Process Design and Evaluation for Chemicals Based on Renewable Resources

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Ph.D. Thesis

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Preface

This thesis is submitted as partial fulfillment of the requirement for the PhD degree at the Technical University of Denmark. The work has been carried out in the Center for Process Engineering and Technology (PROCESS) at the Department of Chemical and Biochemical Engineering from March 1st 2008 to July 31st 2011 under the supervision of Professor John M. Woodley, Professor Rafiqul Gani and Associate Professor Anders Riisager. This PhD project is part of the Bio-petrochemicals project which is a cooperation project between DTU Chemical Engineering, DTU Chemistry and Novozymes A/S, sponsored by the Danish National Advanced Technology Foundation (DNATF).

Lyngby, August 2011

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Wenjing Fu

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Last but not least, to my family, thank you so much for all the support over years.

Abstract

One of the key steps in process design is choosing between alternative technologies, especially for processes producing bulk and commodity chemicals. Recently, driven by the increasing oil prices and diminishing reserves, the production of bulk and commodity chemicals from renewable feedstocks has gained considerable interest. Renewable feedstocks usually cannot be converted into fuels and chemicals with existing process facilities due to the molecular functionality and variety of the most common renewable feedstock (biomass). Therefore new types of catalytic methods as well as new types of processes for converting renewable feedstocks to bulk and commodity chemicals are required. In the future, it seems increasingly likely that a combination of biocatalysts (in the form of enzymes) as well as chemical catalysts will be needed in the production of bulk chemicals from renewable feedstocks. In addition, another characteristic of chemicals based on renewable feedstocks is that many alternative technologies and possible routes exist, resulting in many possible process flowsheets. The challenge for process engineers is then to choose between possible process routes and alternative technologies as well as to match different catalyst conditions. These kinds of problems are crucial, especially at the early stages of process development, when information is limited.

This thesis describes a methodological framework for dealing with the challenges and giving direction to research in the process development of chemicals based on renewable feedstocks. As an example, this thesis especially focuses on applying the methodology in process design and evaluation of the synthesis of 5-hydroxymethylfurfural (HMF) from the renewable feedstock glucose/fructose. The selected example is part of the chemo-enzymatic process design of the synthesis 2,5-furandicarboxylic acid (FDA) from glucose.

By using the selected case study, the complexity and challenges for the process engineer to choose between different alternative routes and technologies as well as to combine two different kinds of catalysis (enzymatic catalysis and chemical catalysis) were illustrated.

Different process routes for the synthesis of HMF from fructose in the literature have been analyzed and evaluated. Using an aqueous route for HMF production is not economically feasible due to the low reaction yield. Using an anhydrous solvent for HMF synthesis is associated with high energy consumption and difficulties with solvent recycle in a large-scale production. The synthesis of HMF from fructose using a biphasic route is found to be promising, cost effective and give a better chance to be integrated with chemo-enzymatic cascades for producing FDA from glucose.

A process flowsheet using chemo-enzymatic cascades for HMF production from glucose has been proposed and evaluated. The process flowsheet is characterized by using glucose isomerase (EC 5.3.1.5) to convert glucose into fructose with a biphasic reaction for dehydration of fructose into HMF with recycle of the aqueous phase back to the

enzymatic reaction. Costing analysis indicates the HMF production cost by the designed process is very sensitive to the dehydration reaction yield, the amount of solvent used in the whole process and the glucose price. In addition, increasing scale is also help to decrease the HMF production cost.

Using an ionic liquid (IL) route for HMF production has been evaluated with the dehydration reaction in [BMIm]Cl with different options starting from fructose and glucose with different initial concentrations. The HMF production cost is highly affected by the recycle of IL and catalyst. Processes with a high feed concentration show better economic potential than processes with a low feed concentration. IL processes starting from fructose are more costly than IL processes starting from glucose. A high concentration feed of glucose showed the best economic potential.

To sum up, the dehydration reaction yield is found to be the key important factor to achieve a feasible production cost of HMF. The use of the organic solvent can not be avoided and plays a very important role in determining the process economics. Recycling (unconverted sugar, reaction medium and solvent) become essential issues for HMF processes to reach a feasible production cost. Future directions and suggestions for the synthesis of HMF from sugar in a large-scale have been proposed. The developed methodology is helpful in evaluation and giving research directions. The methodology can be applied to other chemical process design and evaluation problems and in particular those for the next generation of production processes.

Resume på Dansk

Et af nøgletrinnene inden for procesdesign er at vælge i mellem flere alternative teknologier, og særligt i produktionen af store kvantiteter af almene anvendelseskemikalier. Disse tiders stigende oliepriser og formindskede reserver har gjort, at produktionen af almene anvendelseskemikalier fra fornybare råmaterialer har vagt interesse. Fornybare råmaterialer kan som regel ikke omdannes til brændsel eller kemikalier med eksisterende procesanlæg på grund af deres molekylære funktionalitet og variation af de mest almindelige fornybare råmaterialer (biomasse). Grundet disse problemer er der brug for nye katalytiske metoder så vel som nye processer, der kan omdanne fornybare råmaterialer i massefremstilling af almene anvendelseskemikalier. I fremtiden vil det være sandsynligt, at en kombination af biokatalysatorer (med enzymer), så vel som kemiske katalysatorer, vil være nødvendige i massefremstilling af almene anvendelseskemikalier. Herudover har kemikalier baseret på fornybare råmaterialer mange alternative teknologier og fremstillingsveje, hvilket resulterer i mange forskellige muligheder i procesflowdiagrammerne. Udfordringen for procesingeniører er at vælge i mellem de mange mulige procesveje og alternative teknologier og de tilhørende katalyseforhold. Disse typer af problemer er afgørende, særligt i de tidlige faser af procesudviklingen, hvor information ofte er begrænset.

Denne afhandling beskriver et metodisk framework, der adresserer og vejleder forskning i procesudviklingen af kemikalier baseret på fornybare råmaterialer. Som et eksempel på anvendelse af dette framework, fokuserer denne afhandling på procesdesign og evaluering af syntese af 5-hydroxymethylfurfural (HMF) fra det fornybare råmateriale glukose/fruktose. Det valgte eksempel er en del af det kemo-enzymatiske procesdesign af syntesen af 2,5-fuandicarboxylsyre (FDA) fra glukose.

Den valgte case viser kompleksiteten og udfordringerne som procesingeniører står overfor, når de skal vælge i mellem forskellige alternative synteseveje og teknologier. Herudover er en teknologi med to typer af katalyse (enzymatisk og kemisk) illustreret i casestudiet.

Forskellige procesveje til syntese af HMF fra fruktose fundet i litteraturen er blevet analyseret og evalueret. Anvendelse af en vandig syntesevej til HMF produktion er ikke økonomisk mulig på grund af det lave reaktionsudbytte. Anvendelse af et ikke-vandigt opløsningsmiddel til HMF syntese er forbundet med et højt energiforbrug og vanskeligheder med genanvendelse af opløsningsmidlet i stor skala. Syntese af HMF fra fruktose ved en to-fase vej viser sig lovende, lav i omkostninger og giver en bedre mulighed for at integrere processen med kemo-enzymatiske kaskader til produktion af FDA fra glukose.

Et procesflowdiagram af kemo-enzymatiske kaskader til HMF produktion fra glukose er blevet foreslået og evalueret. Det karakteristiske ved dette procesflowdiagram er, at glukose isomerase (EC 5.3.1.5) bliver brugt til at omdanne glukose til fruktose med en to-

fase reaktion, hvor fruktose dehydreres til HMF med recirkulation af den vandige fase tilbage til den enzymatiske reaktion. Omkostningsanalyser indikerer, at prisen af HMF produktionen ved den foreslåede proces er meget følsom i forhold til udbyttet af dehydreringen, i forhold til mængden af opløsningsmidlet, der bliver brugt i hele processen og i forhold til prisen på glukose. Herudover vil en større produktion også være med til at nedbringe omkostningerne.

Anvendelse af en ionisk væske (IL) vej til HMF produktion er blevet evalueret med dehydreringen i [BMIm]Cl med forskellige muligheder startende fra fruktose eller glukose med forskellige begyndelseskoncentrationer. Omkostningerne af HMF produktionen er særligt påvirket af recirkuleringen af IL og katalysatoren. Processer med høje startkoncentrationer viser bedre økonomisk potentiale end processer med lave startkoncentrationer. IL processer, der starter med fruktose som startprodukt har højere omkostninger end processer, der starter med glukose. En høj startkoncentration af glukose viser det bedste økonomiske potentiale.

I sammendrag er udbyttet af dehydreringen den mest betydende faktor i forhold til at opnå en rimelig omkostning af HMF. Brugen af organisk opløsningsmiddel kan ikke undgås og spiller en vigtig rolle i forhold til bestemmelse af den overordnede procesomkostning. Genanvendelse (uomdannet sukker, reaktionsmedium og opløsningsmiddel) bliver essentielle problemstillinger for at HMF produktionen kan opnå rimelige produktionsomkostninger. Fremtidige retninger og forslag til HMF syntese fra sukker i stor-skala er blevet foreslået. Den foreslåede metodik er hjælpsom til evaluering og til vejledning af forskning. Denne metodik kan anvendes til andre kemiske procesdesign og evalueringsproblemstillinger, og særligt i forbindelse med den næste generation af produktionsprocesser.

Abbreviation

[BMIm]Cl	1-Butyl-3-methylimidazolium chloride
[EMIm]Cl	1-Ethyl-3-methylimidazolium chloride
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
E_tOA_c	Ethyl acetate
FCI	Fixed capital investment
FDA	2,5-Furandicarboxylic acid
GI	Glucose isomerase
HFCS	High-fructose corn syrup
HMF	5-(Hydroxymethyl) furfural
IGI	Immobilized glucose isomerase
IL	Ionic liquid
ILs	Ionic liquids
LCA	Life cycle assessment
MIBK	Methylisobutyl ketone
PET	Polyethylene terephthalate
PG-600	Polyethyleneglycol-600
PTA	Terephthalic acid
TCI	Total capital investment
THF	Tetrahydrofuran
TPC	Total production cost
WCI	Working capital investment

Nomenclature

Nomenclature	Description	Unit
P_{Aj}	Values of pure property j of compound A	-
P_{Bj}	Values of pure property j of compound B	-
r_{ABj}	Ratio of the pure physical property j between compound A and B	-
ρ	Density of the MIBK	kg/m^3
τ	a residence time	h
η	The efficiency	%
$\varnothing(X)$	Correction factor for the IGI related with different conversion	-
[HMF]	HMF concentration	kg/m^3
A	The required area of the heat exchangers	m^2
A_t	The activity of IGI	IGIC/g
DS	Dry substance content in the IGI reactor	% w/w
DX	Dextrose content in the feed to the IGI reactor	% w/w
E	The extraction factor	-
F	Flow rate of the syrup in the IGI reactor	g syrup/hour
K	Experimentally determined constant for IGI	% w/w
k'	Constant correction factor for IGI	-
m	Temperature correction factor for calculating the activity of GI	-
N_s	The theoretical stages	-
Q	The required energy	J
R_{HMF}	The partition coefficient of HMF between the organic solvent and the reaction medium	-
S	The reaction selectivity	% mol/mol
T	temperature	°C
U	The typical overall heat transfer coefficient	W/m^2K
V	The volume	m^3
W	Weight of the enzyme	kg
W_p	The work required for the pump	W
X	The reaction conversion	% mol/mol
Y	The reaction yield	% mol/mol

Contents

1 Introduction

1.1 Chemicals based on renewable resources

Driven by the depletion of fossil resources and increasingly unstable oil prices, searching for replacement of oil based feedstocks for energy and chemical production is a major concern. Given concerns about climate change and CO_2 reduction, biomass as CO_2 neutral, renewable resource is considered to be one of the most promising alternative feedstocks to oil (Poliakoff and Licence, 2007; Brown, 2003; Werpy and Petersen, 2004; Corma et al. , 2007; Christensen et al., 2008; Boisen et al. 2009). A biorefinery is a facility that integrates biomass conversion processes and equipment primarily to produce fuels, and value-added chemicals from biomass (Kamm and Kamm, 2004; Kamm et al., 2006; Fernando et al., 2006). The two strategic goals of the biorefinery development are the displacement of petroleum by renewable raw materials (an energy goal) and the establishment of a robust biobased industry (an economic goal) (Bozell and Petersen, 2010). Addressing the defined energy goal, ethanol, biodiesel and some other biofuels production (butanol, algal biodiesel, etc.) has quickly catapulted to the forefront of displacement a portion of the huge amount of transportation gasoline and diesel which address well the defined energy goal (Huber and Corma, 2006 ; Huber et al., 2007). But despite its high volume, fuel is a low value product. As a result, the return on investment in biofuel-only operations presents a significant barrier to realizing the biorefinery's economic goal (Huber and Corma, 2006; Huber et al., 2007 ; Chisti, 2007; Brehmer and Sanders, 2009; Bozell and Petersen, 2010). Thus, it is required to identify and develop a set of high value products besides fuels in the industries to assure a profitable biorefinery operation.

1.1.1 Production of high value added chemicals as supplements of biofuels in biorefinery

High value, low volume bio-based chemicals provide a potential solution to realize the economic goal of the biorefinery. However, it has not gained the same attention as the biofuel yet. Even though chemical production only accounts for a small portion of oil (4%), it has a high market value. In 2002, world chemicals production (excluding pharmaceuticals) was estimated at 1.3 trillion Euros (Cefic, 2004). World chemicals sales in 2009 were valued at 1.9 trillion Euros (Cefic, 2010). Therefore, the partial

substitution of oil-based chemicals by bio-based chemicals has great potential considering the market.

If the market values for different applications of biomass is compared based on the whole sale level on an energy content basis, the bulk chemicals have a much higher value (75 Euros /GJ end product) than fuel (10 Euros/GJ end product), heat (4 Euros/GJ end product) and electricity (22 Euros/GJ end product) (Sanders et al., 2007). Therefore, biomass should not only be used to make biofuels but also chemicals. In a biorefinery, production of high value bio-based chemicals as supplements to the manufacture of low value biofuels can not only enable efforts to reduce non-renewable fuel consumption but also simultaneously provide the necessary financial incentive to stimulate expansion of the biorefining industry (Bozell and Petersen, 2010).

1.1.2 Production of high functionalized chemicals from biomass

When using biomass to produce bio-based chemicals, high functionalized chemicals offer the best potential chance to compete with petrochemicals. This is because high functionalized chemicals can be produced from biomass without major enthalpy differences (Sanders et al., 2007). The annual production for bulk chemicals is approximately 500 million tones per year, of which about 50% in volume are functionalized chemicals (Weissermel and Arpe, 1993; Lange, 2001; Brown, 2003). Today the entire chemical industry is based on seven building blocks or platform chemicals: methanol, ethene, propene, butadiene, benzene, toluene and the xylene (Lipinsky, 1981), which contain only carbon and hydrogen (Figure 1.1). The conversion of these platform chemicals into high functionalized chemicals requires the aid of co-reagents such as ammonia and various process steps to introduce functionalities such as -NH_2 into the simple structures. This involves major enthalpy changes that require additional process energy in the form of heat and electricity (Figure 1.2). These process and reaction steps are always associated with high pressures and high temperatures as well as corrosive and toxic substrates. Conversely, biomass is always regarded as a mixture of a variety of functionalized components due to its complex carbon backbone and existing chemical functionality. Utilizing these biochemical configurations for synthesizing high functionalized chemicals can significantly reduce the heat required in the process and avoid the use of toxic and corrosive co-reagents (Table 1.1) (Ragauskas et al., 2006).

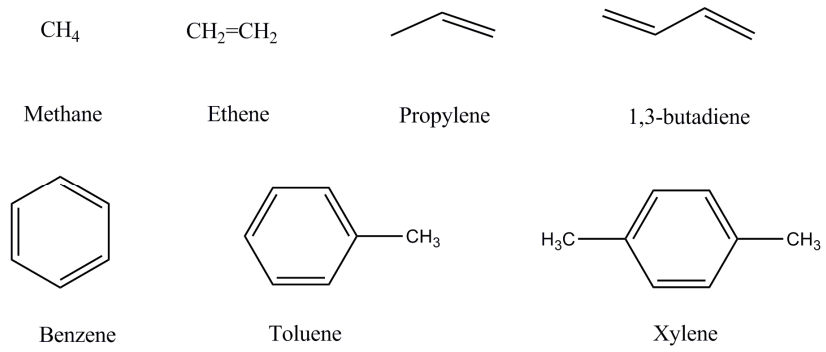


Figure 1.1. Platform chemicals for petrochemical industry.

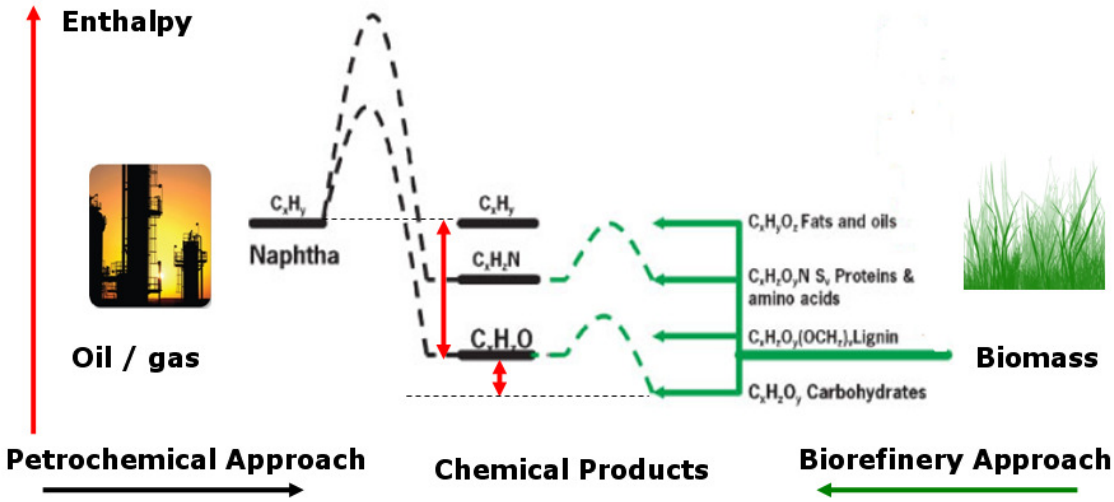


Figure 1.2. Production of functionalized chemicals from oil based feedstocks or from biomass, modified from Sanders et al. (2007).

Table 1.1. Comparison of petrochemicals and bio-chemicals production.

	Petrochemicals	Bio-chemicals
Feedstock	Oil based	Biomass
Chemical structure of feedstock	Only carbon and hydrogen	Rich in functionalized groups
Catalysis methods	Chemical catalysis	Needs to involve biocatalysis
Process condition	High temperature and pressure, use of corrosive and toxic co-reagent	Can be operated in mild condition Can avoid corrosive and toxic co-reagent
Major enthalpy changes	Required	Not required
Renewability	Not renewable	Renewable
CO_2 contribution	Yes	No

1.1.3 CO_2 reduction by replacing fossil feedstock by CO_2 neutral sources

As the issue of climate change has become more prominent on the global agenda, there is further incentive for the replacement of chemicals based on fossil fuels by chemicals based on CO_2 neutral sources such as biomass in order to achieve an overall reduction of greenhouse gas emissions. The fossil feedstocks used as raw materials for products may not immediately end up as greenhouse gas emissions, but will eventually end up as air emissions via incineration (Smith et al., 2001; Lopes et al., 2003; Raymer, 2006; Christensen et al., 2009).

1.2 Synthesis platform chemicals from sugar

Today, the biorefinery is mostly based on simple sugars coming from grain (as in the U.S.) and sugar cane (as in Brazil). By analogy to platform chemicals in petrochemical industry, 12 top chemicals from sugar have also been identified and proposed (Werpy and Petersen, 2004). Some of them are shown in Figure 1.3. Some of the synthesis methods and routes of converting biomass to platform chemicals have been published and reviewed by Corma et al. (2007) and a range of new intermediate chemicals have been identified in order to make the platform chemicals from renewable feedstocks.

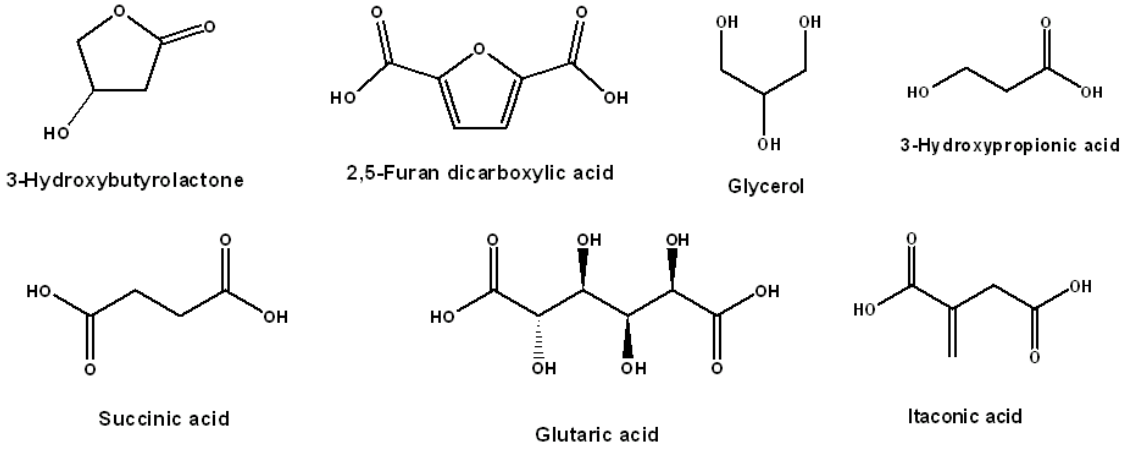


Figure 1.3. Examples of platform chemicals derived from renewable resources.

1.2.1 Glucose – a biorefinery building block

Nature is producing vast amounts of biomass driven by sunlight. However, utilization of biomass for producing chemicals and fuels is still in its infancy with only 3.5% being used for food or non-food purposes. Plant biomass consists mainly of carbohydrates, lignin, protein and fats. Out of an estimated 170 billion metric tons of biomass produced every year roughly 75% are in the form of carbohydrates which makes biomass carbohydrates the most abundant renewable resource (Röper, 2002). Together with their amenability towards enzymatic processes this makes carbohydrates the center of attention when looking for new and greener feedstocks to replace petroleum for producing commodity chemicals as well as fuels. In plant biomass most of the carbohydrates are stored as sugar polymers such as starch, cellulose or hemicellulose.

Starch is the second largest biomass produced on earth and commonly found in vegetables, such as corn, wheat, rice, potatoes and beans. The total world production in 2004 was 60 million tons of which more than 70% came from corn (Boisen et al., 2009). Starch consists of chains of glucose molecules, which are linked together by α-1,4 and α-1,6 glycosidic bonds. The two major parts of starch are amylose (20-30%), essentially linear α-1,4 glucan chains and amylopectin (70-80%), a branched molecule containing 4-5% α-1,6 linkages.

Starch is industrially hydrolyzed to glucose by the 3 enzymes: α-amylase (EC 3.2.1.1), glucoamylase (EC 3.2.1.3) and pullulanase (EC 3.2.1.41) (Schäfer et al., 2007). Cellulose is another glucose polymer consisting of linear chains of glucopyranose units linked together via β-1,4 glucosidic bonds. Hemicellulose is a polysaccharide consisting of short highly branched chains of different carbohydrate units, including five- as well as six-carbon units (e.g. xyloses, galactose, glucose, mannose and arabinose). Hemicelluloses are much easier to hydrolyze than cellulose. The structured portion of biomass, such as straw, corn stover, grasses and wood, is made of lignocellulose composed mainly of cellulose (30-60%), hemicellulose (20-40%) and lignin (10-30%). Both cellulose and hemicellulose consist of carbohydrate components whereas lignin is a highly branched aromatic polymer.

Currently, there is intensive research on the use of a lignocellulosic raw material such as a biomass source for producing chemicals and fuels. However this research still faces considerable challenges due to lignocellulose being remarkably resistant towards hydrolysis and enzymatic attack (Peters, 2007).

Nevertheless, glucose is one of the most abundant monosaccharides in biomass, accessible by enzymatic or chemical hydrolysis from starch, sugar or cellulose. Furthermore, a range of chemical products can be obtained from glucose which gives it a key position as a basic raw material / building block.

1.2.2 Development of a new type of process based on sugar as a feedstock

Development of a new type of process is required in order to shift from oil based chemical industry to the bio-based chemical industry. Clearly, traditional chemical catalytic methods and facilities may not be sufficient since the feedstock (e.g. glucose) is different from the classical fossil based feed-stocks (naphtha). Not to mention that, the most obvious difference between a sustainable biomass-derived platform and the conventional fossil-based one is the much higher oxygen content in the form of hydroxyl, aldehyde, keto and phenol groups, of the former. The appearance of a new generation feedstock requires the development of new types of processes (Table 1.1).

Fermentation of polymer building blocks is already under commercial introduction (Boisen et al., 2009). For example, Cargill produces lactic acid by fermentation and products based on polylactic acid are being introduced to the market. Several companies focus on succinic acid as a polymer building block, but also as a potential raw material for chemicals (e.g. butanediol). DuPont has commercialised a fermentation process for making 1,3-propanediol for its Sorona™ polytrimethylene terephthalate polyester (Hartlep et al., 2002). DuPont is working with Tate and Lyle to scale up the process. Likewise Cargill is working on developing 3-hydroxypropionic acid (3-HP). 3-HP is a potential raw material for existing chemicals such as propanediol and acrylic acid. In addition, DuPont is working with the French starch producer Roquette to commercialize isosorbide, a chemical derivative of sorbitol. Isosorbide is used as a co-monomer for high temperature polyethylene terephtalate. However, even if the commercialization of polymer building blocks made by fermentation is underway, the technology has certain drawbacks such as loss of carbon in form of CO2, low yields and difficult recovery of the products from the fermentation broth (Boisen et al., 2009) (Table 1.2).

To overcome these problems, a new technology is necessary. Chemo-enzymatic synthesis (combined chemical and enzymatic catalysis) has the potential to overcome these problems and represents a promising next generation technology (Vennestrøm et al., 2010).

Table 1.2. Comparison of fermentation and chemo-enzymatic synthesis.

	Fermentation	Chemo-enzymatic synthesis
Feedstock	Biomass based	Biomass based
Selectivity	Low	High
Loss of carbon in process	Yes (as CO_2)	Can be avoided
Toxic substance	Can be produced during fermentation	Can be avoided
Product recovery	difficult	Easy
Product purity	Low	High

Chemo-enzymatic synthetic methods

Simple step synthesis is not sufficient when aiming at the production of the high functionalized platform chemicals from glucose. Production of bio-based chemicals will

require a combination of isomerization, dehydration, oxidation and hydrolysis reactions via a series of intermediate chemicals. It appears essential that the synthetic methods will not rely completely on chemical catalysis but also require the involvement of biocatalysis.

Chemo-enzymatic synthesis offers a great potential for chemical production from sugar. This new synthetic method combines the enzymes together with heterogeneous or homogeneous catalysts together to guide reactions from sugar to high functionalized chemicals. Several advantages such as high selectivity can be gained from such a combination (Vennestrøm et al., 2010). Some of the advantages of chemo-enzymatic synthesis compared with fermentation technology are summarized in Table 1.2.

Although it is evident that both enzymatic catalysis and chemical catalysis must be used, the combination of both has not yet been investigated and used with respect to bulk and commodity chemical production.

1.3 Challenges for process design at the early stage

A key step in process design is to choose between alternative technologies and routes, especially for processes producing bulk and commodity chemicals. This is specially challenging for chemicals based on renewable resources since many possible routes and technologies exist with regard to chemical production from renewable feedstocks. The reasons for this can be explained as following.

First of all, bio-based chemical production is challenged by an overabundance of targets and intermediates (Gallezot, 2007; Bozell and Petersen, 2010). From a fixed material, a range of intermediates can be obtained. These intermediates can further be converted to a range of target products. Integrated biorefinery development is still in its infancy. A core group of primary chemicals and secondary intermediates analogous to those used by the petrochemical industry has just been identified. Even when the final target chemical is fixed, there are still a lot of possible routes via different intermediates. As a consequence, there are always many possible routes from feed stock to the target product (Figure 1.4).

In addition, bio-based chemical production is challenged by a lack of fixed knowledge based conversion technology (Weissermel and Arpe, 2003). Conversion of renewable carbon to chemicals is the least developed and most complicated operation in the biorefinery. For most reactions, suitable catalysts (enzymes, homogenous or heterogeneous chemical catalysts) are still being screened in the laboratory to improve the reaction yield. Most of the reactions are not well developed or optimized. Therefore, the conversion technologies of such reactions are not well defined and many possible alternative technologies exist (e.g. from feedstock to intermediate 1 in Figure 1.4). To choose among the possible technologies, decisions can not be based only on the reaction

yield. How well the reaction steps can fit into the whole process development also needs to be considered.

Another difficulty is to match the operation conditions for different types of catalysis (Hailes et al., 2007). As discussed in Section 1.2.2, bio-chemical production requires involvement of both chemical catalysis and biocatalysis. Consequently, the challenge in this type of process design is how to match the different conditions for different types of catalysis. This includes matching the stability of catalyst, pH, reaction medium, temperature, pressure and reaction rates. In order to match the conditions, certain amount of downstream/up stream process operations is thus required between different reactions.

All these challenges mentioned above result in many possible process flowsheets and options existing for bio-based chemical production. Selecting the right process is critical, especially at the early stage of the process development, when the information is limited. Experiments evaluation is difficult in this case considering the number possibilities. It is slow and expensive. It is hard to judge where the research effort should be placed on.

Therefore, a methodology, which could evaluate quickly different process options with limited information, will be very helpful at the early stage of the process development. Such methodology is also highly required in order to accelerate the development of bio-chemical production.

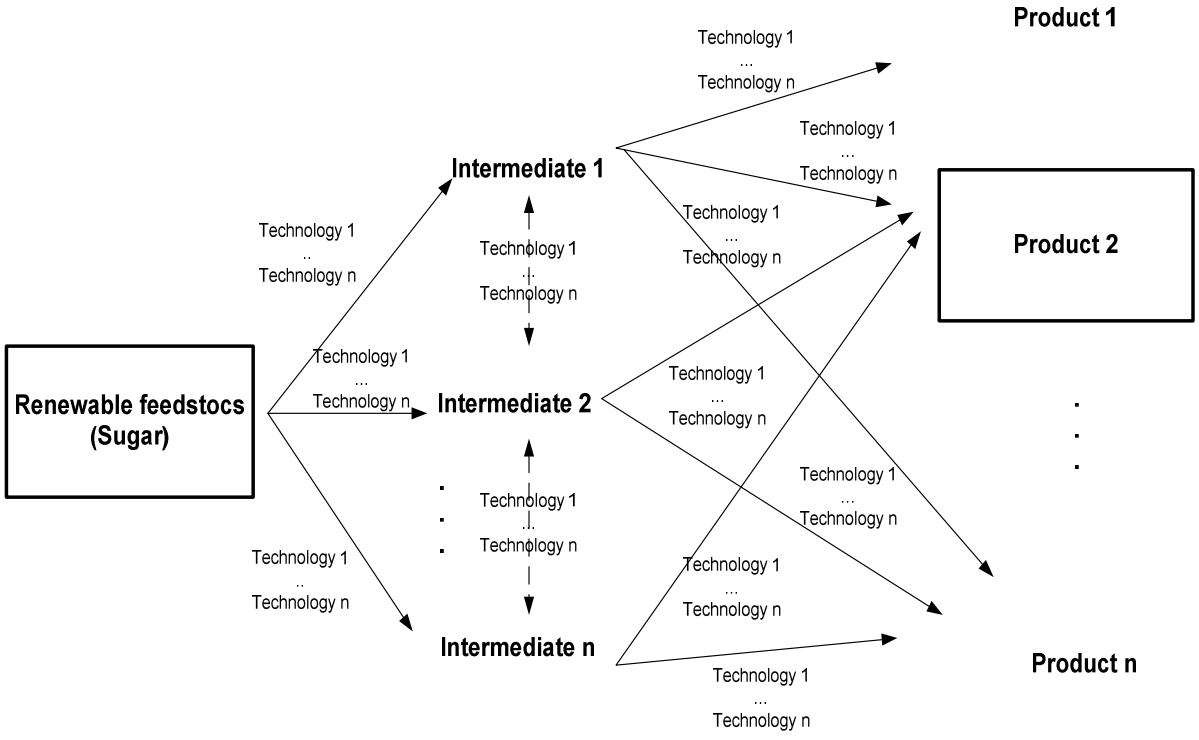


Figure 1.4. Various process technologies and routes exist for the bio-chemical production.

1.4 Objectives of the thesis

The main objective of this PhD is to develop a methodology, which is able to evaluate quickly different process options for production of bio-based chemicals at the early stage of the process development when limited information is available. The aim of the methodology is to understand where the problems are, to identify the important issues in developing a new process, to eliminate some unfavorable options at an early stage, and thus to detect where the research effort should be focused.

This PhD thesis particularly focuses on a case study: process design of synthesis of 5-hydroxymethyl furan (HMF) from glucose with specification and economic constraints. The whole case study is part of the project: process design for production of 2, 5-furandicarboxylic acid (FDA) from glucose via intermediate HMF. The selected case study is used as an example to illustrate:

1. The complexity and the challenge that lies ahead for bio-chemical process development

2. How to evaluate and choose among different options with limited information

3. Issues associated with combining enzymatic catalysis and chemical catalysis in process design

4. Important issues and future requirements in process development for bio-based chemicals in order to be able to compete with oil based chemicals

This case study will provide valuable knowledge for other chemical process design and evaluation problems and in particular those for the next generation of production processes.

1.5 Structure of the Ph.D. thesis

This thesis is organised as follows:

Chapter 1 provides the background information on the importance of producing chemicals from renewable resources. It also highlights the differences between oil-based feedstocks and bio-based feedstocks, and the need for a new type of process and catalytic method for bio-chemical production. The difficulties and challenges with respect to bio-chemical production are introduced.

Chapter 2 describes an early stage evaluation methodology. The methodology is specially developed for evaluating process options at the early stage when limited information is available.

Chapter 3 introduces background information on the synthesis of FDA from glucose via the intermediate HMF. Possible routes and technologies for the synthesis of FDA from glucose are introduced. Using chemo-enzymatic synthetic cascades to produce FDA from glucose is proposed together with the challenges. The three main reactions involved in the whole process are introduced. The bottleneck of the cascade design is identified as the middle dehydration reaction (dehydration of fructose to HMF).

Chapter 4 reviews the literature on the dehydration reaction. Based on this, future researches are suggested for HMF production from fructose. Potential integrated process flowsheets are proposed.

Chapter 5 applies the proposed methodology to evaluate three conventional routes for HMF production from fructose based on the published flowsheets. By evaluating the three process routes, the biphasic process route is identified as the best option to operate the dehydration reaction.

Chapter 6 describes and proposes a new process flowsheet of chemo-enzymatic synthesis of HMF from glucose. The proposed process flowsheet is evaluated by the developed methodology. The feasibility and potential of using a chemo-enzymatic synthetic method for bulk chemical potential is illustrated.

Chapter 7 proposes and examines using ionic liquids for HMF synthesis. A potential process flowsheet of using single phase reaction medium for HMF production is proposed and evaluated by the developed methodology with different process options. The feasibility and future directions for HMF production by the IL route is discussed.

Chapter 8 discusses the key issues with regard to HMF production from glucose/fructose. Future research directions are discussed together with a comparison of all the potential routes for HMF production. The potential for HMF (FDA) to substitute terephthalic acid is stressed. The feasibility and limitation of the proposed methodology is also discussed.

Chapter 9 concludes on the HMF process and the developed methodology.

Chapter 10 provides suggestions for the future directions and developments both for the HMF process and the developed methodology.

2 Methodology

Summary

In this chapter, a methodology for early stage evaluation of different process options for production of bio-based chemicals is proposed. The proposed methodology aims to give a fast evaluation of different process options based on the limited information. This methodology uses cost metrics and sensitive analysis to assess the effects of process parameters on the final production cost. Using this methodology, the most important issues of the process design as well as potential process configurations can be identified. The targets for future research are thus set up.

2.1 Introduction

One of the main challenges for process engineering is how to choose between different process alternatives. This problem becomes even more crucial with process based on renewable feedstocks as discussed in the previous chapter.

In the following sections of this chapter, the existing methodology for both oil-based chemical and bio-based chemical process design is reviewed. The drawback of the existing methods for bio-chemical process design is emphasized. The differences between the proposed methodology and the existing methods are highlighted. Afterwards, the objectives of the proposed methodology are introduced, followed by an overview of the whole methodology. The methodology is then described step by step. In each step, the modeling tools involved and the required input data are described.

2.2 State of the art

2.2.1 Methodologies used for oil-based chemicals

For chemical processes, a large amount of literature on systematic process synthesis and design methods is available. Excellent reviews of process synthesis are given by Nishida et al. (1981), Westerberg (1989), Johns (1987), and Li & Kraslawski (2004).

The heuristic or knowledge based approach is used to narrow the list of possible processing steps based on general experience. There are numerous examples in the literature of the use of heuristics to solve synthesis and design problems in the chemical industry. Particularly, heuristics dealing with the synthesis of separation processes are fairly well developed (Sirrola and Rudd, 1971; Barnicki and Fair, 1990, 1992; Chen and Fan, 1993; Seader and Westerberg 1977; Nath & Motard 1978). Example applications also exist in complete process flowsheets (Siirola & Rudd, 1971; Powers, 1972), and waste minimization schemes (Douglas, 1992). For example, Douglas (1988) applied the hierarchical heuristic method to the synthesis of benzene through the hydrodealkylation of toluene (commonly known as the HDA process).

Thermodynamic/physical insight based methods for synthesis and design rely on thermodynamic data of mixture compounds and analysis of feasible solutions of chemical process flowsheets. The methodology was proposed and applied for design and synthesis of separation processes (Jaksland et al. 1995, Jaksland and Gani, 1996).

Another method, called the driving force approach, makes use of thermodynamic insights and fundamentals of the separation theory, utilizing property data to predict optimum or near optimum configurations of separation flowsheets (BekPedersen, 2002; BekPedersen and Gani, 2004; Gani and BekPedersen, 2000). This approach allows identifying feasible distillation sequences and other separation techniques.

Optimization methods solve an optimization (synthesis/design) problem with a measure of what is needed for the best solution (Biegler et al., 1997). In such an approach, an objective function is defined for the problem, usually a mathematical expression related to the yearly cost or profit of the process. The result of an optimization problem is the optimal value for a set of variables, where some of them may be bounded to lie within a defined set of constraints. This approach has been widely applied in process synthesis and design for chemical processes (Lin and Miller, 2004; Angira and Babu, 2006; Raeesi et al., 2008; Karuppiah et al., 2008; Li et al., 2009). Excellent reviews with respect of suitable optimization techniques for process synthesis were published by Grossmann and Daichendt (1996) and Grossmann (1985, 2002).

The hybrid approach combines thermodynamic insights with mathematical programming based on synthesis algorithms (Hostrup, 2001). Hybrid methods are usually implemented as step by step procedures. The solution of one problem provides input information to the subsequent steps. Finally, such a procedure leads to an estimate of one or more feasible process flowsheets. The final step of hybrid methods is a rigorous simulation for verification of the proposed process flowsheet (d'Anterroches and Gani, 2005; d'Anterroches, 2005). D'Anterroches (2005) illustrated this approach with a set of case studies related to the chemical industry.

2.2.2 Methodologies used for bio-based chemicals

In contrast, the same abundance of literature does not exist for the bio-chemical process design and synthesis.

Regime analysis is an approach to identify bottlenecks and to assess the potential benefit gained from alleviating these. Key to this is the choice of several process metrics which adequately describe the effect of limiting regimes and simultaneously allow for sensitivity analysis of the varying process conditions. This approach was applied to analyze the key process limitations of the Baeyer–Villiger mono-oxygenase catalyzed synthesis of optically pure lactones (Law et al., 2006). In the study, limitations of product concentration, catalyst longevity and reaction rate were quantified and the effect on important process metrics was analyzed. By using this approach, the sensitivity of the metrics to potential changes of the process and the catalyst were successfully analyzed.

Windows of operation is another approach which graphically illustrates how process constraints affect the performance of a process (Woodley and Titchener-Hooker, 1996). Briefly, the windows of operation are found by evaluating how various process variables, e.g. catalyst concentration or stability, influence key process metrics, e.g. the reaction rate and productivity. Defining hurdle (or threshold) values for the process metrics, allows identifying the process conditions that fulfill these constraints (Law et al., 2008). Windows of operation can be used to help understand and optimize biocatalytic processes. The method has been developed and applied in chemo-enzymatic process design (Blayer et al., 1996), pharmaceutical process design and other biocatalytic processes (Law et al., 2008).

However, the current approaches for bio-chemical process development mainly focus on each process step individually and not as a whole. Indeed, the current approach for bio-chemical process synthesis is often performed in a sequential fashion, proceeding from one unit to the next until product specifications are met, subsequently optimizing individual units. This approach may produce economically adequate processes. However, alternative designs that have not been explored yet may be more profitable.

Additionally, the current process design in the bio-chemical industry relies heavily on the use of expensive pilot plant facilities to test out proposed new process sequences. This approach is time consuming and not systematic.

The approaches used in classical chemical process design and synthesis have not been developed for bio-chemical processes. Several major obstacles arise when attempting to apply them to solve bio-chemical synthesis and design problems. These problems are particularly critical at the early stage of the process development.

The heuristic methods are based on a limited number of operational data, and are thus limited to only specific types of operations. On the other hand, since the heuristic rules are based on observations made on existing processes, the application of heuristic methods requires careful consideration because they may lead to the elimination of novel

process flowsheets which seem to contradict prevailing experience, yet having interesting or desirable features. This can be a big obstacle when this approach is applied to bio-chemical process design.

Insights based methods are useful to identify feasible separation. However, if experimental data of the pure compounds or mixture properties are not available in the open literature, the major drawback of these methods is that they rely on the accuracy of models and/or methods to estimate the necessary physical properties. With regard to bio-chemical process design, lack of physicochemical properties is a general problem.

The hybrid approach is very hard to apply to bio-based process design. Biological streams are highly dilute and generally contain a large number of compounds. These characteristics lead to a large number of flowsheet structure candidates and, therefore, a corresponding large search space for the synthesis algorithm. Synthesis problems of this size are difficult to solve using numerical optimization approaches.

2.2.3 Highlights

To conclude, the current methods in bio-chemical process design and evaluation are often not based on a whole process level but focus on one process step. In addition, it relies heavily on experiments and pilot plant facilities. The established systematic approaches for oil based chemical process design are difficult to apply to bio-chemical process design.

Clearly, there is still a lack of methodology in bio-chemical process design and there is a strong need for a systematic framework for a quick and reliable evaluation of a large number of process configurations. The higlights of the proposed methodology are:

1. To apply the evaluation on the whole process level.

2. To evaluate at the early stage of process development.

3. To use costs at the early stage to direct research. In most of oil-based chemical process design and synthesis, costing is always used as an objective function to optimize the designed process configuration in the end. Conversely, the new developed methodology applies costing at the very early stage to direct research instead of optimizing it at the end.

2.3 Aims

The proposed methodology aims at facilitating the design a new type of processes (process started from renewable feedstocks) at the early stage of process development. The main aim is to help understanding where the important issues are with respect to the

whole process design. Hence it helps to direct the research and find out where the research efforts should be placed on.

At the very early stage of process development, the amount of potential catalysts, different types of reaction media, and possible routes or technologies result in a large number of possible process configurations. Carrying out experiments is expensive and time consuming, especially when scaling up. The challenge here is to use the limited information at hand to eliminate the least promising configurations and provide a focus for the investment of research and development effort.

For selected potential process flowsheets, simulations and experimental work are used to obtain the necessary process data for a cost evaluation. The aim is to evaluate the scale up possibility of the potential flowsheets. Costing of the flowsheets is applied together with the sensitivity analysis. By checking the sensitivity of process parameters to the production cost, the important issues related with the process design can be identified. This helps to understand and find out the bottleneck and the problems related with the process configurations. Finally, the future directions are identified.

2.4 Description

The work flow and tools included in the methodology are outlined in Figure 2.1. The whole evaluation methodology contains six steps which include literature research to identify possible process options, data collection for process simulations, data generation if not available, process simulation, evaluations and analysis of process metrics, options kick off and identification of the potential flowsheets for more detailed evaluations.

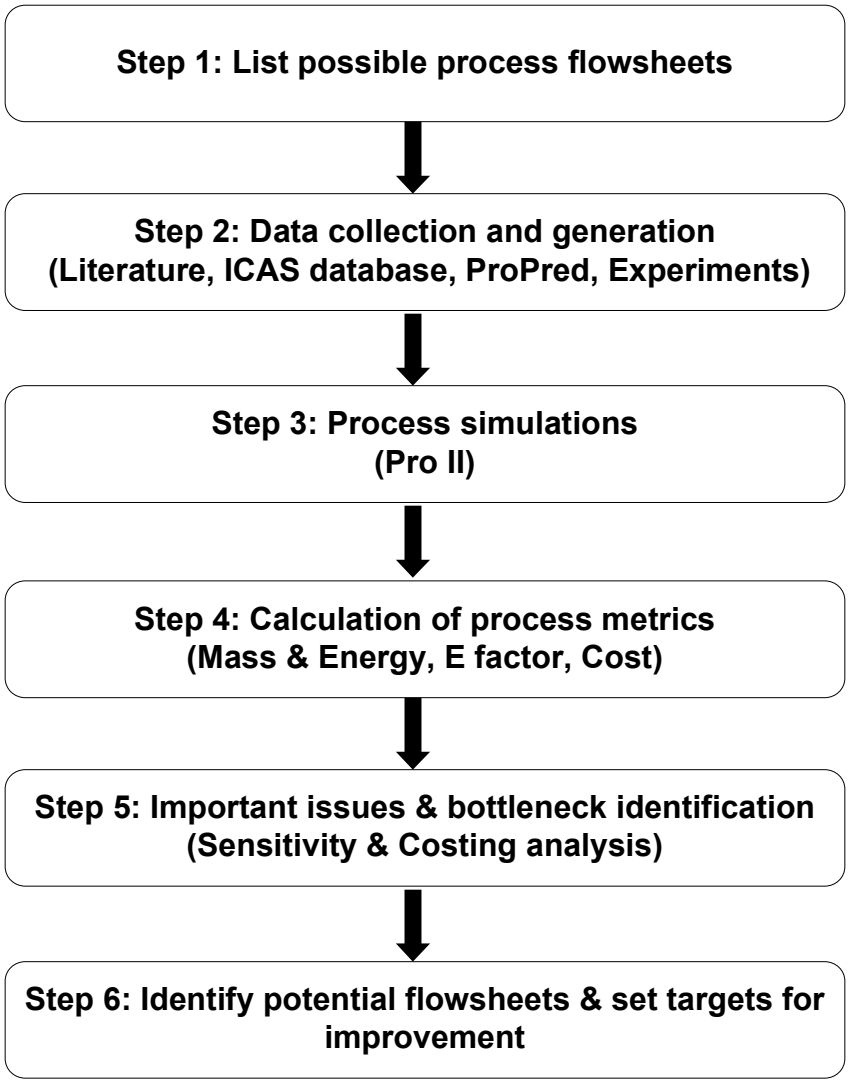


Figure 2.1. An overview of the proposed early stage evaluation methodology.

2.4.1 Step 1: List possible process flowsheets

The first step in the methodology framework requires a literature research to gather information about possible routes from the feedstock to the final products and possible technologies for different process steps. Based on what has been achieved so far, a list of possible process flowsheets and configurations can be identified. These flowsheets include the published literature flowsheets and also potential flowsheets developed based on the literature study.

2.4.2 Step 2: Data collection and generation

In order to compare these different process flowsheets, process metrics such as mass metric, energy metric, environmental metric and cost metric of different process flowsheets are needed. To calculate these metrics (Step 4), data are required. The necessary data can be divided into two types: process data and property data of the chemicals involved in the flowsheets.

Process data

Process data here means the data that describe and characterize a unit step involved in the process flowsheet. Taking a reactor as an example, the required relevant process data are: all the reactions inside the reactor, products information from the desired product as well as the unwanted byproducts, reaction data (the conversion of the main feed and selectivity for each product) and relative reaction condition data (temperature, pressure, pH, reaction time, catalyst amount, raw material initial concentrations). These data can be found in the published literature. If they are not available in open literature, then batch experiments are required to obtain them.

Kinetic information is useful to identify the effects of the operation parameters (temperature, concentration, pH, catalyst amount, inhibition by intermediates) on the yield of each product. At the early stage, a detailed kinetic model of a reaction may not be available in literature, but it is not always necessary to obtain such information by experiments. Basic knowledge of how the parameters affect the yield is sufficient.

For different process steps such as separation steps, basic data like yield, temperature, pressure, pH, amount of feed, feed concentrations and process aids (if there are any) are required for the mass and energy calculations (Step 4). The required data for a unit step are illustrated in Figure 2.2. Basic data of each stream entering the process step and the process step data are required to calculate the data of the outlet streams. If the data of a process step is missing, the data of the inlet and outlet streams are required to calculate the process step data.

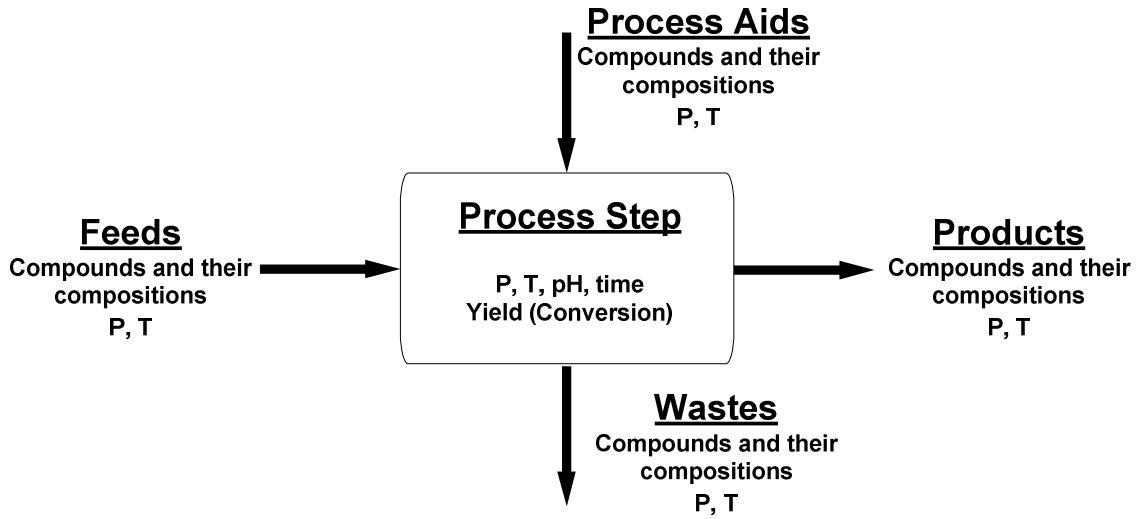


Figure 2.2. Required process data for a process step involved in a process flowsheet.

Compounds' property data and thermodynamic data

Besides process data, another type of required data are physicochemical properties and thermodynamic data of involved compounds. These data include boiling point, density, heat of formation, vapor pressure, enthalpy and so on. Besides the pure property data of the compounds, binary phase diagrams such as vapor-liquid phase diagram between two compounds (design basis of a distillation column/evaporator) and ternary diagrams of compounds (design basis of a liquid-liquid extraction) are also required. Many compounds involved in the processes starting from renewable feedstocks are relatively new compounds compared to oil based chemicals. Therefore, these data are generally not available in the literature. Experimental work to get the missing data can be difficult and time consuming.

An alternative solution is to use available software to estimate the required data. Several software are available to estimate the pure property data and the thermodynamic data of a compound through its chemical structure, e.g. the ThermoData Engine software from NIST (Diky et al., 2007) and ProPred a toolbox from the ICAS software developed by Gani et al. (1997).

The proposed methodology uses ICAS tools. ICAS contains many useful packages and its database contains many property data of chemical compounds. ProPred can be used for missing property data prediction. ICAS is also able to generate the required phase diagrams (both binary VLE diagram and ternary LLE diagram).

2.4.3 Step 3: Process simulations

In order to calculate the required mass and energy of a process flowsheet (Step 4), the process flowsheet can thus be simulated in process design software such as ProII (ProII, 2011), or other packages after gathering all the required data (Step 2). Depending on the complexity of required examinations, sometimes, a simple spread sheet is sufficient. At the early stage of the evaluation, only steady state analysis is required, so ProII, which is a steady state simulator is used.

Short cut model/stream calculators

As mentioned above, one of the major problems is lack of data. Although a lot of pure property data can be predicted, missing parameters between binary groups in the thermodynamic model impedes generating phase equilibrium data between compounds. As a consequence, the unit equipments listed in ProII cannot be applied (ProII, 2006).

For example, an extraction column listed in ProII can not be used to simulate the extraction step in the flowsheet if the binary parameters for the selected thermodynamic models are missing. The missing data can be generated by ProII (ProII, 2006), if all the

compounds can be described properly with the existing UNIFAC groups (and known parameters). However, experimental validation is necessary. Sometimes, the quality of the estimated parameters is not good enough to be used to simulate the process step.

In this case, if the aim of simulating a process step is only to calculate the mass and energy, short cut model (the stream calculator) can be applied in ProII as an alternative. Applying the stream calculator requires knowing the process data of the streams both entering and leaving the process step, such as the pressure, temperature and composition of the streams. With this information, the required mass and energy can be calculated.

2.4.4 Step 4: Calculation of process metrics

In this step, different process flowsheets are evaluated with four process metrics: mass metric, energy metric, environmental metric (the E-factor) and cost metric. The methodology takes into account the required mass of different raw materials, energy and waste for making a given amount of product by different routes. All the metrics are calculated based on the mass and energy calculation of different flowsheets. The mass and energy calculation can be obtained through the previous simulation step (Step 3). By comparison of these metrics for different process options, some unfavorable process configurations can be eliminated.

Mass metric

Mass metric is calculated based on an output of 1 kg of final product. The calculation of process inputs (reactants, reagents, solvent and catalysts) and outputs (products, by-products and waste) are performed by using standard chemical engineering principles and based on the literature process descriptions or experimental results.

Energy metric

The energy metric is calculated based on the energy required for making 1 kg of final product. The energy required for process steps (such as reactors, evaporators) can be obtained from the simulation results of the process configurations in software such like ProII. The energy required for cooling and heating of each individual process step are estimated using typical heat transfer equations. Process temperatures and pressures for estimating heating and cooling enthalpies are based on the process descriptions or conditions at which the experiments took place.

E-factor

The E-factor is used as the environmental metric. It is a widely used and broadly accepted measure of the environmental acceptability of a given chemical process. The E factor is defined as the mass ratio of waste to desired product (Sheldon, 2007; 2008):

E-factor = Total Waste (kg) / Product (kg) Equation 2.1

The E-factor describes the actual amount of waste produced in the process, without regard to the type of waste. The waste is defined as everything but the desired product. The E-factor takes the chemical yield into account and includes reagents and solvent losses. A higher E-factor means more waste and, consequently, a negative environmental impact. Table 2.1 gives some typical E-factors in several sectors of the chemical industry.

Interestingly, there has been controversy about whether the water used in the process (as opposed to utilities) should be excluded in the calculation of the E-factor or not. This is because inclusion of water used in the process can lead to exceptionally high E-factors in many cases and can make meaningful comparisons of processes difficult (Sheldon, 2007;2008; Lancaster, 2002). However, nowadays, one of the major criticisms about biocatalysis is the amount water used in the process (Henderson et al., 2008). So in this thesis, the water is included in the E-factor calculations.

Table 2.1. Typical values of the E factor in chemical industry. Data are taken from Sheldon (2007).

Industry Segment	Product (tons)	E-factor
Oil Refining	106-108	< 0.1
Bulk Chemicals	104-106	<1-5
Fine Chemicals	102-104	5-50
Pharmaceuticals	10-103	25-100

Cost

Both the product cost and the product production cost are used as the process economic metrics.

Product cost

At the screening stage of different process configurations, the product cost which only takes into account the raw material and energy cost is used as the cost metric. The product cost can be written as:

$$\text{Product cost (USD/kg)} = \frac{\text{(Raw material cost + Energy cost)}}{\text{Product production}} \qquad \text{Equation 2.2}$$

The raw material price can be found in some of the publications, or using pricing website such as icis website (icis, 2011) or through personal contact with the chemical companies. The raw material cost here is a sum of the cost of reactants, cost of solvent loss, cost of process reagents and cost of catalyst. Material cost in this metric is calculated by using the required material based on 1 kg product production multiplied by the material price (USD/kg).

The energy cost is the sum of the cost of the heating steams, the cooling water and the electricity. The energy cost is calculated by using the required steams, cooling water and electricity based on 1 kg product production multiplied by their prices.

Product production cost

The product cost is part of the product production cost. However, the product production cost is a more detailed economic metric. Here, it is applied to the identified potential flowsheets for a more detailed evaluation. The following paragraphs describe the calculation of a product production cost.

Step 1: Design information collection
The first step in the calculation of a product production cost of a potential process flowsheet is to set the design scale (the capacity of the designed plant). Once the capacity information is settled, the designed flow rate of the plant can thus be calculated with designed working days. Further information with the plant location, raw material supply information, and labor cost should also be collected. At the early stage, this information is hard to get and thus always based on hypotheses.

Step 2: Estimation of the raw mater & energy supply
The required mass and energy flows are calculated according to the previous parts of mass and energy calculation. Annually required raw material, annually produced products, byproducts and produced wastes can be estimated based on the mass calculations. Annually required cooling water, steams, electricity can also be estimated based on the energy calculations.

Step 3: Estimation of the purchase equipment cost
With the designed capacity of the plant, the size of equipment required in the flowsheet can be estimated with knowing the residence time of each unit. Sizing, selection and design calculation of the equipment can refer to handbooks of chemical engineering. After sizing the equipment, the cost of purchase of the equipment can be estimated according to Equation 2.3. The equation is a correlation derived from a log-log plot of the equipment size vs. capacity, which is a common equation to calculate the equipment prices.

$$\text{Cost(equip.a)} = \text{MFPCost(equip.b)}\left(\frac{\text{capac.equip.a}}{\text{capac.equip.b}}\right)^{c} \qquad \text{Equation 2.3}$$

In this equation, the c is the exponent and it varies with different equipment. The MFP is the correction factor, which relates the base equipment to the relative designed condition. The value of MFP depends on material selection, pressure, and temperature. The cost references can be taken from Peters et al. (2004) and the website www.matche.com.

Step 4: Estimation of the total capital investment (TCI)
The capital cost includes the fixed capital investment (FCI) and the working capital investment (WCI). The fixed capital investment consists of the cost of purchase equipment (including delivery cost), equipment installation, instrumentation and controls, piping, electrical systems, building, yard, land, service, engineering and supervision, legal expense, construction expense, contractor's fee and contingency. The working capital investment on the other hand is the sum of the money invested in raw materials,

supplies carried in stock, finished products in stock, semifinished products in the process of being manufactured, accounts receivable, cash kept on hand for monthly payment of operating expenses, account and taxes payable.

There are many methods for estimating the total capital investment. Most of the methods are based on the purchase equipment cost. In this early stage evaluation method, it is chosen to estimate the fixed capital investment by using percentages of the delivered-equipment cost (E) (Equation 2.5).

$$TCI = FCI + WCI \qquad \text{Equation 2.4}$$

$$FCI = E\sum(1 + f_1 + f_2 + f_3 + ... + f_n) \qquad \text{Equation 2.5}$$

Where f_1, f_2, …, f_n are multiplying factors for piping, electrical, engineering and supervision etc. Table 2.2 lists some typical percentage values for estimating the capital investment based on delivered equipment cost. For some categories, the percentage values have a large range. They depend on the type of plants (liquid processing plant, solid processing plant or solid-liquid processing plant). Typical values for different processing type of plant can be found in Peters et al. (2004).

Typically, in plant design, the fixed capital investment (FCI) is around 80% to 90% of the total capital investment (TCI). And the working capital investment (WCI) is around 10% to 20% of the total capital investment. The TCI and WCI can be calculated with the FCI using the mentioned percentage values.

Table 2.2. Typical percentage values for estimating the capital investment based on delivered-equipment cost. Values are taken from Peters et al. (2004).

Fixed capital investment (FCI)	Percentage of Purchased Equipment
Purchased equipment (delivered, E)	100%
Installation	25-55%
Instrumentation (installed)	8-50%
Piping(installed)	16-68%
Electrical (installed)	15-30%
Building (including service)	5-68%
Yard improvement	10-20%
Service Facilities (installed)	30-80%
Engineering and supervision	32-33%
Construction expenses	34-41%
Legal expenses	4%
Contractor's fee	17-22%
Contingency	35-44%

Step 5: Estimation of the product production cost

The product production cost consists of the variable production cost, the fixed charges, the plant overhead costs and the general expenses.

The variable production cost includes the cost of raw material, of catalysts and solvents, of utilities (electricity, steam, process water and cooling water etc.), of waste disposal, of labor and labor supervision, of plant maintenance and repair, of operating supplies, of laboratory charges, of royalties, and of patents.

The fixed charges include the taxes of the property, financing, rent, insurance and depreciation charge.

The plant overhead cost is the cost directly related to the production operation. Normally, it is about 50% to 70% of the total expenses of the operating labor, supervision and maintenance cost.

General expenses are classified as administrative expenses, distribution and marketing expenses and research and development expenses.

For estimating the product production cost, the costs of raw material, solvent, catalysts, utilities and waste disposal are calculated with respect to the mass and energy balance of the process flowsheet. The labor requirement can be estimated from the capacity and the type of the equipment in the plant. Other remaining variable costs, fixed cost without depreciation, plant overhead cost and general expenses can be estimated using typical percentage values. Some typical used percentage values are listed in Table 2.3.

The equipment, buildings and other fixed capital investment requires an initial investment that must be paid back. This is charged by the depreciation cost. The most widely used method of the depreciation calculation is the MACRS method, in which the amount of depreciation changes year by year (Peters et al., 2004). For a quick estimation at the early stage, a constant yearly depreciation rate is acceptable.

Table 2.3. Typical percentage values for estimating the product production cost. Values are taken from Peters et al. (2004).

	Type of expenses	Typical values
Variable cost (some)	Labor supervision	15% of the labor cost
	Maintenance and repair	2-10% of the fixed capital investment
	Operating supplies	15% of the cost of the maintenance and repairs
	Laboratory charges	10-20% of the labor cost
	Royalties	0-6% of the product production cost
Fixed cost (without depreciation)	Taxes (Property)	1-2% of the fixed capital investment
	Financing	5-10% of the total borrowed capital
	Rent	8-12% of the total rented property
	Insurance	1% of the fixed capital investment
Plant overhead cost	Plant overhead cost	50-70% of the total labor, supervision and maintenance cost
General expense	Administrative cost	15-25% of the operating labor cost
	Distribution & marketing cost	2-20% of the product production cost
	Research & development cost	5% of the product production cost

2.4.5 Step 5: Important issues and bottleneck identification

The process metrics calculated above can give a rough evaluation of different process routes. Some unattractive process options can be eliminated at this stage. The promising process options can also be identified. The next step is to use sensitivity analysis together with cost metrics to find out the important issues of the potential process flowsheets. By estimating the sensitivity of different process parameters (such as different process unit yield, amount of the solvent, different process temperature, pH, pressures) on the final cost, important issues and bottleneck of a process flowsheet can be identified.

By using the methods described above, the potential of a process flowsheet for scale up and industrialization can be evaluated. By fixing the acceptable product cost, changing the process parameters of a process flowsheet can be used to identify the acceptable range of the parameters. Therefore, research targets of different process steps can be identified in this way. On the other hand, the sensitivity analysis of different process parameters can be used to identify the most important process steps of a process flowsheet (Figure 2.3). This step is useful to identify the improvement targets. It also helps to understand better the problems related with the evaluated process flowsheet.

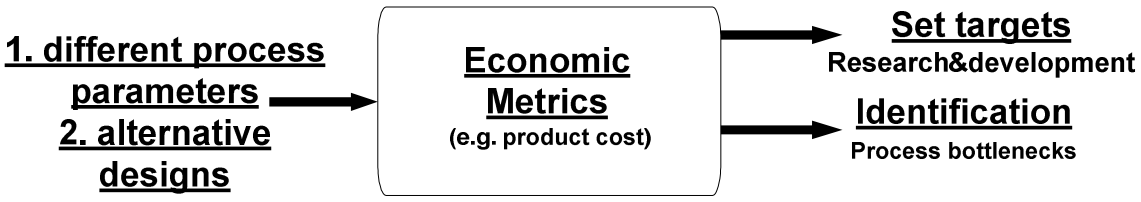


Figure 2.3. Using economic metrics to analyze the important issues and identify the targets for improvements.

2.4.6 Step 6: Identify potential flowsheets and set targets

Potential process flowsheets as well as alternative designs can be identified by using the analysis in Step 5. The research focuses for future improvements in different research areas in process design (reaction design, catalyst design, solvent selection, and downstream unit design) can be concluded.

Concluding remarks

In this chapter, a methodology framework for bio-chemical process design at the early stage is proposed. In the following chapters, a case study is used to illustrate the application of the methodology.

3 Introduction of the Case Study: Synthesis of FDA from Glucose

Summary

In this chapter, a particular interesting case of synthesis of 2,5-furandicarboxylic acid (FDA) from glucose via an intermediate 5-hydroxymethyl furfural (HMF) are introduced as an example with content in the biorefinery for the production of a bulk chemical from sugar. The first part of this chapter introduces the application of HMF, FDA and gives an overview of a series of possible synthetic routes from glucose FDA via HMF. After the overview, the focus is placed on a particular chemo-enzymatic route with cascade reactions from glucose to FDA. The second part of this chapter focuses on discussing the difficulties and challenges in process design for the chemo-enzymatic synthesis FDA from glucose.

3.1 Introduction

A particularly interesting example in biorefinery in the content of production of bulk chemicals with sugar as feedstock can be production of 5-hydroxymethylfufural (HMF) or 2,5-furandicarboxylic acid (FDA) from glucose. The selected specific example with a defined starting and endpoint is an excellent example to illustrate the complexity and the challenge that lies ahead in the process development for production of platform chemicals from biomass (sugar) as stated in the introduction. Great value is obtained by going the whole way from glucose to FDA.

However, even in this small reaction pathway, there are many possible routes from glucose to FDA. Among each route, there are many alternative technologies as well. Some can be integrated together, some give the required yield and selectivity, some are difficult to implement and others are untested at scale. This illustrates very well the challenges that design engineers face.

To date glucose finds its major application in food applications (as a feedstock for sorbitol and high fructose corn syrup). The possibility of non-food products like HMF or FDA implies the use of other technologies not governed by the strict food regulations.

Nevertheless all the potential technologies need to be able to overcome the pH and temperature instability and limited solubility in organic solvents. It is because of the nature of glucose therefore that one obvious starting point is to use enzymatic catalysis (water based and under mild conditions).

In this chapter, the possible routes and the alternative technologies from glucose to FDA are reviewed. The challenges of using chemo-enzymatic route are discussed.

3.1.1 Introduction of HMF, FDA

Recently, there are great of interests in research on developing the methods of synthesis HMF and FDA (Boisen et al., 2009; Cheda et al., 2007; Werpy and Peterson, 2004; Corma et al., 2007; Moreau et al., 2004). FDA is a promising new biomass derived chemical building block. One of the attractions of synthesis FDA is that it can potentially replace terephthalic acid (PTA) in the production of polyethylene terephthalate (PET) (Gandini and Belgacem, 1997; Kamm, 2007; Moreau et al., 2004). This replacement has recently been emphasized, because adding layered silicates improves the properties of the final polymer (Gandini, 2009; Fushiya, 2008). The annual production of terephalic acid in 2004 is 1.8 million tonnes indicating a huge potential market of FDA. Other applications of FDA also include the preparation of furanic-modified amine-based curatives for polyureas, hybrid epoxy- and urea-urethanes (Benecke et al., 2008) and polyester polyols for the manufacture of coatings providing corrosion- and flame-resistance (King II et al., 2008). With its broad potential as platform chemical, FDA was listed as one of the 12 bio-based potential platform chemicals (Werpy and Peterson, 2004).

FDA can be synthesized by oxidation of 5-hydroxymethyl-2-furfural (HMF), produced by fructose or glucose dehydration (Boisen et al., 2009). HMF is seen as a key element for the development of several bio-based chemicals with multiple applications. For example, by a subsequent hydration reaction, HMF can also be converted into levulininc acid, which is another molecule on the list of the 12 bio-based potential platform chemicals (Werpy and Petersen, 2004). In addition, HMF can be chemically converted into a range of other valuable chemicals (Figure 3.1) including bio-solvent, bio-fuel, pharmaceuticals, antifungal compounds, and polymer precursors (Corma et al., 2007). Although the partially oxidized compounds from HMF can also be used as polymer building blocks, these are more difficult to produce selectively. FDA is with particular interest because chemically, it is a very stable compound. Its only current uses are in small amounts in fire foams and in medicine where it can be used to remove kidney stones.

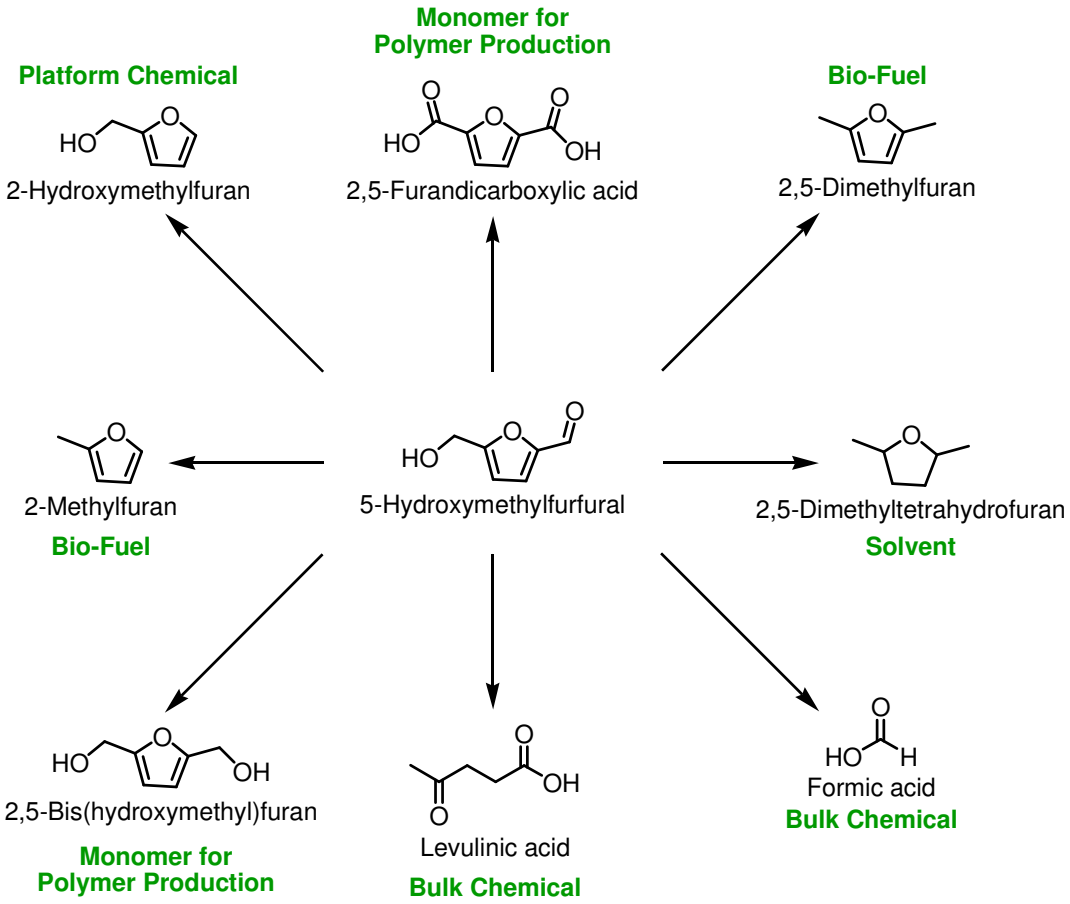


Figure 3.1. HMF as a precursor for a range of commercial products, published in Boisen et al. (2009).

3.1.2 Introduction of the possible routes to HMF, FDA

Dehydration of glucose or fructose can yield HMF. In general, dehydration of fructose can obtain much higher yield (selectivity) and reaction conditions are much easier than dehydration of glucose (Boisen et al., 2009; Kuster, 1990). However, glucose in much cheaper, more abundant and more preferred refinery building block since it can be commercially obtained via the enzymatic hydrolysis of starch which is rich in plant biomass (Pedersen, 2007). Glucose can also be obtained by hydrolysis of cellulose, but this process is not yet commercially practical (Schenck, 2006). Besides, alternative route of enzymatic or acidic hydrolysis of sucrose can result in both frucotse and glucose. In industry, High-fructose corn syrups (HFCSs) are mainly produced from isomerization of glucose derived from starch by the enzyme glucose isomerase (EC 5.3.1.5) (Bhosale et al., 1996). Besides this process, highly pure fructose can also be produced using the Cetus process from glucose via the intermediate 2-keto-D-glucose (Neidleman et al., 1981). In Cetus process, glucose is first oxdised to glucosone catalyzed by the immobilized enzyme pyranose 2-oxidase (EC 1.1.3.10). The glucosone is then converted to fructose by catalytic hydrogenation. The davatagde of the cetus process, is that the process produce

almost 100% pure fructose directly as product. In addition, enzymatic hydrolysis inulin is another competitive process to produce fructose (Kunz,1993 ; Ricca et al., 2007).

Besides dehydration fructose/glucose to obtain HMF, various polysaccharides have also been reported as HMF sources with water as reaction media (Rapp, 1987). However, the selectivity to HMF is in general too low and the reaction condition is quite difficult. Recently, with the increase research interests on ionic liquids, many types of ionic liquids have been screened for synthesis HMF. The investigated feedstock covers not only glucose, fructose but also cellulose, inulin, starch and other biomass (Lansalot-Matras and Moreau, 2003; Moreau et al., 2006; Zhao et al., 2007; Bao et al., 2008; Hu et al., 2008; Binder and Raines, 2009; Hu et al., 2009). There are several examples of ionic liquids that have the ability to solubilize natural polymers such as cyclodextrins, cellulose, starch and chitin. This opens an excellent opportunity to convert crude biomass direct into chemicals (Liu et al, 2005; El Seoud et al, 2007). Producing HMF directly from polysaccharides in ionic liquids has already obtained some good results. For example, yield of 47 % HMF was obtained directly from starch in $SnCl_4$/[EMIm][BF_4] system (Hu et al., 2009). Worth to mention, high yield up to 91% directly from glucose has also been obtained in ionic liquids (Zhang and Zhao, 2010). Nevertheless, for synthesis HMF so far, dehydration fructose is still much easier than other feedstocks and offers the highest reaction yield among them.

HMF can then be oxidized into FDA using a variety of technologies. A review by Lewkowski (2001) described some of the methods, including electrochemical oxidation, use of barium and potassium permanganates, nitric acid and chromium trioxide. In addition, using co-solvent (e.g. acetic acid) besides water, initiators (e.g., cetaldehyde), and homogeneous metal salts (e.g., Co/Mn/Br) have also been reported for oxidation HMF to FDA (Partenheimer and Grushin, 2001). Moderate yield around 60% to 70% are associated with the described homogenous system. High yield of 100% from oxidation HMF to FDA can be obtained with the use of heterogeneous catalysts (e.g. Pt/C-based) able to work in water and with the use of oxygen as oxidant. However, the chemical synthesis of FDA are in general considered with requiring high pressure, sometimes high temperature, metal salts, organic solvents, polluting catalysts (e.g. Pb) or high amount load of catalysts (e.g. Pt/C based catalysts), rendering the process expensive and polluting (Taarning et al.,2008; Carlini et al., 2005; Casanova et al., 2009; Gorbanev et al., 2009; Kroger et al., 2000; Partenheimer and Grushin, 2001; Ribeiro and Schuchardt, 2003). With the debate of this, efficient whole-cell biotransformation of HMF into FDA has also been reported. With glycerol as the carbon source in fed-batch experiments, FDA was produced from HMF at a yield of 97% (Koopman et al., 2010). The relative recovery method of FDA was also reported in the paper. To sum up, although the oxidation reaction has just been caught with attention very recently, good success in terms of yield has already been obtained.

The synthesis of FDA directly from fructose has also been attempted, without much success up to now. Ribero and Schuchardt (2003) obtained 99% selectivity to FDA, at 72% conversion of fructose with an encapsulated cobalt acetylacetonate as a bi-functional acidic and redox catalyst in silica in an autoclave at 160°. Kröger et al. (2000) described a

way of producing FDA via acid-catalyzed formation and subsequent oxidation of HMF in an MIBK/water mixture using solid acids for fructose transformation and PtBi-catalyst encapsulated in silicone and swollen in MIBK for HMF oxidation. The reaction was carried out in a reactor divided with a PTFE-membrane in order to prevent the oxidation of fructose. However, the resulting yield of FDA was only 25% based on fructose.

The described possible routes from biomass to FDA are illustrated in Figure 3.2. Besides what is described above, there are other routes as well. For example, FDA can also be obtained from furan as well as other furan derivatives. This thesis only focuses on the route from glucose to FDA.

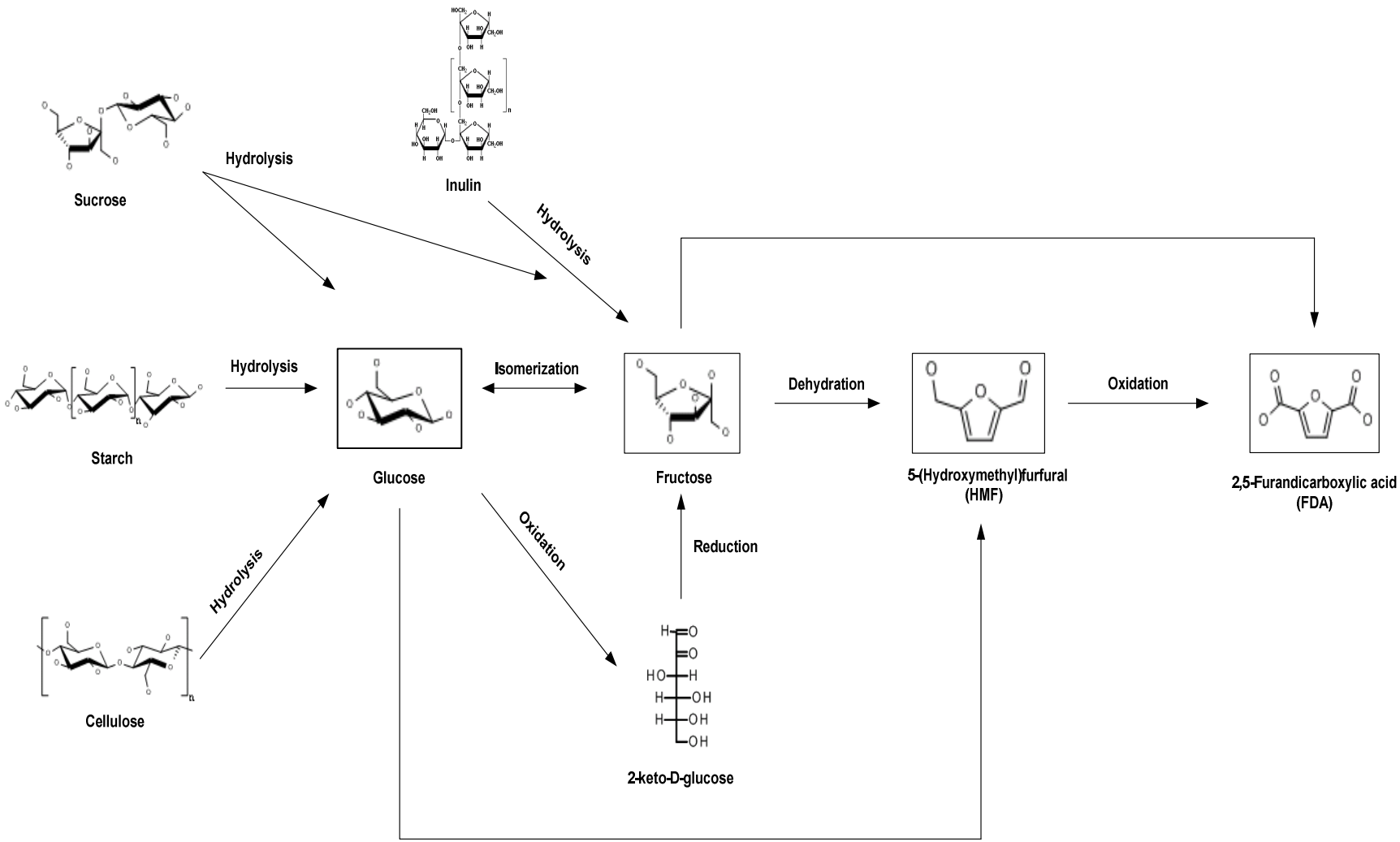


Figure 3.2. Selection of possible routes from biomass to FDA.

3.2 Chemo-enzymatic synthesis of FDA from glucose

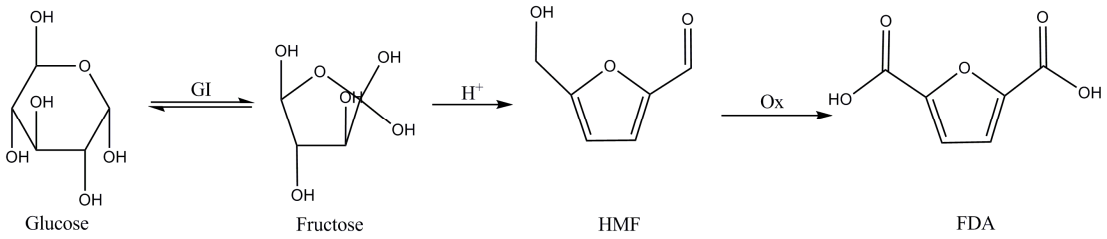


Figure 3.3. Chemo-enzymatic synthesis of FDA from glucose.

As stated in chapter 1, chemo-enzymatic synthesis creates good selectivity and has a great potential in producing platform chemicals from biomass. This method has not yet been discussed for bulk chemical production. In this case study, using the chemo-enzymatic route for synthesizing HMF or FDA from glucose is examined.

Due to the fact that dehydration of glucose is much harder than dehydration of fructose, glucose isomerase (EC 5.3.1.18) is used to convert glucose initially to fructose. Subsequently the fructose is dehydrated to HMF. Afterwards, HMF is oxidized to FDA (Figure 3.3). The isomerasion process is chosen for converting glucose to fructose, because this process has been well developed and has many industrial applications. Glucose in this step can be obtained commercially from hydrolysis of starch as described before.

As described in the previous section, oxidation of HMF to FDA is not a difficult reaction. Both chemical catalytic way and the whole cell oxidation seem promising. The major problem with the selected route is that the efficient preparation of pure 5-hydroxymethylfurfural from fructose is still unresolved. Although plentiful of methods have been reported, no one has found an inexpensive and easy-to-use method for producing this compound. Therefore, chemists today are still keeping on trying to develop new technologies of its synthesis, especially that the field of its application is immense. A detailed study which summarizes what has been done so far in dehydration fructose to HMF can be found in Chapter 4. What still needs to be done in dehydration process development in the future research is also stressed in Chapter 4.

3.2.1 Challenges for process design

Specifically in this case study, one of the major challenges in such a chemo-enzymatic combination is the mismatch of conditions in the three catalytic steps as shown in Table 3.1.

The isomerization step requires mild operating conditions (pH around neutral and temperature around 50-60 °C, at normal pressure) and water as the reaction media due to the nature of glucose isomerasen (Bhosale et al., 1996).

However for the dehydration reaction, in order to keep a high selectivity, it is preferable to operate the reaction over 100 °C and under very acidic conditions. Sometimes, high pressure is necessarily required in this reaction depending on the type of the reaction medium. The aim is to keep the dehydration reaction medium liquid at high temperature so that the dehydration reaction can take place. The dehydration reaction can be operated in water, organic solvent, water and solvent mixture (a one phase system or a biphasic system) or ionic liquids. Several approaches reported in the literature with the application of different reaction medium are shown in Figure 3.4 (M'Bazoa et al., 1990; Rapp, 1987; Roman-Leshkov et al., 2006; Kuster and van der Steen, 1977).

The conditions for the oxidation reaction are also quite different from the other two reactions. Chemical catalytic oxidation of HMF to FDA in organic solvent (e.g. acetic acid, MIBK) has been reported. However, it is more preferred to operate this reaction in water for safety reasons, sincce the oxidation of HMF to FDA requires high pressure and oxygen. Heterogeneous catalysts are much more preferred since they show better selectivity. Heterogeneous catalysts are also easy to recover. Using basic solution provides high yields and selectivity to FDA, fast reaction rates and good product solubility (Lilga et al., 2010).

Table 3.1. Typical reaction conditions for the three main reactions involved in the synthesis of FDA from glucose.

Reaction	Temperature (°C)	pH	Catalyst	Media
Isomerization	50 – 60	7 – 8	Glucose isomerase	Water
Dehydration	Room temperature to more than 200	Acidic	Heterogeneous, Homogeneous	Water, Water-solvent, Solvent, Ionic liquids
Oxidation	Room temperature to more than 100	Basic	Heterogeneous (Inorganinc)	Water

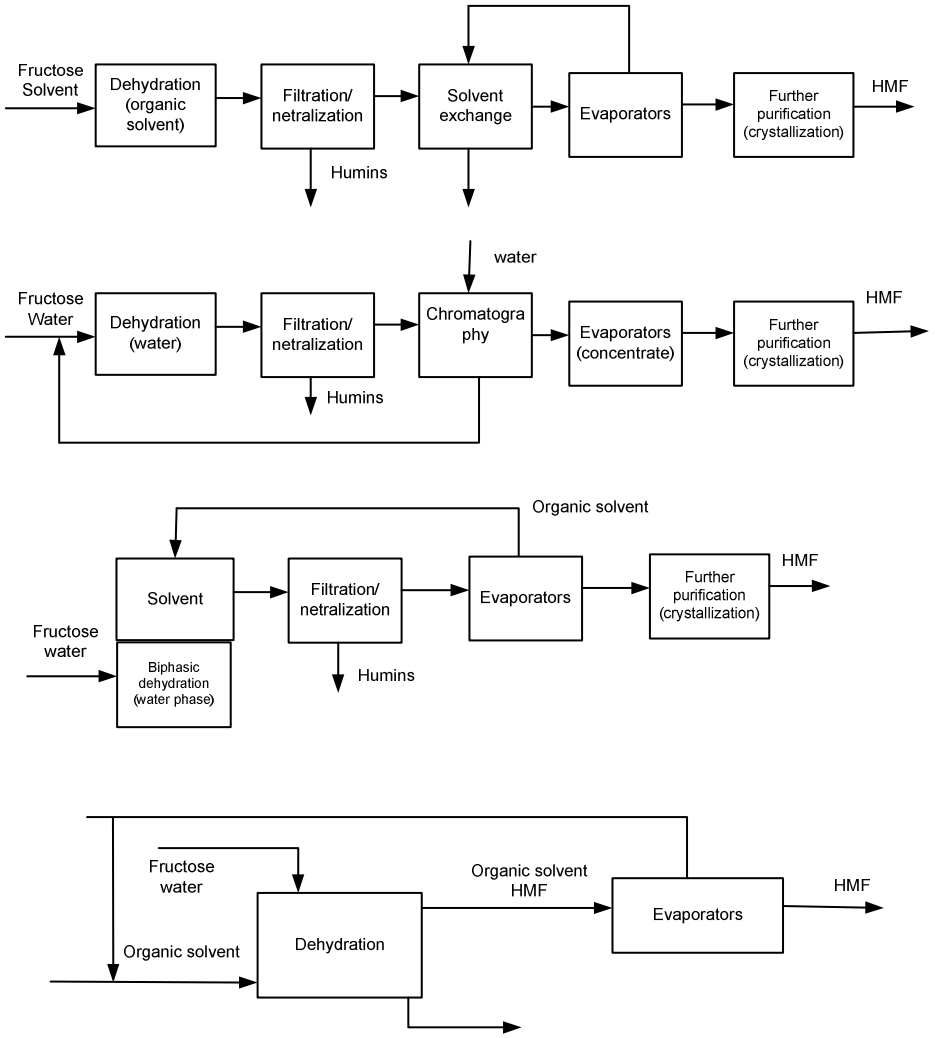


Figure 3.4. A selection of some literature examples of dehydration process flowsheets.

Besides the challenges in process design to match all three reaction conditions, including matching the reaction media, temperature, pH, reaction rate etc., there are many alternative technologies exist in each reaction step in the route from glucose to FDA. As described before, besides the isomerization process for converting glucose to fructose, the Cetus process is another alternative. Similarly, besides chemical catalytic converting HMF to FDA, the whole cell oxidation is another option.

The dehydration step is the most difficult step in the whole route from glucose to FDA in terms of getting a satisfied yield. In addition, the dehydration reaction conditions are far away from both isomerization and oxidation reactions. The reaction has so many different options in terms of reaction medium and choice of catalysts. Some technologies have very good yield, but hard to be applied in a large scale. Some are good to be applied but have unsatisfied yield.

Although, water seems to be the most convenient reaction medium and make the reaction much easier to be combined with the other two reactions, the selectivity in water as medium for dehydration is not satisfied. This is because HMF is not a stable compound and it decomposes to levulinic acid and formic acid in the presence of water. It also forms polymerization compounds (both soluble and insoluble) (Roman-Leshkov et al., 2006; Kuster and Temmink, 1977; Kuster and van der Baan, 1977; Kuster, 1977; Vinke and van Bekkum, 1992). Adding organic solvent into dehydration reaction medium can help to suppress the side reactions and increase the reaction selectivity as well as the dehydration reaction rate (Kuster, 1990; Antal et al., 1990; Boisen et al., 2008). If the solubility of the reactant is high enough, completely avoiding water (such like using neat organic solvent and ionic liquids) in dehydration medium, results in the best yield of HMF from fructose. However, using the neat solvent or ionic liquids requires solvent swaps when combining the three reactions together. Recently, dehydration fructose in a biphasic reactor system catches a lot of attention. With the aqueous phase where the dehydration reaction takes place gives a chance to combine the first reaction. The organic phase where HMF is extracted is sent to distillation/evaporator to isolate HMF from the organic solvent. Afterwards, HMF can be oxidized to FDA. However, due to the poor partition coefficient of HMF between organic solvent and water, large amount of solvent are in general required in order to have an efficient extraction. This leads to the large energy expense later on to isolate the solvent.

In principle, several routes to integrate the steps together in one-pot conversions are possible but the practicalities preclude such an approach in this case.

Concluding remarks

Therefore, the key necessity from the viewpoint of design is to work out the best way of running the process in such a way that the changes between process steps are minimized. Consequently, in order for the entire process to be effective the requirement for minimum temperature, pH and solvent swaps is essential.

In the later chapters, the selection of either an aqueous or organic solvent or biphasic based dehydration step (the middle reaction) are discussed. Any decision made here has a direct influence on the preceding step (isomerization) or the following step (oxidation). Indeed, it affects directly how much up-stream and down-stream processing is required in order to run the whole process from glucose to FDA (Table 3.2). For example, if the solvent based route is used for the second step, it then requires a solvent removal, or swap back to water, to match the reaction media to oxidize HMF to FDA. Consequently, such a decision needs to be made early in the design process and therefore with minimum resources.

In the next two chapters, how to choose a reaction medium for the dehydration step are discussed. Based on the choice of the reaction medium of the dehydration step, the corresponding process design of synthesis of HMF from glucose is illustrated in Chapter 6.

Table 3.2. Effects of the choice of reaction medium of dehydration to the whole process route from glucose to FDA.

Dehydration media	Selectivity to HMF	Backward to IGI	Upstream Processing	Forward to Oxidation	Downstream Processing
Water	Low	Easy (Salts, by products effects on GI)	pH adjustment	Easy/Medium	pH adjustment, HMF separation from unconverted sugar
Organic Solvent	High	Hard	Solvent swap (water to organic solvent)	Medium/Hard	Solvent swap (organic solvent to water), pH adjustment, HMF separation from unconverted sugar
Biphasic	Medium	Easy (Solvent, salts effects on GI)	pH adjustment	Easy	Solvent swap (organic solvent to water), pH adjustment,

4 Dehydration Processes Options: Fructose to HMF

Summary

As discussed in the previous chapter, the dehydration reaction (converting fructose to HMF) is the most difficult reaction step and has the most alternative technologies in the whole route from glucose to FDA. In addition, HMF itself is a very important intermediate for many bio-based chemicals. Thus, a process which is able to produce HMF at a large scale in an economical way is highly demanding.

In this chapter, the synthetic methods in the literature for producing HMF from fructose are reviewed. The dehydration reaction options are divided into five categories based on the type of the reaction medium used. The major research efforts in HMF synthesis are mainly based on the reaction developments. The corresponding downstream separation techniques are discussed. Moreover, the integrated potential flowsheets for scale up are proposed. Moreover, major concerns with respect to scale up are discussed.

4.1 Introduction

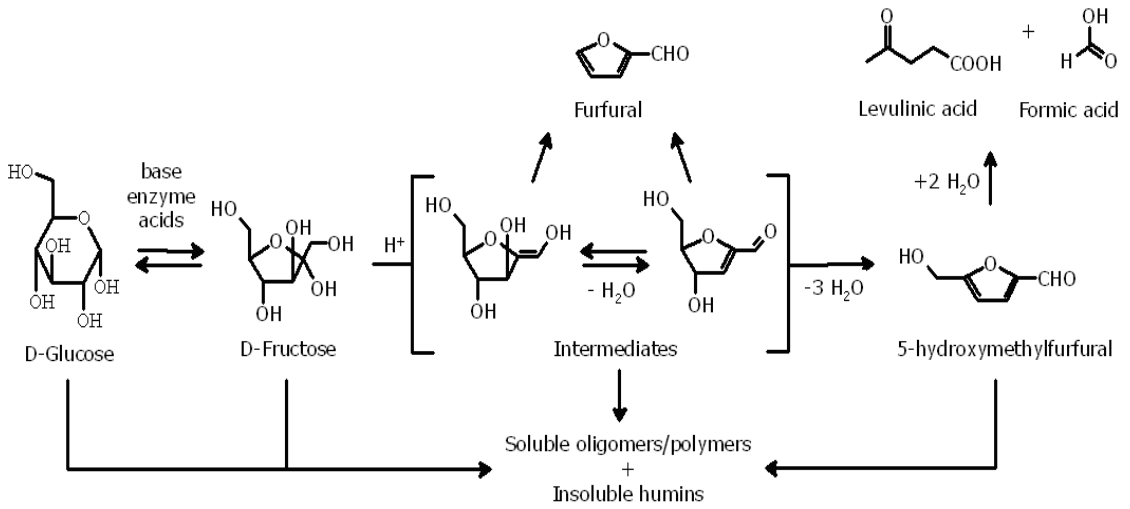
As fossil resources for chemicals and fuels are depleting an intensified search for pathways using renewable feedstocks is taking place in the scientific community (Bozell and Petersen, 2010; Werpy and Peterson, 2004; Corma et al., 2007; Moreau et al., 2004). One compound that has been under particular scrutiny as a future chemical is 5-(hydroxymethyl)furfural (HMF), a six-carbon furan ring obtained from the triple dehydration of hexose sugars (Lewkowski, 2001;Moreau et al., 2004; Bosien et al., 2009). HMF is primarily considered to be a starting material for other chemicals with important applications, such as monomers for plastics, solvents or fuels (Bosien et al., 2009) and therefore represents a potential renewable platform chemical.

The conversion of carbohydrates into furan derivatives has been known for over 100 years (Lewkowski, 2001). Nevertheless, although HMF is considered to be a versatile chemical, commercial process for its manufacture has not yet been realized. Reasons for this include the low reactivity for reactions starting from glucose (potentially the most likely starting material) and the relatively high reactant costs for reactions starting from fructose as well as the fact that simple processes result in low yields (van Dam et al., 1986).

Several extensive reviews about the synthesis of HMF have been published. The most recent of which is based on the development of new catalysts (Tong et al., 2010). Broader reviews include Corma and coworkers (2007) focusing on chemical transformation of biomass to a variety of chemicals with particular emphasis on the dehydration of monosaccharides giving either furfural (from pentoses) or HMF from hexoses respectively. Moreau and coworkers (2004) described the recent catalytic advances in substituted furans from biomass and focused in particular on the ensuing polymers and their properties. A review by Lewkowski (2001) on the chemistry of HMF and its derivatives also appeared recently. Two other older but relevant reviews are from Descotes (Cottier and Descotes, 1991) and Kuster (1990). All these reviews are mainly focused on the chemistry of HMF synthesis. In contrast, this chapter focuses on a discussion of the process options (reaction, isolation and purification) for the synthesis of HMF.

4.2 Synthesis of HMF

At elevated temperatures, hexoses can be dehydrated into HMF with acidic catalysts. In water, HMF can easily decompose into levulinic acid and formic acid. Additionally, it also forms a soluble cross-polymerization substance and an insoluble polymeric substance, so called ‘humins’ (Kuster, 1990; Bosien et al., 2009). The side reactions both rehydration HMF to levulinic and formic acids and the resultant polymerization lowers the yield (and selectivity) of the dehydration. In most cases, dehydration of fructose is much easier than glucose and the selectivity is higher (Bosien et al., 2009). Aside from assistance from catalysts, the dehydration is also affected by the reaction medium used. The reaction has been reported to takes place in water, organic solvents, water - organic solvent mixtures and ionic liquids. Reported temperatures ranges are from 23°C (Lai and Zhang, 2010) up to more than 250°C (Snyder, 1953; Antal and Mok, 1988; Asghari and Yoshida, 2007; Bicker et al., 2005).



Scheme 4.1. Reaction mechanism from dehydration fructose/glucose to HMF.

The mechanism for the dehydration of fructose to HMF has been interpreted to proceed via two alternative routes: one via the fructofuranosyl cyclic intermediate, and the other via an open-chain intermediate (Haworth and Jones, 1944; Kuster, 1990; Van Dam et al., 1986; Antal et al., 1990). In general, evidence supports the former route (Antal et al., 1990; Lewkowski, 2001; Kabyemela et al., 1999). In aqueous mixtures, the acid catalyzed dehydration is non-selective and therefore leads to several other by-products, such as difructodianhydrides and levulosans which are soluble polymers formed from the condensation of two molecules of fructose (Chu and Berglund, 1990) and humins which are insoluble products of the oligomerization of fructose with itself and with HMF (Roman-Leshkov et al., 2006; Kuster and van der Baan, 1977; Vinke and van Bekkum, 1992). In addition, HMF can also rehydrate in the presence of water and yield mainly levulinic and formic acids (Roman-Leshkov et al., 2006; Kuster and Temmink, 1977; Kuster and van der Baan, 1977; Kuster, 1977; Vinke and van Bekkum, 1992).

The reaction mechanism of dehydration of glucose and fructose in acidic solutions are summarized in Scheme 4.1.

From the perspective of establishing a suitable process, this mechanism has provided a useful basis to describe the kinetics of fructose decomposition and HMF formation. A series of first order reactions can describe the kinetics of the intermediate steps between fructose and HMF, with higher order reactions accounting for the formation of soluble and insoluble polymers (Kuster and van der Baan, 1977).

4.3 Process requirements

In a series of experimental studies, both the fructose conversion and HMF selectivity have been found to be determined by a variety of factors, such as initial fructose concentration, temperature (Kuster and van der Baan, 1977) and pH (Kuster and

Temmink, 1977). In order to maximize the yield of HMF on fructose, both side reactions from fructose and decomposition of HMF should be minimized (Table 4.1).

Table 4.1. Reaction parameters related with the dehydration yield based on kinetics from aqueous reactions.

	Initial fructose concentration	Reaction temperature	Medium acidity	Using co solvent/solvent
Suppress side reactions from fructose	Decrease fructose concentration	Increase temperature	Increase acidity	Using water miscible solvent
Prevent HMF from decomposing	Decrease fructose concentration			Using water-immiscible solvent (biphasic system)

4.3.1 Initial fructose concentration and polymerization

An important requirement for this is that in all cases the fructose concentration should be kept as low as possible. Since the polymerization happens on a higher order compared to the HMF formation, keep the concentration of fructose as low as possible during reaction will help to maximize the formation of HMF from fructose and suppress the byproducts formation from fructose. Figure 4.1 showed the effect of fructose concentration to HMF yield and polymerization formation.

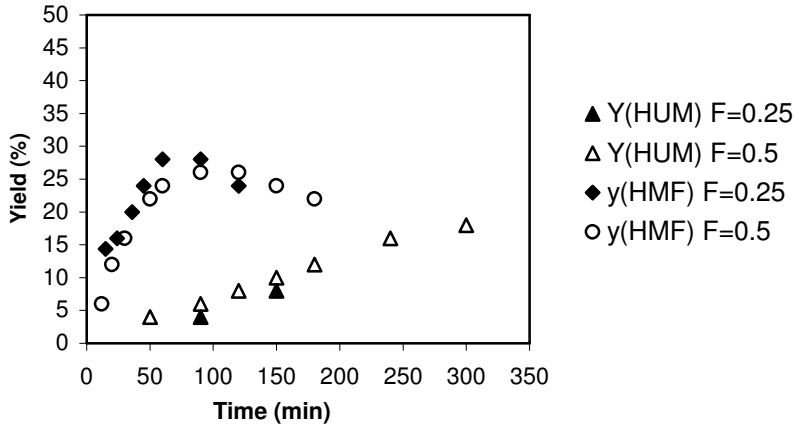


Figure 4.1. Effects of fructose concentration on yield of HMF and humins. Plotted data are published by Kuster and van der Baan (1977). The y(HUM) is the yield of the humins and y(HMF) is the yield of the HMF. The F is the initial fructose concentration. The investigated initial fructose concentration is 0.25 mol/l and 0.5 mol/l.

4.3.2 Reaction temperature

The activation energy for HMF formation and decomposition with H_3PO_4 as catalysts at temperature around 180°C was reported as 129.8 KJ/mol and 100.5 KJ/mol, respectively (Kuster and van der Baan, 1977). Similarly, the activation energy for formation of HMF from fructose in subcritical water catalyzed by hydrochloric acid is 132.2 KJ/mol, and 95.6 KJ/mol for decomposing HMF at 210°C (Asghari and Yoshida, 2007). Due to the fact that the activation energy for formation HMF is higher than that for decomposition HMF, therefore, increasing temperature will help to maximize the ratio between HMF formation rate and HMF decomposition rate. Thus, it increases the selectivity to HMF. The improvement of HMF yield with increased temperature is shown in Figure 4.3.

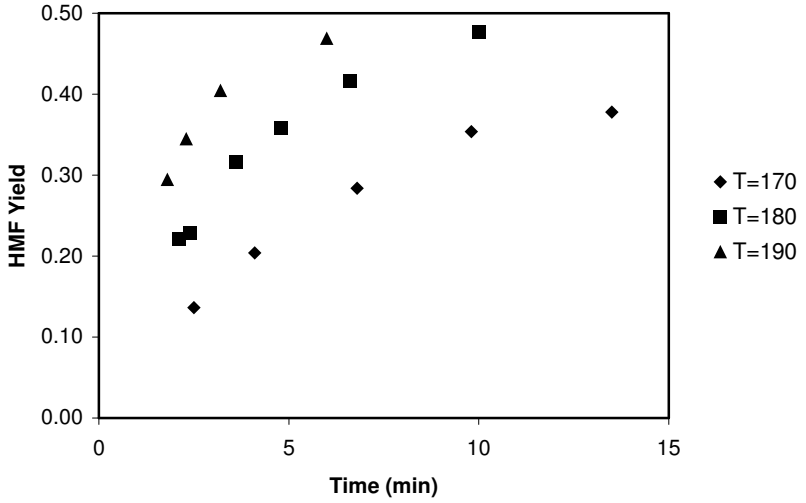


Figure 4.2 Effects of temperature of dehydration yield for HMF. Plotted data are published by Kuster and van der Baan (1977). T is the temperature of the dehydration reaction.

4.3.3 Medium acidity

Choosing the right acidity of the reaction media is another important issue to improve the selectivity. Fructose decomposition rate is found to be proportional to the acidity of the reaction medium. When pH is less or equal to 3, increase the acidity (reduce pH) has a pronounced accelerate effect on the dehydration rate of fructose, and a somewhat smaller effect on the rehydration rate of HMF (Mckibbins et al., 1962; Kuster and van der Baan, 1977). These findings were further confirmed by van Dam et al. (1986).

In addition, the acidity of the reaction medium also affects the composition of final dehydration products. Kuster and van der Baan (1977) concluded that more acidic conditions are needed for the formation of levulinic acid than for HMF. For instance, they found out when the pH of the reaction medium exceeded 2.6, there was no formation of levulinic acid. No formation of HMF was observed when the pH was more than 3.9. They

also found out when the pH was above 4.5, small amount of fructose isomerised to glucose.

4.3.4 Using co-solvent

Since water is the one of the reactants of rehydration of HMF to levulinic acid and formic acid, the effect of water plays a significant role in improving the selectivity to HMF of dehydration fructose. Adding water miscible solvent (to displace water) in dehydration reaction is found to be very beneficial to the formation of HMF because it accelerates its formation and retards its hydrolysis (Kuster, 1977; van Dam et al., 1986; Antal et al., 1990; Lewkowski, 200; Román-Leshkov et al., 2006; Bosien et al., 2009; Tong et al., 2010).

Using water-immiscible solvent in dehydration reaction extracts HMF into organic phase once it is formed. Consequently, it reduces the formation of rehydration and polymeric by-products (Kuster and van der Steen, 1977; Rigal et al., 1981; Moreau et al., 1996; Roman-Leshkov et al., 2006; Roman-Leshkov et al., 2009).

4.4 Reaction schemes

There are many options in implementation the dehydration reaction due to variety choices of the reaction medium and the catalysts. According to the aqueous dehydration reaction mechanism, the type of the reaction medium (using co-solvent or not) plays the most significant role in improving the selectivity of the dehydration reaction among all the four factors (fructose concentration, temperature, acidity and using solvent) (Lewkowski, 2001; Kuster, 1977; van Dam et al., 1986; Antal et al., 1990; Román-Leshkov et al., 2006; Bosien et al., 2009; Tong et al., 2010). Based on this reason, the existing options for operating the dehydration reaction are divided into 5 categories based on the type of the reaction medium they used. These 5 categories include aqueous system, aqueous-solvent system, anhydrous solvent system, sub/supercritical system and ionic liquids.

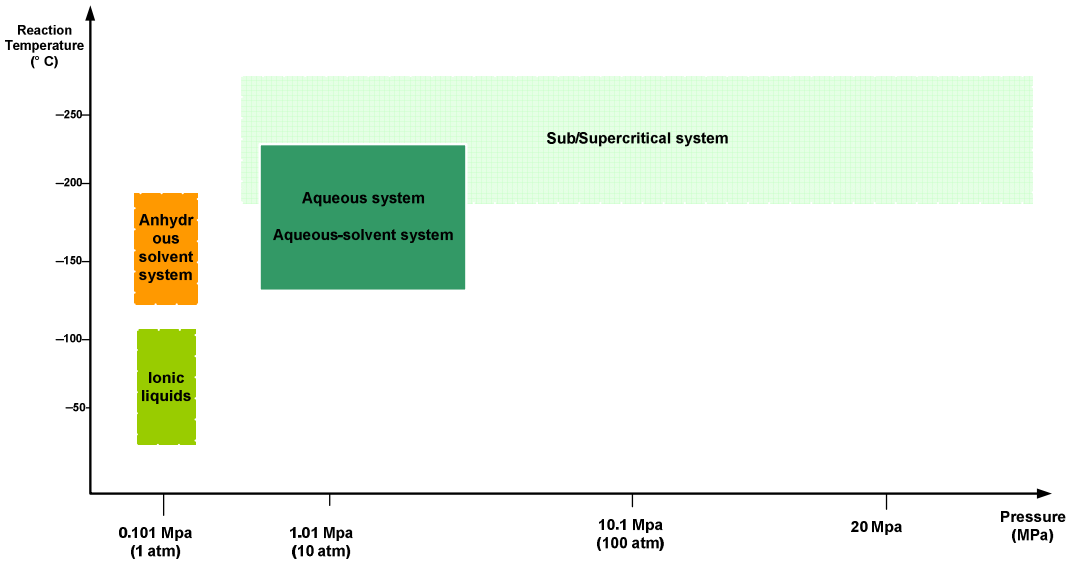


Figure 4.3. Reaction temperature and pressure profile for different reaction systems.

4.4.1 Aqueous system

By definition, the aqueous system means using only water as reaction medium and this division does not include using water at their sub/super critical temperature or pressure. In order to get the acceptable selectivity in aqueous system, high temperature over the boiling point of water is always required. Therefore, the aqueous system is always associated with pressure over 1 atm in order to keep the reaction medium liquid at the reaction temperature (Figure 4.3) since the reaction requires liquid medium to dissolve the reactant and give contact for the reactant and catalyst used.

Water is the preferred green solvent since it is abundant and non-hazardous (Hailes, 2007). In addition, it is a good solvent for dissolving the monosaccharide substrates (fructose and glucose) as well as the product, HMF. However, the dehydration of fructose to yield HMF in aqueous system is hampered by a competitive HMF rehydration and the self- and cross polymerization of HMF, fructose. The byproducts including levulinic acid, formic acid as well as the soluble and insoluble polymerization products are found to be more pronounced in an aqueous reaction medium than an organic one (van Dam et al., 1986). The yield to HMF from fructose by using homogenous catalysts such as mineral acids HCl, H_2SO_4 and H_3PO_4 (Newth, 1951; Mednick, 1962; Román-Leshkov et al., 2006) in aqueous system is generally low and around 20%. The selectivity in aqueous system can be further improved by using heterogeneous catalysts such as highly acidic cation-exchange resins, titanium oxides (TiO2), zirkornium oxides (ZrO2) and H-form zeolites (Carniti et al., 2006, Moreau et al., 1996, Rigal et al., 1981). However, as the reaction time increases, the selectivity drops fast because the catalyst is deactivated by the precipitation of the formatted insoluble polymeric by-products on its surface.

4.4.2 Anhydrous system

Anhydrous system means using the neat organic solvent as the reaction medium if the solubility of hexoses are high enough. Most of this type of solvents reported in the literature so far, are associated with high boiling points over 180ºC (Kuster et al., 1990; Bosien et al., 2009; Tong et al., 2010). Therefore, the reaction with such type of medium is operated at normal pressure (Figure 4.3).

The invested anhydrous solvents cover dimethylformamide (Bonner et al., 1960), quinoline (Morikawa, 1978), acetonnitrile (Brown et al., 1982) and dimethyl sulfoxide (DMSO) (Nakamura and Morikawa, 1980; Brown et al., 1982; Gaset et al., 1985; Musau and Munavu, 1987). Among them, DMSO is the most popular one and creates the highest dehydration yield. High yield of 90% based on fructose was obtained at 80ºC by using strongly acidic ion-exchange resin as the catalyst in DMSO (Nakamura and Morikawa, 1980). A yield up to 92% based on fructose was obtained at 150 ºC after 2 hours in DMSO even without using any catalyst (Musau and Munavu, 1987).

Using the anhydrous system successfully suppresses the unwanted side reactions and creates high reaction yield to HMF. However, there are some drawbacks in stopping using this system in a large scale. The high boiling point solvents cause difficulty and require special treatment for the product removal and purification, e.g. it is difficult to use vacuum distillation to separate HMF from DMSO (Brown et al, 1982; El Hajj et al., 1987). Besides, some of the solvents are very expensive and have some risk for health and environment.

4.4.3 Aqueous-solvent system

The aqueous-solvent system is to use organic solvent together with water as dehydration reaction medium. This type of reaction media includes one phase system and biphasic system. High pressure is always required in order to keep the reaction medium liquid at the high reaction temperature around 150ºC to 180º C (Cope, 1959; Kuster and van der Steen, 1977; Rigal et al., 1981; Moreau et al., 1996; Roman-Leshkov et al., 2006; 2009) (Figure 4.3).

The one phase aqueous-solvent system is defined by adding water miscible solvent such as butanol (Peniston, 1956), 1,4-dioxan (Hales et al., 1963; Mednick, 1962), triethylene glycol (Atlas, 1960) and polyethylene glycol-600 (Kuster, 1977) in to reaction mixture. The aim is to diminish the risk to polymerization by decreasing the water concentration (Kuster, 1990; Antal et al., 1990). The dehydration yield to HMF is much more improved compare to the same condition in aqueous system (Cottier and Descotes, 1991).

Biphasic aqueous-solvent system is by adding a water immiscible solvent to create a second phase. The organic phase extracts the HMF from the aqueous phase as it is produced and consequently reduces the formation of rehydration and polymeric by-

products (Cope, 1959; Kuster and van der Steen, 1977; Rigal et al., 1981; Moreau et al., 1996; Roman-Leshkov et al., 2006). High yield up to 75% were obtained from dehydration of Fructose by using MIBK continuously extract HMF from the reaction mixture when it was formed (Kuster, 1977; Fleche et al., 1979; Mercadier et al., 1981; Rigal et al., 1981). The yield can be further improved by adding phase modifiers (e.g. DMSO) into aqueous phase (Roman-Leshkov et al., 2006; Chheda et al., 2007). However, due to the poor partition coefficient of HMF between the organic solvent and water, large amount of solvent is required in order to get an efficient extraction of HMF from the aqueous phase (Vinke and van Bekkum, 1992; Roman-Leshkov et al., 2006). The partition coefficient of HMF between the organic solvent and water can be improved by addition of phase modifiers (e.g. 2-butanol) into the organic phase (Roman-Leshkov et al., 2006) or addition of an inorganic salt (e.g., sodium chloride NaCl) to the aqueous phase, so called ‘‘salting-out effect’’ (Roman-Leshkov et al., 2007; Roman-Leshkov et al., 2009). The addition of salt largely improves the partition of HMF between the organic solvent and water (Figure 4.4). In addition, it also creates biphasic systems with solvents that are miscible with water if no salt is added.

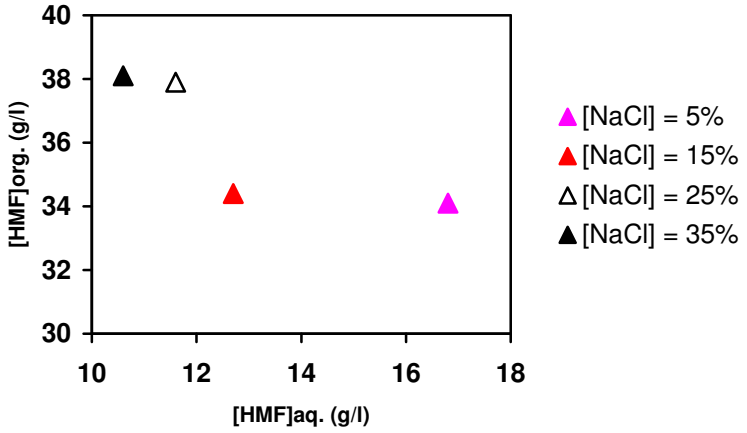


Figure 4.4. Plot of ‘‘salting-out effect’’ to HMF distribution between the organic phase (2-butanol) and water. Data are taken from published data from Roman-Leshkov et al., (2007). The salt concentration is a weight based concentration in the aqueous phase.

4.4.4 Sub/super critical system

Sub/super critical system includes using water or water and water-miscible solvents (low boiling point solvents) at their sub- or super critical state. The unique intrinsic acidic and basic properties showed by sub-super critical water or water-solvent mixture, makes it particularly interesting as a reaction medium for the dehydration of carbohydrates. Depends on the type of the reaction medium, pressure varies from 4 MP_a (Asghari and Yoshida, 2007) to 30 MP_a (Bicker et al, 2003). The investigated temperature is from 180°C up to 300°C (Kabyemela et al., 1999; Asghari and Yoshida, 2007; Chuntanapum et al., 2008) (Figure 4.3).

Improved dehydration selectivity results of glucose compared to the same conditions with normal water were reported (Simkovic et al, 1987; Watanabe et al, 2005a; 2005b; Takeuchi et al., 2008; Aida et al., 2007). The highest yield from glucose obtained was around 40% with mineral acids (Takeuchi et al., 2008).Yields of up to 50 % were obtained when using fructose as the starting sugar with different zirconium phosphates as catalysts in subcritical water (Asghari and Yoshida, 2006). Nevertheless, the overall results from sub- and super critical water have so far been unsatisfactory in terms of yields. Bicker et al. (2003) explored other low-boiling solvents such as acetone, methanol and acetic acid. An acetone/water mixture at 180° C and 20 MP_a gave 99 % conversion of fructose and a selectivity of 77 % to HMF which is the highest yield obtained in sub/super critical system (Bicker et al, 2003; Bicker et al, 2005).

4.4.5 Ionic liquids

Recently, dehydration carbohydrates in ionic liquid have quickly caught the research attentions (Ståhlberg et al., 2011). Their unique physical properties such as very low vapor pressure and non-flammability make them particularly suitable as solvents for large-scale production (Wasserscheid and Welton, 2008). There is a possibility to design and functionalize the ions of the ionic liquid, giving it an ability to work both as solvent and reagent for certain reactions. There are several examples of ionic liquids that have the ability to solubilize natural polymers such as cyclodextrins, cellulose, starch and chitin. This opens an excellent opportunity to convert crude biomass into fine chemicals (Liu et al, 2005; El Seoud et al, 2007). Compared to other dehydration systems, a high yield of dehydration of fructose/ glucose can be obtained at a low temperature. The reported range of temperature is from room temperature (Lai and Zhang, 2010) to 100°C (Chidambaram and Bell, 2010) at normal pressure (Figure 4.3).

During the last 8 years, many types of ionic liquids have been screened for synthesis of HMF. The investigated feedstocks cover not only glucose, fructose but also cellulose, inulin, starch and other biomass (Lansalot-Matras and Moreau, 2003; Moreau et al., 2006; Zhao et al., 2007; Bao et al., 2008; Hu et al., 2008; Binder and Raines, 2009; Hu et al., 2009). A high yield (more than 90%) has been achieved from fructose with many types of ionic liquids (Moreau et al., 2006; Hu et al., 2008; Yong et al., 2008). Remarkably, good yields of 70% (Zhao et al., 2007), 80% (Yong et al., 2008) and up to 91% (with microwave (Zhang and Zhao, 2010)) were achieved with CrCl2/CrCl3 as catalysts directly from glucose. This makes ionic liquid superior than other systems since a good yield can be directly obtained from glucose.

4.4.6 Catalysts

Catalysts are not always required in the dehydration reaction. A good yield over 80% of dehydration fructose in reaction medium such as DMSO and some ionic liquids can be obtained given enough reaction time. However, using catalysts can dramatically reduce

the required reaction time. Choosing the suitable catalysts for some reaction systems (e.g. aqueous system) can become very critical, because for such systems, to drive reactions into the main reaction to yield HMF can be very hard and require very hash process condition without the help of catalysts.

A variety of catalysts such as mineral and organic acids, salts, and solid acid catalysts (ion-exchange resins and zeolites) have been intensively investigated in the dehydration reaction.

Most processes chose to use cheap mineral acids and followed by neutralizing acids with base. The investigation of the separation or reuse of homogenous catalysts (besides reactions with ionic liquids as reaction medium) has not been touched. Besides this, the corrosion of plant of using homogenous catalysts may be expected.

Heterogeneous catalysts have several advantages over homogenous catalysts. They are easy for separation and recycle. In addition, they are more selective to HMF due to the ability of adjusting the surface acidity (Carlini et al., 1999). The risk of using heterogeneous catalysts is the deactivation of catalysts by humins. In dehydration reaction catalyzed by heterogeneous catalysts, the reaction can stop if the formatted humins precipitated on the surface of the catalysts. Therefore, the use of heterogeneous catalysts is limited in the reaction systems such like anhydrous solvent DMSO, ILs and aqueous mixture with continuous solvent extraction so that humins can be avoided (Nakamura and Morikawa, 1980; Lansalot-Matras and Moreau, 2003; Moreau et al., 1996). Moreover, often polystyrene based resins, can only tolerate temperatures up to around 130 °C, which reduces the range of their application.

4.5 Downstream processing schemes

In order to commercialize the manufacture of HMF, it requires not only the information related with reaction conditions and yields, but also full details about how to isolate HMF from a reaction mixture in a more or less pure form.

Chemical and physical properties (pure components or mixtures) are related to the separation process principles. The differences in the values of properties among the compounds of the mixture to be separated are exploited by the separation techniques. Some main components' pure physical property data are listed in Table 4.2. These data are mainly collected form CAPEC database (Gani et al., 1997) or predicted by ProPred (Gani et al., 1997) if no measured values are available. The most frequently used solvent MIBK in the aqueous-solvent system and the most popular anhydrous solvent DMSO were selected as examples. Based on the pure property data, the relative physical property ratio for binaries can be calculated by the following equation.

$$r_{ABj} = \frac{P_{Aj}}{P_{Bj}} \qquad \text{Equation 4.1}$$

where r_{ABj} is ratio of the pure physical property ratio between component A and B. P_{Aj} and P_{Bj} are the values of pure property (j) for component A and B, respectively. Some computed r_{ABj} data are listed in Table 4.3. r_{ABj} can be used to evaluate one kind of separation technique is suitable or not for separating the binary A and B. When r_{ABj} is too close to 1, the differences between the certain property of the two components is too close. Thus a certain kind of separation technique based on this physical property is not feasible for separating A and B (Jaksland et al., 1995; Jaksland and Gani, 1996). For example, both the boiling point and melting point ratios between Levulinic acid and HMF are too close to 1 (Table 4.3). Normal distillation and crystallization can not separate them. On the other hand, liquid-liquid extraction is a good option to separate HMF from fructose, since the difference between the solubility parameters of these two components is quite big.

Table 4.2. Lists of some physical-property data of the main compounds, collected from Database, ICAS (ICAS, 2009)* .

Compounds	Density (kg/L)	Melting point (°C)	Boiling point (°C)	Solubility parameters (MPa½)	log kow	vapor pressure (Pa)
Fructose	1.60	103.00	350.12	65.64**	-2.95**	0.00**
HMF	1.29	30 - 34	303.98	31.31**	-0.10	0.08
Formic Acid	1.22	8.40	100.80	35.57	-0.54	5686.57
Levulinic acid	1.14	33-35	245-246	21.96	-0.08	0.29
Water	1.04	0.00	99.97	47.81		3170.39
MIBK	0.80	-84.70	117-118	17.51**	1.31	2642.89
DMSO	1.10	18.50	189.00	21.45	-1.35	80.19

*All the data are values taken at room temperature (298.15 K). **Data are predicted by ProPred, ICAS (Gani et al., 1997).

Table 4.3. Relative physical property ratios between the binaries.

Binaries	Boiling point	Melting point	Solubility Parameters	Vapor Pressure
Fructose-HMF	1.25	1.23	2.10	23.61
Levulinic acid-HMF	1.04	1.01	1.43	2.00
HMF-Formic acid	1.33	1.08	1.14	71082.13
HMF-Water	1.33	1.12	1.53	0.275862
HMF-MIBK	1.27	1.62	1.79	39629.88
HMF-DMSO	1.08	1.05	1.46	1.75
MIBK-Water	1.05	1.45	2.73	1.20
DMSO-Water	1.24	1.55	1.23	39.53

Based on the physical property, the common used separation techniques are evaluated for the separation of the different binaries (Table 4.4). Clearly, one separation technique alone may not be sufficient to isolate HMF form such complex reaction mixture. It requires the combination of several separation techniques.

4.5.1 Distillation / Evaporation

Distillation or evaporation is a conventional way to separate target compound from a reaction solution. However, using distillation directly for an aqueous reaction mixture can not separate HMF from fructose. High vacuum distillation of HMF together with presentence of sugar causes further Humin formation (Jones and Lange, 1958; hunter, 1965). To distillate DMSO from HMF was approved to be very difficult and require special treatment. This is because of the high boiling point of DMSO and the possibility of causing the decomposition of DMSO at such a high temperature (Brown et al., 1982; El-Hajj et al., 1983). Moreover, the ratio of boiling points between DMSO and HMF is also close to 1 (Table 4.3), indicating that the distillation/evaporation is not feasible to separate DMSO from HMF. For ILs based process which can reach a full conversion of fructose/glucose, high vacuum distillation to distillate HMF from ILs can be a possible choice (Ståhlberg et al., 2011), due to the very low vapor pressure of ILs (Lansalot-Matras and Moreau, 2003), Of course, it requires that the ILs are stable enough.

Table 4.4. Lists of separation options for binaries[*].

	HMF	MIBK	DMSO
HMF	-	Evaporation, Distillation, Crystallization	Evaporation, Distillation, Extraction
Fructose	Extraction, Adsorption, Crystallization	Evaporation, Distillation, Crystallization	Evaporation, Distillation, Crystallization
Levulinic acid	Extraction, Adsorption,	Evaporation, Distillation, Crystallization	Evaporation, Distillation,
Formic acid	Evaporation, Distillation, Extraction, Crystallization	Crystallization	Evaporation, Distillation,
Water	Evaporation, Distillation, Extraction, Crystallization	Evaporation, Distillation, Crystallization	Evaporation, Distillation,
MIBK	Evaporation, Distillation, Crystallization	-	Evaporation, Distillation, Crystallization
DMSO	Extraction,	Evaporation, Distillation, Crystallization	-

[*] Only the binary compounds related with the separation of HMF from the reaction mixture and the separation of solvents from the reaction mixture are shown. Extraction here means liquid-liquid extraction.

4.5.2 Liquid-liquid extraction

On the other hand, a combination of liquid-liquid extraction followed by a distillation or an evaporator will be a better solution for most of the reaction systems. Middendorp (1919) first and later by Haworth and Jones (1944) reported using ethyl acetate (E_tOA_c) to extract HMF from the reaction mixture, and then followed by vacuum distillation. Bazao et al. (1990) reported using dichloromethane (DCM) to extract HMF from the

reaction mixture with DMSO as a reaction medium. And afterwards, the volatile solvent can be removed easily. Mostly, MIBK is one of the most popular solvent to extract HMF from an aqueous mixture (Kuster and van der Steen, 1977; Kuster, 1990; Roman-Leshkov et al., 2006; Roman-Leshkov et al., 2007). A combination of liquid-liquid extraction together with distillation/evaporation is also frequently used to separate HMF from the reaction mixtures with ILs as a reaction medium**.** HMF is usually extracted from the IL by an immiscible organic solvent (e.g. ethyl acetate (Hu et al., 2008; Qi et al., 2009), toluene (Lansalot-Matras and Moreau, 2003) or diethyl ether (Moreau et al., 2006). Thereafter distillation/ evaporation can be applied to isolate HMF and recover the organic solvent**.**

With respect to the biphasic system, the co-solvent also works as an extraction solvent. After the phase separation, distillation/evaporation is applied to purify HMF and recover the solvent.

4.5.3 Adsorption

Using chromatography to separate HMF, sugar, salts and water mixture was proposed by Rapp (1987). Fractionation of reaction mixture is possible using ion-exchanger column in the Ca-form, and the obtained HMF was pure enough for crystallization (Rapp, 1987). The use of ion-exchangers (Chromatography), common technique in sugar industry practice, offers some interesting possibilities. However, the generally high dilution of the resulting HMF solutions is a huge disadvantage and requires further improvements in order to use it at a large scale.

Another alternative downstream separation for aqueous system involves the utilization of selective adsorbents. Activated carbon treatments have been largely used for the removal of the HMF produced in the thermal treatment of honey and fruit juices (Roy, 1994). Vinke and van Bekkum (1992) studied the adsorption and desorption properties of HMF in different types of activated carbon. The study indicated that HMF could be selectively adsorbed from aqueous solutions in the presence of fructose and levulinic acid, and desorbed by extraction of the activated carbon with an organic solvent miscible in water. Besides activated carbon, the use of zeolites to separate HMF from fructose is also addressed in the literature. As an example, the ability of H-form zeolites to act as specific adsorbents of HMF is mentioned when using them as catalysts in the hydrolysis of sucrose (Moreau et al., 2002). More recently Ranjan et al. (2009) showed that HMF readily adsorbs in certain zeolites, whereas sugars adsorb to a much less extent.

Like chromatography, more effort is required to solve the generally high dilution of the resulting HMF solutions. It thus requires further evaporation to concentrate the solution. In addition, the investigation of the reusability and of the materials suffices is also required.

4.5.4 Crystallization

Depending on the required purity of HMF, application of crystallization after the evaporator can lead to highly purified HMF. Rapp (1987) reported the crystallization of a concentrated HMF rich aqueous stream. A purity of 97% crystalline was obtained after two times crystallization. Using crystallization for purifying a concentrated solvent-HMF mixture was also reported by M'Bazoa et al. (1990).

4.6 Integrated process flowsheets and scale-up concerns

To date the process and applications related for the conversion of carbohydrates into HMF has been limited to the laboratory, using small scale apparatus. While the reaction selectivity still remains the unsolved issue for the possibility of scale up of water based system, scale up of anhydrous solvent reaction system is limited by the difficulty of separation and lack of industrial interests for such type of solvents (Kuster, 1990). ILs based process seems to be one of the future solution. Using ILs as reaction medium, a good yield can be obtained directly from cheaper feedstocks such as glucose. However the availability of some ILs, the expensive costs of ILs, stability and environmental concerns still require a lot of investigation for scale-up. The requirement of large amount of organic solvent becomes one of the limitations for the further industrialization of the biphasic system.

However, the potential interests of how to synthesis HMF from sugars can be made to operate in an economic fashion have never been stopped. Hence, possible processes for scale-up are postulated here in an attempt to highlight some of the future research required in the field. Potential economic and scalable processes can be divided into two types, dependent upon whether the reaction is carried out in biphasic or single phase media. Both types will have the common feature of requiring effective product recovery and solvent (organic solvent and ILs) recovery (and recycle) in order to keep the cost contribution from the solvents used to a minimum.

4.6.1 Biphasic process

The biphasic process (both the conventional aqueous-solvent biphasic system and IL-solvent biphasic systems) is characterized by the dissolution of the feedstock in the reaction medium (aqueous or IL) such that the reaction can be carried out in a second reactor vessel with the addition of an immiscible organic solvent and the catalyst (homogeneous or heterogeneous).

The agitation in the vessel is of key importance to enable adequate mass transfer via the creation of a dispersion of one phase in the other. This is particularly critical for the

biphasic process of using ILs instead of aqueous. Unlike conventional biphasic reactions with an aqueous phase and a water-immiscible organic solvent, the values in the IL biphasic reactor show a considerable difference in viscosity and density and if the mixing is too vigorous then a stable emulsion may be formed which will be difficult to separate in the subsequent settler unit (Ståhlberg et al., 2011). Besides, for conventional biphasic reaction system, enough mixing is crucial when using a heterogeneous catalyst. A good and adequate mixing in such a case can help to avoid possible formatted humins blocking the surface of catalysts.

Following the settler the solvent phase is distilled to separate HMF and the solvent is recycled. The IL is stripped of water and recycled. When the extraction solvent can not assure a good extraction yield, a second counter-extraction unit can be added before recycle back the aqueous/ILs stream. Process flowsheets for both conventional biphasic reactor and ILs biphasic reactor systems are shown in Figure 4.5 and Figure 4.6, respectively.

Another key concern is the high pressure and temperature used for the conventional biphasic system. This can lead to potential leak in the process systems. Besides, high amount of salts used in the conventional biphasic system to improve the selectivity and partition coefficient of HMF to the solvent phase, may cause the corrosion of the plants. For the conventional biphasic system, filtration of the humins may be required before recycle back the aqueous stream.

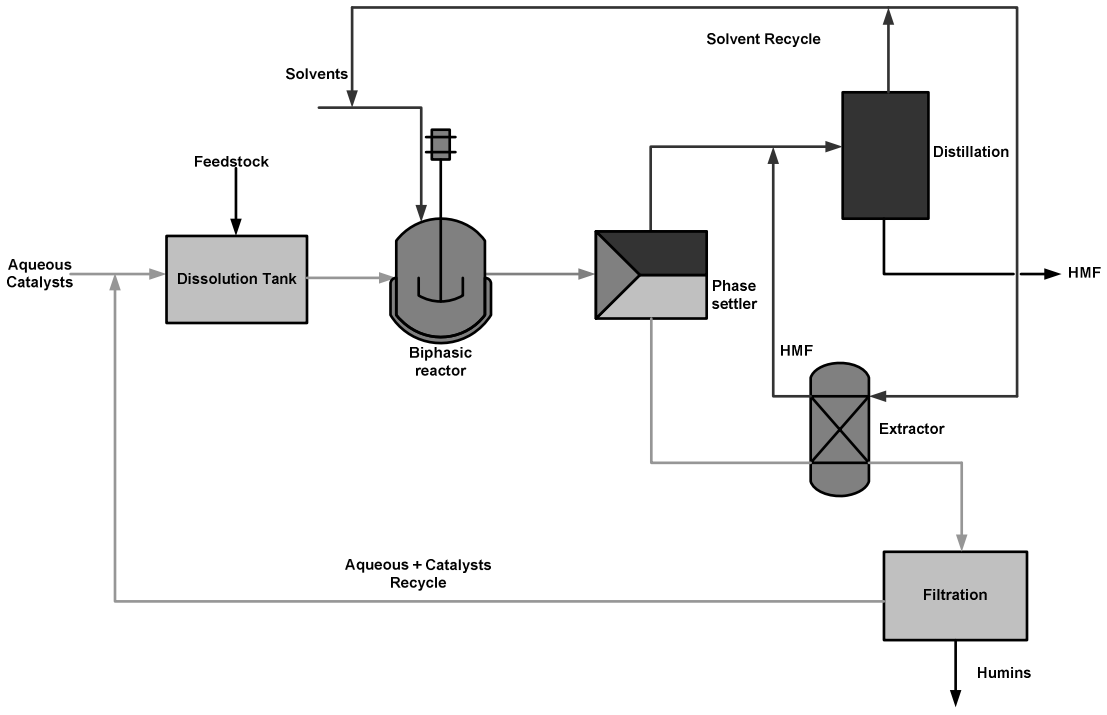


Figure 4.5. Potential process flowsheet for conventional biphasic reactor system.

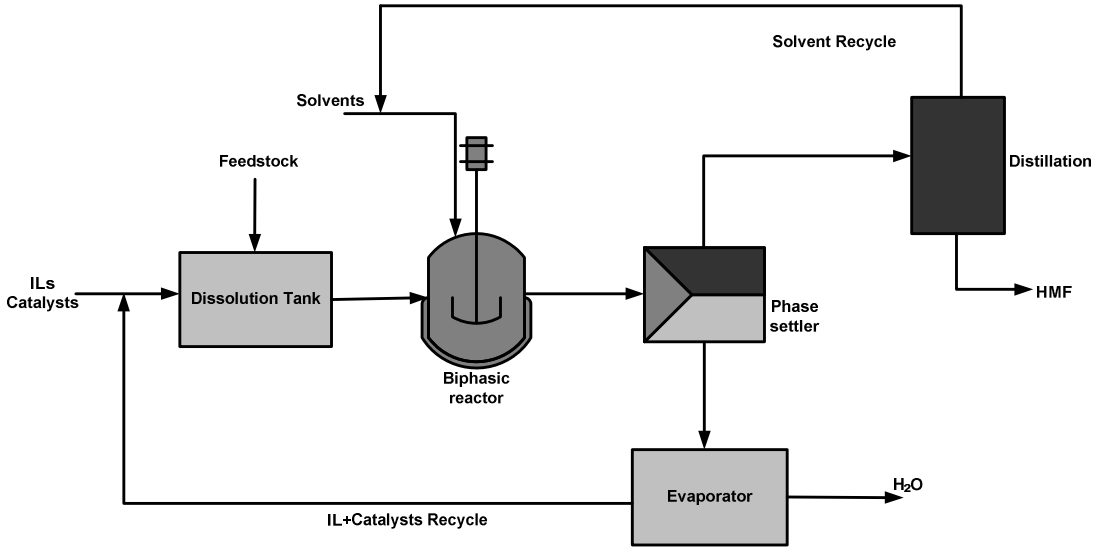


Figure 4.6. Potential process flowsheet for IL-solvent biphasic reactor system.

4.6.2 Single phase process

The single phase process is characterized by the dissolution of the feedstock in the reaction media (either water, or water in the presence of a water miscible solvent, or completely anhydrous organic solvent such as DMSO or neat ionic liquids or ionic liquids with miscible co-solvent) such that the reaction can be carried out in a second reactor vessel with the addition of the catalyst. If the catalyst is heterogeneous, the stirred reactor with a filter can be used. A packed bed is unlikely to be chosen for ILs based reaction medium because it leads to a high pressure drop, given the viscosity of the IL (Ståhlberg et al., 2011). However, the use of heterogeneous catalysts in some reaction medium such as water or water and water miscible solvent, should be well considered. This may require special operation and reactor design to avoid the deactivation of catalysts by the formation of humins. Furthermore, due to the high temperature and high pressure required for reaction medium with water or water-solvent, the design of the reactor should be carefully considered.

After reaction, neutralization of acids formatted in the reaction or homogenous acid catalysts may be needed before the extraction-setter unit in order to stop the HMF rehydration for the reaction medium with water, water-solvent and neat solvent. This may result in the accumulation of salt in the system and thus a risk of corrosion.

After extraction of HMF from the reaction medium by an immiscible organic solvent, distillation/ evaporation will be applied to get crude HMF, and the solvent would be stripped of water and recycled.

The extraction-settler unit needs to be carefully designed as discussed before. A potential process flowsheet for single phase reaction systems is outlined in Figure 4.7.

For IL based reaction system, if a high HMF selectivity can be maintained at almost full conversion of the feedstocks, another alternative for product recovery is to use distillation of HMF from the IL. The reaction mixture needs to be first sent to an evaporator to remove the water formed in the reaction prior to distillation. A potential process flowsheet based on this option is shown in Figure 4.8. Although distillation of HMF from IL has not been reported yet, due to the low vapor pressure of ILs, this option should potentially be possible.

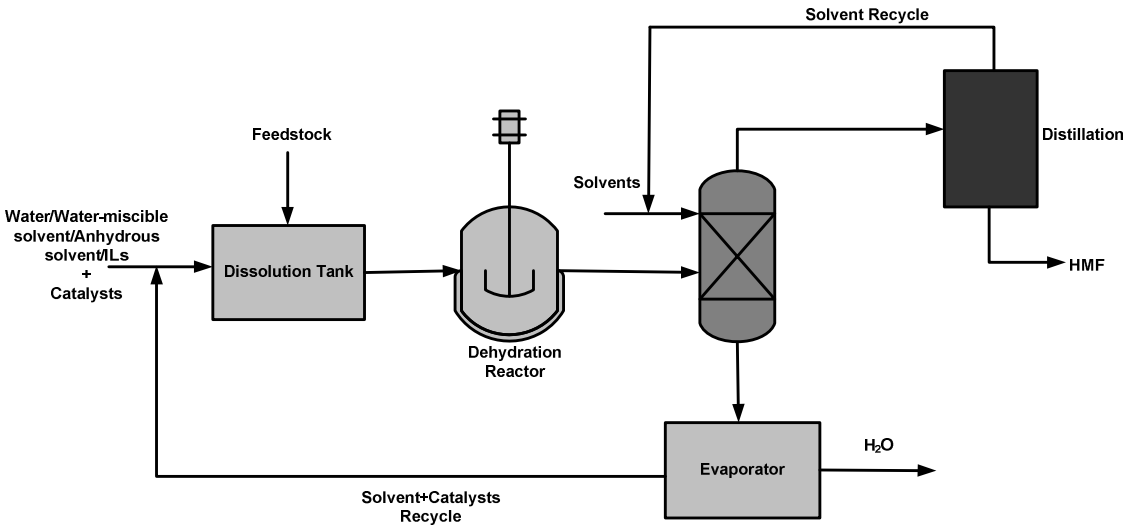


Figure 4.7. Potential process flowsheet for single phase reactor system with reaction medium as water, water-miscible solvent, anhydrous solvent and ILs.

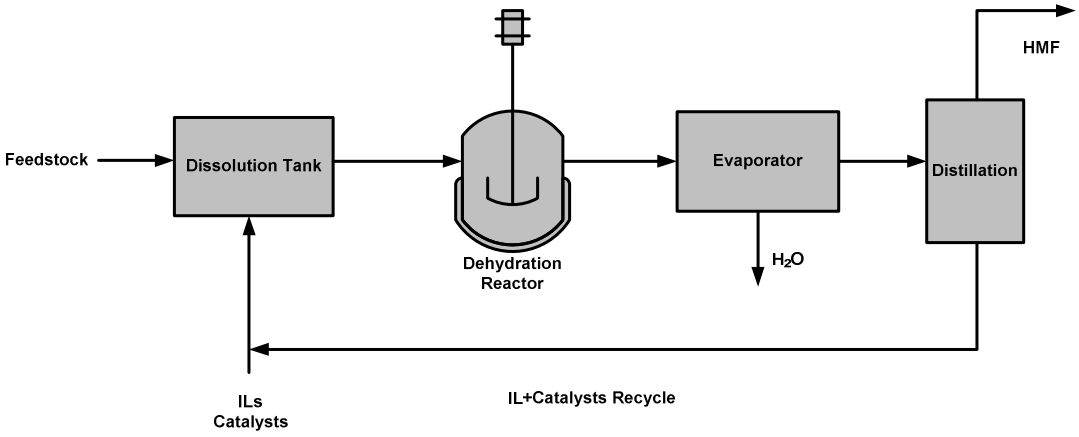


Figure 4.8. Alternative potential process flowsheet for single phase reaction system with ILs as reaction media.

Clearly the feedstock choice, the reaction medium choice will affect the HMF yield and separation requirements in downstream and a relatively simple process can be envisioned. However, critical to economic operation is that the processes are dependent upon solvent (and IL) recycle and the utilization of feedstocks. From the perspective of design, the biphasic reactor (or liquid-liquid extractor) needs careful consideration. Given the potential market size for HMF it is clear that continuous operation will be required. Mixer-settler units lend themselves to such an operational mode but by definition will operate at less than full conversion in order to ensure the reaction is completed in an adequate time. Potentially corrosion (leads by salts accumulation or some of the ILs) and leak (caused by high pressure and high temperature) for some relative types of the reaction medium will require the selection of suitable materials of construction for those parts of the plant.

4.7 Conclusion and outlook

The rapidly growing field of HMF synthesis from carbohydrates holds great promise for the future. The field, however, is still immature and a number of issues need to be investigated in detail in the continuous search for realistic large-scale processes. Future research should target an economic analysis of the potential processes outlined herein. In addition, some specific subjects concerning the chemistry and process engineering should be addressed as follows:

Reactor selection and design

Up to now, all the researches concerning about HMF synthesis, have mainly focused on the catalyst and reaction medium screening driven by obtaining good dehydration selectivity and yield at the laboratory scale. However, besides few exceptions (Kuster and van der Steen, 1977, Kuster and Laurens, 1977), studies about designing and selecting the suitable reactors for the catalytic systems are still rare.

- For the new type of reaction medium (ionic liquids), examining the feasibility of using the conventional reactors may be required.

- In order to reach a good selectivity and reaction rate, high temperature is always required for the conventional solvent mixture. This is always accompanied with the high pressure in order to keep the reaction mixture in liquid phase. When scale up such kind of processes, the safety issue related with high pressure and high temperature for the reactor system needs to be considered.

- The commonly use of salt in conventional biphasic system, and using some types of ionic liquids, may result in corrosion and needs further investigation in reactor design.

- The risk of polymerization may result in deactivation of heterogeneous catalysts. In addition, it also brings the risks in blocking the reactor.

Purity of HMF

The required purity of HMF will highly be dependent on the use of HMF. HMF is an intermediate compound for many important compounds. Therefore the requirements may vary with the final use of HMF. For example, if the final use of HMF is to make biofuels or solvent such as DMF, the required purity may be low. On the other hand, if the use is for polymerization via oxidation to 2, 5-furandicarboxylic acid, the purity of the final HMF maybe very high. The investigation of the application of HMF for different purpose together with the required purity of HMF products is highly required. This is crucially important since this will form the basis for the downstream separation design. Directions in this area is still scare and requires more efforts.

Market size and economic models

The market size, one of the key information for process design, is still not clear for HMF. Economic models should be developed to assess the market size of HMF with different applications. Commercial values of HMF based on different applications are also required. Such information will form the basis of choosing between different process options as well as the feedstocks.

Issues related with different reaction medium

Reaction medium with neat water, the process is mainly limited by the low selectivity. Unless new catalysts appear, avoidance of organic solvent in the whole process may never lead to success. For other reaction medium, such like water-solvent or anhydrous solvent system, besides maintaining a good selectivity, minimizing the solvent use and loss becomes the key issue for the successful scale up.

Although, using sub/super critical system increases the reaction rate. However, compared to the same reaction medium under the conventional condition, the increased selectivity is not that much noticeable. Other issue related with the decreased solubility of sugars and high energy cost for pressurized and high temperature can not really be compensated by the gain in the reaction rate and slightly increased yield.

More knowledge of ILs and more property data of the relevant ILs are required, e.g. the toxicity and the stability (as well as density and viscosity) of the ILs and studies of decomposition at high temperatures.

Concluding remarks

In this chapter, different process options for dehydration carbohydrates to HMF are discussed. Based on what has been achieved so far, what needs to be done in the future to develop a commercial process for HMF production at a large scale is highlighted.

In the next chapter, using different reaction options (aqueous system, anhydrous solvent system and aqueous-solvent system) discussed in this chapter are evaluated respectively with a selected a process synthesis example.

5 Process evaluation: fructose to HMF

Summary

In this chapter, using aqueous system, anhydrous solvent system and aqueous-solvent system based process routes for HMF production from fructose are evaluated with selected typical process synthesis examples. The selected examples are evaluated with the process metrics (mass, energy, E-factor and HMF cost) described in Chapter 2. By analyzing metrics of each process route and their comparisons, the bottleneck for each route is discussed. The strategies for future improvement are proposed. Finally the potential process technology in operating dehydration reaction is selected in the content of process design for chemo-enzymatic synthesis of HMF (FDA) from glucose.

5.1 Introduction

To further stress the problems discussed in a more specific way, in this chapter, using aqueous, anhydrous solvent and aqueous-solvent based process routes for HMF production from fructose are evaluated with selected published lab-scale process synthesis examples.

One process was preparation of high purity HMF but through an aqueous based route, patented by Rapp and co-workers (Rapp, 1987) (water route). The second was patented by M'Bazoa and co-workers for the preparation of high purity HMF through An anhydrous solvent based route (M'Bazoa et al., 1990) (solvent route). And the third one is using water- (water immiscible) solvent route to synthesis HMF with hydrogen chloride as catalyst by Roman-Leshkov et al. (2006) (Biphasic route).

5.2 Process descriptions

The process descriptions here are summarized from the published patents and articles.

5.2.1 Aqueous based synthetic route

The process flow-sheet for the aqueous-based synthetic route is outlined in Figure 5.1. The feed to the dehydration reaction for this process is fructose and water. The feed concentration is around 25 wt% fructose (on a wet weight basis). Oxalic acid is added as a catalyst.

The mixture was stirred mechanically and maintained at around 135 °C to 142 °C for 2.1 hours. The yield for the dehydration of fructose in water was 0.34 mol HMF / mol Fructose (0.24 g HMF/g Fructose), with a 61 % conversion (mol HMF/mol Fructose) and 55% selectivity (mol HMF/mol Fructose). Afterwards, the reaction mixture was cooled down to 40 °C and the solids (poly-HMF) were filtered by pressure filtration. The filtrate was then neutralized with calcium carbonate. After filtration and neutralization, the mixture is then sent to chromatography to separate HMF and unconverted fructose from the mixed fractions. 78% of HMF was recovered in this way. The separated HMF solution is then sent to evaporators for concentration, prior to crystallization. The concentrated syrup containing mainly HMF in water was slowly stirred and cooled to 4 °C to produce crystals of HMF. After filtration of the crystalline HMF, the mother liquor is sent to evaporators to concentrate further prior to a second crystallization. The total crystallization yield was 66% (mol HMF/mol HMF) and the purity of obtained HMF crystals was 97wt% (weight based).

The aqueous stream rich in unconverted fructose together with the remained HMF after Chromatography is then sent to evaporators to strip off the water before recycled back to dehydration reactors.

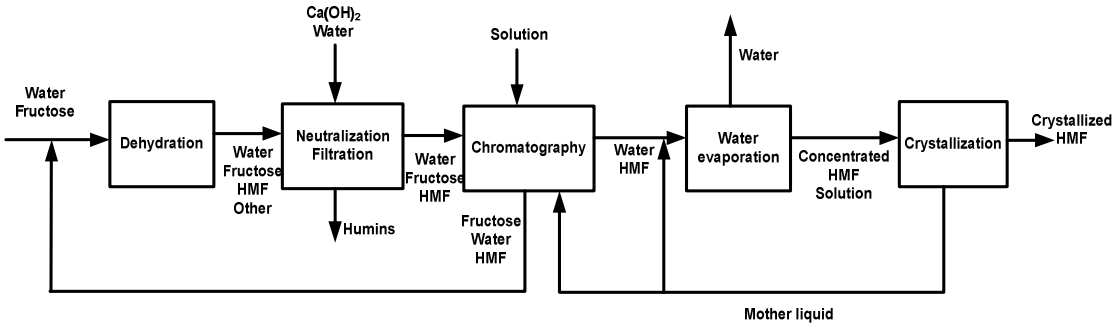


Figure 5.1. Process flowsheet of dehydration fructose in water, modified from the published flowsheet by Rapp et al. (1988).

5.2.2 Anhydrous solvent based synthetic route

The selected example case of anhydrous solvent based synthetic route is based on a French patent published by M'Bazoa et al (1990). The process flow-sheet for synthesis HMF from fructose in DMSO with DCM as extraction solvent is outlined in Figure 5.2.

The feed to the dehydration reaction for this process is fructose and the organic solvent is DMSO. In this case no catalyst was added.

The mixture was stirred mechanically at 160 °C for 8 hours. The yield for the dehydration of fructose in DMSO was 0.8 mol HMF/mol fructose (0.56 g HMF/g fructose), with a 100% conversion and 80% selectivity. Afterwards, the reaction mixture is cooled down to room temperature and neutralized with 50 g / L KOH solution. Water is added in the same amount of DMSO prior to filtration to remove any precipitates. The mixture is then extracted with dichloromethane (DCM) (same amount as the mixture) at 8 °C in a column extractor unit (with 6 theoretical extraction stages). 97% HMF in the mixture was extracted by DCM into the organic layer. The organic layer was concentrated at 20 °C in a vacuum evaporator (50 mm Hg) to separate HMF from DCM. The concentrated syrup containing mainly HMF in the dissolved DCM is passed to the crystallization step (with slow mechanical stirring). The solution was cooled to -5 °C to produce crystals of HMF. After filtration of the crystalline HMF, the mother liquor is sent to vacuum distillation to concentrate it further before sending it for a second crystallization. After two times crystallization, the final crystallization yield was 90%, with a purity of 97 wt%. (M'Bazoa et al., 1990).

Based on the conditions given by the patent, the vacuum evaporator (20 °C, 50 mm Hg) after solvent extraction was sufficient to recover DCM. Around 95% of DCM used in the downstream process was recovered.

No experimental information was given on the recovery of DMSO from water-DMSO mixture. The process step of recovering DMSO form the DMSO-water mixture was simulated in ProII 8.0 (ProII, 2011). A distillation column was used to separate DMSO and water. The design data of the distillation column were taken from the published data by Cho and Kim (2007). Cho and Kim (2007) reported a distillation column design for separation of DMSO and water. In this publication, the designed distillation column had thirteen theoretical stages including condenser and reboiler. The overhead reflux drum was operated at temperature 45 °C and at pressure 0.32 atm. The column had a top pressure about 0.52 atm and the Reflux ratio was 3.49 (by mole). The simulation of the recovery of DMSO from water-DMSO mixture with the designed distillation column data, showed that nearly 98% DMSO was recovered with a purity of 99 wt%.

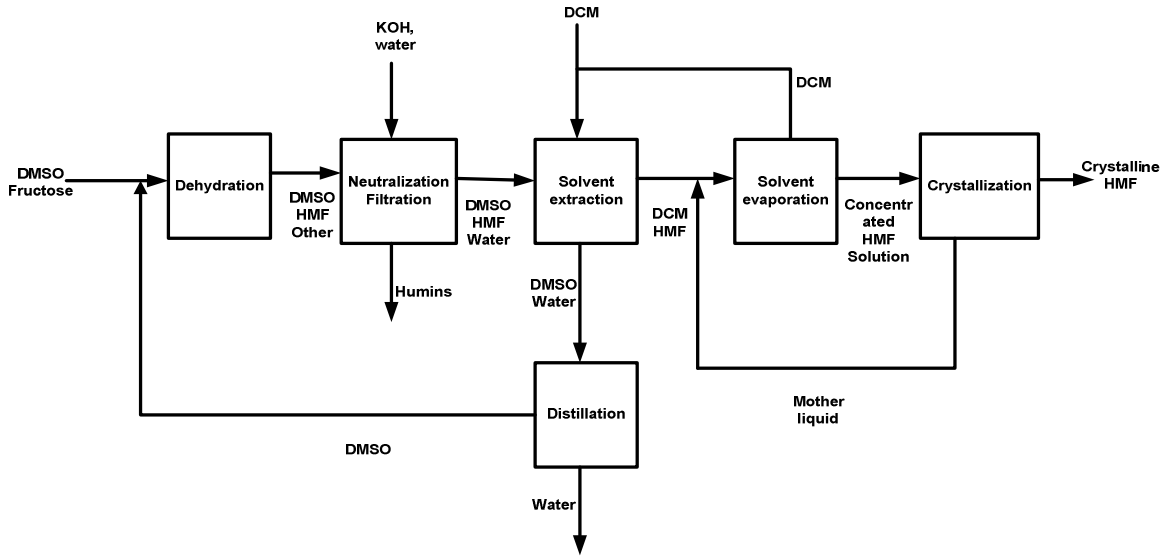


Figure 5.2. Process flowsheet of dehydration fructose in DMSO, modified from the published flowsheet from M'Bazoa et al. (1990).

5.2.3 Water-solvent based synthetic route

The process example of the water-solvent route is a process example of using biphasic reactor system for HMF synthesis published by Roman-Leshkov et al. (2006). The process flowsheet for the biphasic based synthetic route is outlined in Figure 5.3.

The aqueous feed to the biphasic reactor contains fructose and water. The feed concentration was around 30wt% fructose (on a wet weight basis). Hydrochloric acid was added into the aqueous solution as a catalyst with a concentration around 0.25 mol / L. The organic feed to the biphasic reactor is MIBK. The amount of MIBK added into the biphasic reactor was around 2 times amount (weight based) of the aqueous feed. The mixture was heated up and maintained at around 180 °C for 3 minutes. The reaction yield was 0.55 mol HMF / mol Fructose (0.38 g HMF/g Fructose), with a 75% conversion (mol HMF/mol Fructose) and 73% selectivity (mol HMF/mol Fructose). Afterwards, the reaction mixture is cooled down to room temperature for the phase separation.

The partition coefficient of HMF (R_{HMF}) between MIBK and water is poor and close to unity. Only 78% of produced HMF was extracted into the organic phase. There is still some amount of HMF in the aqueous phase. The aqueous phase is then sent to a liquid-liquid extractor for the second extraction. The performance of the second extractor was based on the calculation since no experimental results was available. In the calculation, the feed of MIBK to the second extractor was half of the amount of MIBK used in the biphasic reactor. At room temperature in a column extractor unit (with 9 theoretical extraction stages), 97% of the remained HMF in the aqueous phase was recovered.

Afterwards the aqueous rich in fructose are recycled back after stripped off the excess water produced in dehydration reaction. Organic phase both form the biphasic reactor and the second extractor are sent to a vacuum evaporator. Based on the simulation results in ProII 8.0 (ProII, 2011), at 13 mbar and 343 K, 99.9% of the MIBK solvent was recovered in this way with a 5.0 % loss of HMF. Thus, 95% of HMF was recovered from the evaporator and had a purity of 96 wt%.

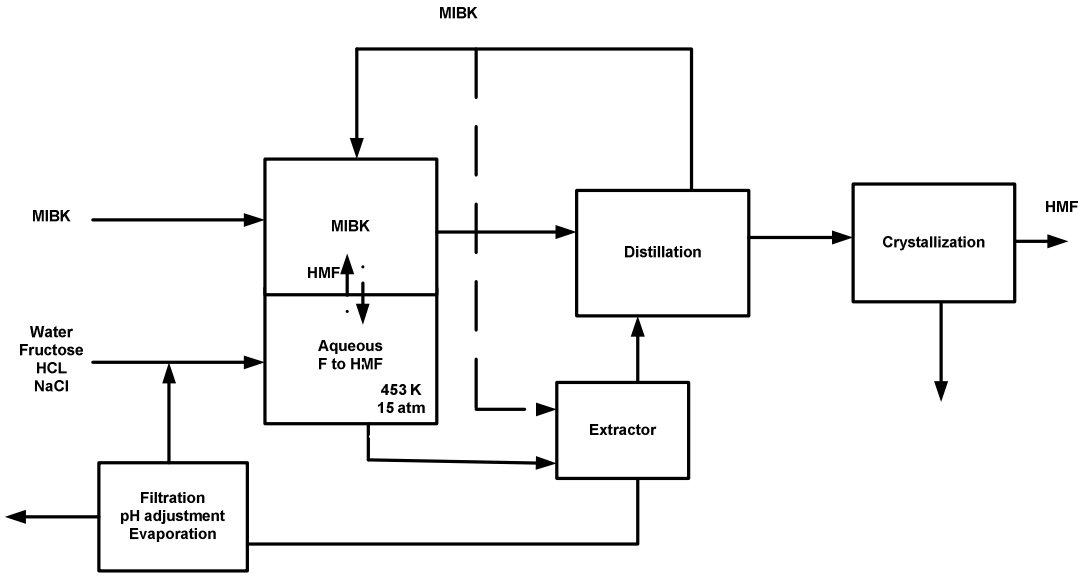


Figure 5.3. Process flowsheet of dehydration fructose in biphasic reactor (MIBK-water), Modified from published flowsheet from Roman-Leshkov et al. (2006).

5.3 Results

The process flowsheets were simulated in ProII 8.0 (ProII, 2011) based on the process descriptions above. All the results presented below were based on the simulation results. The model was validated with the mass balance based on the published experimental data described above if available. The simulation results of the three process flowsheets are listed in the Appendix3.

5.3.1 Mass metric

Table 5.1 summarizes the feed concentration and the yield of each process step (both reaction and downstream processing) of the three process synthesis examples described above.

The mass metric was done on the basis of 1 kg HMF production by the three routes described before. The required amount of reactant, solvents and process reagents of the three different routes are listed in Table 5.2.

Table 5.1. Process parameters of the three routes form producing HMF.

Item	Water route	Solvent route	Biphasic route
Fructose feed concentration (wt%)	25	38	30
Dehydration conversion (mol HMF/mol Fructose)	0.61	1.00	0.75
Dehydration selectivity (mol HMF/mol Fructose)	0.55	0.80	0.73
Solvent extraction yield (g HMF/g HMF)	-	0.97	0.99
Chromatography yield (g HMF/g HMF)	0.78	-	-
Evaporation + crystallization yield (g HMF/g HMF)	0.66	0.90	0.95
Overall process yield (g HMF/g Fructose)	0.32	0.49	0.51

Table 5.2. The required amount of raw material for 1kg HMF production by the three synthetic routes.

Raw material (kg/kg HMF)		Water Route	Solvent Route	Biphasic Route
Reactant	Fructose	3.12	2.05	1.97
Solvent	DMSO		0.08	
	DCM		0.21	
	MIBK			0.11
Catalysts	Oxalic acids	0.05	-	-
Reagents	Ca(OH)2 or KOH	0.05	0.09	

For both solvent route and biphasic synthetic route, around 2 kg of fructose are required for 1 kg HMF production. Although the solvnet route has a better reaction yield than the biphasic route, the biphasic route requires less fructose (1.97 kg Fructose/ kg HMF) than that for the organic route (2.05 kg Fructose/kg HMF). This can be explained by two reasons.

First, when the unconverted sugar is recycled back to the dehydration reactor, the real yield of the dehydration reaction is then equal to the selectivity of the reaction. This makes the difference less in the reaction yield for both routes. The advantage of using DMSO as dehydration reaction medium to gain a better yield is then reduced.

Second, the mass calculation for the solvent route was completely based on the patent descriptions. In this process, after extracting the HMF with DCM from the reaction mixture, a combination of evaporation and crystallization was used in the purification of HMF. The mother liquid was crystallized twice and gave a final yield of 90% HMF form the HMF-DCM mixture. The remained mother liquid still contained some DCM as well as HMF, which could be further purified. This leads to the loss of some produced HMF as well as the organic solvent DCM. On the other hand, HMF was separated from the

organic phase in the biphasic route by vacuum evaporation only. The calculation was based on the simulation results of the suggested downstream process by Roman-Leshkov et al. (2006). According to the simulation results, around 95% HMF in the organic phase can be recovered with a purity of 97.5% similar to other process routes. In addition, 99% MIBK in the organic phase were recovered. The solvent loss in the biphasic route was also less. As a result, the overall yield (g HMF/g HMF) of the downstream separation in the biphasic route (94.1%) was higher than that in the solvent route (87.1%). Therefore, less fructose was required in the biphasic route than that for the solvent route.

The water route requires the most fructose (3.1 kg) for 1 kg HMF production among the three routes. This is because of a low selectivity (55%) in dehydration reaction and a low yield in downstream purification. The chromatography was able to separate 78% of HMF from the total produced HMF in dehydration reaction. The aqueous stream containing the remained HMF together with the unconverted fructose was recycled back to the dehydration reactors after stripped off the water. Evaporation combined with crystallization was used to isolate HMF from the separated stream rich in HMF from chromatography. The total yield is 66% after twice crystallization. The mother liquid still contained certain amount of HMF. The total yield of the downstream separation in the water synthetic route is 64.5% (g HMF/g HMF) which is the lowest among the three routes. The water route has the lowest overall process yield.

5.3.2 Energy metric

The required energy of 1kg HMF production by using the three process routes are listed in Table 5.3. The energy calculation was based on the simulation results, which can be found in the Appendix3.

The required energy by the biphasic route and the solvent route are quite similar. The required energy of the biphasic route (86 MJ/kg HMF) is a bit less than that of the solvent route (92 MJ/kg HMF). The water route is an energy intensive process. It requires 2604 MJ for 1 kg HMF production, which is around 28 times of the energy required by the solvent and the biphasic route.

Figure 5.4 shows the energy consumption of each process step in the three routes. In dehydration reaction, organic route uses the least energy among the three routes. This is because of the high feed concentration used and no energy requirement in this route for pressuring the reaction medium due to a high boiling point of DMSO (189°C). The other two routes require the energy of pumping to make the reaction medium pressurized. Besides, the biphasic route also requires extra energy for heating up the organic phase in the biphasic reactor.

With respect to the downstream separation, the water route demands the highest energy. The reason for this is that using chromatography in the downstream separation leads to significant dilution. In this process step, washing 1 kg HMF out of the reaction mixture

requires 115 kg water. The large dilution therefore requires a lot of energy to evaporate the water to concentrate the solution before crystallization. Moreover, the aqueous stream rich in unconverted fructose was further diluted 12 times after the chromatography. Large amount of energy is thus required to recycle the sugar as well as to recovery of the process water.

The major energy requirement in the solvent route is the energy used for reaction medium recovery. In this case, it is recycling DMSO from a DMSO-water mixture. Distillation was applied here to separate DMSO from water. Large amount of energy (81% of the total energy in the organic route) is required in this process step. DMSO is a high-boiling solvent (Kuster, 1990; Roman-Leshkov et al., 2006) and is not easy to separate from water (Cho and Kim, 2007). Harsh process conditions and high energy is required in order to reach a good recovery and purity of DMSO (Roman-Leshkov et al., 2006; Cho and Kim, 2007). The advantage of using a low-boiling solvent as MIBK can be found here. Even though the amount of MIBK used in the biphasic route is around 11 times of the amount of DMSO used in the solvent route, the energy of DMSO recovery (74.1 MJ/kg HMF) is 4.3 times of that of MIBK recovery (17.2 MJ/kg HMF).

Table 5.3. Energy balance for producing 1kg HMF by using three synthetic routes, the energy unit here is MJ/kg HMF.

Energy (MJ/kg HMF)	Water route	solvent route	Biphasic route
Pumping & Preheating	6.18	0.34	10.89
Dehydration	4.60	1.01	2.55
Cooling	8.06	2.59	34.32
Extraction		0.39	
Chromatography	29.56	-	-
Evaporation	397.69	3.05	18.60
Crystallization	0.23	0.04	
Extraction Solvent recovery	-	3.03	17.17
Reaction medium recycle	896.54	74.1	2.28
Process water recovery	1261.48	7.4	
Total Heating, pumping, evaporation	1305.25	42.26	34.33
Total Condenser, cooling	1299.10	49.68	51.49
Total energy	2604.34	91.94	85.82

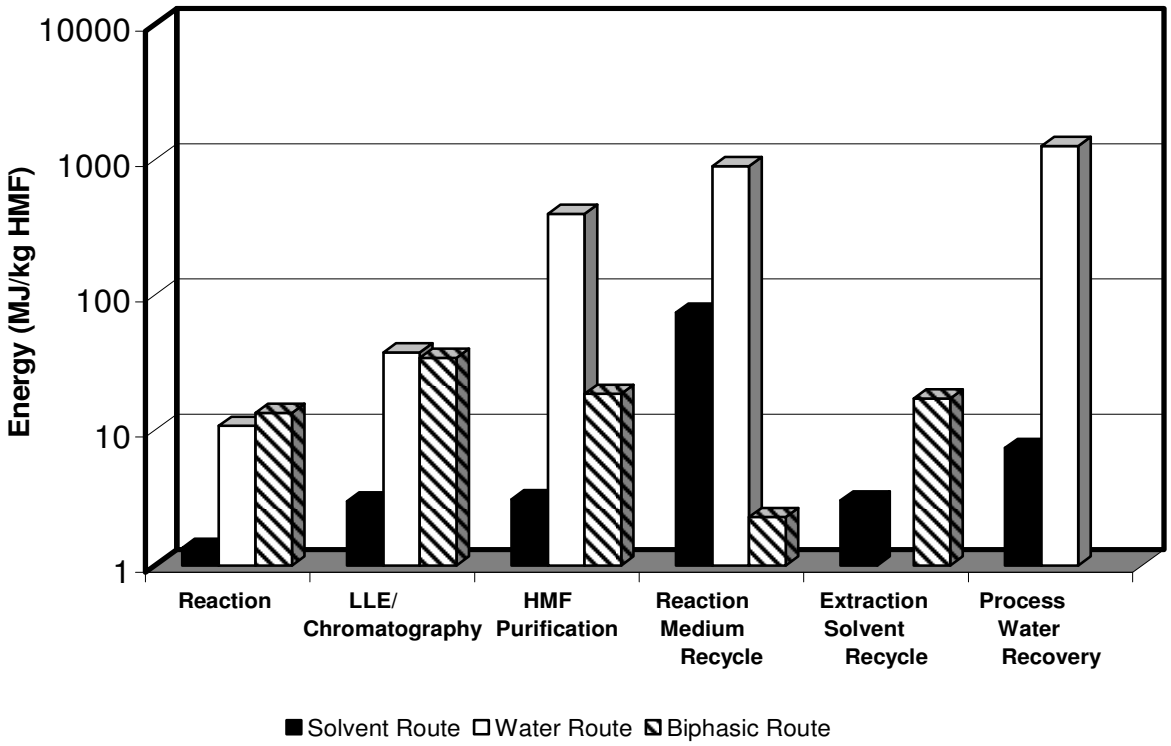


Figure 5.4. Comparison of energy consumption of each process steps for three routes, unit MJ/kg HMF.

5.3.3 E-factor

The E-factor of the three process routes were calculated based on the mass balance results (Table 5.4). The E-factor is 2.22 for the water route, 1.43 for the solvent route, and 1.20 for the biphasic route. For chemical industry process, the typical E-factor for bulk chemical industry is in the range of 1 to 5 (kg waste/kg product) (Sheldon, 2007). The E-factor of the three routes are all inside this range. However, the E-factor for the water route is still the highest among all three synthetic routes. The E-factor indicates the efficiency of the usability of the raw material. Although, avoiding organic solvent is a big advantage, the low usability of the raw material makes the water route unfavorable.

Table 5.4. Calculated E-factors for making 1kg HMF of three synthetic routes.

	Water Route	Solvent Route	Biphasic Route
E-factor	2.22	1.43	1.08

5.3.4 HMF cost

Based on mass and energy requirement for 1kg HMF production, the HMF cost of the three routes was estimated. The raw material and energy price used in the calculation of

the HMF cost is listed in the Table A1.3 in the Appendix1. The HMF cost which is a sum of raw material and energy cost of the three routes are listed in Table 5.5. The HMF cost is 11.52 USD/kg HMF for the water route, 1.62 USD/kg HMF for the solvent route and 1.44 USD/kg for the biphasic route.

The cost distribution of the solvent route and biphasic route are quite similar (Figure 5.5). For both two routes, the reactant (fructose) cost dominates the HMF cost and covers more than 60% of the HMF cost. The energy cost covers around 20% of the HMF cost. The rest HMF cost comes mainly from the solvent loss.

The HMF cost for the water route is mainly dominated by the energy cost. The energy cost in the water route covers 86% of the HMF cost. Most of the energy cost is used for concentrating the highly diluted solution after the chromatography. In the water route, the energy cost after chromatography to concentrate HMF-water solution before crystallization is 2.39 USD/kg HMF, to recycle fructose is 5.38 USD/kg and to recycle the process water is 0.52 USD/kg HMF. All these energy cost contributes to 84.8% of the HMF cost. The dilution caused by the chromatography separation results in such a high energy cost, indicating that the separation technique here is very inefficient and infeasible. The energy cost for recovering fructose is around 2.66 USD/kg fructose, which is much higher than the cost of fructose itself.

The HMF cost of the solvent route was calculated mainly based on the patent description. The cost can be lower than the calculated value (1.62 USD/kg HMF) given the condition that the mother liquid after the second crystallization still contains 10% produced HMF and some organic solvent (DCM), as explained by the section 5.3.1.

Table 5.5. HMF cost of the three process routes (unit USD/kg HMF).

Item	Water Route	Solvent Route	Biphasic Route
Fructose cost	1.56	1.03	0.99
Solvent loss		0.27	0.21
Catalyst cost	0.05		
Process reagent cost	0.01	0.02	
Total raw material cost	1.62	1.31	1.19
Heating, evaporation, pumping	9.23	0.30	0.23
Cooling, condenser	0.55	0.02	0.02
Total energy cost	9.73	0.32	0.25
HMF cost	**11.43**	**1.62**	**1.44**

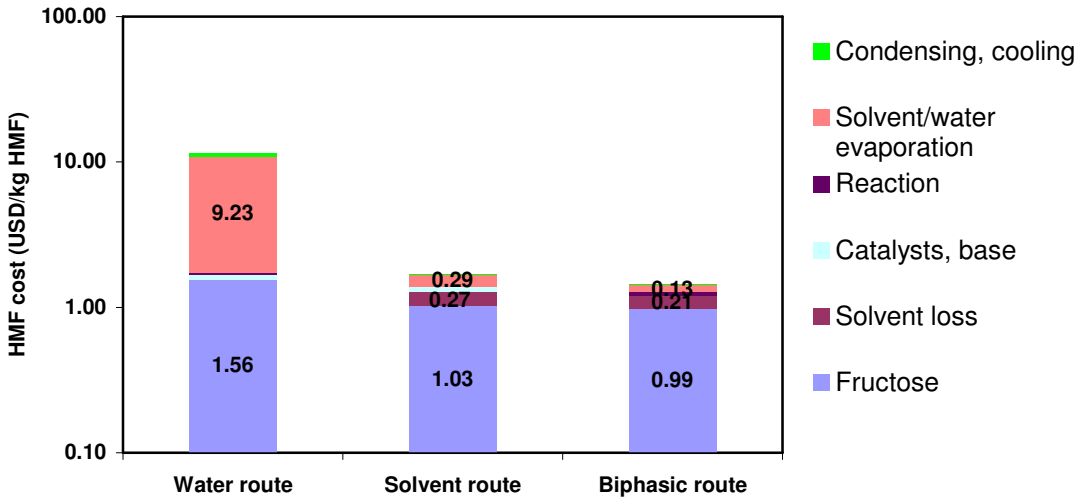


Figure 5.5. HMF cost distribution of each synthetic route.

5.4 Discussion

5.4.1 Important issues and future improvement

Water Route

Both solvent based synthetic route and biphasic route are much more superior to the water synthetic route. The limitation of the water route is mainly the low reaction yield and very inefficient downstream separation. Although the wide application of chromatography in sugar and food industry may offer the great potential for HMF production, the high dilution with the selected ion exchange resin in this study was not applicable.

Besides, even with other more efficient separation technique in the downstream, the reaction yield is too low to compete with the other two routes. Although using water and avoiding organic solvent in the process route sounds more environmental friendly, the inefficient usability of the fructose due to the low selectivity of the reaction will not make this process route economically feasible. The dehydration in water is problematic since water is a reactant of HMF rehydration. The selectivity is always too low to make the process industrialized unless a new catalyst appears which can help to overcome the problem. Based on what has been achieved so far in dehydration, the water route is not a scalable process.

Solvent Route

For the solvent based synthetic route, using DMSO assures very high reaction yield and little solid (humins) formation even with a high feed concentration. Besides, dues to the high boiling point of DMSO, the system can be operated at normal pressure.

Since the fructose dominates the HMF cost of this route, any improvement in the yield will help to reduce the cost. The HMF cost of this process is based on a reaction yield of 80% (mol HMF/mol fructose). A reaction yield up to 92% (mol HMF/mol fructose) was obtained at 150 ºC after 2 hours in DMSO even without using any catalyst (Musau and Munavu, 1987). Based on this reaction yield and the same downstream separation, the calculated HMF cost was 1.47 USD/kg HMF. The fructose cost was 0.89 USD/kg HMF.

The mother liquid still contains 10% of the produced HMF can be recovered. If a third crystallization is added and gives a final crystallization yield of 97%, the HMF cost can be further reduced to 1.40 USD/kg HMF. The cost distribution based on this assumption is shown in Figure 5.6.

The energy cost for recovery DMSO covers 20% of the HMF cost. It also contributed to 82% of the total energy cost. Besides, the cost of DMSO loss contributes to around 60% of the cost of solvent loss, which covers around 11% of the HMF cost. In total, the cost with DMSO in downstream (energy and DMSO loss) contributed around 31% of HMF cost. This indicates the disadvantage of using a high energy intensive solvent (DMSO) in the downstream separation. This cost related with DMSO separation is hard to reduce since reducing the DMSO loss in the process requires more energy cost (Cho and Kim, 2007). Due to a high viscosity of DMSO, water was required to mix with DMSO before the extraction process (M'Baozoa et al., 1990), resulting in a high energy requirement to separate DMSO from water. However, vacuum distillation of DMSO from HMF is difficult (Brown et al., 1982; El Hajj et al., 1987). It is also a high energy required process (Roman-Leshkov et al., 2006). Roman-Leshkov et al. (2006) predicted that an efficient separation of HMF from pure DMSO required 40% more energy as compared with pure MIBK by using Aspen Plus Simulation Software (Version 12.1, Aspen Technology Inc.). Besides, distillation of DMSO is associated with the risk of decomposition and has risk for health and environment (Kuster, 1990). Moreover, DMSO is an expensive solvent as well. All these drawbacks stop the application of DMSO at a large scale for bulk chemical production.

Apart from the problems associated with DMSO, DCM has already been banned due to the environmental concerns. Studies related with finding a suitable solvent to substitute DCM for extraction HMF from DMSO reaction mixture are required. Nevertheless, the main bottleneck in the solvent synthetic route is still the use of DMSO. In order to make the solvent route applicable for a large scale production, research in the future should be placed on finding an alternative solvent. This alternative solvent should assure a high reaction yield with a high feed concentration of fructose. It should also be easy for separation and easy to handle at a large scale. The required properties for the alternative solvent for the synthetic purpose are listed in Box 5.1.

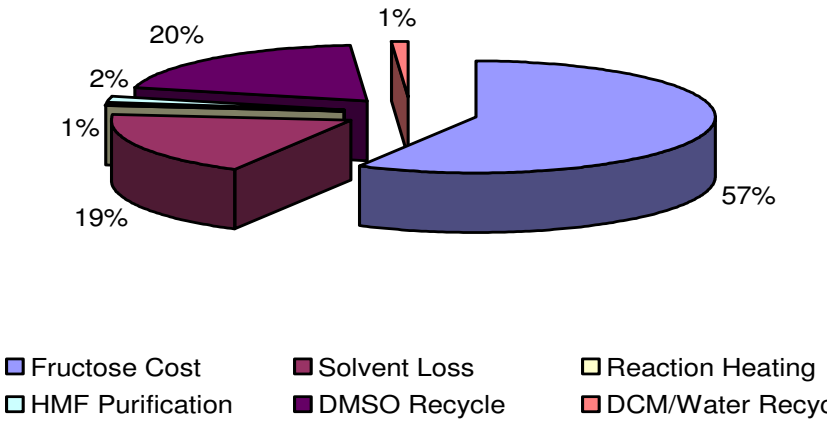


Figure 5.6. HMF cost distribution of the solvent route. The HMF cost is based on an improved reaction yield of 92% and a crystallization yield of 97%.

Box 5.1. Required solvent properties for alternative solvent to DMSO.
Dissolve Fructose (prefer can up to 30% by weight)
High boiling point, normal boiling point between:120˚C < Tb < 200˚C
Stable at high temperature, acidic conditions.
Environmental friendly, no halogenated compounds, prefer no S
Exclude some other functional groups, such as: nitriles, amines, epoxides, alkynes, carbonates, azides.
Easy for separation and to be handled in large scale
Cheap

Biphasic Route

Compared to the other two routes, the biphasic route offers a good potential for scale up. Economically, the HMF cost of this route is cheapest among the three routes examined here. Like the solvent route, the fructose cost dominates the HMF cost. The yield of the process is very critical. The HMF cost calculated here is based on a selectivity of 73% with a conversion of 75%. There is still a lot of room for improvement.

Phase modifiers

For example, adding phase modifiers can improve the selectivity. A high selectivity of 85% with a conversion of 89% was obtained with the aqueous phase (7:3 (8:2 Water:DMSO): Polyvinylpyrrolidone) and organic phase (7:3 MIBK:2-butanol) (Roman-Leshkov et al., 2006). In addition, adding 2-butanol into the organic phase also improves the partition coefficient of HMF. In this way, the amount of solvent used in this route can also be reduced. The HMF cost can thus be reduced with the improved reaction yield as well as the partition coefficient of HMF.

On the other hand, the cost of the solvent loss and energy for solvent evaporation, heating and cooling is another big contribution to the HMF cost. Specially, due to the low partition coefficient of HMF, large amount of MIBK is required in order to assure an

efficient extraction. In the simulated process, 39.6 kg MIBK was required in the process for 1 kg HMF production. With such amount of solvent used in the process, even 1% solvent loss would result in significant cost (0.8 USD for 1% MIBK loss in this case). Besides, Purification of the diluted HMF product thus causes large energy expenditure in the subsequent process (Roman-Leshkov et al., 2007). Optimizing the solvent use (reducing the amount of solvent and minimizing the solvent loss) is very critical for the biphasic route.

One way to reduce the amount of solvent in the process is by improving the partition coefficient of HMF (R_{HMF}). However, solvents which have better R_{HMF} than MIBK are more soluble in water. For example, the R_{HMF} of 1-butanol is 1.7 and the R_{HMF} of MIBK is only 0.9. But the solubility of 1-butanol in water (7.7 g/100 ml water at 20℃) is much higher than that of MIBK in water (1.9 g/100ml water at 20℃). This makes 1-butanol an unfavorable solvent for the biphasic system.

Addition of salts

Roman-Leshkov et al. (2007) reported a method for increasing R_{HMF} by addition of a salt (e.g., sodium chloride (NaCl)) to the aqueous phase. After the addition of inorganic salts (such as NaCl) into the reactive aqueous phase, the partitioning of HMF was largely improved. For example, the R_{HMF} of MIBK with aqueous phase saturated with NaCl is 1.6 (Roman-Leshkov et al., 2007). The R_{HMF} of MIBK is only 0.9 (Roman-Leshkov et al., 2006) when no salt is added. The biphasic route using MIBK-water with saturated NaCl had a selectivity of 77% with a conversion of 72% (Roman-Leshkov et al., 2007). Using the same downstream processing, the HMF cost of the biphasic route with salt is 1.22 USD/kg HMF (Table 5.6).

Table 5.6. Calculated HMF cost for biphasic route with addition of salt (MIBK-water).

Item	(USD/kg HMF)	Percentage (%)
Fructose	0.94	77.05
Solvent loss	0.08	6.56
Electricity	0.00	0.00
Heating steam	0.19	15.57
Cooling water	0.01	0.82
HMF cost	**1.22**	**100.00**

The reduced HMF cost by adding salt is mainly from the reduced cost of the energy and fructose. Since R_{HMF} increases with the addition of NaCl, the total amount of MIBK required in the process is reduced. This leads to a less energy requirement for evaporation and heating. Besides, the improved selectivity also results in less fructose requirement.

Another advantage of addition of salt is that it also helps to decrease the solubility of the solvents in water (Roman-Leshkov et al., 2009). In this way, other alternative solvents with better R_{HMF} than MIBK can also be used in the biphasic route.

From the reduced HMF cost by adding salt, the importance of reducing the amount of solvent to the process economic can be observed. Alternative solvent with big R_{HMF} as well as low solubility in water will favor the process economic. The required properties of alternative solvents to MIBK for biphasic system are listed in Box 5.2. Nevertheless,

reducing the amount of the solvent in the process and minimizing the solvent loss is still a key important issue for biphasic route.

Box 5.2. Required solvent properties for biphasic system (separation purpose).
High extracting power R_{HMF}
Create two phase, needs phase split
Low fructose/glucose solubility
Low water miscibility (below 10% H_2O)
Easy to be distillated, normal boiling point Tb<160°C
Environmental friendly, no halogenated compounds, prefer no S
Exclude some other functional groups, such as: nitriles, amines, epoxides, alkynes, carbonates, azides.

5.4.2 Comparison and alternative process

The advantages together with the drawbacks of the process routes are listed in Table 5.7. The suggestions for future work up issues are also pointed out.

Table 5.7. Comparison and evaluation of three routes for fructose production.

	Main advantages	Drawbacks	Further work up issues
Water route	No organic solvents needed Syrups as feedstock	Low selectivity Demanding product recovery	Develop new catalytic system to improve the reaction yield, improve the efficiency of downstream processing, increase concentrations
Solvent route	High yields Operates at low pressures Little/no solid formation	Hard product recovery High energy require Sulfur by-products	Find the alternative solvent to DMSO
Biphasic route	Good yields In situ product recovery Syrups as feedstock	Complex multiphase reactors needed Large amount of solvent needed	Improve the reaction yield, Find the right extraction solvent, optimize the solvent use and minimize the solvent loss

In this thesis, the HMF use is to make FDA which can potentially substitute PTA. The PTA cost (raw material and energy) of a PTA process from p-xylene by bromine-promoted air oxidation is around 1 USD/kg (Detailed information of this process as well as the cost is shown in Chapter 8). If this is chosen as a criterion, none of the process routes can reach this cost (Figure 5.7).

The cost of the solvent route (with improved reaction yield as well as the solvent recovery) is still 1.40 USD/kg, which is much higher than a cost of 1 USD/kg. The biphasic route with addition of salt has a cost of 1.22 USD/kg which is the lowest cost among all the routes from fructose presented here. But, still, it can not reach 1 USD/kg. Even with a reaction yield nearly 100%, the HMF cost is still around 1.02 USD/kg. This is due to a high reactant cost of fructose (0.5 USD/kg). Therefore, alternative process which can start from a cheaper raw material is thus required.

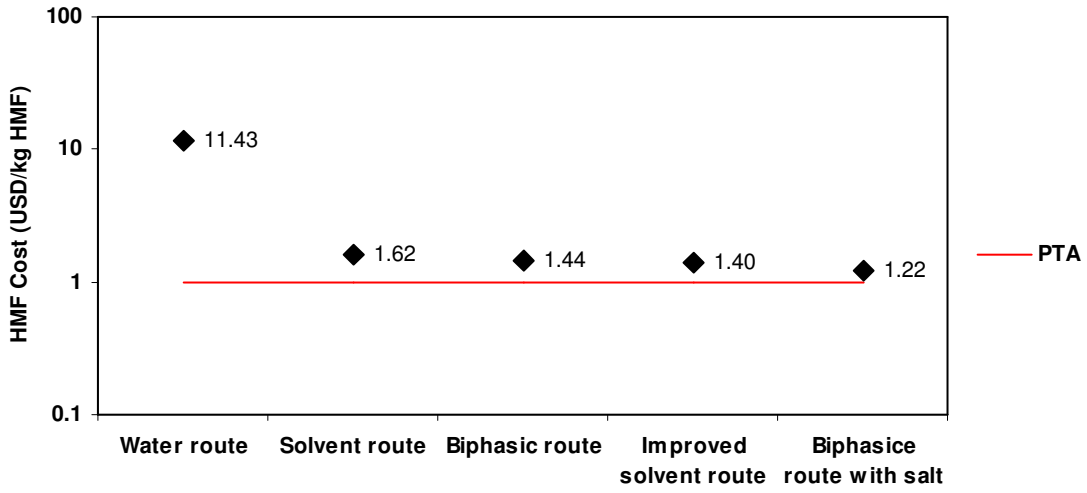


Figure 5.7. HMF cost of the three process routes as well as the improved cost of solvent route and biphasic route with salt. The red line is the PTA cost.

5.4.3 Back/forward integrations with other process

Since none of HMF cost by the process routes presented here is cheap enough to compete with PTA process. Dehydration reaction needs to be integrated with other reactions together to produce HMF (FDA) from a cheaper material: glucose.

To consider the whole cascades (described in Chapter 3), decisions can not be completely made just with the performance of one single reaction. It has to be considered as a whole, how easy the chosen route can be integrated with other reactions and how much down/up stream processing are required.

Obviously, using water route provides the simplest solution for the whole cascades. However, considering the large dilution in separation HMF from the unconverted sugar resulting in the high energy requirement and the low selectivity of the reaction, the process economic is not good.

Solvent route offers a better improvement in the feed concentration, high reaction yield and very good process economic as well. However, if putting the enzymatic reaction together with the dehydration in organic solvent, it then requires the solvent swap. The feed from the enzymatic reaction to the dehydration reaction is an aqueous mixture with glucose and fructose. Consequently, this feed requires completely removal of water before entering the dehydration reactor. Moreover, after the produced HMF in dehydration reaction is separated from the unconverted sugar, the unconverted sugar (rich in glucose) will require completely removal of the solvent to recycle back to the enzymatic reaction. As showed in the example, it requires a high energy to separate high-boiling solvent (e.g. DMSO) from water mixture. Specially, considering the sensitivity of

enzyme to solvents, the purity of the recycled stream will be very high. This can make the downstream processing very costly.

Biphasic route, on the other hand, with a system containing both the aqueous phase and the organic phase gives a much better chance to be integrated into the whole cascade reactions. The aqueous stream from the first enzymatic reaction can be used as the aqueous feed in the dehydration reactor with pH adjustment. If the third reaction is operated in water, the organic phase (rich in HMF) from the dehydration reactor requires the solvent swap before the oxidation reaction. However, this type of solvents used in this route is low-boiling solvents. The removal of the solvents from HMF is easy and requires low process energy as showed in this Chapter.

Table 5.8. Comparison and evaluation of three routes for chemo-enzymatic cascades design.

Dehydration	Backward to IGI	Forward to Oxidation	Process Energy	Process Economic	Solvent Swap
Water Route	Easy (Salts, by products effects on GI)	Medium	High	Not good	No
Organic Route	Hard	Easy	Medium	Good	Required
Biphasic Route	Easy (Solvent, salts effects on GI)	Easy	Low	Good	Required

5.5 Conclusion

For the dehydration of fructose to HMF, both the organic synthetic route and biphasic route are superior to the water synthetic route. Both the two routes have better usability of both raw material and energy. However, due to the limitation with DMSO for the organic route, biphasic route is more promising.

For biphasic route, the emphasis and challenge in process design should then be placed on improving the reaction yield and optimizing the solvent use (reducing the amount of solvent and minimizing the solvent loss) or finding alternative extraction solvents. For the organic route, finding the alternative solvent (more environmental friendly and easy to recover) is the key issue. For the water based synthetic route, maintaining a high yield and keeping a high concentration are very critical. Although the uses of ion-exchangers (chromatography) are common practice in the sugar industry, the generally high dilution of the resulting HMF solutions is a disadvantage and requires further improvements in order to use it at a large scale for bulk chemical production.

None of the process routes examined here is cheap enough for HMF production due to a high fructose cost. New alternative process is required. The biphasic route offers the best potential to be integrated in the cascade reactions mentioned in Chapter 3.

Concluding remark

In this chapter, three process routes for HMF production from fructose are evaluated. Biphasic route is found to be promising for HMF production and shows the best to be integrated with a whole cascade reactions described in Chapter 3. Based on the selected medium for operating the dehydration reaction, a new process which uses chemo-enzymatic synthetic method to produce HMF from glucose is designed and evaluated in the next chapter.

6 Chemo-enzymatic Synthesis of HMF from Glucose

Summary

A process flowsheet using a chemo-enzymatic route for synthesis of HMF from glucose is proposed and evaluated in this chapter. The process flowsheet is characterized by using glucose isomerase to convert glucose into fructose, and followed by a biphasic route for dehydration fructose into HMF. After extracting HMF with MIBK, the aqueous phase rich in unconverted glucose is recycled to the enzymatic reaction.

The process flowsheet is evaluated with process metrics. In the economic metric, besides the HMF cost, the HMF production cost is used to evaluate the feasibility of the proposed flowsheet for large scale production. The HMF production cost is calculated based on a hypothesis with a production scale of 250,000 tons HMF per year. For the base case, the total capital investment is approximately 196 million dollars. Based on a glucose price of 0.3 USD/kg, the HMF production cost of the base case is around 1.48 USD/kg.

The HMF production cost is found to be very sensitive to the dehydration reaction yield, the amount solvent used in the whole process, and the glucose price. Reducing the amount of solvent to half amount of the solvent used in the base case can decrease the HMF production cost to around 1.21 USD/kg. In addition, increasing scale also contributes to decrease the HMF production cost.

6.1 Introduction

In the previous chapter, the biphasic route is selected for operating the dehydration reaction in the whole cascade reactions described in Chapter 3. Based on a biphasic reaction medium in dehydration, a process flowsheet of chemo-enzymatic synthesis of HMF from glucose is proposed. The designed process flowsheet is outlined in Figure 6.1.

In the flowsheet, glucose is first dissolved in the aqueous solution. The aqueous stream passes then through to a fixed bed reactor where glucose is converted to fructose

catalyzed by the immobilized glucose isomerase (IGI) (E.C. 5.3.1.5). After reaching equilibrium, the aqueous stream containing a mixture of glucose and fructose is pumped into a second reactor vessel followed by the addition of a water-immiscible organic solvent and the catalyst (homogeneous). The second reactor is a pressurized vessel. In this reactor vessel where the dehydration reaction takes place, fructose is converted to HMF. Most of glucose remains unconverted, although a small amount of glucose reacts together with fructose, HMF and forms humins (insoluble polymers). Following the settler, the aqueous phase is sent to a second extractor where the remaining HMF is extracted by a water-immiscible solvent. The organic phase rich in HMF, both from the dehydration reactor and the second extractor, passes by the evaporator to separate HMF and recycle the solvent. The aqueous phase rich in unconverted sugar (mainly glucose) is stripped of water and recycled back to the fixed bed reactor after the pH adjustment.

6.2 Highlights

The designed process flowsheet is characterized by using glucose isomerase to convert glucose into fructose, and using afterwards a biphasic route for chemically catalytic dehydration of fructose into HMF. After extracting HMF with MIBK, the aqueous phase rich in unconverted glucose is recycled back to the enzymatic reaction. The innovation of this designed process flowsheet is highlighted in below:

1. The designed process flowsheet combines an enzymatic reaction together with the chemically catalytic reaction for a bulk chemical production.

2. The aqueous phase from the dehydration reactor is recycled back to the enzymatic reaction after a second extraction to remove the remained HMF.

3. The designed process flowsheet uses glucose as feedstock for HMF production.

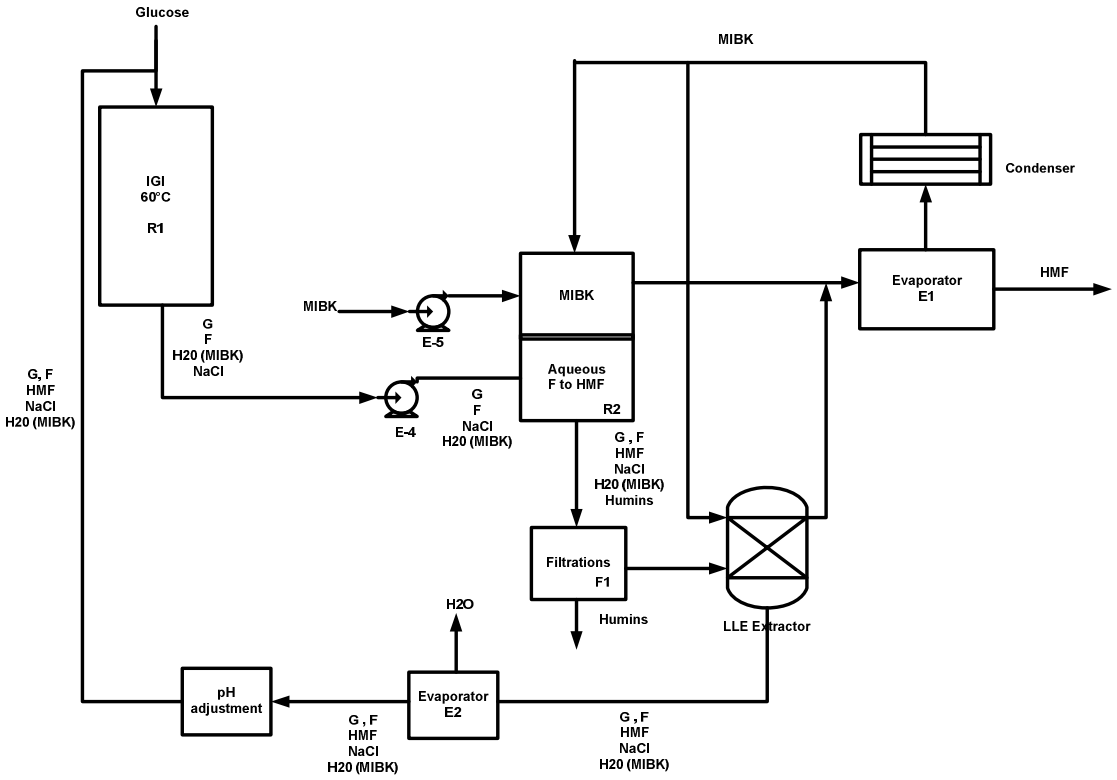


Figure 6.1. Process flowsheet of chemo-enzymatic synthesis of HMF from glucose.

6.3 Methodology

In order to evaluate the designed process flowsheet, process metrics described in Chapter 2 need to be calculated. The process metrics are calculated according to the methodology presented in Chapter 2. This methodology section mainly describes the assumptions and process data which are used to calculate the process metrics.

The economic metric in this Chapter uses the HMF production cost which contains the HMF cost as well as the capital cost. The capital investment is calculated based on the purchase of equipment cost (Chapter 2). Equipment sizing is required to estimate the purchase of equipment cost. In section 6.3.3, the procedures of sizing the major equipment involved in the designed process flowsheet as well as the assumptions are described.

6.3.1 Mass Metric

The process parameters and assumptions used for calculating the mass metric are listed as bellows:

Isomerization reaction

The feed aqueous stream to the IGI reactor (which is a mixture of the recycled aqueous stream and new glucose feed) contains around 30 wt% of saccharide (both glucose and unconverted fructose from the recycled stream). The salt (NaCl) concentration is around 50g/l. The NaCl in the feed comes from the recycled aqueous stream because it is used as the catalyst in the dehydration reaction. The inlet fructose concentration of the total dry substance is around 1.68%. The isomerization reaction conditions are listed in Table 6.1.

Table 6.1. Reaction conditions for the IGI reaction.

Reactor type	Fixed bed reactor
Dextrose content, (DX)	99.9% (dry basis)
Dry substance content, (DS)	30% w/w
Catalyst	Immobilized glucose isomerase
Temperature	60°C
pH	7.5-8.2
NaCl concentration	50 g/l
Magnesium	0.15 g MgSO4•7H20/l
Inlet fructose content	1.68%(on dry basis)
Outlet fructose content	42% (on dry basis)

Dehydration reaction

The dehydration reaction takes place in the aqueous phase catalyzed by the salt NaCl. MIBK is used to form a water-immiscible phase and to extract HMF from the aqueous phase to the organic phase when it is formed.

The levulinic acid and formic acid are always formed during very acidic conditions (Kuster, 1977). Using NaCl as catalyst avoids this very acidic condition. The formation of both levulinic acid and formic acid is thus very small (Boisen et al., 2010) and can be negligible.

The byproducts of the dehydration reaction in this route are mainly considered to be polymers (both soluble and insoluble humins). To simplify the calculation, it is assumed that all the formed HMF is converted from fructose. The structures of the formed polymers are rather complex. Still, there is not an agreed molecular structure for the formed polymers (Roman-Leshkov et al., 2006). The experiments carried out in this study indicate that a large amount of water is the formed during the reaction. Therefore, it is assumed that all the polymers have the same structure as HMF. By converting 1 mole of the polymers, 3 moles of water are produced. It is also assumed that all the converted glucose forms polymers. The soluble polymers can also be removed as humins by adding water into the reaction mixture (Kuster, 1990). In calculating the mass metric, it is assumed that all the formed polymers are insoluble and can be fully removed by filtration.

The overall dehydration reaction can be written as:

Fructose --> HMF + 3H2O

Fructose --> Polymers + 3H2O

Glucose --> Polymers + 3H2O

Conversion (X), selectivity (S) and yield (Y) are defined as:

For fructose: $X_F = \frac{F_{in} - F_{out}}{F_{in}}$ Equation 6.1

$$S_{HMF} = \frac{HMF_{in} - HMF_{out}}{F_{in} - F_{out}}$$ Equation 6.2

$$Y_{HMF} = \frac{HMF_{in} - HMF_{out}}{F_{in}} = X_F \times S_{HMF}$$ Equation 6.3

$$S_{Polymers\_F} = 1 - S_{HMF}$$ Equation 6.4

For glucose: $X_G = \frac{G_{in} - G_{out}}{G_{in}}$ and $S_{Polymers\_G} = 1.00$ Equation 6.5

F_{in} , $F_{out,}$, G_{in}, G_{out} and HMF_{in}, HMF_{out} are the mass flow rates of fructose, glucose and HMF entering and leaving the dehydration reactor. HMF_{out} is the sum of HMF mass flow rate in the aqueous and in the organic phase.

The reaction conditions together with the reaction yield from the dehydration experiments in this study are summarized in Table 6.2.

Table 6.2. Reaction conditions and results from dehydration reaction.

Reactor type	Batch biphasic reactor
Feedstock	Fructose and glucose
Reaction medium	Water-MIBK
Catalyst	NaCl
Catalyst amount (concentration in aqueous)	50 g/l
Reaction temperature(°C)	180
Residence time (h)	0.5
Total sugar concentration (wt%)	30 (aqueous)
Phase ratio in volume (MIBK/aqueous)	4
X_F	0.96
S_{HMF}	0.80
X_G	0.10

HMF distribution and phase separation

The distribution of HMF between the solvent and water is described by R_{HMF}, which is the ratio of the HMF concentration between the organic phase and the aqueous phase:

$$R_{HMF} = \frac{[HMF]_s}{[HMF]_A}$$ Equation 6.6

The measured R_{HMF} at room temperature between MIBK and water with the applied salt concentration (50g/L) is 1.35.

It is assumed that no sugar or formed polymers enter the organic phase. To simplify the calculation, it is assumed that with the addition of salt, the solubility of MIBK in water is 0 and the solubility of water in MIBK is also 0.

The experiments examined the effects of the aqueous stream with saturated MIBK at this salt concentration on the glucose isomerase performance. The effect on the activity of IGI is small. The IGI is stable with the recycled aqueous saturated with MIBK at a salt concentration of 50 g/L. Therefore, neglecting the small amount MIBK in the aqueous phase does not affect the process evaluation.

Liquid–liquid extractor (LLE)

The remaining HMF in the aqueous phase after the dehydration reactor is extracted again with fresh MIBK in a liquid-liquid extraction column.

The liquid-liquid extractor is designed with an extraction yield of 0.99 HMF/HMF. The designed extraction solvent volume of MIBK is 2 times of the volume of the aqueous. For the extraction calculations, equilibrium at each stage is assumed, thus the separation obtained in the extractor is related to the number of theoretical stages N_s and can be calculated as (Perry and Green, 2007):

$$\frac{[HMF]_{aqueous\_in}}{[HMF]_{aqueous\_out}} = \frac{E^{N_S}(1-E)}{1-E^{N_S+1}}$$ Equation 6.7

Where $[HMF]_{aqueous\_in}$ and $[HMF]_{aqueous\_out}$ are the mole concentration of HMF in the diluted reaction mixture entering and leaving the extractor. E, the extraction factor, can be calculated as:

$$E = \frac{\rho_{MIBK} V_{aqueous\_in}}{R_{HMF} \rho_{aqueous} V_{MIBK\_in}}$$ Equation 6.8

where ρ_{MIBK} and $\rho_{aqueous}$ ares the densities of the organic solvent and of the aqueous phase, respectively. The V_{MIBK_in} and $V_{aqueous\_in}$ are the volumes of the extraction solvent and of the aqueous phase, respectively.

It is also assumed that both phases must have the same residence time. The parameters in the extraction process are listed in Table 6.3.

Table 6.3. Summarized process parameters for the second extraction column.

Item	Value
Extraction temperature (°C)	25
Extraction yield (mole HMF_{mibk}/mol $HMF_{aqueous\_in}$)	0.99
Phase volume ratio (MIBK/aqueous)	2
R_{HMF}	1.35
ρ_{MIBK} (kg/m^3)	804
$\rho_{aqueous}$ (kg/m^3)	1270

HMF isolation and solvent recycle (solvent evaporation)

After extraction, the organic phase rich in HMF is sent to a vacuum evaporator to evaporate MIBK and isolate HMF. The vapor-liquid equilibrium (VLE) phase diagram of HMF-MIBK under different pressures generated by ICAS (Gani et al., 1997) with UNIFAC model is shown in Figure 6.2.

From the phase diagram, it indicates that lowering the pressure favors the separation of HMF and MIBK. For example, at 1 atm, with a purity of 96 mol% in the HMF product results in 16.9 mol% HMF loss in the vapor phase. In order to decrease the HMF loss in the vapor phase, and simultaneously achieve a high purity of the crude HMF product, vacuum evaporation should be applied.

The evaporation process was simulated in ProII 8.0 (ProII, 2011). The simulated process has a temperature of 47 °C and a pressure of 0.01atm. The simulation result with UNIFAC as thermodynamic model shows that around 95% HMF in the organic phase can be recovered with a 5% HMF loss in the vapor phase with MIBK. The obtained HMF has a purity of 97 wt%. The solvent vapor phase after passing by the condenser is recycled back to the extractor and dehydration reactor.

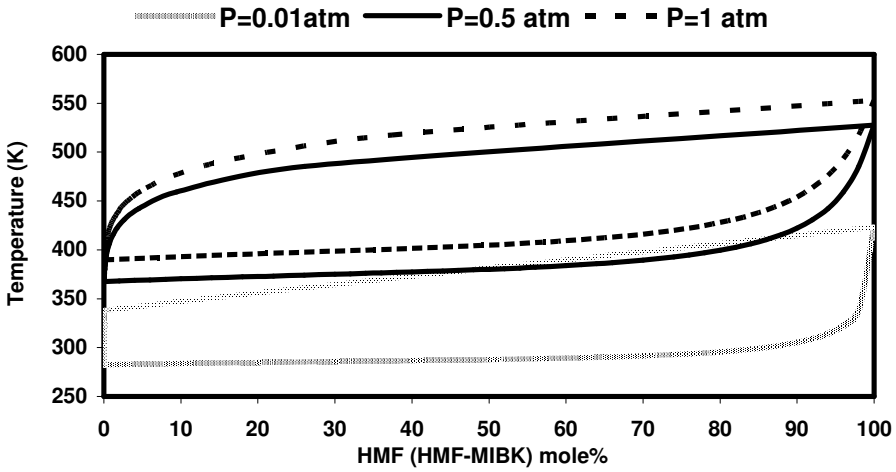


Figure 6.2. HMF-MIBK VLE phase diagram under different pressure profile, generated by ICAS (Gani et al., 1997), using UNIFAC model.

Aqueous recycle

After the extractor, the remaining aqueous phase, rich in unconverted glucose together with a little fructose, is sent to the vacuum evaporator to evaporate all the water formed during dehydration reaction. Afterwards, new glucose feed is added to match the sugar concentration (30wt%) and the aqueous stream is recycled back to the isomerization reactor after cooling down to 60℃.

6.3.2 Energy Metric

Based on the process description above, the process flowsheet is simulated in ProII 8.0 (ProII, 2011). The required energy is calculated for 1 kg HMF production. The energy required for cooling and heating of each individual unit operation is obtained directly from the simulation results (Appendix3).

Major heating and cooling energy include: cooling energy for the recycling aqueous stream from 79℃ to isomerization reaction 60℃, heating energy for both aqueous (from isomerization reaction) from 60 ℃ to 180℃ and the recycled MIBK from 116 ℃ to 180 ℃, heating energy for dehydration reaction to maintain a temperature at 180 ℃, cooling energy for cooling the dehydration reaction medium (both aqueous and MIBK) from 180℃ to room temperature for phase separation, and cooling energy for the recycled MIBK in the second extractor from 116 ℃ to room temperature.

Other major energy consumptions for process units are the energy for evaporating MIBK and water that formed during dehydration and the pumping energy for increasing the pressure of both MIBK and the aqueous phase (from 1 atm up to 10 atm) for dehydration reaction.

6.3.3 Economic metric

The economic metric here uses both the HMF cost and the HMF production cost.

The HMF production cost takes into account the cost of the capital investment, main raw material, utilities costs for the operation of the main units, the required labor cost and other expenses (such as plant overhead cost).

The major hypotheses for the HMF production cost are based on the following assumptions.

The designed plant has a capacity of 250000 tons HMF/year. The working days are assumed to be 328.5 days. The location is assumed in US and with easy access to the raw material and energy supply. Therefore, the transportation of the raw material supply is not considered. The detailed methods for estimation the HMF production cost can be found in Chapter 2. The cost of purchase of the equipment is estimated according to Peters et al. (2004) and Matches (www.matche.com). The prices of the raw material, labor, wastewater disposal and utilities are listed in Table A1.3 in the Appendix1.

Major Equipment Sizing

The major process equipment (feed tanks, buffering tanks, reactors, settlers, extractors, evaporators, pumps and heat exchangers) in the process flowsheet are sized with a designed capacity. The designed plant has a capacity of 250,000 tons HMF/year with a stream factor of 0.9 (328.5 working days /year). The designed capacity is based on an assumption to substitute 1% of PTA by FDA. By 2006, the demand for global purified terephthalic acid (PTA) had exceeded 30 million tonnes. To substitute 1% of PTA, the annual production of FDA should be 300, 000 tons. Assuming a process yield of 96% (mole based) from HMF to FDA, the annual production of HMF is thus calculated as 250, 000 tons.

With the designed capacity of the plant, the mass flowrate for different process units can be quantified based on the process parameters. The size of equipment required in the flowsheet is estimated with the residence time of each unit. Detailed equations and descriptions for sizing of the major equipment are listed in the Appendix4.

6.4 Results

6.4.1 Mass Metric

The process flowsheet was simulated in ProII 8.0 (ProII, 2011). The mass metric is calculated based on the assumptions listed above. The block of mass flow in the designed process flowsheet for 1 kg HMF production is shown in Figure 6.3.

The main reactant in the process is glucose. For 1 kg HMF production, the feed to the IGI reaction contains 4.6 kg of glucose. After the IGI reaction, 1.96 kg of fructose is formed. 96% of fructose is consumed in the dehydration reaction. Meanwhile 10% of the remained glucose is also consumed. After extracting the HMF from the aqueous phase, the remaining 2.44 kg glucose together with a small amount of fructose is completely recycled.

In total, 2.15 kg of glucose is required for 1 kg HMF production. The amount of MIBK used in the dehydration reactor is 40 kg and in the second extractor is 20 kg. Around 99.9% of MIBK is recycled. The solvent loss is mainly in the crude HMF product, which is around 0.031 kg MIBK/kg HMF. Around 0.45 kg humins are formed together with 1 kg HMF. And around 0.65 kg of water is formed during the dehydration reaction.

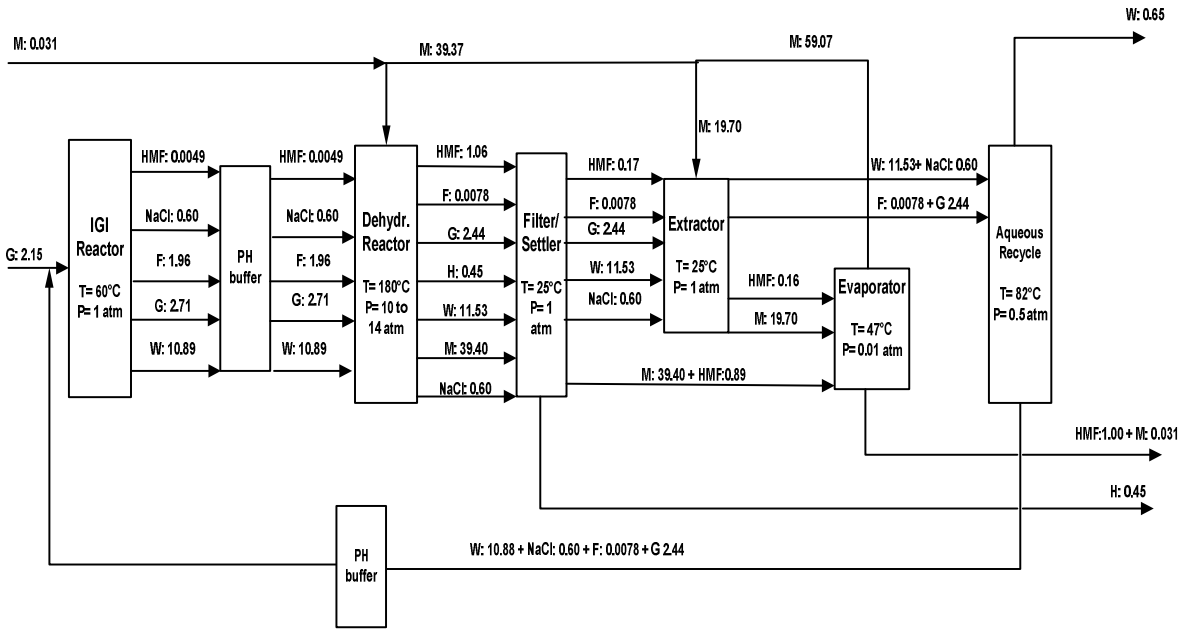


Figure 6.3. Process flowsheet with mass flow for 1 kg HMF production.

6.4.2 Energy Metric

The calculated energy of each process step for 1 kg HMF production is listed in Table 6.4. The total energy consumption for 1kg HMF is around 88.6 MJ. The contribution of each process step to the total energy consumption is plotted in Figure 6.4.

The most energy demanding part of the flowsheet concerns the solvent recycling (MIBK evaporation together with MIBK condensing and cooling) which uses 49% of the total energy consumption. This is mainly due to the large amount of solvent used in the process, leading to a high energy requirement for recycling the solvent.

The second biggest share of energy consumption is used for preheating the streams before dehydration and the cooling for phase separation after dehydration. These two parts together contribute with other 45% of the whole energy consumption. In the dehydration reaction, in order to achieve the desired selectivity and a relatively short residence time, the temperature needs to be high enough. In this case, the reaction is operated at 180℃. On the other hand, the temperature for the phase separation is at room temperature. This requires large amount of energy first to heat up the reaction medium to 180℃ and then to cool the reaction mixture to room temperature for separation. The energy use in this part of the process flowsheet is therefore not efficient.

Table 6.4. The required energy for 1 kg HMF production.

Units	Energy requirement	MJ/kg HMF	Energy Supply
IGI	Cooling	0.98	Cooling water
Dehydration	Pumping	0.06	Electricity
	Preheating & Reaction	16.51	Steam
Phase separation & extraction	Cooling	22.60	Cooling water
Evaporator	Evaporation	26.14	Steam
MIBK recycle	Condenser & Cooling	17.91	Cooling water
Aqueous recovery	Evaporation	4.41	Steam
Total	Heating & Pumping	47.11	Steam, Electricity
Total	Cooling	41.49	Cooling water
Total	Energy	88.61	

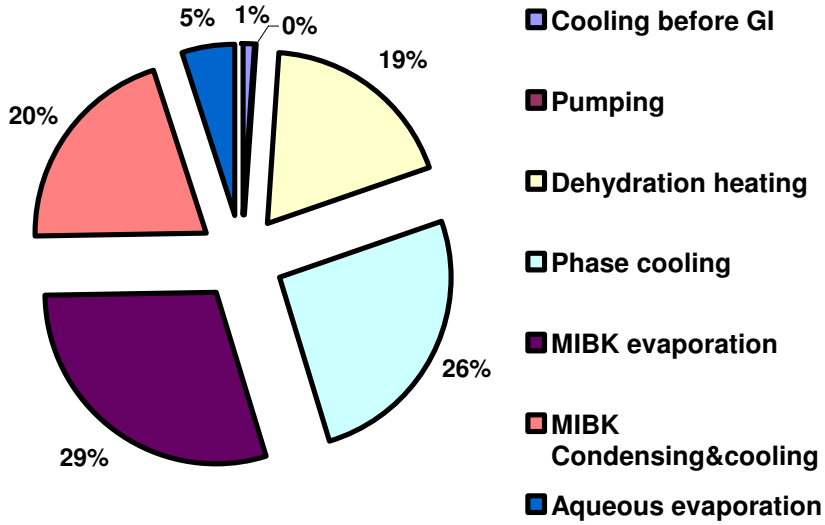


Figure 6.4 Plot of energy contribution of different process units to the total energy consumption of 1 kg HMF production.

6.4.3 E-factor

The E-factor calculated for this process flowsheet is around 1.18. The E-factor of this chemo-enzymatic route is higher than that of the biphasic route (1.08). This can be

explained by the lower process yield of the chemo-enzymatic route (2.15 kg glucose/kg HMF) than that of the biphasic route (1.97 kg fructose/kg HMF).

In the dehydration reactor, the aqueous feed contains both glucose and fructose. 10% of the glucose in the aqueous feed is converted to the byproduct humins instead of HMF. This decreases the whole process yield of the chemo-enzymatic route, which is a disadvantage.

6.4.4 HMF cost

The cost of HMF when using the chemo-enzymatic route for synthesis of HMF is around 1.07 USD/kg (Table 6.5). The overall process yield of the chemo-enzymatic route is lower than that of the solvent route and the biphasic route examined in Chapter 5. However, the chemo-enzymatic route is the cheapest route for HMF production among all the examined routes in Chapter 5 and this Chapter (Figure 6.5). It indicates the big advantage with using a cheap feedstock of glucose (0.3 USD/kg) for HMF production.

In addition, the HMF cost of the chemo-enzymatic route is very close to the PTA cost. Since this cost is calculated for the base case described above, there is still a lot of room for reducing it. The chemo-enzymatic route shows a great potential for HMF production in an economic feasible way.

In the following sections, the HMF production cost is calculated to give a more detail evaluation of this process route.

Table 6.5. List of the raw material and energy cost.

Item	Cost (USD/kg HMF)	Percentage (%)
Glucose	0.65	60.19
Glucose isomerase	0.00	0.07
MIBK	0.06	5.56
Electricity	0.00	0.00
Steam (MP 200 Pigs)	0.25	23.15
Steam (HP 600 Pigs)	0.11	10.19
Cooling water	0.01	0.93
HMF cost (total raw material and energy cost)	1.07	100.00

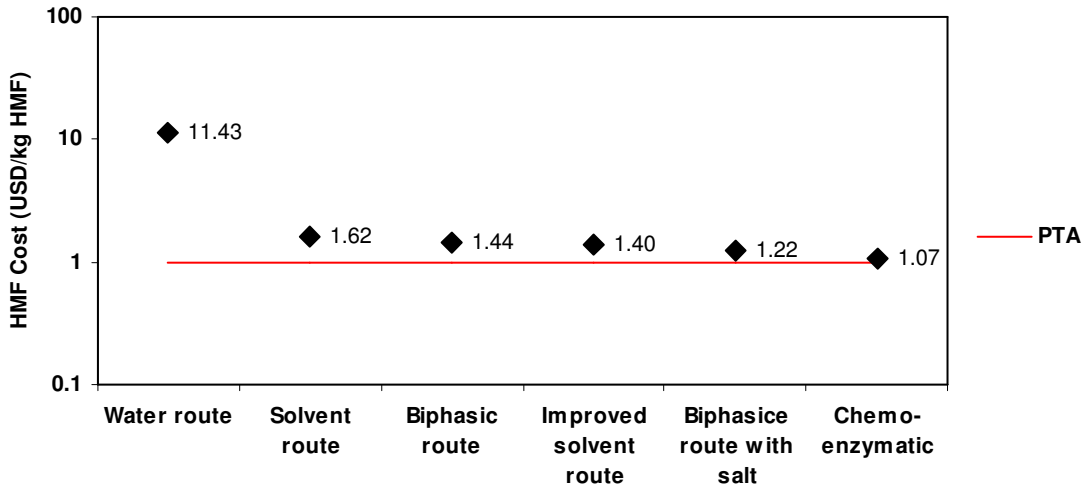


Figure 6.5. Plot of the HMF cost of different process routes. The red line is the PTA cost.

6.4.5 HMF production cost

Major equipment sizing and costing

The result of the calculated size of the major equipment involved in the process flowsheet is shown in Table A5.1 in the Appendix5. Based on the designed capacity, the total required volume of the enzyme is around 555m^3. The required volume of the enzyme is divided into 48 IGI reactors (in total 12 lines, 4 reactor each line). Each IGI reactor has a volume of 14 m^3, with a bed diameter of 1.72 m and a bed height of 6m.

The total required volume of the dehydration reactor is 1078 m^3. Since the dehydration reactor is a pressurized vessel, the suggested maximum volume of a pressurized vessel with stainless steel 316 as material at the operating pressure of the dehydration reaction is around 67 m^3 (Perry, 1994). Hence, the required number of the dehydration reactors is 16, with a volume of 67 m^3 each.

There are three extractors (Sieve tray type). Each extractor has a designed diameter of 2.83 m, a total height of 11.4 m and a tray number of 10.

The purchase of equipment cost is presented in Table 6.6. The cost is estimated with the required size of the equipment, using www.matche.com and Peters et al. (2004) for the cost reference. The cost of all the equipment is around 35 million USD. Assuming 10% of the total equipment cost as the delivery cost, the total cost of the delivered equipment is around 39 million USD.

According to the cost distribution of the total equipment cost, the cost of dehydration reactors covers the largest part (35%) due to a high cost of purchasing of the pressurized

vessels. The second largest part of the cost distribution is the cost of the IGI reactors (38%). The fixed bed reactors are operated at normal pressure. However, a large number of the reactors are required, leading to a high cost.

Table 6.6. Cost of the major equipment.

Item	Number	Million USD	Percentage (%)	Reference
pH Buffering Tank	2	0.2	1	www.matche.com
MIBK Feed Tank	1	0.004	0	www.matche.com
IGI Reactors	48	12.5	35	www.matche.com
Dehydration Reactors	16	13.2	38	www.matche.com
Settlers	16	1.7	5	www.matche.com
Vacuum Evaporators	2	1.6	4	www.matche.com
Extractor Column	3	0.68	2	Peters et al. 2004
Heat Exchangers	6	5.2	15	www.matche.com
Pumps	2	0.055	0	Peters et al. 2004
Total equipment cost		35.1	100	
Delivery cost	10% equipment cost	3.5	10	
Total delivered equipment cost		38.6	110	

Estimation of total capital investment

Based on the delivered equipment cost, the total capital investment is calculated (Table 6.7). The total capital investment is around 196 million USD.

Table 6.7. List of items considered in the estimation of total capital investment.

Total capital investment	Percentage of purchased equipment (100%)	Cost (million USD)
Purchased equipment (delivered)	100	39
Installation	39	15
Instrumentation (installed)	43	17
Piping(installed)	31	12
Electrical (installed)	10	4
Building (including service)	12	5
Yard improvement	15	6
Service Facilities (installed)	55	21
Total direct cost (D)		118
Engineering and supervision	32	12
Construction expenses	34	13
Legal expenses	4	2
Contractor's fee	19	7
Contingency	37	14
Total indirect plant cost (I)		49
Fixed capital investment, D+I	85% of total capital investment	167
Working capital	15% of total capital investment	29
Total capital investment (TCI)		**196**

Estimation of the HMF production cost

The items considered in the calculation of the HMF production cost are presented in Table 6.8. The HMF production cost of the proposed process flowsheet is around 1.46 USD/kg. The reactant cost is the largest part in the cost distribution which covers around 44% of the total HMF production cost (Figure 6.6).

The second largest cost in the HMF production cost is the cost of the utilities which contributes 26% to the total HMF production cost. In total, the raw material cost together with the energy cost (HMF cost) cover around 74% of the total HMF production cost. The cost calculated based on the capital investment such as the fixed cost, the maintenance cost, operating supplies and part of the plant overhead cost (related with maintenance cost) covers around 12% of the HMF production cost. Other cost related with labor, labor supervision, part of the plant overhead cost (related with labor and laboratory charges) together contributes 3% cost of the HMF production cost.

In sum, the most important share in the HMF production cost is the cost of raw material and utilities.

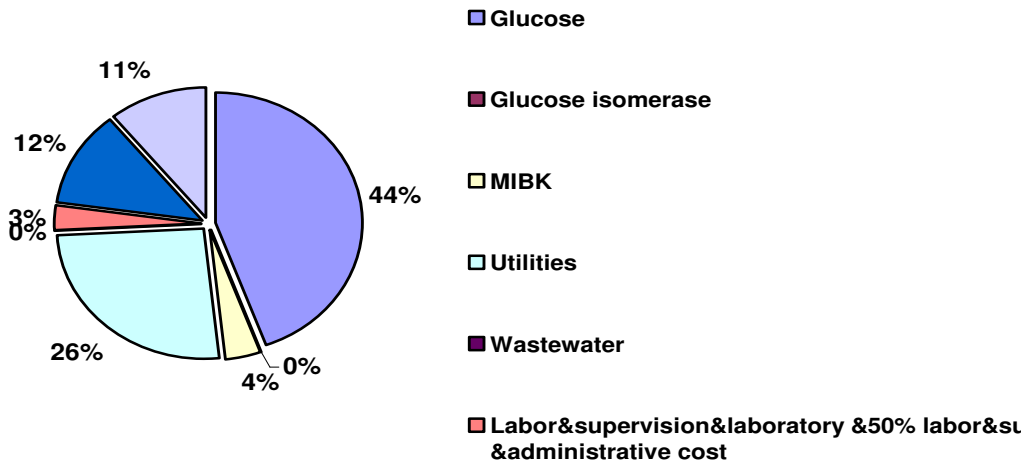


Figure 6.6. Plot of the distribution of the HMF production cost.

Table 6.8. List of all the items considered for estimation of the HMF production cost.

Item		Annual requirement (tons/year)	Cost (USD/tons)	USD/kg HMF	Percentage (%)
Reactant	Glucose	537986	300	0.65	44.33
Catalyst	Glucose isomerase	10369	19	0.00	0.05
Solvent	MIBK	7732	1890	0.06	4.01
Utilities	Electricity	5610	0.05	0.00	0.00
	Steam (MP 200 Pigs)	4357311	14.23	0.25	17.03
	Steam (HP 600 Pigs)	1768091	16.04	0.11	7.79
	Cooling water	165198593	0.03	0.01	1.00
Wastewater	Disposal	171845	0.53	0.00	0.03
Labor		183960[a]	28.13[b]	0.02	1.42
Labor supervision	15% of labor cost			0.00	0.21
Maintenance and repair	7% of FCI			0.05	3.20
Operating supplies	15% of maintenance and repair			0.01	0.48
Laboratory charges	15% of labor cost			0.00	0.21
Royalties	4% of TPC without depreciation			0.05	3.77
Total Variable Cost				**1.22**	**83.54**
Taxes (Property)	2% of FCI			0.01	0.92
Depreciation	10% of TCI			0.08	5.38
Insurance	1% of FCI			0.00	0.46
Total Fixed Cost				**0.10**	**6.76**
Plant overhead cost	**50% of labor, supervision of labor, maintenance**			**0.04**	**2.42**
Administrative Cost	20% of labor			0.00	0.28
Distribution and marketing cost	2% of TPC			0.03	2.00
Research and development cost	5% of TPC			0.07	5.00
Total General Expense				**0.10**	**7.28**
Total Production Cost (TPC)				**1.46**	**100.00**

6.5 Discussion

The sensitivity of the different process parameters to the HMF production cost is discussed here.

6.5.1 Effect of the selectivity to HMF production cost

The plot of HMF production cost distribution indicates that the cost of glucose covers the largest part of the whole production cost. Thus, the efficiency of using glucose (fructose) becomes very critical to the process economic.

The efficiency of the designed downstream processing is very high. In the designed process flowsheet, the total extraction yield of HMF is 99.8% and the recovery yield of HMF from the evaporator is 94.6%. Thus, the total HMF recovery yield in downstream is 94.4%. The unconverted sugar is assumed to be recycled completely. The inefficient consumption of the sugar is mainly in the dehydration reaction. 10% of glucose in the aqueous feed is converted to the byproduct humins. 20% of the converted fructose also contributes to the formation of humins. The overall process yield of HMF is thus decreased.

The effect of the selectivity (fructose to HMF) of the dehydration reaction to the HMF production cost is plotted in Figure 6.7. The calculated HMF production cost is based on a fructose conversion of 0.96 and a glucose conversion of 0.10. The size of all the equipment is considered to be fixed and thus the capital cost is fixed as well.

The HMF production cost is very sensitive to the selectivity of the dehydration reaction. The HMF production cost of the base case is 1.46 USD/kg based on a selectivity of 80%. If the selectivity is not good enough, the HMF production cost will increase. For example, if the selectivity drops to 60%, the HMF production cost will be increased to 1.95 USD/kg. On the other hand, the HMF production cost will decrease to 1.19 USD/kg, if a selectivity of 100% can be reached (Yield 96% from fructose).

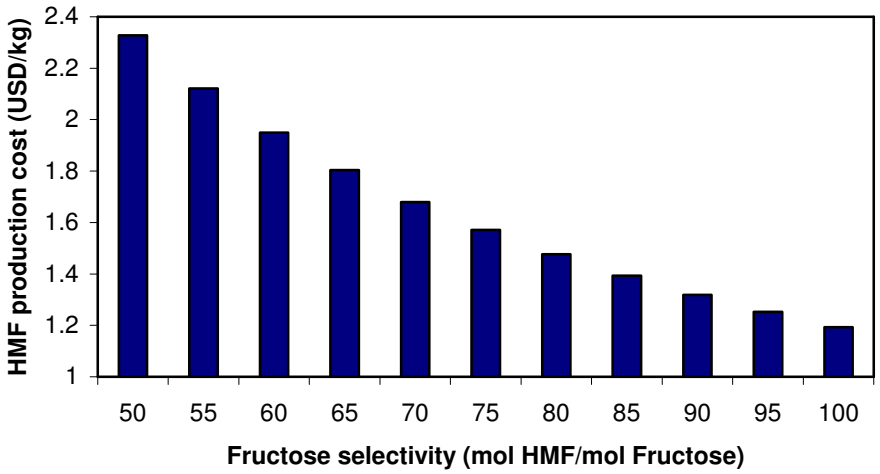


Figure 6.7. Plot of the effect of the selectivity (fructose to HMF) of dehydration reaction to HMF production cost.

6.5.2 Effect the solvent to HMF production cost

In Figure 6.7, even with a high dehydration yield of 96% (from fructose), the HMF cost is still around 1.20 USD/kg. One reason accounts for this high production cost is due to the humin formation from glucose. Another reason for this high production cost is the high energy cost. The total energy required for 1kg HMF production of the designed process is around 88.6 MJ. This high energy is related with a high amount of the solvent used in the process. Therefore, the use of solvent is another big issue after the yield.

Large amount of the solvent is used in two parts of the process flowsheet. The first part is in the dehydration reactor, where the solvent is used to extract HMF once it is formed so that a good selectivity of dehydration can be ensured. The second part is in the second extractor, where the solvent is used to isolate the remained HMF from the aqueous phase before recycling back to the IGI reactor. The second reactor is required here, because the organic phase from the biphasic reactor can only recover 85% of the produced HMF.

The aim of adding the second extractor here is for two reasons. First of all, HMF in the aqueous phase can decrease the activity of the GI when it is recycled back to the IGI reactor. The maximum concentration of HMF allowed in the aqueous is 0.1 wt% in order to not affect the performance of GI (Boisen et al., 2010). It is thus required that at least 98.7% of the produced HMF is extracted to the organic phase before HMF is recycled back to the IGI reactor. On the other hand, HMF is not a stable compound in the aqueous phase during the dehydration reaction. It can react with both fructose and glucose, and form humins (Van Dam et al., 1986; Kuster, 1990). This can decrease the whole process yield. Therefore, a second extractor is also needed to exact the remained HMF from the aqueous phase in order to keep a high process yield. The second extractor is designed to extract 99% of the remained HMF from the aqueous phase. The total extraction yield of HMF from both the biphasic reactor and the second extractor is 99.8%.

In this section, the effect of the solvent use to HMF production cost is examined based on varying the partition coefficient of the solvent and the amount of the solvent used in the process. However, the total exaction yield (both from the biphasic reactor and the second extractor) is fixed to 99.8% in order to maintain a high process yield as well as not to affect the GI performance. Changing the R_{HMF} or the amount of solvent used in the biphasic reactor can result in different extraction yield of HMF in the biphasic reactor. This is adjusted by increasing or decreasing the yield of the second extractor by changing the number of the required theoretical stages.

Effect of R_{HMF}

The effect of R_{HMF} is examined based on the same amount of solvent applied in both the biphasic reactor and the extractor. The variable parameter in this analysis is the required number of the theoretical stages of the second extractor (variable capital cost). Other assumptions in this analysis include no effect on the dehydration selectivity and no change of the phase miscibility.

When the amount of the solvent and the total extraction yield is fixed, the effect of R_{HMF} on the HMF production cost is not significant (Figure 6.8). When the R_{HMF} is small, more

stages in the second extractor are required to maintain the same extraction yield. However, the cost of the extractor is quite cheap compared to other equipment (Table 6.6). The increased total capital investment caused by increasing 1 or 2 stags in the extraction column is very small. At the examined scale of production, the increased capital investment does not show any significant effect to the HMF production cost.

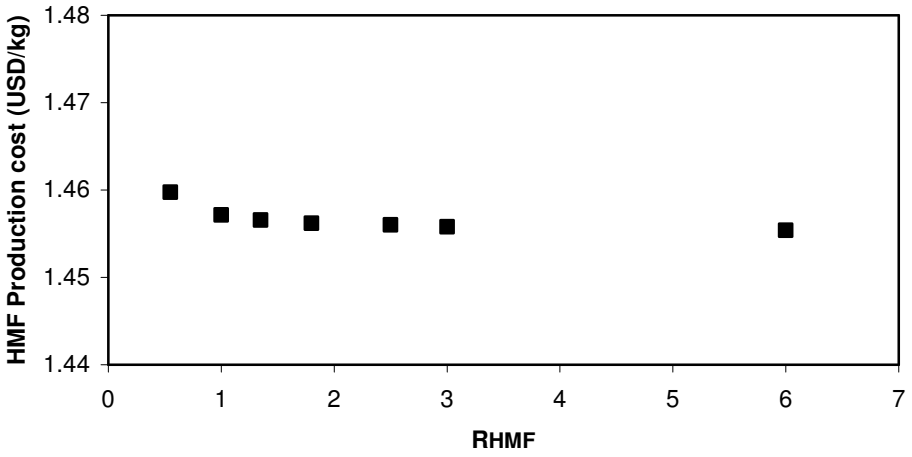


Figure 6.8. Plot of the effect of R_{HMF} to HMF production cost.

Effect of the amount of solvent

Due to a high energy cost (0.38 USD/kg HMF) of the designed flowsheet, reducing the amount of solvent used in the process to reduce the amount of energy is very important for the process economic. The solvent is applied in two parts of the process flowsheet as described before. In this analysis, 4 different process options related with the amount of solvent used in the process are compared. The base case which has a HMF production cost of 1.46 USD/kg, has a phase ratio of MIBK/ water equal to 6 (Table 6.9). Case option 1 reduces the solvent amount to 2 times of the volume of the aqueous phase. Both case option 2 and option 3 use the same amount of MIBK (Table 6.9).

In this analysis, it is assumed that there is no effect of the reduced amount of solvent in the reactor to the selectivity of the dehydration. The total extraction yield is fixed. The changes in the amount of the solvent used in the process result in the changes of the required energy, as well as the size of some equipment (volume of dehydration reactor, volume of settlers, number of extractors and number of stages required in the extractor, pump capacity and efficiency, and the areas required for some of the heat exchangers).

The HMF production cost of the four options are plotted in Figure 6.9. Clearly, reducing the amount of the solvent used reduces the HMF production cost dramatically. By reducing the amount of solvent to 2 times of the aqueous phase, the energy cost is reduced from 0.38 USD/kg HMF to 0.20 USD/kg HMF. The total capital cost is reduced from 196 million USD to 140 million USD. Therefore, the costs that are related with

capital cost such as maintenance cost, supplies, and fixed cost are also reduced. The final HMF production cost with case option 2 is around 1.21 USD/kg.

For case option 2 and option 3, the total amount of MIBK applied in both cases is the same. The production cost of case option 2 and option 3 is around 1.25 USD/kg HMF and 1.27 USD/kg HMF, respectively. Applying more solvent in the reactor (option 3) results in high volume required both for the dehydration reactor and the settler. Similar to the option 2, more solvent in the extractor requires more volume of the extractor. However, the cost of the extraction column is much cheaper than the cost of the dehydration reactor, since the dehydration reactor is high pressurized vessel. The cost related with the capital cost of option 2 (0.13 USD/kg HMF) is lower than that of option 3 (0.14 USD/kg HMF). In addition, when using the solvent in the dehydration reactor, it requires extra energy for pumping the solvent, extra energy for increasing the solvent temperature to reaction temperature (180℃), and extra energy for cooling the solvent to room temperature for phase separation. The extra consumption of energy results in the energy cost of option 3 (0.25 USD/kg HMF) is higher than that of option 2 (0.23 USD/kg HMF).

Table 6.9. Phase ratio (V_{MIBK}/ $V_{aqueous}$) applied in dehydration reactor and second extractor.

	Dehydration reactor	Second extractor
Base case	4	2
Option 1	1	1
Option 2	1	2
Option 3	2	1

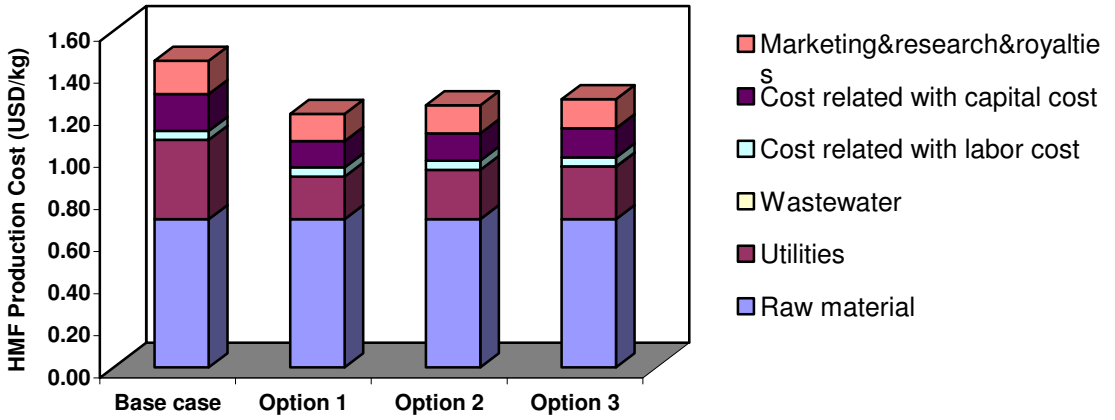


Figure 6.9. Effects of different options of using solvent to HMF production cost.

Due to the fact that the HMF production cost is sensitive to the amount of the solvent used, reducing the amount of solvent in the process becomes one of the key issues to reduce the HMF production cost. The calculation is based on the assumption that there is no effect on the dehydration selectivity with the reduced amount solvent in the dehydration reactor.

However, reducing the amount of solvent in the dehydration reactor may decrease the selectivity. Román-Leshkov, et al. (2006) reported a selectivity of 73% with a conversion of 75% with a phase ratio of MIBK/water around 3.10 in the biphasic reactor. When he reduced the amount of solvent to half in the reactor, the reported selectivity was around 60% with a conversion of 90%. It is hard to draw the conclusion that the selectivity will decrease with the amount of solvent inside the reactor, because the reported high selectivity was obtained at a lower conversion.

The effect of the selectivity of the dehydration reaction to HMF production cost of the different options is plotted in Figure 6.10. Even with a reduced selectivity of 60%, the HMF production cost of option 1 (1.42 USD/kg HMF) is still lower than that of the base case (1.46 USD/kg HMF). At a selectivity of 70%, both option 2 and option 3 have a lower HMF production cost than that of the base case. At a selectivity of 60%, the cost of option 2 is similar to that of the base case.

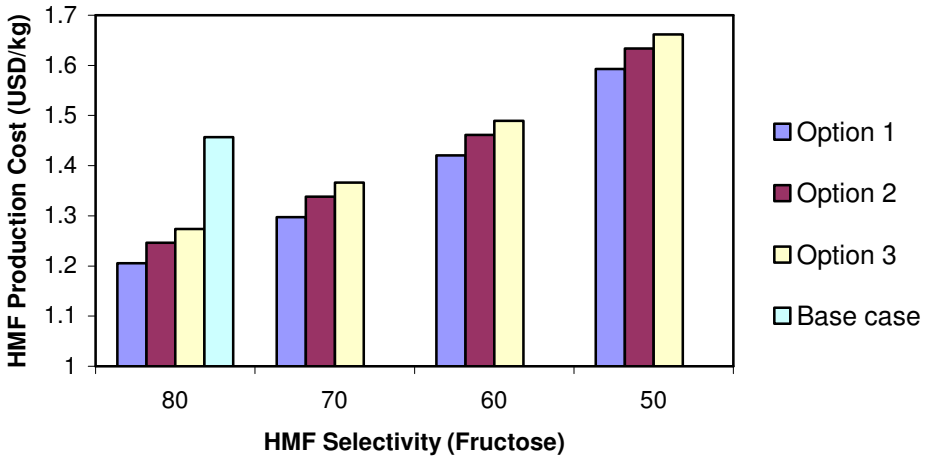


Figure 6.10. Effect of the selectivity to HMF production cost of different case options.

6.5.3 Effect of the scale to HMF production cost

The plot of the effect of the designed HMF production scale on the HMF production cost is shown in Figure 6.11. With the increasing scale, both the cost related with labor and capital decreases. If the scale increases to 2500000 tons HMF per year, the HMF production cost will decrease from 1.46 USD/kg to 1.30 USD/kg. This analysis is based on the same price of the material and utilities. On the other hand, a production cost with a scale of 25000 tons/year is around 1.97 USD/kg, indicating the small scale is not economic feasible.

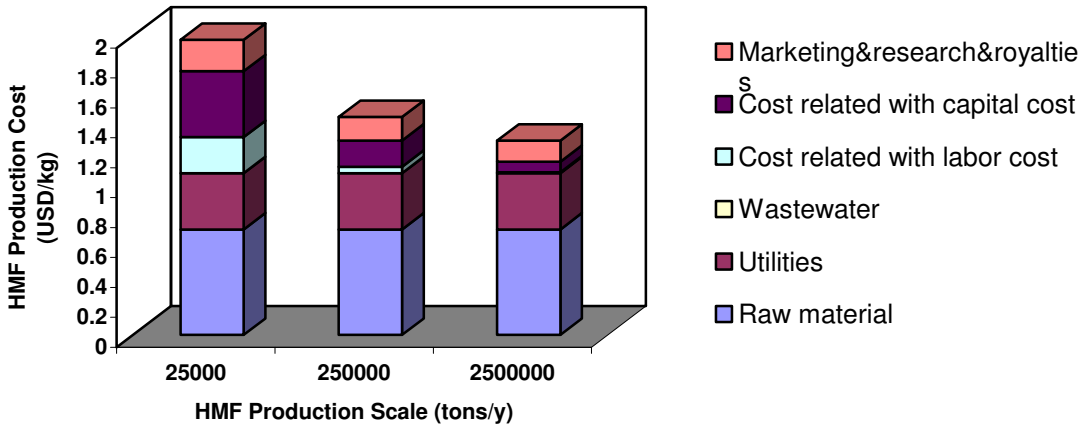


Figure 6.11. Effect of the scale to HMF production cost.

6.5.4 Effect of the glucose price to HMF production cost

The effect of the glucose price on the HMF production cost is shown in Figure 6.12. The HMF production cost is highly dominated by the glucose price. If the glucose price reaches 0.5 USD/kg, the HMF production cost would increase to around 2 USD/kg. A production cost around 1USD/kg can be reached if the glucose price is around 0.1 USD/kg.

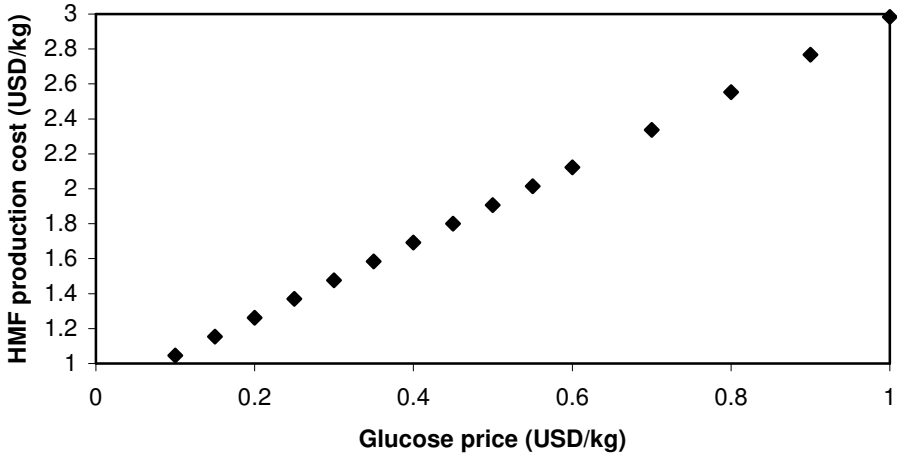


Figure 6.12. Effect of the glucose price to the HMF production cost.

6.6 Conclusions

In this chapter, a process flowsheet for chemo-enzymatic synthesis of HMF from glucose has been proposed and evaluated. Process metrics are calculated to evaluate the designed

process flowsheet. The HMF cost by the designed flowsheet is around 1.07 USD/kg. The chemo-enzymatic route is so far the cheapest route for HMF production among all the examined routes. It shows a great potential for HMF production in an economic feasible way.

Based on a production scale of 250,000 tons HMF per year, the total capital investment is around 196 million USD. The HMF production cost of the base case is around 1.48 USD/kg. The effects of different parameters to the HMF production cost are examined. The HMF production cost is very sensitive to the dehydration reaction yield, the amount of the solvent used in the whole process and the glucose price. Reducing the amount solvent used in the process is very useful to decrease the HMF production cost. In addition, the effect of the scale to the HMF production cost is also evaluated. The HMF production cost decreases with the increased scale.

Concluding remarks

In this Chapter, a potential process flowsheet of chemo-enzymatic synthesis of HMF from glucose is illustrated and evaluated. In the next Chapter, using IL route for HMF production from both fructose and glucose is examined.

7 Assessment of an Ionic Liquid based Process for the Synthesis of HMF from Carbohydrates

Summary

Recently, using ionic liquids (ILs) for the HMF synthesis has gained increased attention. Examples in the literature on scale-up and process development on the topic are, however, still scarce. In this chapter, the potential IL process flowsheet for the single phase reaction system is evaluated with different options starting from fructose and glucose with different initial concentrations. The HMF cost and the HMF production cost of the IL route is founded to be highly affected by the number of reuses of the IL and the catalyst. Processes with a high feed concentration show better economic potential than processes with a low feed concentration. IL processes starting from fructose are more expensive than IL processes starting from glucose due to a higher cost of fructose than glucose. The IL route from glucose with a high feed concentration shows the best economic potential.

7.1 Introduction

In recent years, the limitations of the world's oil reserves and the increased threat of climate change have intensified research in production of fuels and chemicals from renewable resources via so–called biorefineries (Corma et al., 2007). One of the most interesting potential platform chemicals that could be produced in a future biorefinery is 5-(hydroxymethyl)furfural (HMF) which can be synthesized via the dehydration of hexose sugars (Werpy and Petersen, 2004; Bozell and Petersen, 2010).

Synthesis of HMF from fructose proceeds readily at elevated temperatures in high-boiling anhydrous solvents and is catalyzed by Lewis or Brønsted acids (Lewkowski,

2001). Product recovery from these solvents is nevertheless difficult (El-Hajj et al., 1983). However, an alternative water-based process is also problematic due to the potential hydrolysis of HMF into formic acid and levulinic acid as well as polymerization products (Boisen et al., 2009; Kuster, 1990). This problem can be overcome to some extent by the use biphasic liquid - liquid system, such as water - methyl isobutylketone (MIBK), together with phase modifiers or addition of salts that favor the extraction of HMF into the organic phase (Roman-Leshkov et al., 2006; 2007; 2009) The scientific literature reports many attempts to synthesize HMF, but in spite of the work undertaken none of the methods proposed to date has led to a commercial process. Furthermore, the current price of fructose hinders a cost competitive process. Indeed, use of a cheaper feedstock such as glucose might open up an opportunity for a process that could be economically feasible (eg. chemo-enzymatic route examined in Chapter 5). Indeed, if it were possible to establish a successful synthesis from glucose, other processes based on the natural polymers of glucose (such as starch and cellulose) as a feedstock would also become feasible. Some studies of the synthesis of HMF from glucose have also been reported in scientific lifetime but these processes require the use of special catalysts to achieve yields that are adequate for scale-up (Zhao et al., 2007; Yong et al., 2008; Watanabe et al., 2005).

In recent years ionic liquids (ILs) have become important in many synthetic schemes as alternative solvents due to their negligible vapor pressure, non-flammability and unique dissolving abilities (Wasserscheid and Welton, 2008). Interestingly, the synthesis of HMF from fructose and glucose could benefit from the use of certain ILs as the reaction media (Ståhlberg et al., 2011; Zakrzewska et al., 2010). In IL media, investigated feedstocks cover not only fructose and glucose but also sucrose (IIgen et al., 2009; Lima et al., 2009; Hu et al., 2009), starch (Hu et al., 2009; Chun et al., 2010) and cellulose (Binder and Raines 2009; Zhang and Zhao 2010), although reaction yields were usually far from adequate, resulting in significant by-products and unconverted sugars in the product stream. The dehydration from fructose or glucose shows better yields (Ståhlberg et al., 2011). For example, the use of solvents like 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) and 1-butyl-3-methylimidazolium chloride ([BMIm]Cl) together with chromium catalysts provide excellent yields from both fructose and glucose (Zhao et al., 2007; Yong et al., 2008). While, the research on the synthesis of HMF in ILs has attracted considerable attention, these methods have so far only been investigated on a laboratory scale and few examples of the necessary process requirements have been discussed in the literature.

In this Chapter, a potential process flowsheet of HMF synthesis in ILs reported in Chapter 4 is selected and used to examine process feasibility. Using the selected example as a base case, alternatives using different starting feedstocks and alternative feedstock concentrations are explored. Four alternatives have been evaluated from the perspective of mass, energy and economic metrics. Such an approach helps evaluate the feasibility of such processes and also identifies future research directions to assist in their eventual implementation.

7.2 Process Description

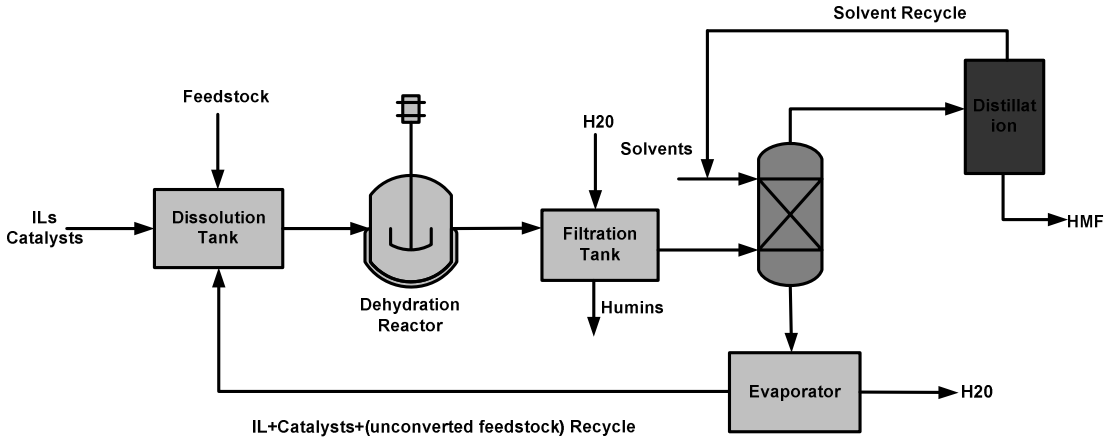


Figure 7.1. Potential process flowsheet using neat IL as reaction media for the synthesis HMF (Based on the published flowsheet from Ståhlberg et al., (2011)).

Some potential process flowsheets of using IL for HMF synthesis have been proposed in Chapter 4. In this Chapter, one of the flowsheets that uses neat IL as reaction medium for the synthesis of HMF is selected as a base case design.

The feedstock (either fructose or glucose) is dissolved in an ionic liquid [BMIM]Cl. A homogeneous catalyst (NHC-CrCl2) is used in the dehydration reaction to convert the sugar into HMF. After the dehydration, the HMF in the reaction mixture is extracted using ethyl acetate (EtOAc). Due to the high viscosity of the IL, water is added prior to extraction. After extraction, the organic phase (rich in HMF) is sent to a vacuum evaporator to evaporate EtOAc and isolate HMF. Meanwhile, the IL phase together with the catalyst and unconverted sugar is sent to the vacuum evaporator to remove the process water added prior to extraction before recycling back to the dehydration reactor (Figure 7.1).

7.3 Materials and methods

The process data (such as reaction yield and temperatures) are the basis for the calculation of the mass and energy balance. The flowsheet in Figure 7.1 is the conceptual design flowsheet, which is proposed based on what has been achieved so far in HMF synthesis using ILs (Chapter 4). Process data related with all the process units have not been published yet except for the reaction part where most of the research has been placed. However, other process data such as extraction yield, evaporation temperatures are necessary in order to calculate the mass and energy so that the process can be evaluated.

For the extraction part, no one has published the partition coefficient of HMF between IL and solvent (R_{HMF}). However this is the base for the extraction calculation. Consequently, experiments were done to measure R_{HMF} between IL and solvent. This experimental value is the basis for simulation of the extraction process and the calculation for mass balance of the downstream. Based on a designed extraction yield (99% HMF) and a fixed amount of solvent, the required number of theoretical stages is calculated.

The process step for evaporation of the solvent, in order to isolate HMF is simulated in software ProII 8.0 (ProII, 2011) since no experimental results related with the mass recovery has been published. The required energy for the solvent evaporation and IL recovery is obtained by simulation these operations.

7.3.1 Experimental

Extraction experiments were made with 12 different experimental conditions based on different compositions of HMF (0.312, 0.711, 1.077 or 4.850 g), [BMIm]Cl (10.0 g), water (5, 10 or 20 mL) and E_tOA_c (30 mL). Phase separations of these compositions were examined at 30, 50 and 70°C to investigate the influence of temperature. HMF was dissolved in [BMIm]Cl at 70°C in a 100 mL round bottom-flask equipped with a condenser. Water was added and the temperature adjusted to 30 °C (50 or 70 °C). E_tOA_c was added and the biphasic mixture was stirred with a magnetic stirrer for 1 hour after which the two phases were left to equilibrate for 1 hour. Samples of 1 mL from each phase were collected and analyzed by HPLC (Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm x 7.8 mm pre-packed column, 0.005 M H_2SO_4 mobile phase, 60 °C, 0.6 mL/min). The amount of HMF was confirmed by calibration with standard solutions.

7.3.2 Mass metric

The mass metric is calculated according to the methodology presented in Chapter 2. The basis for the mass metric is an output of 1 kg of final product. The defined assumptions of different process units are listed or described as bellows:

Dehydration

The mass balance assumptions for the reaction are taken from published results (Yong et. al., 2008). Four different alternatives are listed for a comparison (see Table 7.1).

Table 7.1. Published reaction selectivity to HMF with different choice of feedstock and feed concentration with catalyst amount 9mol%, reaction temperature of 100°C and batch reaction time of 6 hours (Yong et al., 2008).

Case	Feedstock	Feed concentration (wt%)	Selectivity	Conversion
F1	Fructose	17	96	100
F2	Fructose	50	70	100
G1	Glucose	17	81	100
G2	Glucose	50	73	100

Liquid–liquid extractor (LLE)

The extraction process was designed by using a liquid-liquid extractor. For the calculations, equilibrium at each stage was assumed, thus the separation obtained in the extractor is related to the number of theoretical stages and can be calculated as follows (Perry and Green, 2007):

$$\frac{[HMF]_{(IL+H\,20)in}}{[HMF]_{(IL+H\,20)out}} = \frac{E^{N_S}(1-E)}{1-E^{N_S+1}} \qquad \text{Equation 7.1}$$

Where $[HMF]_{(IL+H20)in}$ and $[HMF]_{(IL+H20)out}$ are the mole concentration of HMF in the diluted reaction mixture enter and leave the extractor. E is the extraction factor can be calculated as:

$$E = \frac{\rho_{EtOAc} V_{(IL+H\,20)in}}{R_{HMF}\,\rho_{IL+H\,20} V_{(EtOAc)in}} \qquad \text{Equation 7.2}$$

Where ρ_{EtOAc} and $\rho_{IL+H\,20}$ are the density of the organic solvent and IL/water mixture and $V_{(EtOAc)in}$ and $V_{(IL+H\,20)in}$ are the volume of the extraction solvent and IL/water mixture.

Other assumptions are that both phases must have the same residence time. The defined assumption parameters in the extraction process are listed in Table 7.2.

Table 7.2 Summarized process parameters for second extraction column.

Second extraction	Extraction column
Extraction temperature (°C)	50
Extraction yield (mole HMF_{mibk}/mol $HMF_{aqueous\_in)}$	0.99
Phase feed volume ratio (EtOAc /IL+H_2O)	4
R_{HMF}	Experimental results of this work
ρ_{EtOAc} (kg/m^3)	897 (Perry and Green, 2007)
ρ_{IL+H20} (kg/m^3)	1000 (Chen et al., 2010)

Solvent evaporation

Solvent evaporation was simulated in software ProII 8.0 (ProII, 2011). By choosing a temperature at 55 °C, a pressure at 0.1atm, the simulation result showed that more than 99% HMF can be recovered with less than 1% loss in the vapor phase with E_tOA_c. The obtained HMF has a purity of 95 wt%. The solvent vapor phase after passing through the condenser is cooled to 50 °C and recycled back to the extractor again.

H20 Evaporation

Water can be separated from IL and catalyst by using vacuum evaporation (Qi et al., 2009; Lai and Zhang, 2010). Due to lack of vapor-liquid phase equilibrium data between IL and water, it is assumed that all the water can be removed in vacuum evaporation and there is no loss in IL. The vapor phase after condensing and cooling can be recovered as process water (with a small amount E_tOA_c) and reused again before extraction.

7.3.3 Energy metric

The energy required for cooling and heating for each individual process step was estimated using typical heat transfer equations. Process temperatures, pressures for estimating heating and cooling enthalpies were based on the process descriptions and assumptions above. The energy metric related with solvent evaporation and condensing was obtained directly from the simulation of the process configuration in process simulator ProII 8.0 (ProII, 2011) (Appendix3). The energy related with water evaporation was considered as the energy requirement for evaporating all the water inside the IL and water mixture and the energy requirement for heating the mixture to the required operating temperature and pressure.

7.3.4 HMF production cost

Mainly the HMF production cost is used as the economic metric in this chapter. To assess the feasibility of using ionic liquid for HMF production at a large scale, and to compare different options (case F1, F2, G1 and G2), HMF production cost was calculated. The HMF production cost took into account the cost of the equipment of the process flowsheet (reactor, extractor and evaporators) which is the base for estimating the total capital investment, main raw material (glucose/fructose, solvent, [BMIM]Cl and catalyst), utilities for the operation of the main units (energy and cooling water), the required labor and other expenses (such like plant overhead cost et al.).

The global purified terephthalic acid (PTA) demand has exceeded 30 million tones in 2006. Based on the assumption of replacing 1% PTA by FDA per year, the required amount of HMF is 250 000 tons/year (based on a total process yield of 97 mol% from HMF to FDA). If 10% of the required HMF is produced by using IL process route, the designed plant has a capacity of 25,000 tons/year. The working days are assumed to be 350 working days a year. The location is assumed to be a place with the easy access to the raw material and energy supply. Therefore, the transportation of raw material supply was not considered in this analysis.

With the designed capacity of the plant, the size of the equipment required in the flowsheet was estimated based on the residence time in each unit. The cost references can be taken from Peters et al. (2004) and www.matche.com. Based on the cost of purchase of the equipment, the capital investment was estimated according to the methodology described in Chapter 2.

The costs of raw material, solvent, catalyst, utilities and waste disposal were directly related with the mass and energy balance of the process flowsheet. Labor requirements were estimated from the designed equipment in the plant using the method from Peters et al. (2004). Other remaining variable costs, fixed cost without depreciation, plant overhead costs and general expenses were estimated with using typical percentage values. The depreciation was calculated with a constant yearly depreciation rate based on a 10 year schedule.

7.4 Results

7.4.1 Experimental determination of partition coefficient

In the experiments, it is found that the partition coefficient R_{HMF} is affected by the composition of the mixture of IL and water phase. Addition of water into the IL to decrease the viscosity of [BMIM]Cl, increases the R_{HMF} (Figure 7.2). Decreasing the extraction temperature also increases the R_{HMF}. However, the effect of the dilution ratio with water shows much more significant effect on the rate of R_{HMF}.

Dilution will lead to energy consumption to dry the IL prior to recycle back. Since the energy to evaporate water (boiling point 100°C) is higher than that for E_tOA_c (boiling point 77.1 °C), it is better to use less water for the dilution and more solvent for the extraction process. Therefore, it is decided to add an equal amount volume of water into the IL. 70°C is close to the boiling point of E_tOA_c. Extraction at this temperature led to some solvent evaporation making the process control quite difficult. The exaction temperature is then chosen as 50°C. Although R_{HMF} at 30°C is slightly higher, considering the required energy related with temperature change (cooling for extraction and heating for evaporation), a comprise temperature is selected.

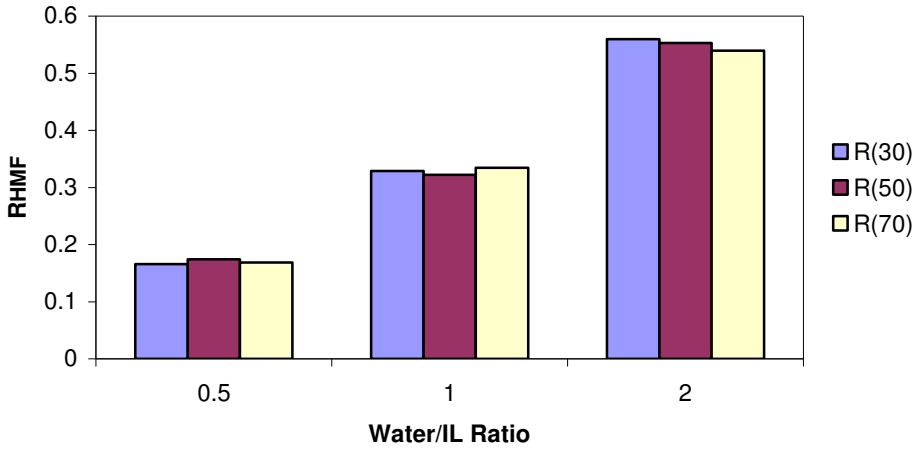


Figure 7.2. Plot of the effects of water/IL volume ratio and temperature to the partition coefficient.

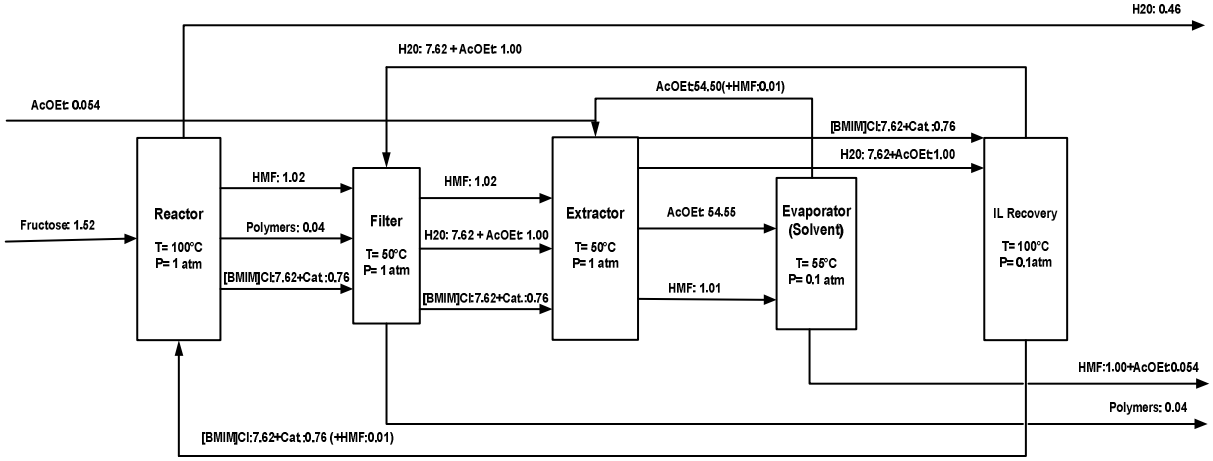
7.4.2 Mass metric

The mass metrics for 1 kg HMF output for the four reaction options are plotted in Figure 7.3. It can be seen that both process options with low concentration (17wt%) require less reactant (fructose/glucose) than the cases with high concentration (50 wt%). This is attributed to a lower selectivity towards HMF at a higher concentration. As a consequence, the byproducts (humins) and water formed from the reaction options with a low feed concentration are lower than that from the options with a high feed concentration.

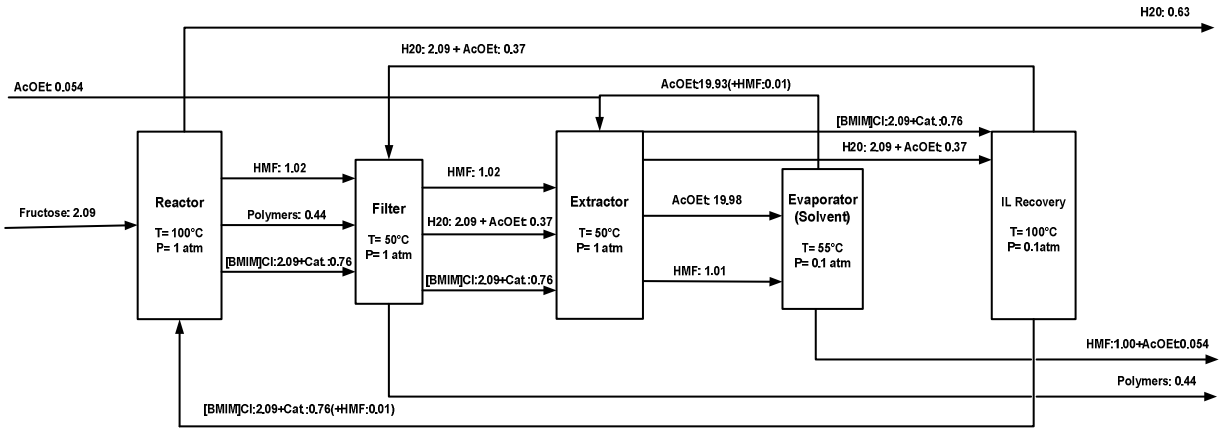
It is commonly believed that glucose is converted first to fructose, and subsequently to HMF (Yong et al., 2008; Ståhlberg et al., 2011). As a result, the reaction condition is harder and always associated with lower selectivity to HMF and more byproducts (mainly humins) are formed (Boisen et al., 2009; Ståhlberg et al., 2011). Interestingly, the selectivity to HMF was more affected by the initial feed concentration for fructose than from glucose (Table 7.1). At a concentration of 50 wt%, the selectivity to HMF from

glucose (73%) is better than from fructose (70%). This gives a less sugar requirement with Case G2 than Case F2 (Plot b and Plot d, Figure 7.3).

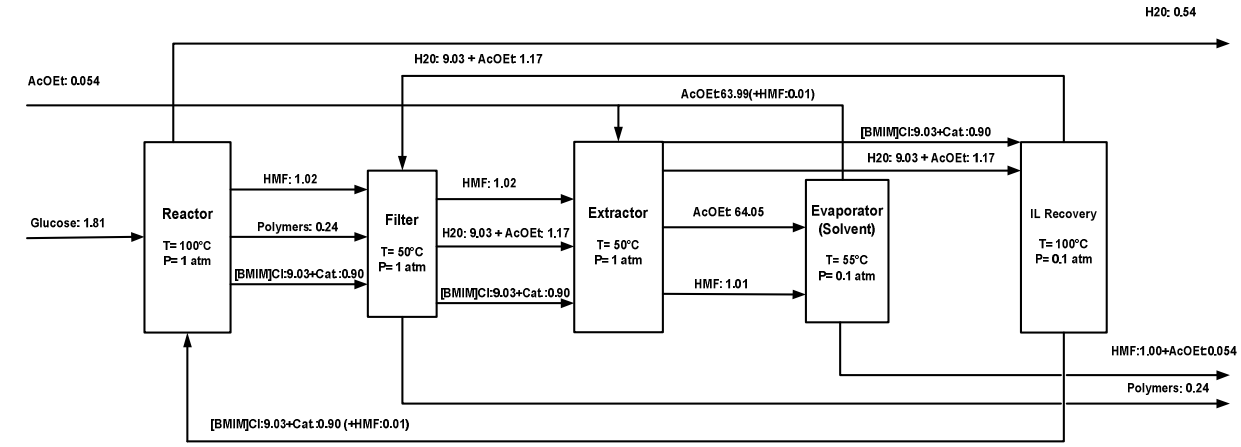
Although using a low concentration feed shows more efficient use of reactant (less byproducts), the disadvantage with low concentration options is large dilution which requires more reaction medium, solvent and process water in the whole production process. For example, it requires 7.62 kg [BMIM]Cl /kg HMF and 55.55 kg E_tOA_c /kg HMF respectively in the process option with a fructose feed concentration of 17wt%. On the other hand, the required amount of [BMIM]Cl is only 2.09 kg/kg HMF and the amount of EtOAc is 20.35 kg/kg HMF for the process option that employs fructose with a feed concentration of 50wt% .



b)



c)



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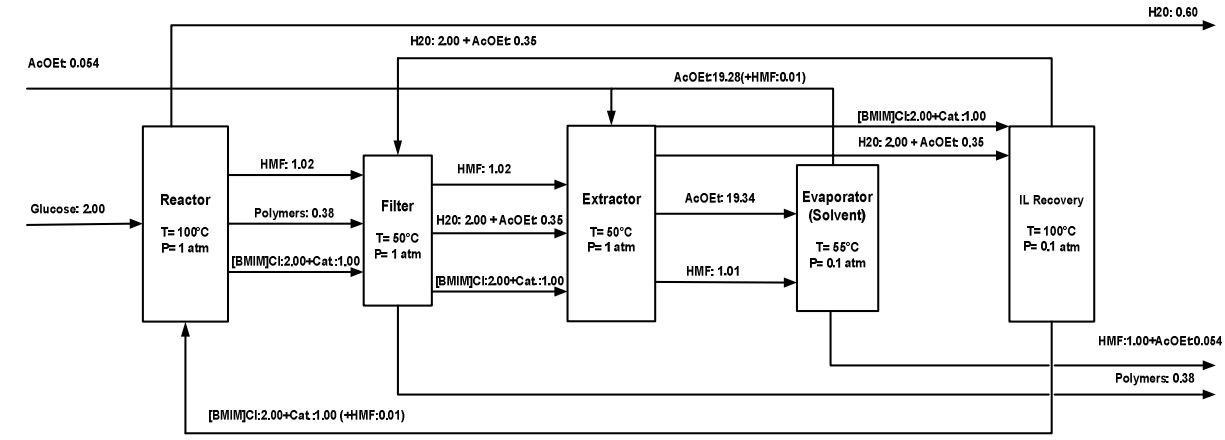

Figure 7.3. Block scheme diagram of mass flow balance for 1 kg HMF production of different process options. Plot a) is for process starting with fructose with initial concentration of 17 wt% (case F1), Plot b) is for process starting with fructose with initial concentration of 50 wt% (case F2), Plot c) is for process starting with glucose with initial concentration of 17 wt% (case G1) and Plot d) is for process starting with glucose with initial concentration of 50 wt% (case G2).

7.4.3 Energy metric

The calculated energy requirement for major process units are listed in Table A6.1 (Appendix6). The energy metrics for the four alternative options are shown in Figure 7.4. The difference for energy requirements between a high concentration feed and a low concentration feed for both glucose and fructose are significant. A high dilution leads to higher energy consumption for recovering the reaction medium, the process water and the solvent. For process options from fructose, the total energy consumption for a feed concentration of 17wt% is 85 MJ/kg HMF which is 2.7 times of that for a feed concentration of 50 wt%. For process options from glucose, the energy consumption for a feed concentration of 17 wt% (101 MJ/kg HMF) is also around 3.3 times of that for a feed concentration of 50 wt% (30 MJ/kg HMF).

For all the four process options, the largest energy consumption is attributed to condensation (over 40% of the total energy). The calculated condensation energy here is the sum of the energy required to condense the solvent vapor and the vapors of process water. Due to a low partition coefficient of HMF, large amount of the solvent is used in the extraction process in order to reach an efficient extraction. The energy for evaporating and condensing the solvent are therefore significant. Other major energy consumptions besides condensation are the energy for E_tOA_c evaporation followed by the energy for IL recovery (process water evaporation).

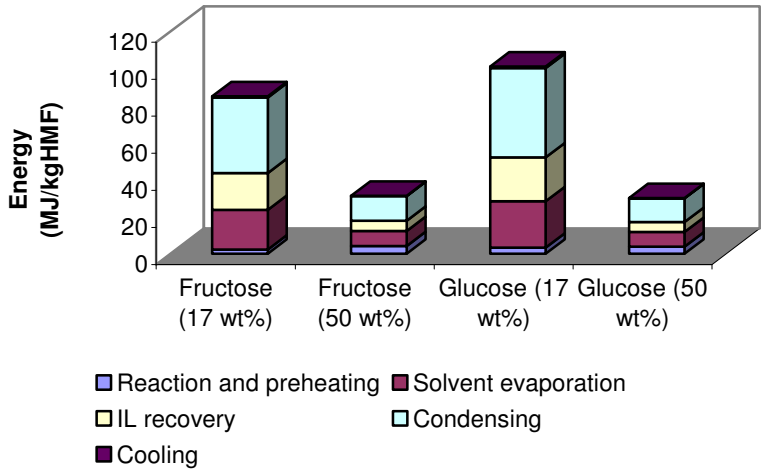

Figure 7.4. Plot of the required energy for major process units in process flowsheets for four process options.

7.4.4 HMF production cost

Equipment sizing and estimation of the capital cost

The calculated size and capacity of the major equipment involved in the process flowsheet of the four options is shown in Table A5.2 in the Appendix5. Due to the dilution with a low concentration feed, the required volume of all the equipment for process options F1 and G1 are around 2 to 3 times of that for process options F2 and G2. The heat exchanger 2 and 3 are used to condense the vapor solvent and the vapor process water, respectively. Since the required amount of energy for condensing both the solvent and water is large, the required areas for these two heat exchangers are also large. The required volume of the dehydration reactor is huge, because it is calculated with a residence time of 6 hours for all the four options. Since the dehydration reaction in IL process has not optimized yet, there is still scope to reduce the residence time. The required volume of the dehydration reactor can consequently be reduced.

The calculated total capital investment for different process options is shown in Table 7.3. The capital investment is highly related with the required capacity of the equipment. Obviously, a low feed options (F1 and G1) have much higher capital cost than that for a high feed concentration options (F2 and G2). The total capital investment for the options with the same feed concentration is similar.

Table 7.3. Total capital investment for HMF IL process options.

Item	Cost (Million USD)			
	Case F1	Case F2	Case G1	Case G2
Total direct plant cost[a]	7.5	4.6	8.4	4.5
Total indirect plant cost[b]	3.1	1.9	3.5	1.9
Fixed capital investment (85% TCI)	10.6	6.5	11.9	6.4
Working capital (15% TCI)	1.8	1,2	.2.1	1.1
Total Capital Investment	12.5	7,7	14.0	7.6

a)Includes: Purchased equipment (PE), installation equipment (39%PE), instrumentation(43%PE), Piping (31%PE), electrical (10%PE), yard improvement (15%PE) and service facilities (55%PE).
b)Includes; engineering and supervision (32%PE), construction expense (34%PE), legal expense (4%PE), contractor fee (19%PE) and contingency (37%PE).

HMF production cost

HMF cost

The calculated HMF cost of the IL route is a cost consisting of the raw material and the energy cost. The HMF cost of the IL route from fructose is around 1.15 USD/kg HMF at a feed concentration at 17wt% and 1.23 USD/kg HMF at a feed concentration at 50wt%. The HMF cost of the IL route from glucose is around 0.99 USD/kg HMF at a feed concentration at 17wt% and 0.78 USD/kg HMF at a feed concentration at 50wt% (Table 7.4, sum of the raw material and the utility cost). The HMF cost of the IL here is without considering the cost of the IL and the catalyst.

HMF production cost

The calculated HMF production cost of HMF consists of variable cost (mainly the material cost, utility cost, labor cost and maintenance cost), fixed cost (tax, insurance and depreciation), plant overhead cost and general expense. The depreciation cost is calculated as 10% of total capital investment per year (assuming a recovery period of 10 years). The calculated HMF production cost without adding the cost of IL and catalyst for each process option is listed in Table 7.4.

The HMF production costs of process options with glucose as feedstock (G1 and G2) are cheaper than those with fructose (F1 and F2). The lowest HMF production cost without considering the cost of the IL and catalyst is 1.12 USD/kg HMF (Option G2). The highest HMF production cost is 1.62 USD/kg HMF, obtained from Option F2.

For all the four options, the cost of reactant (glucose/fructose) dominates the whole HMF production cost, followed by the cost of utilities (heating steam and cooling water)

(Figure 7.5). The fixed cost and other variable cost, which are related to the total capital investment covering the whole HMF production cost is around 7 to 11% for all four process options. This indicates the effect of the total capital investment to the HMF production cost is not significant. This effect can be further decreased by increasing the production scale. The major HMF production cost (without the IL and the catalyst cost) still comes from the cost of the reactant and utilities. The cost of utilities for processes with low feed concentration (F1 and G1) is around 3 times that of processes with high feed concentration (F2 and G2). However, the decreased selectivity with a high feed concentration increases the required amount of reactant. Consequently the cost of reactant increases. For processes starting from glucose, the decreased utilities cost with a high feed concentration is bigger than the increased cost of reactant. Therefore, the HMF production cost (without considering IL and catalyst) of G2 is lower than that of G1. On the other hand, for processes from fructose, the savings in terms of energy cost with a high feed concentration (F2) can not pay back the increased cost of fructose due to a high fructose cost.

Table 7.4. HMF production cost without adding the IL and the catalyst cost for the four process options.

Item	HMF production cost (USD/kg HMF)				
		Case F1	Case F2	Case G1	Case G2
Material cost	Glucose/Fructose	0.76	1.04	0.54	0.60
	Solvent	0.05	0.05	0.05	0.05
Utilities	Steam (MP 200 Pigs)	0.31	0.13	0.37	0.12
	Cooling water	0.03	0.01	0.03	0.01
Labor and Labor supervision		0.08	0.08	0.08	0.08
Other variable cost		0.11	0.10	0.10	0.07
Fixed cost		0.06	0.04	0.07	0.04
Plant overhead cost		0.06	0.05	0.06	0.05
General expense		0.12	0.13	0.11	0.09
Total		1.58	1.62	1.42	1.12

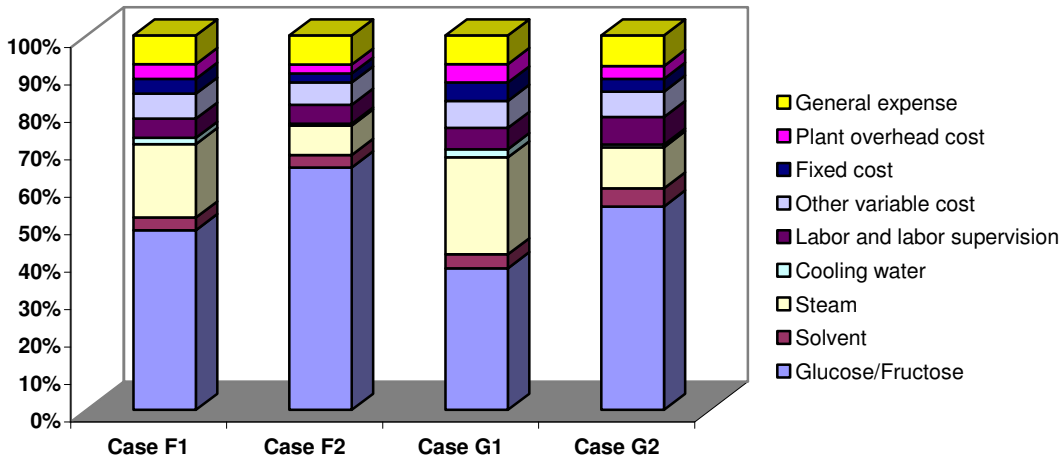

Figure 7.5. Plot of the cost distribution of the HMF production cost (without adding the IL and the catalyst cost).

7.5 Discussion

The required amount of the IL and the catalyst for HMF production is highly dependent on the number of recycles. Successful reuse of the [BMIM]Cl and the catalyst for 6 or 7 times without affecting any selectivity of HMF production have been reported (Qi et al., 2009; Lai and Zhang, 2010). However, for a large scale production, 6 or 7 reuse times is far from sufficient due to a high cost of IL.

If the cost of [BMIM]Cl is 11USD/kg and the catalyst is 2 USD/kg, the effect of reuse times of the IL and the catalyst to the HMF production cost is plotted in Figure 7.6. In Figure 7.6, the HMF production cost is highly affected by the number of reuses of the IL system. The reuse here is assumed as the number of times that the IL and the catalyst can be reused for HMF production without affecting the selectivity.

The HMF production cost decreased dramatically with the increased number of reuses of the IL and the catalyst until the reuse time reaches 50. After 50 times of reuse of the IL and the catalyst, the HMF production cost for processes with a high feed concentration (case G2 and case F2) declines gradually with the number of recycles. After recycling the IL and the catalyst for 150 times, the effect of recycling on the HMF production cost is not significant anymore. The cost of sugar starts to dominate the HMF production cost again. If the IL and the catalyst can be reused for around 200 times without significant effect on the selectivity of HMF production from sugar, the HMF production cost for F1, F2, G1 and G2 is around 1.97 USD/kg HMF, 1.74 USD/kg HMF, 1.88 USD/kg HMF and 1.23 USD/kg HMF, respectively. Clearly, when considering the IL and the catalyst cost, processes with a high feed concentration are more competitive than process with a low feed concentration. This advantage decreases with the increase in IL and catalyst reuse (Figure 7.6).

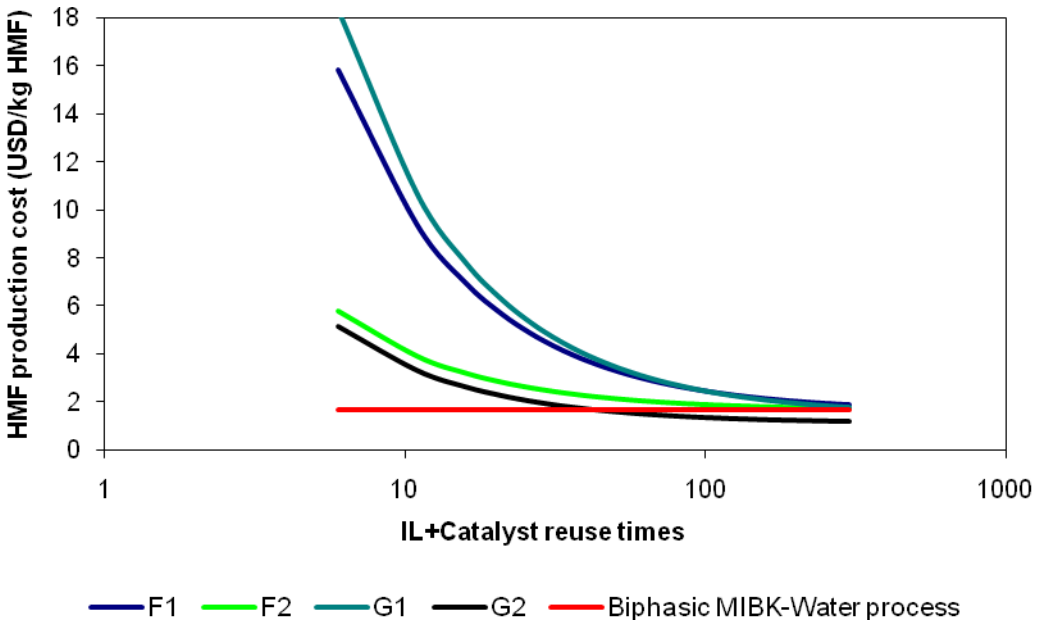

Figure 7.6. HMF production cost versus. IL+ catalyst reuse times.

7.5.1 Comparison with biphasic HMF production process

Besides using IL as reaction medium for HMF production from sugar, HMF can also be produced from fructose in water (Rapp, 1987), neat high boiling point solvent such like DMSO (Nakamura and Morikawa, 1980; Brown et al., 1982; Musau and Munavu, 1987), one phase water-solvent mixture (Kuster, 1977; Bicker et al., 2003; Bicker et al., 2005) and biphasic water-solvent mixture (Roman-Leshkov et al., 2006; Roman-Leshkov et al., 2009). Due to a low selectivity in water as medium, and no industrial interest in DMSO as reaction medium for HMF production, using biphasic reaction medium such as water-MIBK with addition of salt or phase modifier appears to be one of the most promising processes for HMF production from fructose (Roman-Leshkov et al., 2006; Roman-Leshkov et al., 2007; Roman-Leshkov et al., 2009; Bosien et al., 2009; Tong et al., 2010). This has also been approved in Chapter 5. The HMF production cost by using MIBK-water as reaction medium, HCl as catalyst with addition of salt (NaCl) was calculated.

The biphasic MIBK-water process flowsheet is outlined in Figure 7.7. The aqueous feed to the biphasic reactor consists of fructose and water. The feed concentration is around 30wt% fructose (on a wet weight basis). Hydrochloric acid is added into the aqueous solution as a catalyst with a concentration around 0.25 mol/L. The aqueous phase is saturated with salt (around 35 wt% based on water) to improve the partition coefficient of HMF between water and MIBK[31]. The mixture is heated up and maintained around 180 °C for 3 minutes. The selectivity for the dehydration of fructose to HMF is 77% (mol

HMF/mol Fructose) at 72% conversion (mol HMF/mol Fructose). Afterwards, the reaction mixture was cooled down to room temperature for the phase separation. The aqueous phase is then sent to a liquid-liquid extractor for the second extraction to remove the leftover HMF in aqueous phase. 99% of HMF can be recovered in this way. Afterwards, the aqueous phase rich in fructose will be recycled back after the excess water produced in dehydration reaction is stripped off. Organic phases from both the biphasic reactor and the second extractor will be sent for vacuum evaporation. Based on the simulation results in ProII at 0.01 atm and 314 K, 99.8% of the MIBK solvent can be recovered in this way with a 1.6% loss of HMF. The total distillation yield for HMF is 98.4% and the purity of obtained HMF is around 95 wt%.

The total capital investment calculated for biphasic process is around 13.5 million USD (detailed equipment sizing, costing can be found in the appendix), which is higher than the calculated capital investment for IL processes with high feed concentration (Case F2 and Case G2) and IL process with low feed fructose concentration. The required dehydration reactor size is around 6 m^3, which is much smaller than that calculated for IL processes due to a short residence time (3 minutes) and a high feed concentration (30 wt%). However, since the reactor is high pressurized, the equipment cost is also high. Besides, since the required reaction temperature is quite high, the required total area for heat exchangers is also much bigger than that for IL processes. The calculation for HMF production cost with biphasic process is listed in Table 7.5. The production cost for HMF by biphasic route is around 1.68 USD/kg HMF.

The HMF production cost by biphasic route was also plotted in Figure 7.6 (red line). Using IL processes for HMF production, only the process start with glucose with a high concentration (Case G2) is competitive to the biphasic route with the assumption if the IL system can be reused for around 45 times. Clearly, the more times that IL system can be reused, the HMF production cost by IL process is more close to the cost by biphasic production. The production cost for case G2 starts to be lower after IL reuse times reaches 45 times. However, as it can be seen in Figure 6, besides G2, none of the other three IL processes are able to reach a lower HMF production cost than the biphasic process even if the IL recycle time reaches 300. The dominating factor in HMF production cost by biphasic system is the sugar cost (0.94 USD/kg HMF), which is bigger than that for the IL process options F1, G1 and G2. The second biggest part is the cost of the utilities (0.21 USD/kg HMF) which is bigger than that of IL processes with high feed concentrations (F2 and G2) but smaller than that of IL processes with low feed concentrations.

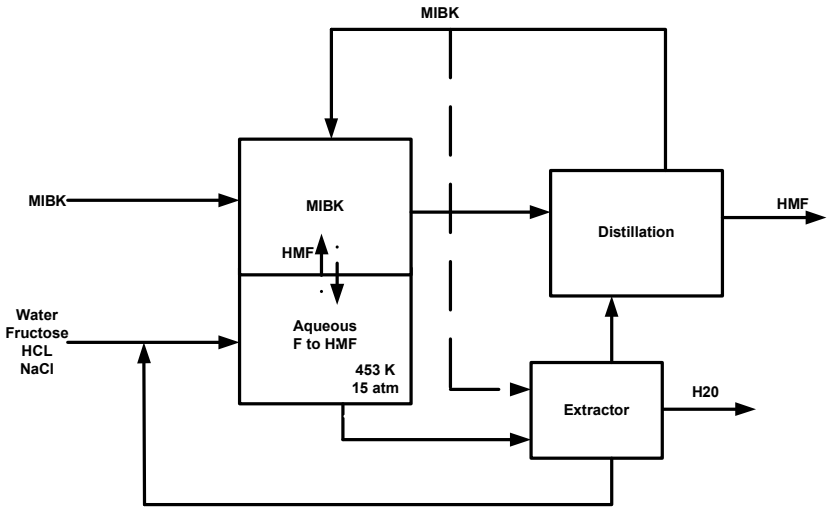

Figure 7.7. Process flowsheet of dehydration fructose in biphasic reactor (MIBK-water), Modified from Roman-Leshkov et al. , 2006.

Table 7.5 Calculated HMF production cost for biphasic process (MIBK-water) for HMF production.

Item		**(USD/kg HMF)**	**Percentage (%)**
Material Cost	Fructose	0.94	56.24
	Solvent	0.08	4.76
Utilities	Electricity	0.00	0.04
	Steam	0.19	11.56
	Cooling water	0.01	0.79
Labor	Labor and supervision	0.08	4.85
Other variable cost		0.11	6.71
Fixed cost	Tax, depreciation, insurance	0.07	4.04
Plant overhead		0.06	3.39
General expense		0.13	7.62
HMF total production cost		1.68	100.00

7.5.2 Improvement for process option G2

The cost distribution chart of the HMF production cost using the IL process option G2 with the IL and the catalyst recycle for 200 times is shown in Figure 7.9. The glucose cost covers 48% of the total cost, followed by cost of utilities (steam and cooling water) which is 11%. The cost of the IL and the catalyst together is around 10%. Other cost related with the capital investment is the sum of other variable cost (maintenance, repair and laboratory) and fixed cost, which all together covers around 9%. Since the whole process is still based on some lab unit operation results, there is still a lot of room for further improvement.

For example, the reaction residence time is based on a batch reaction with a residence time of 6 hours, leading to a reactor volume of 90 m^3. On the other hand, the reaction volume required for the biphasic process is only 6 m^3. This can be improved with a better understanding of the kinetics of the decomposition sugar inside the IL. The IL cost used for calculation is around 11 USD/kg. In the future, with the demanding scale, the cost may reduce. It then demands less recycling times if IL's price is cheaper. However, based on the price now, recycling more than 46 times can lead to a competitive IL based process which has a lower cost than that of the biphasic process with salt. The cost can be even more appealing if more than 200 reuses can be reached. The reaction selectivity for the calculation is chosen as 73%. In the future, this can be further improved. Figure 7.8 shows the HMF production cost decreasing with the increased dehydration reaction yield. If the yield is able to reach 93%, the HMF production cost can reduce to 1 USD/kg HMF. In large-scale production, the process may be operated in a continuous mode due to many advantages (Ståhlberg et al., 2011). The reaction yield in continuous processes would be equal to the selectivity when the unconverted sugar is fully recycled. This offers great potential for the dehydration glucose to reach the selectivity of 93%. Of course, this requires better understanding of the reaction kinetics.

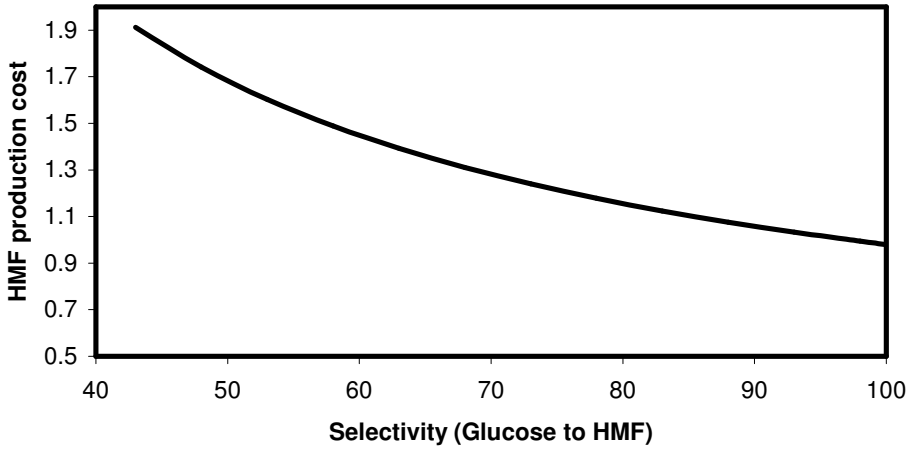

Figure 7.8. Effects of the dehydration selectivity from glucose to HMF to the HMF production cost.

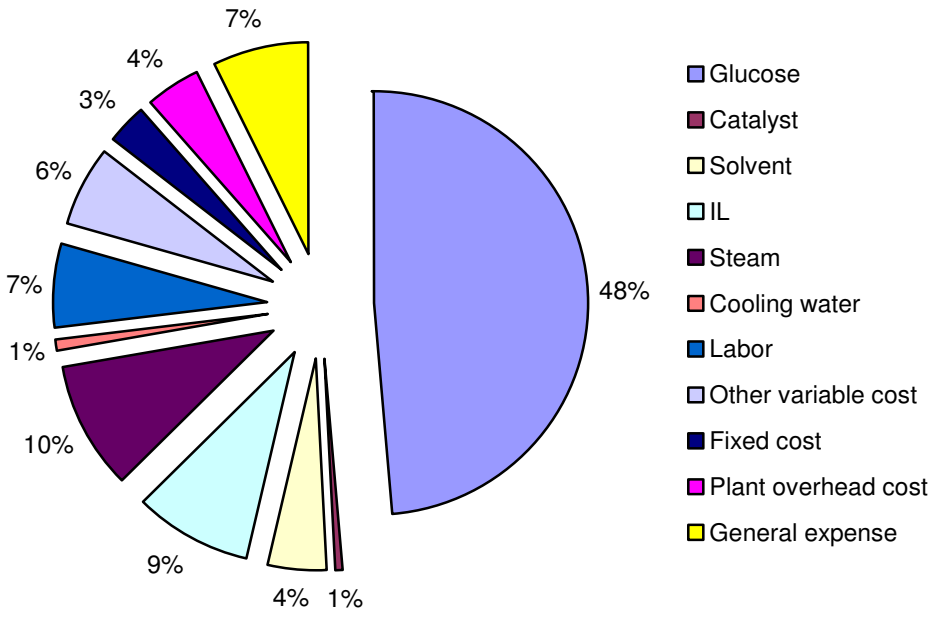

Figure 7.9. Total HMF production cost breakdown. The production cost is obtained by using the IL process option G2 with the IL and catalyst recycled for 200 times.

7.6 Conclusions

Using the IL route for the HMF production with different process options starting from fructose and glucose with different initial concentrations were evaluated in this study. The mass and energy metrics were calculated for the four examined options. The HMF production cost of the four options was calculated. The HMF production cost is highly affected by the number of times that the IL and the catalyst are recycled. Processes with a high feed concentration show better economic potential than processes with a low feed concentration. IL processes starting from fructose are more costly than IL processes starting from glucose due to a high cost of fructose.

Using IL processes for HMF production from glucose with a high feed concentration with IL and catalyst recycle of at least 46 times can be competitive with the biphasic processes proposed by Roman-Leshkov et al. (2006; 2007) which corresponds to have a production cost of 1.68 USD/kg HMF in this study.

In the future, in order to realize the HMF production at a large industrial scale, studies should focus on investigating the recycle of the IL medium and using cheap starting material such as glucose for HMF production. Although the recycle of the ILs together with catalysts have been investigated, the reported number of recycle is only around 6 or 7 times which is far away from the requirement for industrial scale-up. For using IL liquid for the bulk chemical production, the number of recycle of the IL should be at least 150 times so that a production cost of chemicals can be economical feasible. A high concentration feed of glucose showed the best economic potential. The recent research in using IL for synthesis HMF always uses very low feed concentration. In the future, research should put more emphasis on understanding the kinetics of decomposing sugar in IL in an effective manner in order to be able to maintain a good selectivity even with a high concentration feed.

The main advantage of an IL based process is the possibility to use glucose as feedstock. The attained HMF selectivity together with possible product recovery can not be achieved in other solvent systems. In addition, the choice of feedstock could be expanded to even cheaper bioresources such as the glucose polymers cellulose and starch. These can be dissolved in ILs (unlike in organic solvents and water) and can be directly converted to HMF. The use of such feedstock might lower the cost even further and reduce the number of IL cycles required to obtain a cost competitive process.

Concluding remarks

In this chapter, using the IL route for the HMF production from both fructose and glucose is evaluated. Using the IL synthetic route to produce HMF from glucose is found to be very promising. In the next chapter, the important issues related with the HMF production process routes and the limitations of the methodology are discussed.

8 Discussion

Summary

In this chapter, the most important issues related with the HMF synthetic process design are discussed here. Afterwards, all the process routes for HMF production examined in this thesis are compared. Their future possible improvements are discussed. Finally, the most promising routes are identified. The potential routes are also compared with PTA production process.

8.1 Evaluation of the important issues

Here, the important issues related with the HMF synthetic process design, such as the selectivity, conversion, recycle (solvent, unconverted sugar, reaction medium) and use of the solvent are discussed.

8.1.1 Selectivity versus Conversion

In all the HMF synthetic process routes, irrespective of the feedstock, the yield is one of the key parameters dominating the HMF production cost as well as the HMF cost. By using the economic metrics, clearly, all the processes that have a good yield in dehydration reaction show the economic potential for HMF production in a large scale. A good dehydration yield means not only a good selectivity, but also a good conversion. They are both important.

However, due to the polymerization and hydrolysis of HMF, with the increasing conversion of the sugar, HMF starts to convert to polymers or levulinic and formic acids, resulting in the decrease of the selectivity. Figure 8.1 is the plot of conversion versus selectivity of different reaction systems for dehydration of fructose to HMF. For reaction media that could completely avoid water, such as using DMSO or ionic liquids, the selectivity does not decrease so much with the increase of the conversion. However, when water is present in the reaction medium, the selectivity is more affected with the conversion. This makes it very hard to maintain a high selectivity while trying to reach a high conversion for reaction medium such as water or biphasic system. It then becomes the choice in process design which parameter is more important? A high conversion will save the energy for recycling the aqueous, and some downstream capital investment. On

the other hand, a high conversion can lead to a loss in the selectivity, leading to an inefficient use of reactants. This can increase the cost of the reactants and also give difficulties in the downstream separation. Thus, a final decision should be a compromise between the selectivity and the conversion, which leads to the lowest production cost.

Figure 8.2 shows the effects of the selectivity and conversion to the HMF production cost by using the designed process flowsheet in Chapter 5. The calculation of the effect of the conversion on the HMF production cost is based on the assumption that the selectivity is maintained at 80% and the unconverted sugar is recycled. The calculation of the effects of the selectivity on HMF production cost is based on the assumption that the fructose conversion is 96%. It can be seen that, at the same reaction yield (conversion x selectivity), a high selectivity will lead to a low HMF production cost. For example, at the dehydration yield of 72%, the HMF production cost with a selectivity of 75% is around 1.57 USD/kg and the HMF production cost with a selectivity of 80% is around 1.53 USD/kg. On the other hand, when the selectivity is around 80%, the HMF production cost with a conversion of 96% is around 1.46 USD/kg, and the HMF production cost is with a slightly lower conversion of 95%, is around 1.49 USD/kg.

However, for the chemo-enzymatic synthesis of HMF from glucose (Chapter 6), the dehydration reaction needs to have a high conversion so that the aqueous stream can be recycled back to the IGI column. If the conversion of fructose is not high enough, the fructose concentration in the sugar mixture will be too close to the equilibrium concentration (42 wt% fructose in the dry sugar concentration) and there will be no need to recycle the mixture sugar aqueous stream to the IGI column. The calculation showed in Figure 8.2 takes into account that the enzyme consumption will increase by 6% if the initial fructose content in the recycled aqueous stream increases by 5% (Novo Nordisk, 1985). On the other hand, if the conversion of dehydration reaction is not high enough (less than 50%), the aqueous stream alternatively can be recycled back to the aqueous phase in the dehydration reactor. However, this alternative option may lead to some extra consumption of glucose. Besides the formation of HMF from fructose in the dehydration reactor, some amount of the glucose will also react and form humans, leading to an extra consumption of glucose. Therefore, for the chemo-enzymatic process proposed in Chapter 6, the dehydration reaction should aim at maintaining a good conversion and keeping the selectivity as high as possible.

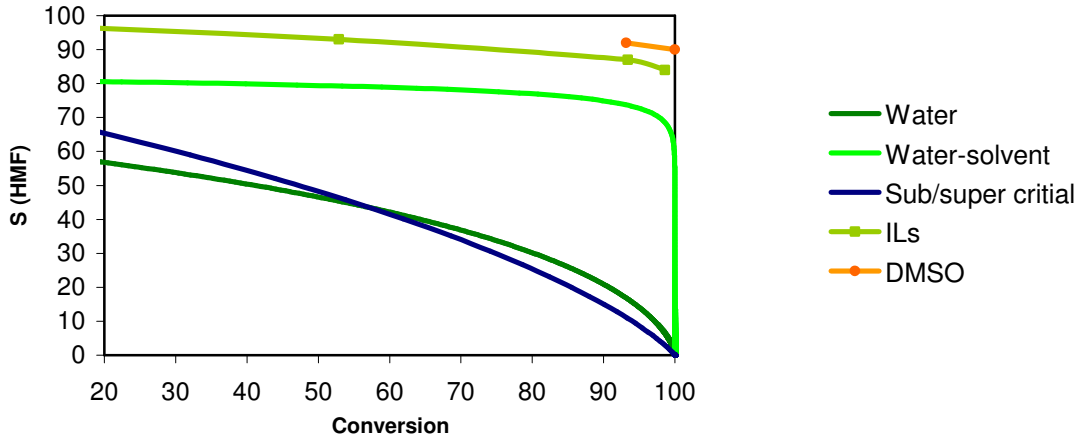

Figure 8.1. Selectivity versus conversion for different reaction media systems. The curve of the water reaction medium is calculated by using the kinetic model proposed by Kuster and van der Baan (1977); the curve of the water-solvent reaction medium is calculated by using the kinetic model from Kuster (1977). The curve of the sub/super critical reaction system is calculated by using kinetic model from Asghari and Yoshida (2007); the IL reaction system is plotted by using the published experimental data from Tong and Li (2010) and the DMSO system is plotted using the experimental data from Musau and Munavu (1987).

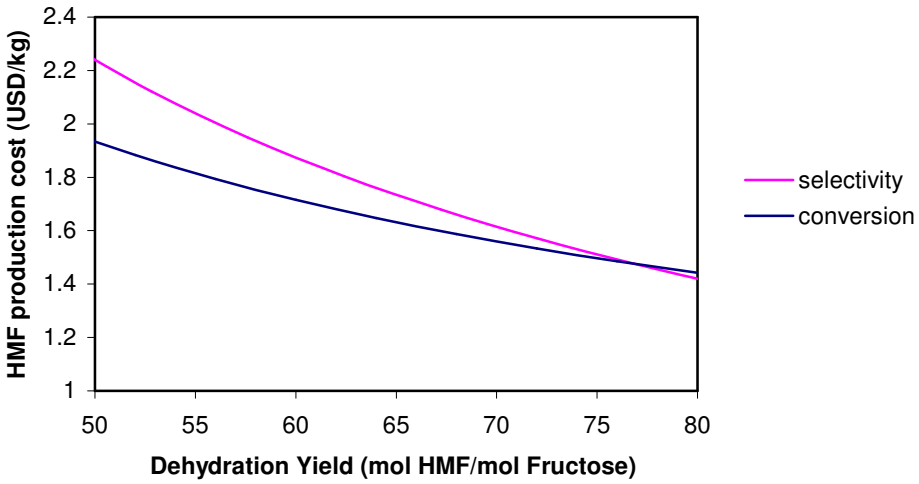

Figure 8.2. Plot of the effects of the dehydration selectivity and the conversion to HMF production cost.

8.1.2 Effect of the recycle rate

Effect of the recycle rate of the aqueous stream (unconverted sugar)

According to the cost distribution of the HMF production cost, the reactant is the major cost contributor. Thus, recycling the unconverted sugar is very important. Specially as discussed in the previous section, some times, in order to maintain a good selectivity, the conversion can not be very high. Therefore, recycling the unconverted sugar in the aqueous phase becomes another very important factor that affects the HMF production cost. Figure 8.3 shows the effect of the recycling rate of the aqueous phase to the HMF production cost of the chemo-enzymatic route. In the chemo-enzymatic route, a mixture of fructose and glucose after IGI reactor is sent to the dehydration reactor where mainly the fructose is reacted. Thus the aqueous stream after the dehydration still contains around 2.4 kg glucose/kg HMF (with a value of 0.72 USD). The recycle rate of the aqueous phase is then very important to the HMF production cost. In Figure 8.3, increasing the aqueous recycle rate, the energy cost increases and the cost related with the capital cost also increases (due to the investment on a second evaporator, heat exchangers). However, the decreased reactant cost is much higher than the increased energy and other cost. The HMF production cost is very sensitive to the aqueous recycle rate.

On the other hand, the effect of the aqueous recycle rate on the HMF production cost of the biphasic process with addition of salt proposed by Román-Leshkov et al. (2007) is less sensitive than that on the HMF production cost of the chemo-enzymatic route (Figure 8.4). Although the HMF production cost of chemo-enzymatic route (1.46 USD/kg) is cheaper than that of the biphasic route (1.68 USD/kg) at 100% recycle rate of the aqueous phase, the HMF production cost of the chemo-enzymatic route (2.14 USD/kg) is higher than that of the biphasic route with salt (2.09 USD/kg) when there is no aqueous recycle. This can be explained as with a conversion of 75% in the biphasic route, there is only around 0.78 kg fructose/kg HMF in the aqueous stream (with a value around 0.4 USD/kg). The value of the aqueous phase of the biphasic route with salt is not as high as that of the chemo-enzymatic route.

The HMF cost (only material and energy) of the water route by Rapp (1990) with no recycle of the unconverted sugar is lower than that when the unconverted sugar is fully recycled. Due to a high dilution in the downstream by using chromatography to separate HMF from sugar mixture, the energy used to concentrate the aqueous stream before recycle costs more than the value of the remained sugar in the aqueous stream.

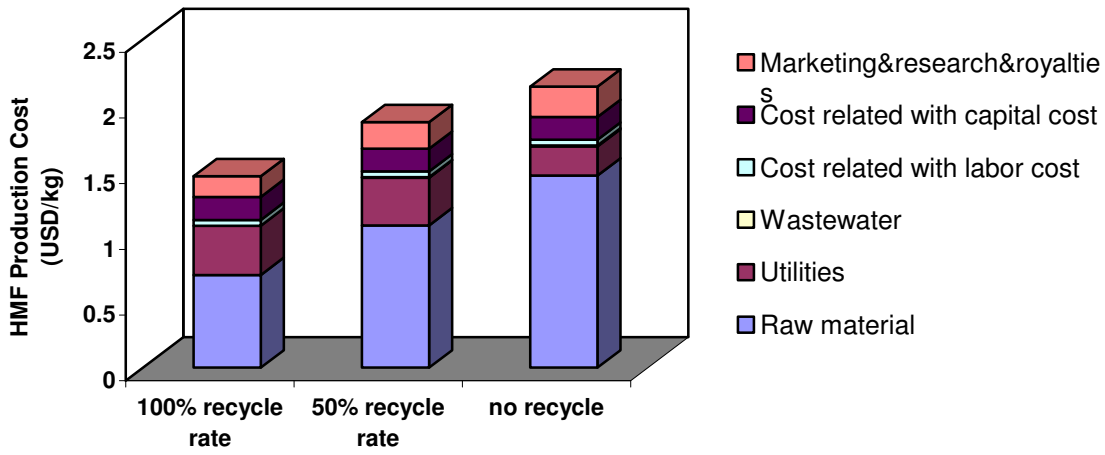

Figure 8.3. Plot of the effect of the aqueous recycle rate to the HMF production cost of the chemo-enzymatic process (Chapter 6).

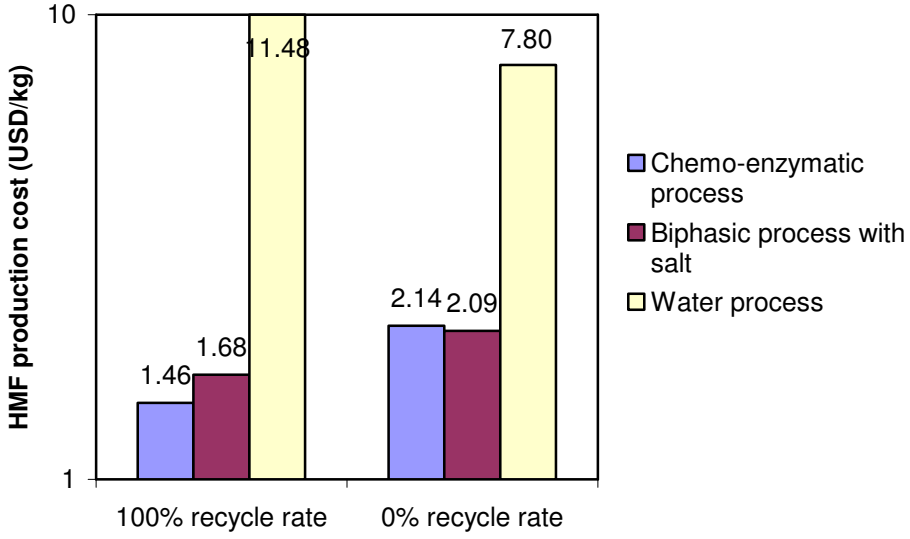

Figure 8.4. Effects of the aqueous recycle rate to HMF production cost of different processes.

Effect of the recycle rate of the organic solvent

In most of the process routes developed for synthesis of HMF, it seems that using organic solvent can not be avoided. The solvent is applied in the process routes either for the purpose of synthesis or separation. Due to the low partition coefficient between HMF and solvents, it always results in a large amount of solvent used in the process routes for separation. This makes it very important for the downstream design to recycle all the organic solvent. The whole production cost is very sensitive to the recycling ability of the

solvent in the process. Any loss in the solvent will lead to a big increase in the HMF production cost.

HMF is a bulk chemical, and the production cost of HMF should be low enough in order to compete with the chemicals based on oil. For example, using the chemo-enzymatic route proposed in Chapter 6, the required amount of MIBK in the process is around 59 kg for 1 kg HMF production. The market price for MIBK is around 1.89 USD/kg (ICIS, 2009). With such amount of solvent, every 1% of solvent loss will increase the production cost by 1.12 USD. On the other hand, the market price of PTA is only around 1 USD/kg. This indicates the importance of recycling solvent in order to make the chemicals from biomass to be able to compete with the oil-based chemicals.

On the other hand, based on the annual production rate of 250 000 tons HMF per year, if there is no solvent recycled at all, there will be around 14 750 000 tons organic solvent waste per year. The cost of buying and decomposing such large amount of solvent waste will increase the production cost dramatically. Assuming the market value of HMF is 2 USD/kg, 250 000 tons HMF gives a value of 500 million USD per year. This is far away to cover just the cost of buying MIBK, which is around 27 877 million USD if the MIBK is not recycled. On the other hand, the whole chemical production industry today has put a lot of the emphasis and efforts on minimizing the waste production during the whole production life. Recycling solvent is definitely a very important way to reduce the amount solvent required and the amount of waste produced during production.

Sometimes, the choice of solvent may bring difficulties in recycling and thus consume a lot of energy. For example, recovering DMSO from water is kind of difficult. In Chapter 5, we have cost and analyzed the solvent route that uses DMSO for synthesis of HMF. DMSO is used as the reaction medium in this route. The consumption of DMSO is around 3.5 kg for 1 kg HMF production. The energy consumption to recover all the used DMSO is 75 MJ (21 MJ/kg DMSO). Although the energy consumption for recycling DMSO is high, the energy cost to recycle 3.5 kg DMSO is around 0.28 USD. If there is no recycle of DMSO, the cost for only buying DMSO is around 7 USD for 1 kg HMF production. This example shows the importance of recycling solvents to the process economy even though the solvent is an energy intensive solvent. On the other hand, it also shows how the choice of the solvent affects the process design. Using biphasic route for HMF production as proposed by Roman-Leshskov et al. (2006), the consumption of MIBK is around 40 kg MIBK for I kg HMF production. However, the energy to recover all the MIBK (around 40 kg MIBK) is around 36 MJ (0.9 MJ/kg MIBK) which is much less than that required to recover 3.5 kg DMSO. This indicates the benefit of using a low-boiling solvent in the downstream separation.

8.1.3 Use of the solvent

Effect of the R_{HMF}

A low R_{HMF} always results in a large amount of solvent used in the process route in order to get a sufficient extraction of HMF from the reaction medium (aqueous phase, DMSO-water mixture, IL phase). If a R_{HMF} is higher, the amount of solvent used will be reduced. There are some ways of improving the R_{HMF}.

For biphasic system (water-solvent), R_{HMF} can be improved by adding salt into the aqueous phase (Roman-Leshskov et al., 2007) or using phase modifiers (eg. adding 2-butanol into MIBK) (Roman-Leshskov et al., 2006). Alternatively, use of solvents with better R_{HMF} can be combined with addition of salts into the aqueous phase. In general, solvents have better values of R_{HMF} are more hydrophilic. MIBK is a good solvent in the biphasic process, because the solubility of MIBK in water is very low. Solvents have better values of R_{HMF} than MIBK are more soluble in water. Adding salt not only improves the R_{HMF} but also decreases the miscibility between the solvent and water. For example, by adding salt into the aqueous phase, the water solubility in 2-butanol decreased from 31.4 wt% to 7.4 wt% (Roman-Leshskov et al., 2007).

These methods work well with process directly started from fructose. The drawback with adding salt is that it may lead to corrosion due to a high concentration of salt in the aqueous phase. Moreover, for the salty aqueous phase, it may require to use special material for the equipment design, which may lead to a high capital investment and a high maintenance cost.

For process using chemo-enzymatic route to produce HMF from glucose (Chapter 6), since the salt affects the stability of glucose isomerase, the use of salt is limited to a certain concentration (7wt%, 50 g/L) in the aqueous phase. This limits the use of adding salt to improve the R_{HMF} and reduce the miscibility between the solvent and water. Therefore, solvents with better values of R_{HMF} than MIBK, like THF, 2-butanol are not suitable solvents to be applied in this process route proposed by Chapter 6. These solvents are more miscible with water than MIBK, leading to more solvents entering the aqueous phase. In order to not affect the stability of the glucose isomerase, more downstream processing will thus be required to reduce the amount of the organic solvent in the aqueous phase when the aqueous phase is recycled to the enzymatic step. Alcohol solvents always have a better R_{HMF} and have positive effects on the selectivity of the dehydration reaction (Roman-Leshskov et al., 2009). However, alcohol solvents normally form azeotrope with water making it difficult to be separate from the aqueous phase before recycling back to the enzymatic reaction.

For process routes with ILs as reaction medium, the R_{HMF} between ILs and extraction solvents are lower than R_{HMF} between aqueous and solvents. Adding water in ILs will help to decrease the viscosity of the reaction mixture and thus increase the R_{HMF} between reaction mixture and the extraction solvents (Chapter 7). The drawback is then the dilution in reaction mixture, which will in turn increase the energy costs related to

evaporate water when ILs is recycled. Evaporating water may require more energy than evaporating the solvent. In such process design, the decision should then be aiming at to find the best operation condition: to which content the ILs should be diluted, and to which content more solvents should be used. This point should be identified by using cost-effective methods. It is not always to maximizing the R, but minimizing the energy use (process cost).

Effect of the amount of the solvent use

The amount of solvent used in the synthetic routs affects the process economics by the energy cost for heating, cooling and recycling the solvent and the cost related with capital investment. According to the energy consumption distribution for different process routes of synthesis HMF, the energy used for recycling solvents (evaporation and condensing) always covers more than half of the total energy consumption. Large amount of solvent used in the process leads to high energy cost. In addition, in the biphasic route, large amount of solvents used in the biphasic reactor results in a large volume required for the dehydration reactor (Chapter 6). The dehydration reactor is a pressurized reactor. For safety reasons, the size of the dehydration reactor is limited to a certain volume, based on the selected material. Many reactors are thus required due to a large volume in total. This makes the dehydration reaction the most costly part of the whole process. As discussed in Chapter 6, Figure 6.9 shows the effects of reducing the amount of solvent in the process route on the process economics. Reducing the amount of the solvent in the process design (specially the amount in the biphasic reactor) decreases the HMF production cost effectively (in terms of energy savings, capital investments, maintenance costs and so on).

However, as also mentioned in Chapter 6, the main role of the solvent in the biphasic dehydration reactor is not confirmed yet. There is no clear evidence that a reduced R_{HMF} or a reduced amount of the solvent in biphasic system will lead to a selectivity drop. Thus, if there is no clear effect on dehydration selectivity by reducing the amount of the solvent inside the biphasic reactor, it is more economically feasible to reduce the amount of the solvent used in the dehydration reactor and combine a second extractor to assure the designed extraction yield. One the other hand, if reducing the amount of the solvent inside the dehydration reactor decreases the selectivity, it then requires the detailed cost analysis. The aim is to see if the saved cost on energy and the capital can compensate for the increased cost of the reactant. As also shown in Figure 6.9, even with a reduced yield in dehydration reaction, reducing the amount of solvent can still decrease the HMF production cost to certain extent.

The amount of the solvent can also be reduced by increasing the stages in the liquid-liquid extractor. This method is applicable to both biphasic system and single-phase processes (eg. IL process) which use solvent to extract HMF from the reaction mixture. The capital investment for adding more stages in the extractor is low.

To sum up, using a solvent with a high R_{HMF} will definitely reduce the amount of the solvent needed for the process. However, as discussed before, solvents with a higher

R_{HMF} than MIBK will be more miscible with the aqueous solution. This may increase the difficulty in the downstream processing depending on the routes for HMF production. The overall effect of applying a solvent with a better R_{HMF} on the process economic needs to be evaluated. Some process routes (biphasic routes starting from fructose) may benefit from choosing a solvent with better R_{HMF} value. Some process routes may not benefit.

Effect of the second extractor

The second extractor here means adding the liquid-liquid extraction column in biphasic route after the biphasic reactor (eg. chemo-enzymatic process route proposed in Chapter 6 and the biphasic route proposed by Roman-Leshskov et al. (2006)). The overall yield is crucial to the HMF production cost. Thus, an efficient extraction yield is also important to keep the overall process yield high. Due to the low R_{HMF}, large amount of the solvent is required to reach a sufficient extraction. Large phase ratio requires high volume of the biphasic reactor resulting in a high capital investment and a high maintenance cost. In the chemo-enzymatic route described in Chapter 6, only 84% of the total produced HMF is extracted to the organic phase with the amount of MIBK which is 4 times the volume of the aqueous phase. The extraction yield inside the biphasic reactor is not satisfied even with this large amount of the solvent. If no extractor is used afterwards, the rest 16% of the produced HMF in the aqueous will be mixed with the feed of glucose and recycled back to the IGI reactor. The effect of HMF on the stability of glucose isomerase was examined with experimental work (Boisen et al., 2010). The remaining HMF in the aqueous phase (1 wt%) decreases the activity of the glucose isomerase from 392 B-IGIU/g to 364 B-IGIU/g. Although this effect is not so significant, the remaining HMF can further form humins with the glucose/fructose mixture (Antal et al., 1990), leading to both the HMF product loss and raw material loss. Since the investment of the second extractor is not high compared to the cost of other process units (Table 6.6, Chapter 6), investing on a second extractor after the dehydration reactor to extract the remaining HMF is benefited to the process economic. In addition, having the second extractor gives the opportunity to reduce the amount of the solvent used in the biphasic reactor.

The effect of the second extractor also depends on the way of designing the process route. For example, if a solvent such as THF (R_{HMF} is around 7.3) is applied as the solvent in the biphasic reactor with aqueous phase saturated with NaCl proposed by Roman-Leshskov et al. (2009), 96% of HMF will be extracted into the organic phase in the reactor (phase ratio between THF and aqueous is 3.2). The effect of the second extractor then becomes less important. However, if the R_{HMF} of solvent is not high or the amount of the solvent is reduced, the effect of having a second extractor will then become important.

8.1.4 Effect of the addition of acids

For dehydration reaction taking place in the aqueous phase, addition of acids into reaction medium increases the dehydration reaction rates (both fructose and HMF decomposition

rates). Fructose decomposition rate increases much faster than the HMF decomposition rate (Kuster and vad der Baan, 1977; Antal et al., 1990). Thus, addition of strong acids is one way to increase the selectivity of the dehydration reaction. Biphasic process route proposed by Roman-Leshskov et al. (2006) using 0.25 mole/l HCl as catalyst, the reaction time required is only 3 minutes at 180 ℃. Drawback with the addition of strong acids is the corrosion problem to the reaction equipment.

In the chemo-enzymatic route described by the Chapter 6, the catalyst is chosen to be NaCl. The proposed process intends to avoid the addition of acids given the condition that the aqueous needs to be recycled back to the enzymatic reaction. Although the reaction is also operated at around 180℃, the reaction time (30 mins) is much longer than that of the reaction with the addition of acids (3 mins). On the other hand, running the reaction at a higher pH reduced the possibility to form levulinic and formic acids (Kuster and vad der Baan, 1977). The byproducts formed during the dehydration reaction are mainly humins and soluble polymers. During recycle, humins and polymers can be removed. No major process step is required to remove the acids before the aqueous is recycled back to the enzymatic reaction. However, the total required volume of the dehydration reactor is then tremendous due to such a long reaction time. This leads to a much higher capital investment and a maintenance cost than that of the biphasic route using acids as catalyst. In addition, the selectivity is also better with the addition of acids.

If acid is added, the dehydration reaction rate would increase and the required reactor volume will decrease. In addition, improvement of the selectivity in dehydration reaction can also be obtained. In industry, the best operating condition for glucose isomerase is around pH 7.4. Any deviation from this point causes a change in stability and activity of the glucose isomerase, leading to more enzyme consumption. In order to maintain this pH, adding base to neutralize the added acid and the formed acids will then be required before recycling back the aqueous phase to the IGI reactor. As a consequence, the whole process starts to accumulate salt in the aqueous phase.

The salt effect on the stability of the glucose isomerase has been examined by the experimental work. Using NaCl up to 50g/l does not affect the glucose isomerase. In fact, this helps to increase the activity of the glucose isomerase a bit. This concentration is the concentration of salt applied in the chemo-enzymatic route. If the acid is added, the salt concentration would increase. It may cause more consumption of glucose isomerase which will increase the production cost. In addition, the whole aqueous phase will need to be completely removed after a certain time due to the accumulation of NaCl. This would increase the production cost as well. It makes the process operation inconvenient.

In sum, although the addition of acids to the dehydration reaction has some advantages, it does not seem to be feasible for the chemo-enzymatic route. This requires more research on the effects of salts on the glucose isomerase. The effect of adding acids in the aqueous phase on the HMF production cost needs to be evaluated.

8.1.5 Effect of the feed concentration

In general, a high sugar feed concentration favours the production of humins (Antal et al., 1990; Boisen et al., 2009; Yong et al., 2008). Using a low feed concentration helps to improve the selectivity for HMF in dehydration reaction. This has been approved in the aqueous systems, the aqueous-solvent systems, ionic liquids, the anhydrous solvent systems and sub/super critical systems. However, the feedback with a decreased concentration is a high consumption of energy for heating and cooling. It also leads to more solvent consumption while using the solvent to extract HMF from the reaction mixture. In addition, a high capital investment is also expected with a diluted system due to a big size of the equipment.

As discussed before, the yield of the dehydration reaction is the key point to the HMF production cost. In order to get a better yield (selectivity), the feed some times can not have a high concentration. A high feed concentration saves the cost on energy consumption, capital investment and the maintenance cost, but increases the cost of the reactant. It is hard to judge for all the process routes if a high concentration is better or a low concentration is better. This needs to be evaluated.

If the saved cost by increasing the concentration can pay back the loss in the reactant, then using a high concentration favours the process. In Chapter 7, the feed concentration effects on the HMF production cost were evaluated. For the examined IL process route starting from fructose, the HMF production cost at a high concentration is higher than that at a low concentration. For the examined IL process route starting from glucose, the HMF production cost with a high feed concentration is much lower than that with a low feed concentration.

Besides the feed concentration, dilution in the downstream also leads to high energy expenditure. The water route for thesis of HMF described in Chapter 5, has a very high-energy cost because of the high dilution from the use of chromatography for separation. Sometimes, the dilution may help to improve the efficiency of the downstream separation. For example, adding water into IL reaction mixture improves the efficiency of the HMF extracting process. The amount of the extracting solvent can thus be reduced. It can also help to precipitate the formed polymerization byproducts (Kuster, 1990).

Therefore, there is no straight answer to the concentration effects. The decision is a compromise for the whole process. If the gain by the dilution can not compensate the extra increased cost, dilution should be avoided. In the chemistry synthesis research, especially in the IL reaction development, most published results are for reactions at a very low concentration. Although the high selectivity is obtained in that way, it makes the scale-up very difficult.

8.2 Comparison of all the process routes

8.2.1 Chemo-enzymatic process (integration) versus biphasic process (non-integration)

The HMF cost of the biphasic route with salt from fructose is 1.23 USD/kg HMF. The cost is based on an overall process yield of 75% (mole yield). On the other hand, the overall process yield of the chemo-enzymatic route from glucose is 66% (mole yield). However, even with a lower process yield, the HMF cost of the chemo-enzymatic route is cheaper than that of the biphasic route with salt due to a cheaper price of glucose (Table 8.1).

Since the chemo-enzymatic route integrates together two different kinds of reactions (enzymatic reaction and chemical catalyzed reaction), the operation choice of the second dehydration reaction (biphasic route) is much more limited compared to the biphasic route directly from fructose.

First, the pH of the dehydration reaction medium in chemo-enzymatic route is limited to neutral. This also affects the choice of catalysts, meaning acids catalysts are not suitable in chemo-enzymatic route. Using acidic medium can help to improve the selectivity from fructose to HMF and accelerate the reaction rate. In spite of these advantages, addition of acids in dehydration reaction in chemo-enzymatic route is avoided. Because addition acids here requires adding base to neutralize the acids before the aqueous is recycled back to the enzymatic reaction. This leads to salt accumulations in the aqueous phase.

Second, the addition of NaCl in the aqueous phase in the dehydration reaction improves the R_{HMF} and reduces the miscibility of the solvent and the aqueous phase. However, the NaCl concentration in chemo-enzymatic route is only limited to 50 g/l (7 wt%) in aqueous phase in order to not affect the stability of the glucose isomerase.

Third, the choice of solvents in the biphasic reactor is very limited in the chemo-enzymatic route. This can be explained by two reasons. First, due to the sensitivity of the glucose isomerase to the solvent, very little amount of the solvent can affect the activity of the glucose isomerase. Therefore, the allowed concentration of the solvent in the aqueous phase is very little. Some solvents like alcohols are not allowed to appear in the aqueous phase. Second, due to the salt concentration here is limited to 7 wt%, many solvents that potentially can be applied in the biphasic route with salt can not be applied in the chemo-enzymatic route. In sum, if the solubility of the solvent in water (at 7 wt% of NaCl) is more than that of MIBK, extra step is required to remove the solvent before the aqueous is recycled to the enzymatic reaction. In addition, certain types of solvents that would harm the enzyme can not be applied unless it is very easy to remove it completely from the aqueous phase.

To sum up, the freedom of operating the biphasic reaction in the chemo-enzymatic route is limited compare to the biphasic route. The choices of the catalysts, the solvents and addition of salts are all limited to certain extent. As a result, at the same temperature, the rate of the dehydration reaction in the chemo-enzymatic route is much slower than that in the biphasic route. The overall process yield is also lower. With the presence of glucose in dehydration reaction, some of the glucose forms byproduct humins, leading to a reactant loss.

Despite all these discussed above, the chemo-enzymatic route is still superior to the biphasic route since it starts from a cheaper feedstock. It creates the opportunity for HMF synthesis in a cost-effective way.

Table 8.1. Comparison of biphasic route with addition of salt and chemo-enzymatic route for HMF production.

	HMF (biphasic route with salt)	HMF (chemo-enzymatic route)
Feedstock	Fructose	Glucose
Feedstock price (USD/kg)	0.50	0.30
Reaction steps	1	2
Catalyst	HCl	Glucose isomerase, NaCl for dehydration
Salt concentration	35 wt%	7 wt%
Dehydration temperature	180℃	180℃
Dehydration reaction time	3 minutes	30 minutes
Solvent choice	Many	Limited
Total mole yield	0.75	0.66
Raw material cost (USD/kg HMF)	1.02	0.71
Utilities cost (USD/kg HMF)	0.21	0.36
HMF cost (USD/kg)	1.23	1.07
Operation freedom	High	Low

8.2.2 Comparison of all the routes for HMF production

According to the HMF production cost distribution (Chapter 6 and Chapter 7), the raw material and energy cost in all these cases covers over 70% to 80% of the whole production cost. Therefore, the raw material and energy cost (HMF cost) is the key factor in determining the economic feasibility of the production route at the early stage. The HMF cost of the potential routes that has been evaluated before is plotted in Figure 8.5.

In Figure 8.5, the highest HMF cost is obtained by using solvent based synthetic route (DMSO route). By adding the salt into the biphasic reactor, the HMF cost of the biphasic route is decreased from 1.46 USD/kg HMF to 1.23 USD/kg HMF. The HMF cost is further reduced to around 1.07 USD/kg HMF using a chemo-enzymatic route to produce HMF from glucose. By assuming that the IL and the catalyst can be recycle for around 150 times, the HMF cost is around 1.21 USD/kg HMF for a low feed concentration (17 wt%) of fructose and 1.25 USD/kg HMF for a high feed concentration (50 wt%) of fructose. The HMF cost of the IL route is reduced to 1.06 USD/kg HMF if it starts from

glucose (17 wt%). If the glucose concentration is increased to 50 wt%, the HMF cost is then reduced to around 0.80 USD/kg HMF.

Using the PTA cost (1 USD/kg) as a selection criterion, none of the process routes starting from fructose can reach the criterion due to a high cost of the fructose. On the other hand, the HMF cost from all process routes starting from glucose is around this criterion.

For process routes starting from fructose, the IL route does not seem much superior to other conventional routes. The HMF cost of the IL route from fructose is around 1.2 USD/kg HMF which is quite similar to that of the biphasic route with salt. In addition, the obtained HMF cost of the IL route is based on the assumption that the IL can be reused for around 150 times.

For process routes from glucose, using IL route with a low glucose concentration is also not superior to the conventional route (chemo-enzymatic route). However, with a high glucose feed concentration (50 wt%), IL route is much more promising than other routes.

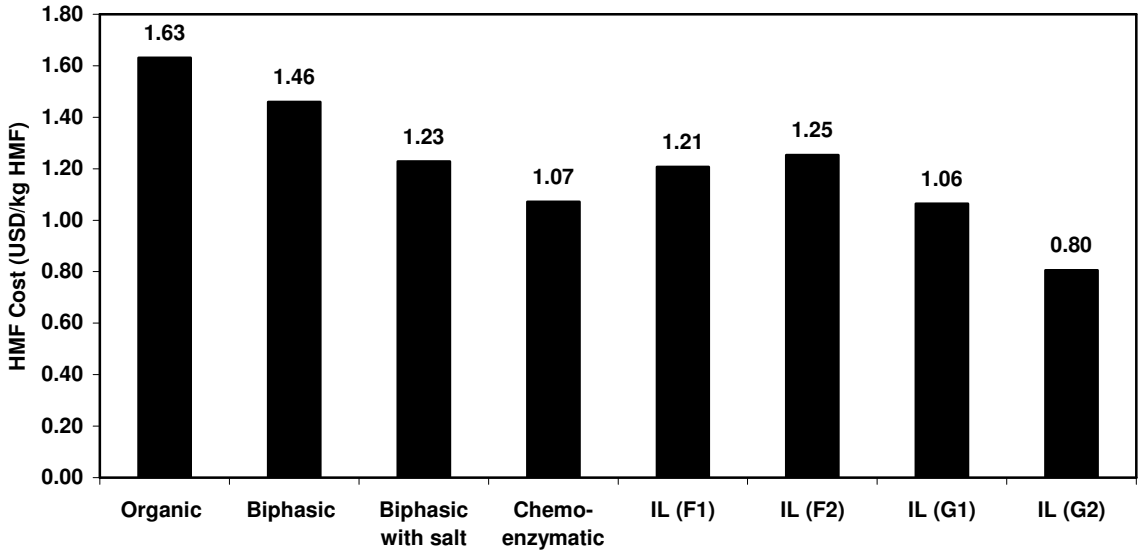

Figure 8.5. Comparison of the HMF cost (raw material and energy cost) of the organic route, biphasic route, biphasic route with salt, chemo-enzymatic route and IL route with different options.

8.2.3 Glucose price

The effect of the glucose price on the HMF cost of all the different routes has also been investigated. Since fructose is commercially produced through glucose by the glucose isomerasion process, fructose price is dependant on the glucose price. With the current

price of glucose (0.3 USD/kg) and fructose (0.5 USD/kg), it is assumed that the fructose cost is equal to the glucose cost (0.3 USD/kg) plus the process cost (0.2 USD/kg).

The variation of the glucose price is from 0.21 USD/kg (decreasing by 30% from the base price 0.3 USD/kg) to 0.39 USD/kg (increasing by 30% from the base price). The relative range for the fructose price variation is then from 0.41 USD/kg to 0.59 USD/kg. The HMF cost with the variation of the glucose price for all the potential routes is shown in Figure 8.6. Clearly, the HMF cost for all the routes is highly affected by the glucose price.

In the future, with the increasing production of biomass, the amount of sugar production is most likely going to increase, especially in Brazil (USDA, 2011). The price for starch may decrease with the increased amount of starch production. On the other hand, with the increasing maturity of the technology, the process cost pertaining to the hydrolysis of starch may also decrease. All this can bring down the price of glucose. With the decreasing price of the glucose, process routes from glucose can all meet the requirement and all have a great potential to compete with the oil-based chemicals. However, for process routes from fructose, the HMF cost still cannot meet the requirement even if the glucose price is lowered to 0.21USD/kg.

Conversely, if the demand for the sugar (in the future) increases faster than the increasing production rate, glucose price may also increase. With an increase in the glucose price, most of the process routes can not meet the selection criterion. But the IL route with a high glucose concentration still indicates great potential. Even with a glucose price of 0.39 USD/kg, the HMF cost is still less than 1 USD/kg. The IL route opens a great opportunity for the bio-based chemicals to compete with the oil-based chemicals. By using IL route, HMF can also be produced from cheaper raw material such like starch and sucrose.

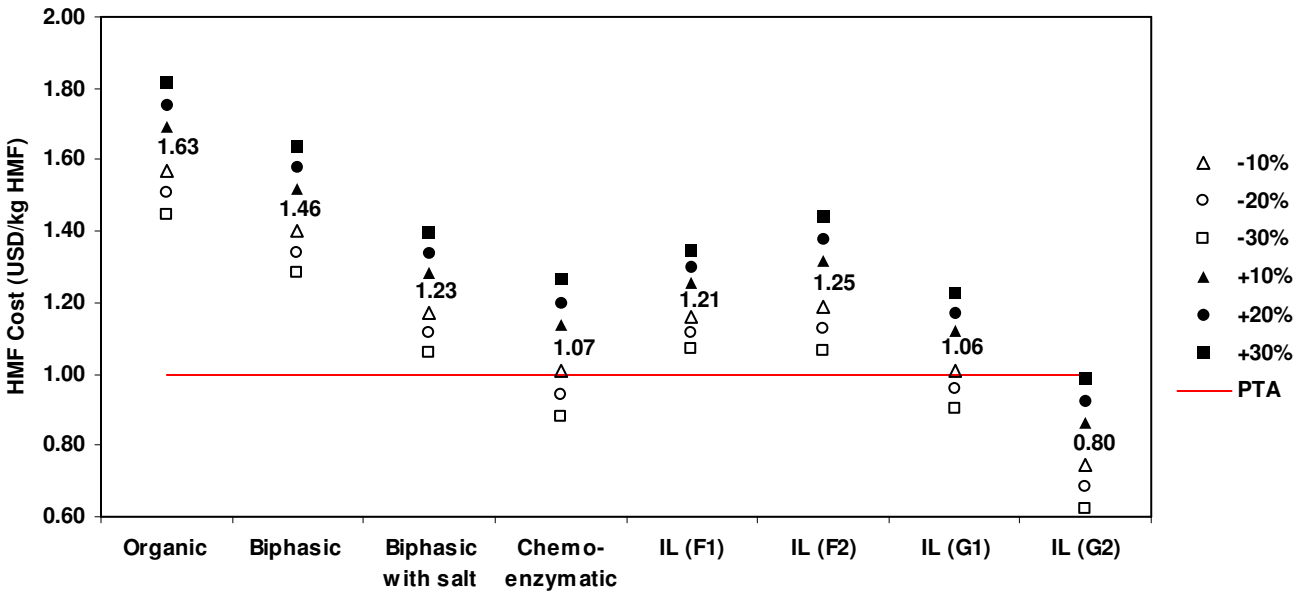

Figure 8.6. Effect of the glucose price on the HMF cost of different routs.

8.2.4 Future improvements

Besides bringing down the price of the glucose, reducing the HMF cost can also be achieved by increasing the dehydration reaction yield and optimizing the use of the solvents.

Since for most of the process routes, the conversion is quite high (over 90%) except for the biphasic route. However, since the unconverted sugar in all the routes is fully recycled, the reaction yield is actually equal to the selectivity. Therefore, the effect of the reaction yield on the HMF cost is examined by varying the selectivity. Better solvent here means better use of the solvent thus the energy used for the solvent evaporation, condensing and recycle can be reduced. This can be achieved by optimizing the amount of the solvent used in the process or using alternative solvents that have a better R_{HMF} (in some cases), so that the total amount of solvent in the process can be reduced. In addition, it also means using alternative solvents, which has a lower boiling point. In this way, the energy for the solvent evaporation, condensing and recycle can be reduced. The effects of using the mentioned approaches to reduce the HMF cost are shown in Figure 8.7 to Figure 8.9.

Clearly, increasing the selectivity of the dehydration reaction is the most important factor to break down the HMF cost. For some routes that already have a very high selectivity, increasing the selectivity by 10% already leads to a value of 1. In that case, the HMF cost is calculated with a selectivity of 99%, when the selectivity exceeds 100%. The effect of the selectivity on the HMF cost is bigger than the effect of glucose price. The better

solvent approach (reducing the energy for evaporation, condensing and recycle the solvent to reduce the HMF cost) is not as significant as the other two approaches.

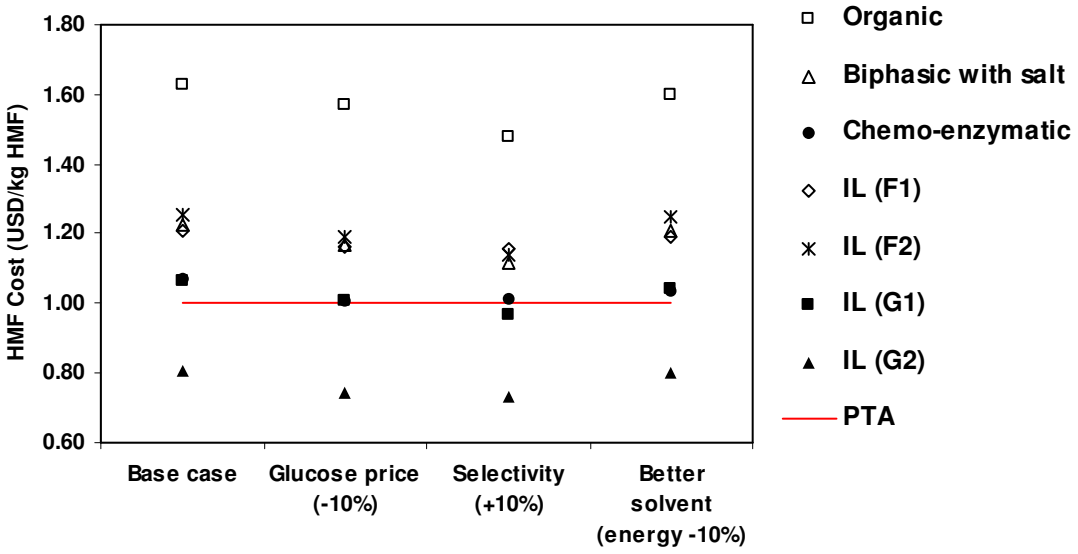

Figure 8.7. Plot of the future improvements of different parameters to the HMF cost (glucose price reducing by 10%, dehydration selectivity to HMF increased by up to 10% and the energy for evaporation and solvent recycle reduced by 10%).

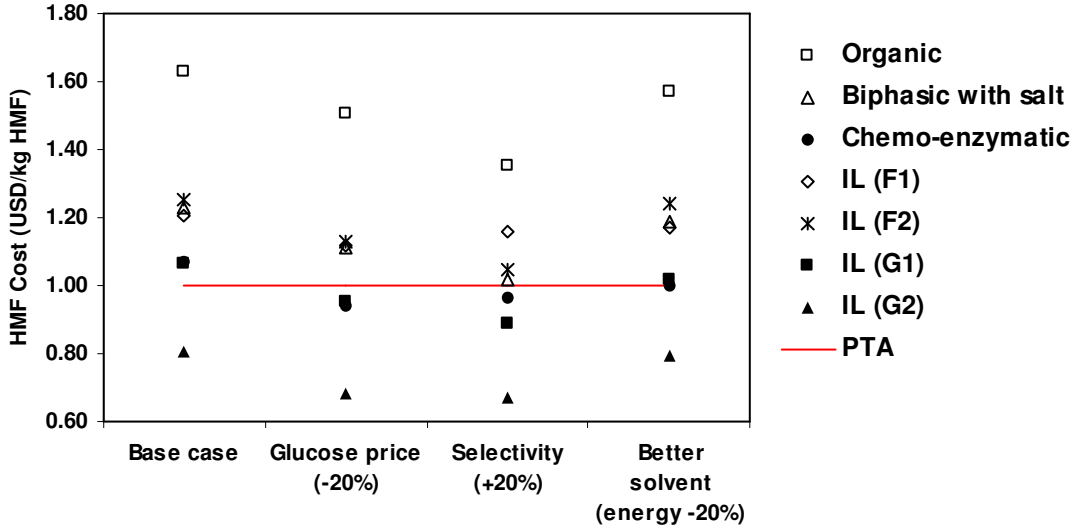

Figure 8.8. Plot of the future improvements of different parameters to the HMF cost (glucose price reducing by 20%, dehydration selectivity to HMF increased by up to 20% and the energy for evaporation and solvent recycle reduced by 20%).

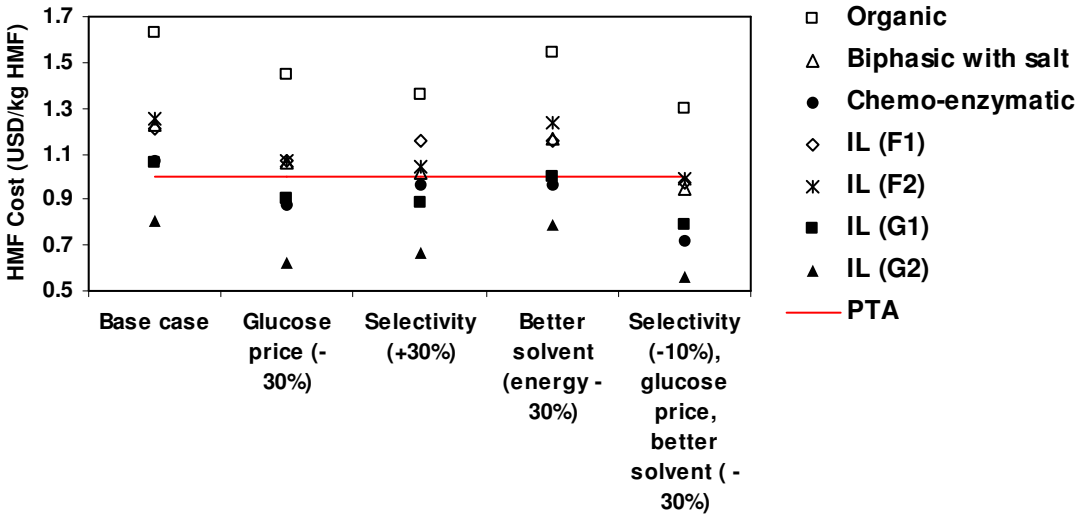

Figure 8.9. Plot of the future improvements of different parameters to the HMF cost (glucose price reducing by 30%, dehydration selectivity to HMF increased by up to 30% and the energy for evaporation and solvent recycle reduced by 30%).

By increasing the selectivity of the dehydration reaction by 10%, HMF cost by all the routes from glucose is below 1 USD/kg. Further improving the selectivity up to 30%, the biphasic route with salt from fructose can also meet the criterion. On the other hand, the IL route from fructose can not meet the criterion even if the selectivity is up to 99%. This indicates the research effort in the future should be placed on improving the selectivity of the process routes from glucose. Specially, in most of the process routes here, the selectivity of the process routes from glucose are lower than that of the process routes from fructose. For example, the selectivity of the IL route with a glucose concentration of 50 wt% is only 70%. There is still a lot of room to improve this selectivity.

Conversely, even with a selectivity of 99%, the HMF cost of the most promising process route from fructose (biphasic route with salt) is still up to 0.97 USD. Process routes from fructose are limited by a high fructose price. In the future, if a cheaper way of producing fructose appears (eg. inulin process), process routes from fructose will then be able to be competed with the PTA process.

The energy use for all the routes has not been optimized yet. The use of the solvent for all the routes has also not been optimized yet. Therefore, it is possible for all the routes to reduce the energy used in evaporation, condensing and recycle the solvent by 30%. If the selectivity of all the routes can be increased by 10%, together with the price of the glucose reduced by 30%, most of the process routes can reach the criterion (last row in Figure 8.9) except for the organic solvent route (DMSO route). In this ideal situation, the HMF cost of the chemo-enzymatic route is around 0.72 USD/kg and the HMF cost of the IL route with a glucose concentration at (50 wt%) is around 0.56 USD/kg.

8.2.5 HMF, FDA versus PTA

Of all the examined process routes from fructose, the biphasic route with salt is the most promising process. Although, the HMF cost by the IL route (F1) indicates a similar cost with 0.02 USD/kg cheaper, the HMF cost of the IL route is based on the assumption that IL can be reused for 150 times. In addition, the HMF cost of the IL (F1) is obtained at a selectivity of 96%. The room to improve the selectivity of this route is much less than that of the biphasic route with salt (Figure 8.7 to Figure 8.9.). The chemo-enzymatic route and the IL route from glucose with a high concentration (G2) are the two most promising routes for HMF production. The current HMF cost of the biphasic route is 1.23 USD/kg. The HMF cost of the chemo-enzymatic route is 1.07 USD/kg and the HMF cost of the IL route (G2) is 0.80 USD/kg.

Assuming a total process yield of 96% from HMF to FDA, and a process cost of 0.1 USD, the FDA cost based on the HMF from the biphasic route with salt is around 1.13 USD/kg FDA. If the HMF is produced by the chemo-enzymatic route from glucose, the FDA cost is around 1.00 USD/kg. The FDA cost can be decreased to 0.77 USD/kg by using the IL route for HMF production (Table 8.2). A high oxidation yield up to 99% has already reported (Casanova et al., 2009; Gorbanev et al., 2009). Therefore, a total process yield of 96% from HMF to FDA in the near future is possible to reach. On the other hand, the temperature of the oxidation reaction is not as high as the dehydration reaction. FDA mostly is isolated by precipitation by adding acids. Therefore, the energy consumption should be much lower compared to the energy cost of the dehydration process. Major reactant apart from HMF is the oxygen. Using air to supply the oxygen is also quite cheap. Therefore, the other major cost apart from HMF cost is mainly the cost of acids, base and the oxidation catalyst. The assumption of a process cost of 0.1 USD/kg should be reasonable to reach in the future.

The PTA cost by bromine-promoted air oxidation from p-xylene is around 1.05 (Table 8.2). The cost is based on a p-xylene price of 1.25 USD/kg and a total process yield of 94% (mole based yield). From p-xylene (106 g/mol) to PTA (166 g/mol), there is a weight gain making the mass yield around 1.47 kg PTA/kg p-xylene. On the other hand, from glucose/fructose (180 g/mol) to HMF (126 g/mol), there is a weight loss. In addition, the total process yield of all the three routes is all around 66% to 75%, which is much lower compared to the process yield of PTA. For all the three process routes, around 2 kg of sugar can make 1 kg HMF.

The utilities cost of PTA process is much lower compared to that of all the HMF routes. In the PTA process, p-xylene is oxidized to PTA in the acetic acid with a cobalt-manganese-bromine catalyst. The crude product is recovered by evaporation together with crystallization. However, in all the HMF routes, the HMF is not recover directly from the reaction medium but extracted by an organic solvent from the reaction mixture, then recovered by evaporation. Due to the low R_{HMF}, large amount of the solvent is used, leading to a high energy consumption. However, as mentioned before, the process routes for the HMF production have not been optimized yet. Energy integration as well as

optimizing the solvent use has not been done yet. There is still a lot of room to improve the utilities cost.

In sum, the PTA process is a well developed industry process. The overall yield is around 94%, which is very high. On the other hand, the three routes for the HMF production are still in the laboratory scale. Especially, the chemo-enzymatic route and the IL route for HMF production form glucose are very new processes. The overall process yield from these two routes is still very low. There is a large room in the future for these two routes to improve and the HMF cost can be further reduced. Even though, the HMF cost is around 1.07 USD/kg of the chemo-enzymatic route and 0.80 USD/kg o f the IL route. If FDA can be oxidized from HMF with a process yield of 96% and a process cost of 0.1 USD/kg, the FDA cost is quite close to the PTA cost (Table 8.2). The FDA oxidized from the HMF made by the IL route has an even lower cost compared to the PTA cost. This indicates a great potential of using FDA to substitute parts of the PTA in the future.

In addition, FDA (HMF) production is based on a renewable and a CO_2 neutral resource. The FDA (HMF) process contributes to a CO_2 reduction in the future if FDA subtitles parts of the PTA production. PTA is produced from p-xylene, which is based on oil-refinery. The feedstock for PTA production is not renewable and not CO_2 neutral. In the future, with the decreasing oil resource, the price of p-xylene is most likely going to increase. Together with the increasing the maturity of the technology, the FDA (HMF) process will be more competitive to the PTA process.

Table 8.2. Comparison of the PTA process with the HMF process routes.

	PTA[a]	HMF (biphasic route with salt)	HMF (chemo-enzymatic route)	HMF (IL route-G2 option)
Feedstock	p-Xylene	Fructose	Glucose	Glucose
Feedstock price (USD/kg)	1.25	0.50	0.30	0.30
Total mole yield	0.94	0.75	0.66	0.71
Total mass yield (kg product/kg feedstock)	1.47	0.53	0.46	0.50
Raw material cost (USD/kg)	0.90	1.02	0.71	0.67
Utilities cost (USD/kg)	0.10[b]	0.21	0.36	0.13
Total cost (USD/kg)	1.00	1.23	1.07	0.80
Potential product cost (USD/kg)	1.00	1.13	1.00	0.77
Renewability	No	Yes	Yes	Yes
CO2 contribution	+	-	-	-

[a] Data taken from the year book 2008 of PTA process from p-xylene by bromine-promoted air oxidation. The detailed data can be found in the Appendix.

[b] The original utilities cost by PTA was 0.14USD/kg in the year book 2008 (Appendix). This was calculated based on a higher steam, cooling water and electricity cost compare to the calculation of utilities cost of HMF production routes. Therefore, the utilities cost of PTA was recalculated using the same utility cost as HMF routes.

8.3 Methodology

The methodology developed in this study is quite useful to give a fast evaluation of different process options based on the limited information. The methodology is very useful to find out where is the bottleneck of the different process routes. Thus, it provides a research focus and it directs the research. Some limitations of this developed methodology are pointed out here.

8.3.1 Lack of data and information

In the application of the developed methodology, data and information collection is a difficult step. However, such information is always required since it is the basis for the mass and energy calculations.

In the evaluation of the HMF process options, since most of the chemicals involved are relatively new chemicals compared to the oil based chemicals, their property data, thermodynamic data are not always available in the literature. The property predication tools (such as Propred in ICAS) are developed from the database based on the oil-based chemicals. Using these predication tools to generate the missing property data for chemicals from renewables is possible. However, the predication is not always satisfied. The process simulator software ProII requires a lot of input data for simulation. This makes it hard to use the software to simulate the process flowsheet because of the missing data.

Due to the lack of the property data, a shortcut model was used to simulate some of the process steps (e.g. liquid-liquid extraction). The shortcut model is useful for the energy calculation. But it requires the information of all the process data of streams that enter and leave the process unit. This means experiments are required if these data can not be obtained from the process descriptions in the literature. In addition, the published process data in the literature is always based on one condition. The effects of the operating parameters such as temperature, pressure and the solvent amount on the mass and energy balance in the unit operation can not be modelled in such situations. Experiments are thus required.

In the present process software such as ProII, most of the thermodynamic model is not valid for modelling the system with salt. This means that the salting-out effects in the solvent extraction or the biphasic system can not be predicated or modelled. In addition, if the R_{HMF} between the solvent and the aqueous phase is not published, the extraction process can not be simulated or calculated. In this work, the generated ternary phase diagram by ICAS for the MIBK-HMF-water is not good enough to describe the system.

Furthermore, due to the lack of the kinetic information and insight of the solvent effects on the dehydration reaction, the application of different solvents as co-solvents in the

dehydration reaction can not be modelled. All the simulations in the HMF process routes are using the published data or experimental data as input.

Collection of the property data related with the IL system is another difficult issue, especially for the IL and sugar mixture. In addition, relative thermodynamic system which can be applied for simulating the IL system is also missing. The IL system was evaluated mainly based on the published literature data and the experimental data. Most of the calculations related with the IL system was performed in the spreadsheet in excel not in the simulation software.

8.3.2 Environmental evaluation

In the methodology, the E-factor is used as the environmental metric as a quick evaluation in the environmental aspect. During the evaluation of the HMF production processes, all the evaluations are based on the assumption that all the streams are recycled. The E-factors of all the process routes meet the requirement for the bulk chemicals. The E-factor can give a quick idea of how much waste is produced in the route and a quick assessment of the efficiency of the use of raw material. However, the E-factor does not distinguish the waste type in the waste. The toxicity and the environmental effect (e.g. CO_2 contribution if the stream is sent to incineration) can not be evaluated by the E-factor. For example, the negative effect of a stream containing the organic solvent on the environment is worse than that of a stream that only contains water and salt.

Alternative metric of the E-factor can be Life Cycle Assessment (LCA). LCA is a standardised methodology (ISO, 1998) used for assessing the environmental impact of a product including the full life cycle from cradle-to-grave as well as the impact during its use-phase. It is crucial to identify the step in a product's life cycle that has the highest impact on the environment so that the efforts for improvements can be focused there and to avoid shifting the environmental burden of one phase into another. However, as discussed in 8.3.1, the data collection for evaluating is always a difficult step. Application of LCA in the early stage of the process development is hard to be implement because of the limited availability of data and decisions. For example, regarding allocation of environmental impact between products and side-products can make it a time consuming task.

However, despite the difficulties in getting data, it is important to design environmental metrics for evaluating process options at the early stage, so that the toxic substance that pose problems to the environment can be avoided at the very beginning of the process development.

A supplement to the E-factor is the climate factor or the C-factor introduced by Christensen et al. (2008). In the C-factor, the amount of CO_2 produced is taken into account for a chemical process, providing a number that reveals its renewability:

$$\text{C-factor} = \frac{\text{kg CO2}}{\text{kg product produced}} \qquad \text{Equation 8.1}$$

This could be further added into the environmental metric for evaluation.

8.3.3 The HMF cost and the HMF production cost

Both of the HMF cost and the HMF production cost are used as the economic metrics in the process evaluation. The HMF cost, which is a part of the HMF production cost, only take accounts of the raw material and the energy cost. The HMF production cost contains also the capital investment, the labour cost, the maintenance cost, plant overhead cost, the operating cost and so on. In most of the case, the HMF cost covers over 70% of the HMF production cost and determines the HMF production cost. Therefore, in most of the cases, the evaluation results obtained by using the HMF cost are the same as that by the HMF production cost.

However, since the HMF production cost is more detailed than the HMF cost. It gives other insights into the evaluation. For example, the dehydration reaction time for the biphasic route from fructose is 3 minutes. The dehydration reaction time is around 30 minutes for the chemo-enzymatic route. This affects the required size of the dehydration reactor. The dehydration reactor of the chemo-enzymatic route is much bigger than that of the biphasic route. The biphasic dehydration reactor is a high-pressurized reactor and it is one of the most costly equipment in the whole process flowsheet. In addition, there is extra capital investment in the chemo-enzymatic route for the isomerisation reaction. Therefore, the total capital investment in the chemo-enzymatic route is much higher than that in the biphasic route. As a consequence, in all the HMF production cost, the cost related with the capital cost as well as the labour cost of the chemo-enzymatic route is higher than that of the biphasic route. Conversely, the HMF cost does not really reflect the differences in the reaction time and the total required size of the process equipment.

In addition, the amount of the solvent used plays a big effect on the HMF production cost of the chemo-enzymatic route. The HMF production cost decreases from 1.46 USD/kg HMF to 1.25 USD/kg HMF (Figure 6.9). Figure 6.9 also indicates that where to reduce the amount of the solvent in the chemo-enzymatic route is crucial to the total capital investment. This can not be reflected so detail in the HMF cost.

8.3.4 Sensitivity analysis

The sensitivity analysis of the parameters to the HMF cost (HMF production cost) in this thesis was done by the variation of one parameter at a time. The sensitivity analysis of the selectivity and the conversion of the dehydration reaction to the HMF production cost were done by varying one of them with the assumption that there is no effect to the other

(Section 8.1.1). The sensitivity analysis at this point is limited by the lack of kinetic model and detailed process knowledge.

Another example is the solvent effect on the HMF production cost of the chemo-enzymatic route. When the amount of the solvent in the biphasic reactor is reduced, the consequent effect on the dehydration reaction (selectivity and conversion) can not be quantified due to a lack of the knowledge in the role of co-solvent in the dehydration reaction. All these lack of knowledge limit the use of the sensitivity analysis.

Concluding remarks

In this chapter, the most important issues related with all the process routes for the HMF synthesis are discussed. Comparisons of different process routes are also discussed. Finally, the limitations of the methodology are mentioned. The next chapter concludes all the important issues mentioned before.

9 Conclusions

In this chapter, all the important issues mentioned before and the central conclusions are shown here.

9.1 Process

In this work, process design and evaluation of the synthesis of 5-hydroxymethylfurfural (HMF) from the renewable feedstock glucose/fructose was selected as an example of process design and evaluation of the chemical production from the renewable resource. The selected example is part of the chemo-enzymatic process design for producing 2,5-furandicarboxylic acid (FDA) from glucose. By using the selected case study, the complexity and the challenges to choose between different alternative routes and technologies as well as to combine the two different kinds of catalytic methods (enzymatic catalysis and chemical catalysis) at the early stage of the process development were illustrated. The central conclusions attained during these evaluations are presented here.

9.1.1 Dehydration fructose to HMF

The development of dehydration of fructose to HMF in literature has been reviewed in the view of process development. By going through the major publications in dehydration of sugar to HMF, most researches have mainly focused on the dehydration reaction development: catalyst screening in different reaction mediums. Most of the researches are mainly batch experiments. Very few publications have investigated the reactor selection, downstream separation and the continuous process design for production of the isolated pure HMF.

Based on the reaction mediums that have been investigated so far, dehydration fructose to HMF is divided into five categories: aqueous system, aqueous-solvent system, anhydrous system, sub/super critical system and ionic liquids. The corresponding downstream schemes for isolating HMF and recycling the reaction medium, process solvent as well as the unconverted sugar has been proposed based on the published methods. In addition, the potential integrated process flowsheets for production HMF from fructose are proposed.

9.1.2 Conventional process routes for HMF production from fructose

The synthesis of HMF from fructose by using the aqueous route, the anhydrous solvent route and the biphasic route were evaluated by simulating the published process flowsheets in literature. The examined water route has a very high reactant and energy cost due to a low dehydration yield and an extremely high dilution in the downstream processing.

Both the organic solvent route (DMSO route) and the water-solvent route (eg. biphasic route) are much more superior to the water synthetic route. Both of the two routes have much higher reaction yields compare to the water route. The energy consumptions of these two routes are also much lower than that of the water route. Therefore, the DMSO route and the biphasic route have better usability of both raw material and energy.

By completely avoiding water in the reaction medium, DMSO route shows better performance in the dehydration yield than the biphasic route. But recycling DMSO is difficult and requires high-energy consumption. The energy used to recycle the solvent in the biphasic route is less than that required for the DMSO route, although the amount of the solvent used in the biphasic route is much more than that in the DMSO route. Both of the two routes have similar HMF cost. Using biphasic route offers a better opportunity to be integrated into the chemo-enzymatic production of FDA from glucose.

9.1.3 The chemo-enzymatic route for HMF production from glucose

After identifying the reaction medium for the dehydration reaction, a process flowsheet of using the chemo-enzymatic route for HMF production from glucose was proposed and evaluated. The process flowsheet is characterized by using the glucose isomerase to convert glucose into fructose with a biphasic route for dehydration of fructose into HMF. After using MIBK to extract HMF, the aqueous phase that is rich in unconverted glucose is recycled back to the enzymatic reaction.

Based on the mass and energy calculation, the HMF cost by the chemo-enzymatic route is around 1.07 USD/kg HMF. Based on a production scale of 250,000 tons HMF per year, the total capital investment is around 196 million dollars. The HMF production cost of the base case is around 1.48 USD/kg based on a glucose price of 0.3 USD/kg. The HMF production cost is very sensitive to the dehydration reaction yield, the amount of the solvent used in the whole process and the glucose price. Reducing the amount of the solvent to half amount of the solvent used in the base case can decrease the HMF production cost to around 1.21 USD/kg. In addition, increasing the production scale of the base case design to around 2 500 000 tons HMF per year, the HMF production cost can be further decreased to around 1.30 USD/kg.

9.1.4 The IL route for HMF production

Recently, using ionic liquids (ILs) for the HMF synthesis has gained increased attention. Examples in the literature on scale-up and process development on the topic are, however, still scarce. By summarizing what has been achieved by using IL for the HMF synthesis from sugar of this new catalytic system, potential process flowsheets for using ILs for the HMF synthesis from sugar have been proposed.

The potential IL process flowsheet for the single phase reaction system was evaluated with different options starting from fructose and glucose with different initial concentrations. The HMF cost and the HMF production cost of the IL route is highly affected by the number of reuses of the IL and the catalyst. Processes with a high feed concentration show better economic potential than processes with a low feed concentration. IL processes starting from fructose are more expensive than IL processes starting from glucose due to a higher cost of fructose than glucose.

The IL route from glucose with a high feed concentration shows the best economic potential.

9.1.5 Most important issues in the HMF production processes

Dehydration yield

For all the process routes, the dehydration yield highly affects the HMF cost. It plays the key important factor for the HMF production process to achieve a feasible cost. Both the conversion and the selectivity are important to the HMF cost. The selectivity affects the HMF cost more than the conversion when the unconverted sugar is recycled. How to maintain a good selectivity at a high conversation rate is essential for the HMF to be produced in a cost-effective way.

Use of organic solvent

The use of the organic solvent cannot be avoided due to the instability of HMF in water during the dehydration reaction condition. The amount of the solvent used in the process routes affects the HMF production cost. How to optimize the solvent amount and reduce the solvent use is very important to the process economic.

Recycle

Recycling (unconverted sugar, reaction medium and solvent) ís another key issue for the HMF production processes to achieve a low production cost. Especially, the feasibility of using the IL route for the synthesis of HMF in a large scale is completely dependent on the recycle and reuse ability of ILs system.

Concentration

A low concentration results in a high energy cost and a high capital investment. However, a high concentration might reduce the selectivity. Therefore, a comprise concentration should be used which favours the HMF production cost most. In addition, dilution in the downstream should be avoided since it costs energy to concentrate the dilution. Sometimes, this can be very critical to the production cost.

9.1.6 Most promising routes

The biphasic route with the addition of salt is the most promising route for HMF production from fructose. However, this process route is still not cost-effective due to a high fructose cost (0.5 USD/kg).

Process routes for HMF production from glucose show better economic potential than process routes from fructose. HMF can be produced in a cost effective way by using the chemo-enzymatic route or the IL route (option G2). A potential FDA cost around 1 USD/kg from HMF by the chemo-enzymatic route and 0.77 USD/kg from HMF by the IL route is possible to be obtained. Both of the two routes still have a lot of room to improve and have a great potential to compete with the PTA process.

In conclusion, HMF (FDA) can be produced by an economical feasible way and has a great potential to compete with PTA. The research efforts should be placed on:

The chemo-enzymatic route

- Improve the dehydration selectivity
- Optimize the reaction rate
- Optimize and reduce the use of the solvent in the process

The IL route

- Investigate on the recycling and reusability of the IL and the catalyst system (up to 150 times)
- Improve the dehydration selectivity for options from glucose with a high concentration

If the IL system can afford to be reused up to 150 times, the IL based process route is the most promising process route for HMF (FDA) production. In addition, the choice of the feedstock could be expanded to even cheaper bioresources such as the glucose polymers cellulose and starch. These can be dissolved in ILs (unlike in organic solvents and water) and be directly converted to HMF. The use of such feedstocks might lower the cost even further.

9.2 Methodology

A methodology framework for aiding process design and evaluation at the early stage of a new process development has been proposed in this thesis. The proposed methodology gives a good overview of the whole production process and is able to evaluate the process in a systematic way.

It is important to apply modeling and costing at the early stage of the process development. By doing this, the methodology is able to use the limited information to give a fast evaluation. It helps to understand the problems in the whole process design and can identify the important issues related with the process development at the early stage. Therefore, the methodology reaches its aim, which is to direct the research.

The bottleneck of applying the methodology for process design, especially for the bio-based process design, is the data and information collection. Applying the model requires basic property data, certain thermodynamic data and so on. This is especially critical for chemicals from the renewable resources due to the lack of the published property data.

Both the HMF cost and the HMF production cost are useful economic metrics. For screening process routes, only HMF cost is sufficient enough. However, for analyzing important process issues of the potential process route, the HMF production cost is more useful since it contains capital cost and reflects more information.

The environmental metric by the E-factor is useful but not enough. Developing other environmental metric is needed.

Despite some limitations, the methodology is very useful and can be applied to other chemical process design and evaluation.

10 Future Work

Based on the discussion and conclusions, some future work is pointed out here.

10.1 Process

10.1.1 Completely understanding the kinetic mechanism

In order to obtain a good selectivity at a high conversion, completely understanding the dehydration kinetic mechanisms of all the reaction systems is very important. Up to now, the published kinetic models are only for the aqueous and the sub/super critical aqueous system. It is generally agreed that the dehydration fructose to HMF and HMF decomposition is a series of the first order and the higher order reactions. However, due to the difficulty in fitting the parameters, the published models are treated as the first order models and cannot describe the whole dehydration process.

Therefore, it is still the lack of the overall assessment of parameters that affect the selectivity and conversion of the dehydration reaction. The reaction is yet to be optimized and relative reactor design has not been investigated much. However, these become more and more important to be sorted out.

Only by completely understanding the kinetic and the mechanism, suitable reactors can be designed. In addition, the best operation conditions can be found out. Through this, a good yield of the dehydration reaction can be reached and the HMF can be produced in a cost-effective way.

10.1.2 Completely understanding the effect of the solvent in the dehydration reaction

Up to now, the solvent effect on the dehydration reaction is still unclear. A kinetic model that could describe the solvent effect does not exist.

Adding water miscible polar solvent into the dehydration reaction is believed to improve the dehydration selectivity by decreasing the relative water activity (Kuster, 1977; van Dam et al., 1986; Antal et al., 1990). However, it is also found that not all the water miscible solvents have the same effect. Solvents which promote the fructose in the

furanoid form of fructose favour the formation of HMF (Bicker et al, 2003; Bicker et al, 2005). Using the biphasic system to improve the selectivity is explained by keeping the HMF inside the organic phase so that it stops HMF from decomposing. However, the selectivity to HMF is not directly linked to the R_{HMF}.

All these motioned issues have not been completely understood. However, it becomes more and more important to investigate all these issues. Because the use of the solvent affects the HMF production cost. Only by real understanding of the solvent effects on the dehydration reaction, favourable solvent type can thus be identified. And finally, the aim to optimize and reduce the amount of the solvent in the whole process can be reached.

10.1.3 Investigation of the reusability of the IL medium

The IL route showed very promising potential for HMF production in a large industrial scale. The HMF production cost is highly dependent on the times of recycle of the IL system. Although the recycle of ILs together with catalysts have been investigated, the reported recycle times is only around 6 or 7 times which is far away from the requirement for industrial scale up. Investigation of recycling the IL reaction medium up to 150 times is required.

10.1.4 Investigation of the IL route from glucose with a high feed concentration

The recent research in using the IL route for the synthesis of HMF always uses very low feed concentration. In the future, researches should put more emphasis on understanding the kinetics of decomposing sugar in the IL, so that a good selectivity can be obtained even with a high feed concentration.

10.1.5 Purity of HMF

The required purity of the HMF will highly be dependent on the use of the HMF. HMF is the intermediate compound for several important compounds. Therefore the requirements may vary with the final use of the HMF. For example, if the final use of the HMF is to make biofuels, the required purity may be low. On the other hand, if the use is for polymerization via oxidation to 2,5-furandicarboxylic acid, the purity of the final HMF maybe very high. The investigation of use of the HMF for different purpose and the requirement of the purity of HMF products needs to be investigated. This is crucially important since this will form the base for the process design. Directions in this area is still scare and requires more efforts.

10.1.6 Humins values

The formation of the polymerization byproducts seemingly cannot be avoided in most of the process routes. Investigations on how to efficiently remove the formed the soluble polymers as humins are required. Also, investigating on the potential value and the use of humins for energy supply will be useful to compensate the HMF cost.

10.2 Methodology

10.2.1 Developing data base and property predication tools for bio-based chemicals

Using simulation and modeling to aid the process design and to reduce the experiments is limited by the lack of the relative property and thermodynamic data. This is a general problem for most of the chemicals from the renewable resources. Developing a data base for bio-based chemicals is important and useful. In addition, developing property predication tools and methods for bio-based chemicals will be very helpful.

10.2.2 Developing thermodynamic model for bio-based process, system with salt involved

Besides the data base, developing the thermodynamic model that could describe and model the bio-based process is important and required. Specially, the thermodynamic model that is capable of predicting a system with salt involved is of interest. Moreover, relative thermodynamic model for the IL based system is also required.

10.2.3 Developing a new environmental metric

Processes need to be developed not only in a profitable way but also in an environmental friendly way. Both the economic and the environmental metrics are needed for the evaluation at the early stage of the process development. The E-factor has its limitation. The life cycle assessment is hard to be applied at the early stage. Therefore, developing a new environmental metric and software, which requires less information but gives insights to the environmental effect will be very helpful. The new metric and software should be easy to be applied at the early stage of the process development.

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Appendix

Appendix1 Data for case study

A1.1 Pure component property data

Table A1.1. Required properties for the simulation of the base case design.

Liquid/gases	Conventional solids
Critical temperature	Heat of formation
Critical pressure	Heat capacity
Vapor pressure	Density
I.G: heat of formation	
I.G. heat capacity	
Heat of vaporization	
Density	

Table A1.2. List of compounds involved in the synthesis problems. ProII library.

ProII library	User defined
Water	Glucose
MIBK	Fructose
DMSO	HMF
DCM	Humins
E_tOA_c	FDA
Levulinic acid	
Formic acid	
Oxalic acid	

A1.2 Prices and miscellaneous

Table A1.3. List of price lists of the items for costing.

Item	Price	Reference
Raw Material		
Glucose	300 USD/tons	Our personal contact with Novozymes, 2010
Fructose	500 USD/tons	Our personal contact with Novozymes, 2010
MIBK	1890 USD/tons	ww.icis.com, February 2011
DMSO	2000 USD/tons	Our personal contact with Novozymes, 2010
DCM	500 USD/tons	Assumed
E_tOA_c	1000 USD/tons	Our personal contact with Novozymes, 2010
[BMIM]Cl	11000USD/tons	Our personal contact with the company, 2011
Glucose isomerase	19.15 USD/tons	Our personal contact with Novozymes, 2010
NHC-CrCl2	2000 USD/tons	Assumed
HCl	500 USD/tons	Our personal contact with Novozymes, 2010
NaCl	100 USD/tons	Our personal contact with Novozymes, 2010
KOH (50 wt%)	200 USD/tons	Our personal contact with Novozymes, 2010
$Ca(OH)_2$ (50 wt%)	200 USD/tons	Our personal contact with Novozymes, 2010
Oxalic acid	1000 USD/tons	Assumed
Utilities		
Process water	0.26 USD/tons	Our personal contact with Novozymes, 2010
Cooling water	0.022 USD/tons	Our personal contact with Novozymes, 2010
Electricity	0.0483 USD/kWh	Our personal contact with Novozymes, 2010
HP Steam (gas), 600 psig	14.23 USD/tons	Our personal contact with Novozymes, 2010
MP Steam (gas), 200 psig	16.04 USD/tons	Our personal contact with Novozymes, 2010
Other		
Waster water disposal	0.53 USD/tons	Peters et al., 2004
Labor	28.13 USD/h	Peters et al., 2004

A1.3 Lists of reactions

Table A1. 4. List of all the reactions considered in the case study.

Item	Reaction
Glucose isomerasion	$C_6H_{12}O_6(Glu\cos e) \overset{IGI}{\rightleftarrows} C_6H_{12}O_6(Fructose)$
Dehydration fructose to HMF	$C_6H_{12}O_6(Fructose) \xrightarrow{H^+} C_6H_6O_3 + 3H_2O$
Humin formation from fructose (assumed)	$C_6H_{12}O_6(Fructose) \longrightarrow C_6H_6O_3(Hu\min) + 3H_2O$
Dehydration glucose to HMF	$C_6H_{12}O_6(Glu\cos e) \xrightarrow{H^+} C_6H_6O_3 + 3H_2O$
Humin formation from glucose (assumed)	$C_6H_{12}O_6(Glu\cos e) \longrightarrow C_6H_6O_3(Hu\min) + 3H_2O$
HMF decomposition	$C_6H_6O_3 + 2H_2O \longrightarrow C_5H_8O_3 + CH_2O_2$
HMF oxidation to FDA	$C_6H_6O_3 + \frac{3}{2}O_2 \longrightarrow C_6H_4O_5 + H_2O$

Appendix2 PTA process information

Table A2.1. Information related with PTA cost.

TEREPHTHALIC ACID (HIGH PURITY) FROM P-XYLENE BY BROMINE-PROMOTED AIR OXIDATION					
RAW MATERIAL AND UTILITY COST, US ¢/KG					
	UNIT	COST	CONSUMPTION/	TONNE	¢/KG
RAW MATERIALS					
ACETIC ACID	75.84	¢/KG	0.06175	TONNE	4.68
CATALYST, Pd On C	10580	¢/KG	0.00005	TONNE	0.53
CATALYST, Rh On C	11880	¢/KG	0.00001	TONNE	0.12
COBALT ACETATE.4H2O	1250	¢/KG	0.00005	TONNE	0.06
HAFNIUM ACETATE.4H2O	3274	¢/KG	0.00004	TONNE	0.13
HYDRAZINE (85%)	382.6	¢/KG	0.00027	TONNE	0.1
HYDROBROMIC ACID (48%)	123.1	¢/KG	0.0017	TONNE	0.21
HYDROGEN.	148.8	¢/KG	0.00008	TONNE	0.01
MANGANESE ACETATE.4H2O	315.3	¢/KG	0.00014	TONNE	0.04
P-XYLENE	124.9	¢/KG	0.67915	TONNE	84.83
GROSS RAW MATERIAL COST					90.71
UTILITIES					
COOLING WATER	3.51	¢/M3	349.672	M3	1.23
ELECTRICITY	7.13	¢/KWH	394.627	KWH	2.81
NATURAL GAS	3.53	¢/MMCAL	475.555	MMCAL	1.68
STEAM	3064	¢/TONNE	2.658	TONNE	8.14
TOTAL					13.86
					1M- 1119

Table A2.2. Information related with PTA production cost, based on bromine-promoted air oxidation process.

SRI CONSULTING PEP YEARBOOK	2008				
LOCATION : U.S.					TEREPHTHALIC ACID
PEP COST INDEX-U.S. : 793					PRICE: 97.47 ¢/KG
THOUSAND TONNE/YR	125		249		499
INVESTMENT, US $ MILLION*					
BATTERY LIMITS	141	0.64	220	0.75	370
OFF SITES	75		119		204
TOTAL FIXED CAPITAL	216	0.65	339	0.76	574
PRODUCTION COSTS, US ¢/KG					
RAW MATERIALS	90.71		90.71		90.71
BY PRODUCT CREDITS	0		0		0
UTILITIES	13.86		13.86		13.86
VARIABLE COSTS	104.57		104.57		104.57
MAINTENANCE MATERIALS	2.71		2.12		1.78
OPERATING SUPPLIES	0.27		0.14		0.07
OPERATING LABOR (9/SHIFT)	2.7		1.36		0.68
MAINTENANCE LABOR	1.8		1.41		1.19
CONTROL LABORATORY	0.54		0.27		0.14
TOTAL DIRECT COSTS	112.59		109.87		108.43
PLANT OVERHEAD	4.03		2.43		1.61
TAXES AND INSURANCE	3.46		2.72		2.3
DEPRECIATION	17.28		13.61		11.5
PLANT GATE COST	137.36		128.63		123.84
G + A, SALES, RES., 5 %	9.5		8.56		8.03
PRODUCTION COSTS					
AT 100% CAPACITY	146.86		137.19		131.87
AT 75% CAPACITY	162.8		149.91		142.82
AT 50% CAPACITY	194.69		175.35		164.71
PRODUCT VALUE					
(COST + 25 %/YR ROI BEFORE TAXES), US ¢/KG					
AT 100% CAPACITY	190.06		171.23		160.63
AT 75% CAPACITY	220.4		195.29		181.16
AT 50% CAPACITY	281.09		243.43		222.23
* INCLUDES 25% CONTINGENCY.					

PROCESS DESCRIPTION

The continuous process described below is PEP process design based on patents issued to Amoco. p-Xylene is oxidized to terephthalic acid in the presence of a cobalt-manganese-bromine catalyst. The reaction is conducted liquid-phase in a stirred reactor using acetic acid as the solvent. The crude product is then recovered by flash crystallization and subsequent solid-liquid separation with countercurrent water washing at super-atmospheric pressure on a belt filter. The moist filter cake is sent to the hydrogenation section without further drying.

In the hydrogenation section, the crude product is reslurried and dissolved in water, then fed to a hydrogenator where insoluble impurities are hydrogenated liquid-phase in the presence of a rhodium and palladiumcontaining catalyst to more soluble impurities. Terephthalic acid is flash-crystallized from the hydrogenation product stream, then the crystals are separated by centrifuge and reslurried in water. The slurry is sent to a final flash crystallization/centrifuge operation, then the product crystals are dried.

In the catalyst recovery section, cobalt and manganese are recovered from distillation residue. Also various waste streams are incinerated and scrubbed to produce an acceptably clean plant vent gas.

Overall yield of terephthalic acid on p-xylene is 94%. Purified terephthalic acid is used as a monomer for manufacture of polyethylene terephthalate (PET).

REFERENCE: PEP Report 9E, SEC 5 (TIM)

1M- 1119

Appendix3 Simulated process flowsheets in ProII

A3.1 Water based synthetic route

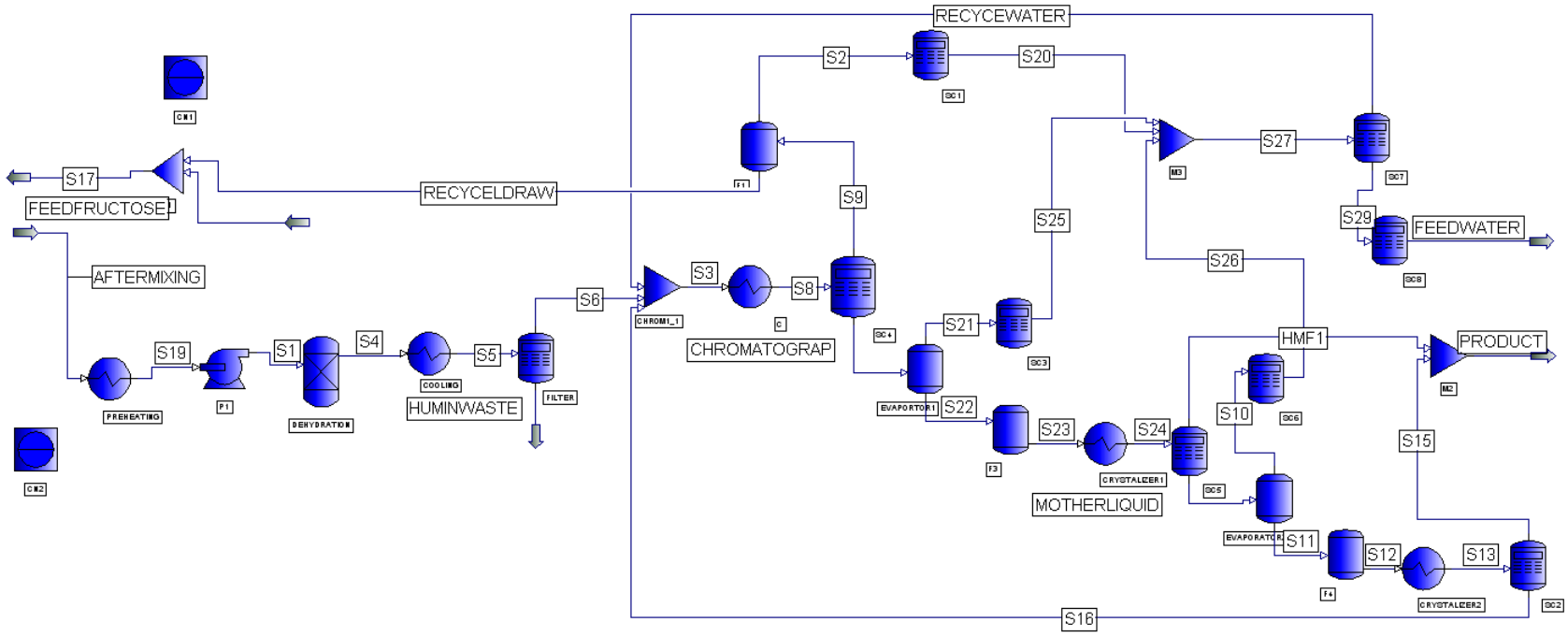

Figure A3.1. Simulated process flowsheet of the selected process example of the water based synthetic route, modified from the published flowsheet by Rapp et al. (1987).

Table A3.1. Lists of the mass and energy information of the main process streams.

Stream name	FEED FRUCTOSE	RECYCEL DRAW	AFTER MIXING	S4	HUMIN	WASTE	S3	CHROMATOGRAP	S9	FEED	WATER	RECYCE	WATER	PRODUCT
Stream description														
Stream phase	Liquid	Liquid	Liquid	Mixed	Unknown		Liquid	Liquid		Liquid	Liquid		Liquid	Liquid
Temperature (°C)	25.00	101.44	52.00	138.00	40.00		77.75	65.00		65.00	79.01		79.01	4.00
Pressure (atm)	1.00	1.00	1.00	3.29	1.00		1.00	1.00		1.00	1.00		1.00	1.00
Enthalpy (MM J/h)	2.05	3.20	5.33	11.59	0.00		179.14	46.57		103.28	3.10		175.61	0.00
Total weight comp. rates (kg/h)														
HMF	0.00	0.38	0.34	1.55	0.00		2.06	1.60		0.45	0.00		0.00	1.00
Levulinic acid	0.00	0.45	0.31	0.60	0.00		0.60	0.00		0.60	0.00		0.00	0.00
Formic acid	0.00	0.00	0.00	0.11	0.00		0.11	0.00		0.11	0.00		0.00	0.00
Water	9.36	5.14	15.35	15.91	0.00		546.68	170.61		376.07	9.36		530.74	0.00
Fructose	3.12	2.02	5.16	2.02	0.00		2.02	0.00		2.02	0.00		0.00	0.00
Oxalic acid	0.03	0.06	0.06	0.06	0.00		0.06	0.00		0.06	0.00		0.00	0.00
Humins	0.00	0.00	0.00	0.96	0.96		0.00	0.00		0.00	0.00		0.00	0.00

A3.2 Solvent based synthetic route

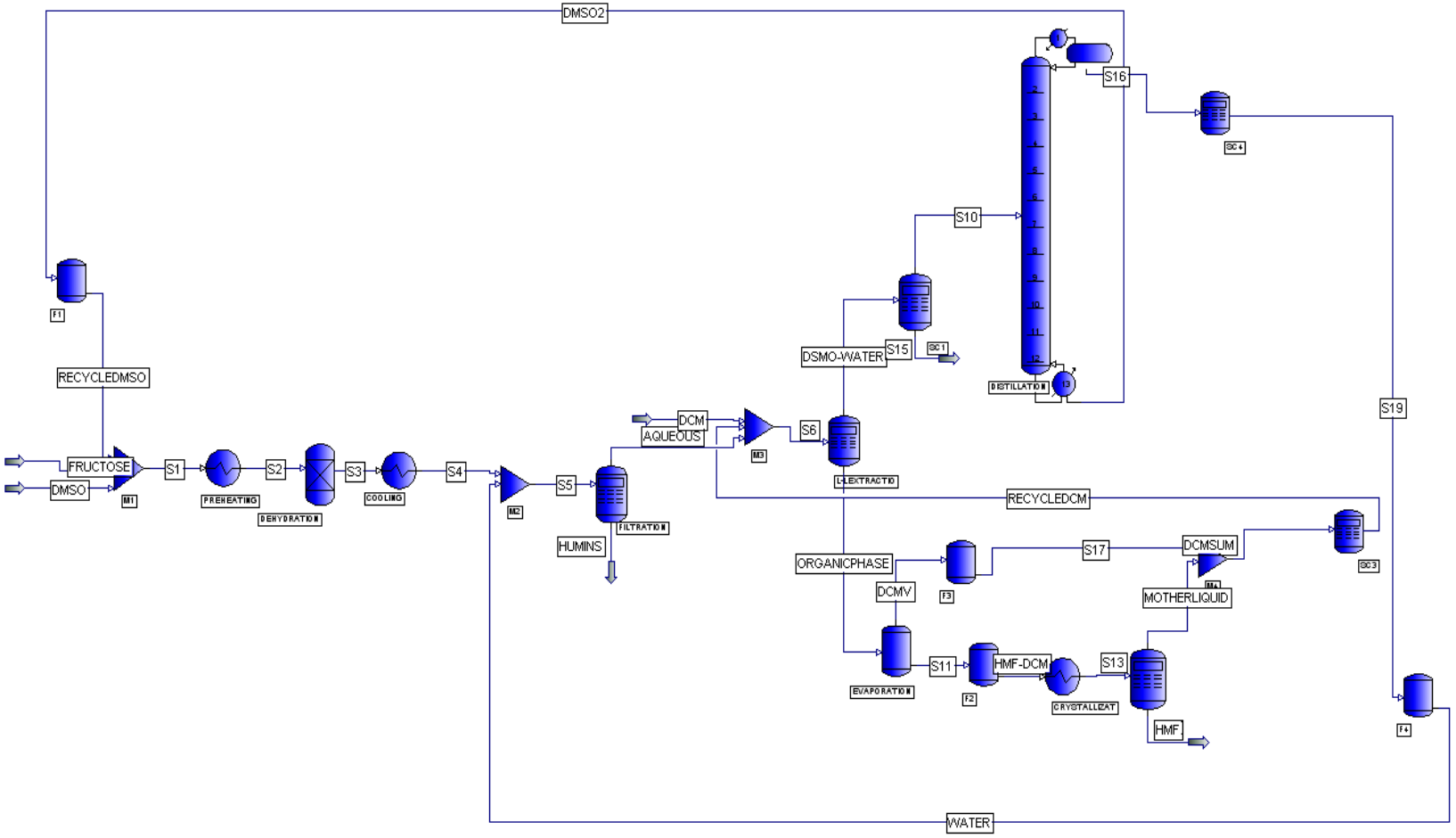

Figure A3.2. Simulated process flowsheet of the selected process example of the solvent based synthetic route, modified from the published flowsheet by M'Bazoa et al. (1990).

Table A3.2. Lists of the mass and energy information of the main process streams.

Stream name	FRUCTOSE	DMSO	RECYCLE DMSO	S3	HUMINS	AQUEOUS	DCM	RECYCLE DCM	ORGANIC PHASE	HMF	DSMO-WATER	WATER
Stream description												
Stream phase	Liquid	Liquid	Liquid	Liquid	Mixed	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
Temperature (°C)	25.00	25.00	159.00	160.00	25.00	25.00	25.00	7.54	8.00	-5.00	8.00	25.00
Pressure (atm)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Enthalpy (MM J/h)	0.70	0.00	1.11	2.85	0.00	0.57	0.01	0.08	0.09	-0.01	0.54	0.31
Total weight comp. rates (kg/h)												
Fructose	2.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
HMF	0.00	0.00	0.00	1.15	0.00	1.15	0.00	0.00	1.11	1.00	0.03	0.00
DMSO	0.00	0.08	3.40	3.47	0.00	3.47	0.00	0.00	0.08	0.07	3.40	0.00
Water	0.00	0.00	0.03	0.54	0.00	3.46	0.00	0.00	0.00	0.00	3.46	2.92
DCM	0.00	0.00	0.00	0.00	0.00	0.00	0.21	8.56	8.56	0.00	0.21	0.00
Levulinic acid	0.00	0.00	0.00	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Formic acid	0.00	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Humins	0.00	0.00	0.00	0.31	0.31	0.00	0.00	0.00	0.00	0.00	0.00	0.00

A3.3 Solvent-water based synthetic route (biphasic route)

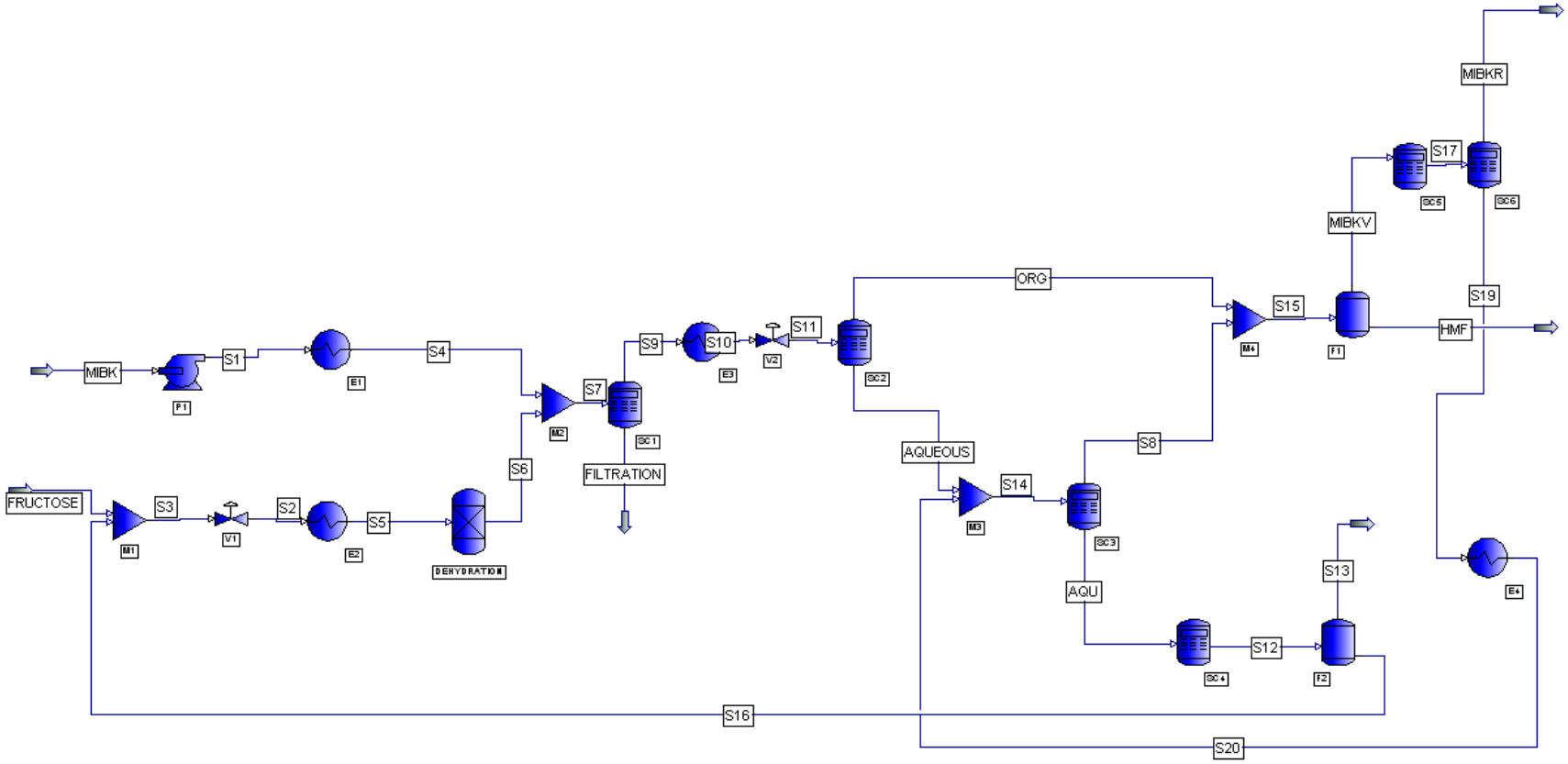

Figure A3.3. Simulated process flowsheet of the selected process example of the solvent-water based synthetic route, modified from the published flowsheet by Roman-Leshkov et al. (2000).

Table A3.3. Lists of the mass and energy information of the main process streams.

Stream name	FRUCTOSE	S16	S5	MIBK	MIBKR	FILTRATION	S11	AQUEOUS	S20	S15	HMF
Stream description											
Stream phase	Liquid	Liquid	Liquid	Liquid	Liquid	Unknown	Mixed	Liquid	Liquid	Liquid	Liquid
Temperature (°C)	25.00	96.35	180.00	50.00	50.00	180.00	25.00	25.00	25.00	25.00	50.00
Pressure (atm)	1.00	1.00	10.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.01
Enthalpy (MM J/h)	0.68	2.91	6.30	2.84	2.83	0.00	2.42	0.98	0.70	2.16	0.07
Total weight comp. rates (kg/h)											
HMF	0.00	0.00	0.00	0.00	0.00	0.00	1.06	0.23	0.00	1.05	1.00
Water	0.00	6.37	6.37	0.00	0.00	0.00	6.84	6.60	0.00	0.37	0.00
Fructose	1.97	0.76	2.73	0.00	0.00	0.00	0.76	0.76	0.00	0.00	0.00
Levulinic acid	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.10	0.00	0.00	0.00
Formic acid	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.04	0.00	0.00	0.00
Humins	0.00	0.00	0.00	0.00	0.00	0.30	0.00	0.00	0.00	0.00	0.00
MIBK	0.00	0.04	0.04	26.39	26.28	0.00	26.43	0.13	13.22	39.52	0.03

A3.4 Chemo-enzymatic synthetic route from glucose

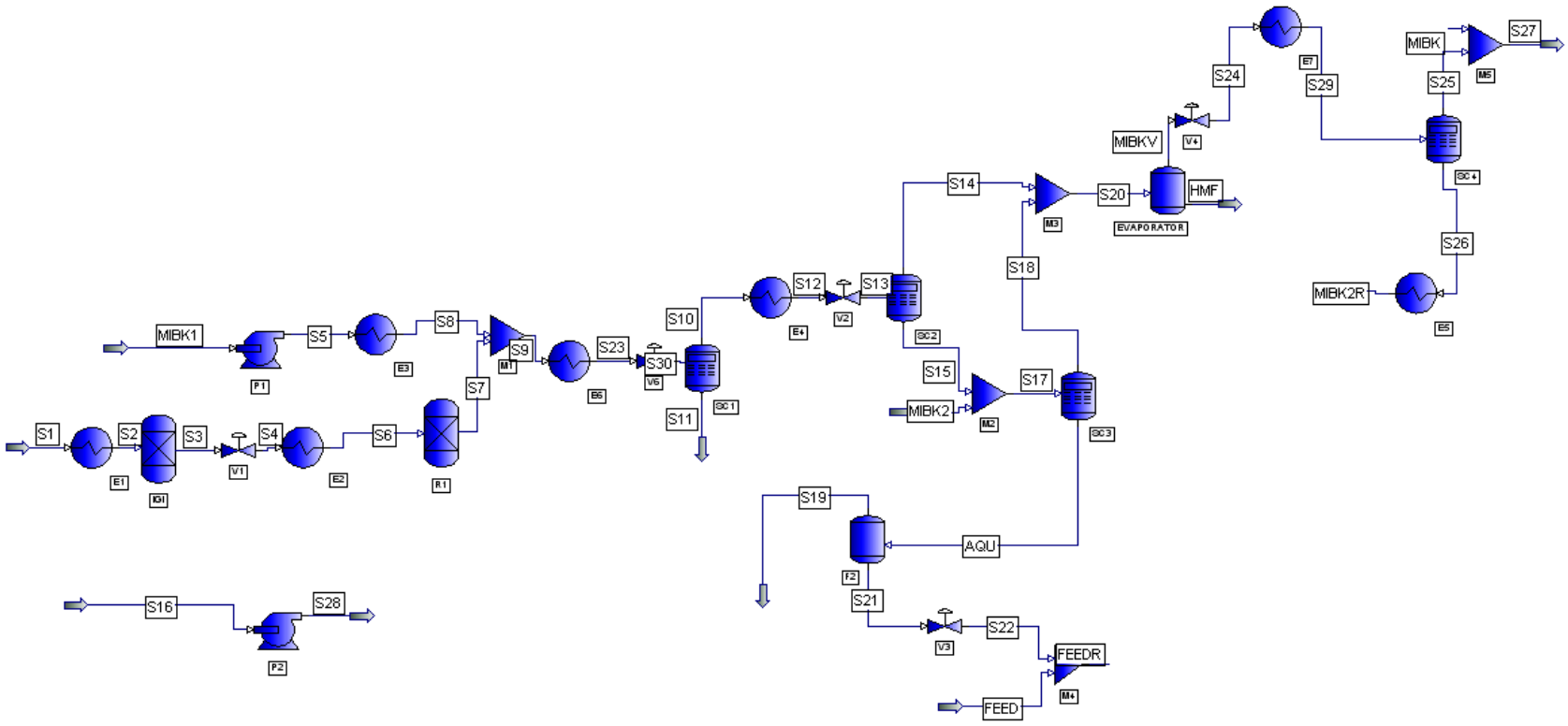

Figure A3.4. Simulated process flowsheet of the chemo-enzymatic synthetic route for HMF production from glucose.

Table A3.4. Lists of the mass and energy information of the main process streams.

Stream name	S22	S1	S6	MIBK1	S11	S13	AQU	S20	HMF	S29	MIBK
Stream description											
Stream phase	Liquid	Liquid	Liquid	Liquid	Unknown	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
Temperature (°C)	82.12	79.29	180.00	115.93	25.00	25.00	25.00	25.00	47.00	116.00	25.00
Pressure (atm)	1.00	1.00	10.00	1.00	1.00	1.00	1.00	1.00	0.01	1.00	1.00
Enthalpy (MM J/h)	4.77	5.51	10.74	10.29	0.00	4.19	2.07	3.16	0.06	15.44	0.00
Total weight comp. rates (kg/h)											
Glucose	2.44	4.59	2.71	0.00	0.00	2.44	2.44	0.00	0.00	0.00	0.00
Fructose	0.08	0.08	1.96	0.00	0.00	0.08	0.08	0.00	0.00	0.00	0.00
MIBK	0.00	0.00	0.00	39.40	0.00	39.40	0.00	59.10	0.03	59.07	0.03
Water	10.89	10.89	10.89	0.00	0.00	11.53	11.53	0.00	0.00	0.00	0.00
HMF	0.00	0.00	0.00	0.00	0.00	1.06	0.00	1.06	1.00	0.06	0.00
Humins	0.00	0.00	0.00	0.00	0.45	0.00	0.00	0.00	0.00	0.00	0.00
NaCl	0.60	0.60	0.60	0.00	0.00	0.60	0.60	0.00	0.00	0.00	0.00

A3.5 HMF separation from E_tOA_c

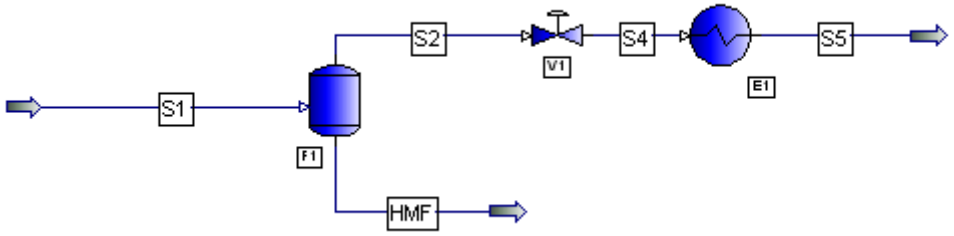

Figure A3.5. Simulated process flowsheet of HMF separation from EtOAc.

Table A3.5. Lists of the mass information of the main process streams.

Stream name	S1	HMF	S5
Stream description			
Stream phase	Liquid	Liquid	Liquid
Temperature (°C)	50.00	55.00	50.00
Pressure (ATM)	1.00	0.10	1.00
Total weight comp. rates (kg/h)			
HMF	1.01	1.01	0.00
E_tOA_c	19.98	0.05	19.93

Table A3.6. Lists of the energy information of the process units.

Process Unit	F1	E1
Description	Evaporator	Vapor Condenser
Temperature (°C)	55.00	-
Pressure (atm)	0.10	1.00
Duty (MM J/h)	7.84	7.84

Appendix4 Sizing the equipment

Reactors

Immobilized glucose isomerase reactors
The volume of the immobilized isomerase reactors are sizing based on the required enzyme volume which is dependent on the daily operating capacity and the activity of the enzyme. The calculation of the immobilized glucose isomerase is using the information with Sweetzyme, Type Q.

For operating conditions it should be taken into account that only part of the dry substance is dextrose, and that the operating temperature normally is lower than 65°C. The dry substance may also differ from the analytical conditions. The activity at 35 and 45% dry substance is 5% less than at 40%.The activity decreases when the temperature decreases and the activity A_t at a temperature t is calculated according to the formula:

$$A_t = A_{65} \times 0.932^{(65-t)} \quad (55°C \le t \le 65°C) \qquad \text{Equation A4.1}$$

Therefore, the activity (in IGIC/g) under operating conditions is transformed to standard conditions and can be calculated as :

$$\text{Correctedactivity} = \frac{F(DX/100)\times[DS\times(DX/100)\times X - K\ln(1-X)]}{m\times k'\times\phi(X)\times W} \text{ IGIC/g} \qquad \text{Equation A4.2}$$

where

F = Flow rate, g syrup/hour
DS = Dry substance content, 30 % w/w (this case)
DX = Dextrose content, % w/w, dry substance, 99.9 (this case)
X = Conversion, fructose/(fructose + glucose), 0.403 (this case)
m = $0.932^{(65-t)}$ (t = actual temperature 55°C ≤ t ≤ 65°C)
K = Experimentally determined constant = 58% w/w
k' = $1.081\times\left(1+\frac{58}{DS}\right)\times\left(1-\frac{\sqrt{(DS-40)^2}}{100}\right)$ Constant, required to give the activity in the desired units. With 30% w/w syrup as substrate k has the value of 2.81
W = Weight of enzyme, 1 kg
∅(X) = $\varnothing(X) = \sqrt{1-3X^2+20X^3-79X^4+75X^5}$ $(0 \le X \le 0.47)$ Correction factor

Afterwards, the required enzyme volume can then be calculated by substituting the enzyme weight, W, with the enzyme bed volume, V:

$$V = \frac{F'(DX/100)\times[DS\times(DX/100)\times X - K\ln(1-X)]}{m\times k'\times\varnothing(X)\times A_v}$$

Equation A4.3

V is the enzyme volume in m^3. Av is the average volumetric activity of the enzyme during the design lifetime (IGIC/ml). If the enzyme is discarded at a residual activity of 12.5% (after three half-lives), AV is 0.43 x 60 IGIC/ml. And F' is the flow in ton syrup/hour.

This calculated enzyme volume equals the total enzyme volume of all reactors. The number and dimensions of the reactors are chosen in accordance with the design criteria given below. Finally an excess of 20% is added to the height of each reactor to give space for settling during loading and to enable enzyme fluidization during emptying.

Lists of design criteria recommended by Novo Nordisk:
Maximum bed height: 5 m
Maximum diameter: 1.8 m (approx.)

A certain minimum height/diameter ratio of each bed is required to ensure good flow distribution. For several reactors in series this restriction becomes less severe. The following design values are recommended by Novo Nordisk (1985):

Table A4.1. Minimum height/diameter ratio for design fixed bed reactors.

No of reactors in series	Minimum H/D
1	3
2	1.5
3 or more	1

Dehydration reactors

Due to lack of kinetic data in this system, for a roughly estimation, dehydration reactor is sized as a batch reactor. The required volume is estimated based on the volume flowrate (both organic phase and aqueous phase) entering the reactor multiplied by the residence time. The reactor volume is then equal to the calculated required volume by adding 0% to 20% extra required volume.

Vessel Sizing (storage tanks, buffering tanks, evaporators)

Vessels include evaporators (flash drums), liquid feed tanks (MIBK feed tanks) and pH buffering tank involved in the process flowsheet. Unless specified by a particular unit requirement, they can be sized according to the following criteria suggested by Biegler et al. (1997):

$$V = 2F_L\tau/\rho_L$$

Equation A4.4

Where F_L is the liquid mass flowrate leaving the vessel (eg. evaporator), ρ_L is the liquid density and τ is a residence time. If not specially specified, typically set to five minutes.

Settlers

Settlers are sizing as with the mass flowrate and a residence time of 30 mins (Peters et al., 2004).

Extraction column

The extraction column is sizing based on the required number of trays (N) for the extraction and the designed diameters of the extraction column. N can be calculated with the required theoretical number of trays (N_s) and the extractor's efficiency (E_0):

$$N = \frac{N_s}{E_o} \qquad \text{Equation A4.5}$$

The Ns is calculated based on the designed extraction yield and extraction power as described before. The extractor's efficiency is depending on the type of extractor. The diameter is estimated based on the maximum designed liquid loading which is to avoid flooding. The maximum designed liquid loading is dependent on the type of extractor. The selected type of extractor and designed parameters for sizing is listed in Table A4.2. The designed height of the column and diameter are calculated with the mass flowrate with the designed parameters.

Table A4.2. Designed parameters of a liquid-liquid extractor (Peters et al., 2004).

Liquid-liquid extraction	Sieve tray tower
Tray efficiencies	30%
Tray space	0.6 m
Tray tack	(N-1)*Tray space
Extra feed space	1.5 m
Disengagement space	3 m
Skirt height	1.5 m
Maximum liquid loading	60 m3/m2/h
Maximum design diameter	3 m

Heat exchangers

The heat exchangers are considered to be the countercurrent, shell and tube heat exchangers. The required area (A) of the heat exchangers can be calculated as (Peters et al., 2004):

$$Q = AU\Delta T_{o,M} \qquad \text{Equation A4.6}$$

Where Q is the required heating or cooling energy, U is the typical overall heat transfer coefficient, and $\Delta T_{o,M}$ is the mean overall temperature difference between the two liquids and can be calculated as:

$$\Delta T_{o,M} = F \Delta T_{o,logmean} \quad \text{Equation A4.7}$$

Where F is the correction factor to account for the type of multipass arrangement that has been selected. For a multipass exchanger with one shell and two or more even-number tube passes, F can be calculated as:

$$F = (R^2+1)^{0.5} \ln(\frac{1-P}{1-RP}) / (R-1) \ln \frac{2-P[(R+1)-(R^2+1)^{0.5}]}{2-P[(R+1)+(R^2+1)^{0.5}]} \quad \text{Equation A4.8}$$

Where R and P are defined as:

$$R = \frac{T_{h,in} - T_{h,out}}{T_{c,out} - T_{c,in}}, \; P = \frac{T_{c,out} - T_{c,in}}{T_{h,in} - T_{c,in}} \quad \text{Equation A4.9}$$

And $\Delta T_{o,logmean}$ is calculated as:

$$\Delta T_{o,logmean} = \frac{(T_{h,in} - T_{c,out}) - (T_{h,out} - T_{c,in})}{\ln[(T_{h,in} - T_{c,out}) / (T_{h,out} - T_{c,in})]} \quad \text{Equation A4.10}$$

Where $T_{h,in}$, $T_{h,out}$, $T_{c,in}$ and $T_{c,out}$ are the temperatures of the hot side liquid/vapor entering and leaving the heat exchanger and the temperatures of the cold side liquid/vapor of entering and leaving the heat exchanger.

The cooling water temperature is assumed to 15℃ when entering the heat exchanger and has a temperature of 30℃ when leaving the heat exchangers. Some typical U values used for sizing calculations are listed in Table A4.3.

Table A4.3. Lists of approximate design values of overall heat transfer coefficients (Peters et al., 2004).

Hot side	Cold side	U (W/m^2K)
light organic	water	375-750
water	water	1250-2500
steam	water	1000-3500
steam	light organic	500-1000

Pumps

The sizing and selection of the pump is based on its capacity (the flowrate, m^3/s) and the head. The head of the pump can be obtained directly from ProII 8.0 (ProII, 2011)

simulation. Centrifugal pump are one of the most commonly used pumps and are for flows with a flowrate from 10^{-3} to 0.3 m^3/s. It can provide a 150-m maximum head. The pump efficiency η_p is from 20% to 90% depending on the flowrate and the type of the pump. The motor efficiency η_m is assumed to be 90%. The required work for pumping can be calculated as:

$$W_p = \frac{W_{theoretical}}{\eta_p \eta_m} \qquad \text{Equation A4.11}$$

$W_{theoretical}$ is the theoretical work for pump to increase the liquid pressure which can be obtained directly from the ProII simulation.

Appendix5 Size of the equipment

Table A5.1. Lists of required size of the major equipment involved in the process flowsheet of chemo-enzymatic synthesis of HMF (Chapter 6).

Plant Capacity: 250,000 tons HMF/y				Stream factor: 0.9		
Item	Pressure (atm)	Capacity		Number	Material[c)]	Mark
pH buffering tank	1	Volume (m3)	65	2	SS 316	pH adjustment before/after IGI
MIBK Feed Tank	1	Volume (m3)	0.20	1	SS 316	
IGI Reactors	1	Volume (m3)	14	48	SS 316	12 lines, and 4 reactors per line
Dehydration Reactors	10	Volume (m3)	67	16	SS 316	
Settlers	1	Volume (m3)	67	16	SS 316	
Vacuum Evaporators	0.01	Volume (m3)	395	1	SS 316	MIBK Evaporation
	0.5	Volume (m3)	56	1	SS 316	Aqueous Concentration
Extractor	1	Design Diameter (m)	2.83		SS 316	Sieve Tray type
		Tray number	10	3	SS 316	
		Tray stack (m)	5.4		SS 316 SS 316	
		Total Height (m)	11.4			
Heat exchangers 1	1	Area (m2)	103	1	SS 316	Cooling the aqueous before recycle back to IGI
Heat exchangers 2	10	Area (m2)	227	1	SS 316	Preheating aqueous before dehydration
Heat exchangers 3	10	Area (m2)	798	1	SS 316	Preheating MIBK
Heat exchangers 4	10	Area (m2)	4739	1	SS 316	Phase separation
Heat exchangers 5	1	Area (m2)	2649	1	SS 316	Condensing MIBK
Heat exchangers 6		Area (m2)	2145	1	SS 316	Cooling MIBK before recycle
Pump 1 (MIBK pressurized)	13[a)]	Flow rate (m3/s)	0.5	1	SS 316	Centrifugal pump
Pump 2 (aqueous pressurized)	13[b)]	Flow rate (m3/s)	0.1	1	SS 316	Centrifugal pump

a) Head: 131m, efficiency 85%, motor efficiency 90%
b) Head: 68m, efficiency 80%, motor efficiency 90%
c) SS 316 means Stainless steel 316

Table A5.2. Calculated size of the major equipment involved in the IL process flowsheet for the four process options (Chapter 7).

Cases	F1	F2	G1	G2
Reactor Volume (m3)	178	94	212	90
Filter Capacity (m3)	29	11	34	11
Extractor Diameter (m)	1.4	2.3	2.5	1.4
Trays number	30	31	31	30
Total Extractor Height (m)	23	24	24	23
Vacuum Evaporator 1 (m3)	30	11	35	11
Vacuum Evaporator 2 (m3)	3.8	1.4	4.5	1.4
Heat Exchanger 1 Area (m2)	11	3	12	3
Heat Exchanger 2 Area (m2)	833	305	980	296
Heat Exchanger 3 Area (m2)	620	177	737	170

Appendix6 Energy metric

Table A6.1. Detailed energy balance of the four process options of the IL process route (Chapter 7).

Energy requirement (MJ/kg HMF)	F1	F2	G1	G2
Reaction and preheating	2.20	4.13	3.17	3.85
Solvent evaporation	21.40	8.10	25.18	7.88
IL recovery	19.95	5.51	23.69	5.29
Condensing	40.66	13.33	48.06	12.88
Cooling	0.78	0.22	0.93	0.21
Total energy	84.99	31.29	101.03	30.10

Appendix7 Publications

Paper I: Process integration for the conversion of glucose to 2,5-furandicarboxylic acid.

Paper II: Synthesis of 5-(hydroxymethyl)furfural in ionic liquids: Paving the way to renewable chemicals.

Paper III: A method of producing hydroxymethylfurfural (Patent application).

Paper IV: Process considerations for the scale-up and implementation of biocatalysis.

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Process integration for the conversion of glucose to 2,5-furandicarboxylic acid

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ABSTRACT

The development of biorefineries means that a key feedstock for many new processes will be sugars in various forms, such as glucose or fructose. From these feedstocks a range of chemicals can be synthesized using heterogeneous catalysis, immobilized enzymes, homogeneous catalysts, soluble enzymes, fermentations or combinations thereof. This presents a particularly interesting process integration challenge since the optimal conditions for each conversion step will be considerably different from each other. Furthermore, compared to oil-based refineries the feedstock represents a relatively high proportion of the final product value and therefore yield and selectivity in these steps are of crucial importance. In this paper using the conversion of glucose to 2,5-furandicarboxylic acid and associated products as an example, alternative routes will be compared with respect to achievable selectivity, and achievable yield.

Keywords: Biorefineries; Glucose isomerase; 5-Hydroxymethylfurfural; 2,5-Furandicarboxylic acid

1. Introduction

While the increasing cost of oil is driving particular interest in the production of new fuels from biomass there is little doubt that today of equal importance is the production of chemicals from biomass. Indeed for the supply of fuels in the future there are many potential sources aside from biomass. In a world with limited (or very expensive) oil it is less clear where the chemicals of the future will originate. There is currently an existing infrastructure based on the use of the seven established platform chemicals (toluene; benzene; xylene; 1,3-butadiene; propylene; ethene; methane). In the short term one could consider if we can use the same infrastructure and just create the seven chemicals from alternative sources. However in the longer term it will be necessary to devise new processes based on a different set of platform chemicals. One group will be based around glucose (the hydrolytic product of starch and therefore readily available from biomass). In a biorefinery it will be necessary to develop a structure which can manage a range of feedstocks, a range of technologies and a range of products. This presents a considerable challenge for design and optimization as well as process integration. In order to illustrate the complexity and the challenge that lies ahead we have studied one specific example with a defined starting and endpoint: the production of 5-hydroxymethylfurfural (HMF) or 2,5-furandicarboxylic acid (FDA) from glucose or fructose. Greatest value is obtained by going the whole way from glucose to FDA. However even in this small reaction pathway there are many alternative technologies. Some can be integrated together, some give the required yield and selectivity, some are difficult to implement and others are untested at scale. This illustrates very well the challenge that design engineers face. To date glucose finds its major use in food applications (as a feedstock for sorbitol and high fructose corn syrup). The possibility of non-food products like HMF or FDA implies the use of other technologies not governed by the strict

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food regulations. Nevertheless all the potential technologies (whether approved for food or non-food production) need to be able to overcome the pH and temperature instability and limited solubility in organic solvents. It is because of the nature of glucose therefore that one obvious starting point is to use enzymatic catalysis (water based and under mild conditions). In this paper we will review the alternative technologies and routes from glucose to FDA, and discuss some of the limitations and challenges.

2. Biomass as a raw material for biorefineries

Nature is producing vast amounts of biomass driven by sunlight via photosynthesis:

$$nCO_2 + nH_2O \rightarrow (CH_2O)_n + nO_2$$

However, utilization of biomass for producing chemicals and fuels is still in its infancy with only 3.5% being used for food or non-food purposes. Plant biomass consists mainly of carbohydrates, lignin, protein and fats. Out of an estimated 170 billion metric tons of biomass produced every year roughly 75% are in the form of carbohydrates which makes biomass carbohydrates the most abundant renewable resource (Röper, 2002). Together with their amenability towards enzymatic processes this makes carbohydrates the center of attention when looking for new and greener feedstocks to replace petroleum for producing commodity chemicals as well as fuels. In plant biomass most of the carbohydrates are stored as sugar polymers such as starch, cellulose or hemicellulose.

Starch is the second largest biomass produced on earth and commonly found in vegetables, such as corn, wheat, rice, potatoes and beans. The total world production in 2004 was 60 million tons of which more than 70% came from corn. Starch consists of chains of glucose molecules, which are linked together by α-1,4 and α-1,6 glycosidic bonds. The two major parts of starch are amylose (20–30%), essentially linear α-1,4 glucan chains and amylopectin (70–80%), a branched molecule containing 4–5% α-1,6 linkages.

Starch is industrially hydrolyzed to glucose by the three enzymes: α-amylase, glucoamylase, and pullulanase (Schäfer et al., 2007). Bacterial α-amylases (EC 3.2.1.1) catalyze the hydrolysis of internal α-1,4 glycosidic bonds. This reduces the viscosity, which is necessary for further processing. Glucoamylase (EC 3.2.1.3) is an exo-amylase that is added to the partly hydrolyzed starch after liquefaction. Glucose units are removed in a stepwise manner from the non-reducing end of the molecule. The third enzyme is pullulanase (EC 3.2.1.41). Industrially used pullulanases are heat stable enzymes, which act simultaneously with glucoamaylase during saccharification. Pullulanases catalyze the hydrolysis of the α-1,6 linkages in amylopectin, and especially in partially hydrolysed amylopectin. Typical process conditions for production of glucose from starch are given in Table 1.

Cellulose is a glucose polymer consisting of linear chains of glucopyranose units linked together via β-1,4 glucosidic bonds. Unlike starch, cellulose is a crystalline material where inter- and intra-molecular hydrogen bonding gives rise to the very stable cellulose fiber. Hemicellulose is a polysaccharide consisting of short highly branched chains of different carbohydrate units, including five- as well as six-carbon units (e.g. xyloses, galactose, glucose, mannose and arabinose). Hemicelluloses are much easier to hydrolyze than cellulose. The structured portion of biomass, such as straw, corn stover, grasses and wood, is made of lignocellulose composed mainly of cellulose (30–60%), hemicellulose (20–40%) and lignin (10–30%). Both cellulose and hemicellulose consist of carbohydrate components whereas lignin is a highly branched aromatic polymer.

Currently, there is intensive research on the use of lignocellulosic raw material as a biomass source for producing chemicals and fuels (as exemplified by many of the other articles in this special edition). However this research still faces considerable challenges due to lignocellulose being remarkably resistant towards hydrolysis and enzymatic attack (Peters, 2007). Energy demanding thermal pre-treatment of lignocellulose is necessary in order to break up the extremely stable cellulose–hemicellulose–lignin composites prior to adding cellulose-hydrolyzing enzymes and the current situation does not allow the efficient use of lignocellulosic materials. Nevertheless, there is little doubt given the great abundance of lignocellulose that in the future this will become an attractive option. It is therefore important to continue to develop processes that can economically convert lignocellulose into chemicals. Moreover, glucose is one of the most abundant monosaccharides in biomass, accessible by enzymatic or chemical hydrolysis from starch, sugar or cellulose. Furthermore, a range of chemical products can be obtained from glucose which gives it a key position as a basic raw material/building block.

3. Glucose – a biorefinery building block

Fermentation of polymer building blocks is already under commercial introduction. For example, Cargill produces lactic acid by fermentation and products based on polylactic acid are being introduced to the market. Several companies focus on succinic acid as a polymer building block, but also as a potential raw material for chemicals (e.g. butanediol). 1,3-propandiol is marketed by DuPont Tate & Lyle BioProducts for Sorona™ polytrimethylene terephthalate (PTT) polyester. Likewise Cargill is working on developing 3-hydroxypropionic acid (3-HP). 3-HP is a potential raw material for existing chemicals such as propanediol and acrylic acid. Polyhydroxyalkanoate (PHA) is marketed by Telles, a J/V between ADM and Metabolix. Roquette, the French starch producer, has commercialized isosorbide, a derivative of sorbitol. Isosorbide is used as a co-monomer for high temperature polyethylene terephthalate. However, even if commercialization of polymer building blocks made by fermentation is commercially underway, the technology has certain drawbacks such as loss of carbon as CO_2, low yields and difficult recovery of the products

Table 1 – Process conditions for production of glucose from starch.

Process	Temperature (°C)	Dry substance content (%)	pH	Process time (h)
Jet cooking/dextrinization	105/95	30–35	5.2–5.6	0.1/1–2
Saccharification	60	30–35	4.3–4.5	25–50

from the fermentation broth. The technology presented here (combined chemical and enzymatic catalysis from glucose) has the potential to overcome these problems and represents a promising next generation technology.

One chemical transformation (besides fermentations) of carbohydrate monomers for the degradation of functionality is the dehydration reaction. This facilitates the removal of some of the functional groups in carbohydrates and allows the formation of defined building blocks. Triple dehydration of glucose yields HMF—a building block molecule that subsequently can be transformed into a multitude of bio-based chemicals. By a subsequent hydration reaction or an oxidation, HMF can be converted into levulininc acid or FDA, respectively. Both of these molecules are on the list of the 12 bio-based platform chemicals identified as being of highest potential to be converted into new families of useful molecules (Werpy and Petersen, 2004). In the following we will focus on the dehydration of glucose to HMF as an example of the need to efficiently combine enzymatic aqueous processes with inorganic heterogeneous catalytic processes that have so far mainly been developed for running reactions within the petrochemical industry.

HMF is in itself a rather unstable molecule. It can be found in natural products such as honey and a variety of heat processed food products formed in the thermal decomposition of carbohydrates. Interestingly, HMF can be chemically converted into a range of other valuable chemicals. The oxidation of HMF is of particular interest. Here, the ultimate objective is to obtain FDA as suggested by Schiwek et al. (1991). The diacid can be used as a replacement for terephthalic acid in the production of polyethylene terephthalate and polybutylene terephthalate (Gandini and Belgacem, 1997; Kunz, 1993) which was recently reviewed by Moreau et al. (2004). The partially oxidized compounds can also be used as polymer building blocks although these are more difficult to produce selectively. FDA is a chemically very stable compound. Its only current uses are in small amounts in fire foams and in medicine where it can be used to remove kidney stones.

Several extensive reviews describing the chemistry of HMF and its derivatives have been reported (see Fig. 1). The most recent review focuses on chemical transformation of biomass to a variety of chemicals with particular emphasis on the dehydration of monosaccharides giving either furfural (from pentoses) or HMF from hexoses, respectively (Corma et al., 2007). Moreau et al. (2004) described the recent catalytic advances in substituted furans from biomass and focused especially on the ensuing polymers and their properties. A review by Lewkowski (2001) on the chemistry of HMF and its derivatives also appeared recently. Two other relevant reviews are from Cottier and Descotes (1991) and Kuster (1990).

The mechanism for the dehydration of fructose to HMF has been interpreted to proceed via two different routes; either via acyclic compounds or cyclic compounds (Haworth and Jones, 1944; Kuster, 1990; Van Dam et al., 1986; Antal et al., 1990). Besides HMF, the acid-catalyzed dehydration can lead to several other by-products such as insoluble polymers, called humins or humic acids. In an industrial process it is very important to find the right process conditions that avoid the formation of humins as these, besides lowering the selectivity of the reaction, potentially can clog up your reactor or deactivate the heterogeneous catalysts.

In spite of all the research carried out within this area an efficient way of producing HMF or its corresponding dicarboxylic acid, FDA, still remains to be found. Traditionally, chemists have been struggling with finding an inexpensive way of producing pure HMF. Given the immense field of its application, it is interesting that relatively few of the listed reviews have described the challenges that might be faced in

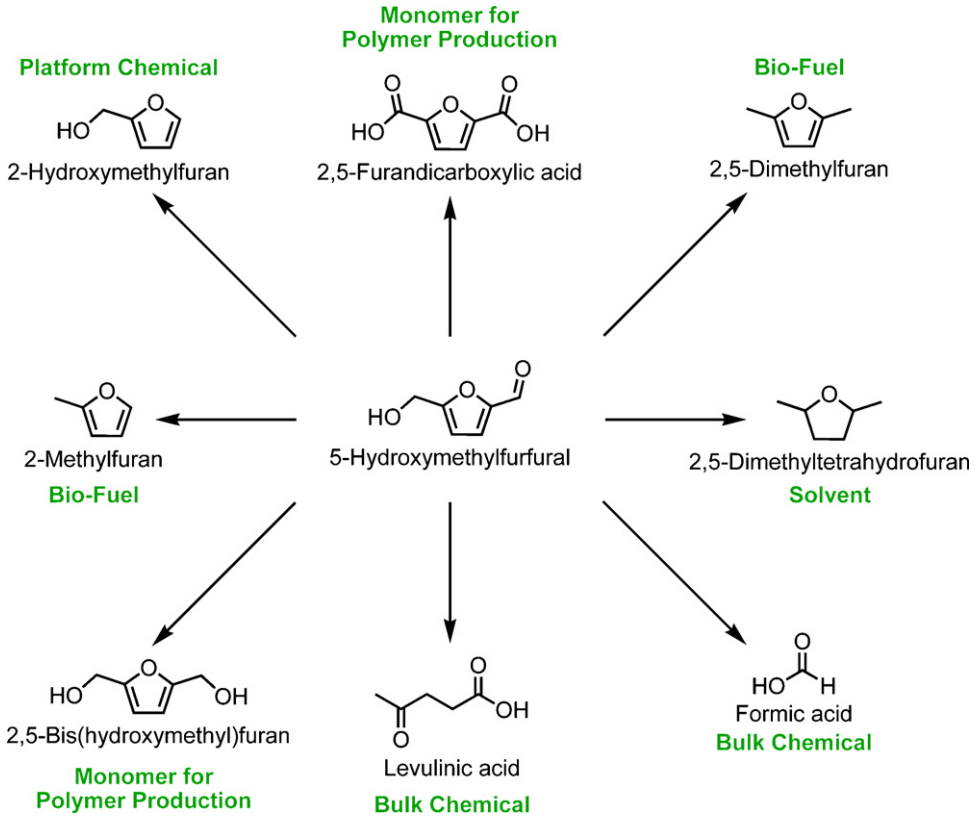

Fig. 1 – HMF as a precursor for a range of commercial chemicals.

Table 2 – Typical reaction conditions for immobilized glucose isomerase.

Process	Temperature (°C)	Dry substance content (%)	pH	Process time (h)
Isomerization	50–60	40–50	7–8	0.3–3

a biorefinery manufacturing HMF or its derivatives. The most likely biorefinery scenario will not be restricted to one product but make a series of high and low value products (including fuel). This allows the biorefinery to shift focus from one product to another if the market changes. In the case of HMF or FDA production this means that producing purely HMF or FDA is not the ultimate target and side-streams producing other valuable products besides HMF or FDA can actually be of benefit. One potential by-product of value is levulinic acid. This is formed via a rehydration of HMF to give levulininc acid along with formic acid. Both of these molecules are valuable products that are potentially worth isolating as side streams. In this respect the goal of completely selective dehydration may in the future be misplaced.

The synthesis of HMF is based on the acid-catalyzed triple dehydration of C6-sugar monomers, mainly glucose and fructose. However, various polysaccharides have also been reported as HMF sources (Rapp, 1987). The most convenient method for the preparation of HMF is by dehydration of fructose. When starting from ketohexoses (such as fructose) the dehydration reaction proceeds more efficiently and selectively. This can be explained by aldohexoses (such as glucose) only being able to enolyze to a low degree which is considered the limiting step in the production of HMF from glucose. However, glucose is the favored source of HMF due to the lower cost of glucose compared to fructose. Fructose may be obtained by enzyme or acid-catalyzed hydrolysis of sucrose and inulin or by the isomerization of glucose to fructose. Inulin is a linear β-2,1 linked fructose polymer which is terminated by a single glucose unit. It is found as a food reserve in a number of plants including Jerusalem artichoke and chicory. Industrially fructose is produced from glucose by the enzyme glucose isomerase (EC 5.3.1.5). The equilibrium conversion under industrial conditions is 50% making chromatographic separation necessary in order to obtain the industrial product of 55% fructose, which has sweetness similar to sucrose. Glucose isomerase is used industrially as an immobilized enzyme with typical reaction conditions as shown in Table 2.

Commercial immobilized glucose isomerase preparations used in a packed column have half-lives between 100 and 200 days. Most columns therefore last for more than 1 year and productivities are typically around 15 tons of syrup dry substance/kg immobilized enzyme.

4. Case studies

4.1. *Case 1: conversion of glucose/fructose to HMF*

To date most of the work regarding the acid-catalyzed conversion of fructose, and to a less extent glucose, into HMF has been carried out in aqueous reaction media. Obviously water being very abundant and non-hazardous is the preferred solvent of choice when exploring green and sustainable chemistry. Furthermore water is a good solvent for dissolving the monosaccharide substrates (fructose and glucose) as well as the product, HMF. However the dehydration of fructose to yield HMF in aqueous media is hampered by a competitive rehydration process resulting in the by-products levulinic acid and formic acid. In addition soluble and insoluble polymerization products (humins), that are thought to arise from the self- and cross-polymerization of HMF, fructose and other by-products seem to be more pronounced in an aqueous reaction medium than an organic one (Van Dam et al., 1986). Nevertheless, several interesting papers have been published on the dehydration of fructose into HMF. The conversion of glucose into HMF is more difficult and as a result there are only a few publications on this process.

4.1.1. *Aqueous media*

Several mineral acids such as HCl, H_2SO_4 and H_3PO_4 have been employed in the homogeneous catalyzed dehydration of fructose to yield HMF (Newth, 1951; Mednick, 1962; Román-Leshkov et al., 2006). So far, however, the yield and selectivity of reactions carried out in aqueous reaction media are not comparable to those observed in aprotic high-boiling organic solvents such as DMSO where the solvent also serves as the catalyst (Musau and Munavu, 1987). Despite high yields and selectivity, the cost of removing high-boiling solvents makes these solvents unsuitable for industrial and large-scale processes. Heterogeneous catalysts have, due to separation and recycling considerations, drawn more attention than homogenous catalysts. The use of various acidic heterogeneous catalysts such as niobic acid ($Nb_2O_5{\cdot}nH_2O$) and niobium phosphate ($NbOPO_4$) have been reported to have an intermediate selectivity of about 30% for the production of HMF at about 80% conversion of fructose (Carniti et al., 2006). Zirconium and titanium phosphates/pyrophosphates have been shown to have a very high selectivity of up to 100% at 100 °C in a period of 18 min for the formation of HMF in water. However as the reaction time increases, the selectivity drops fast which is thought to be due to the formation of polymeric by-products. Additionally, titanium oxides (TiO_2), zirconium oxides (ZrO_2) and H-form zeolites catalyze the dehydration reaction (Moreau et al., 1996). Especially interesting is the direct conversion of glucose to HMF which can be enhanced up to 5-fold compared to the hydrothermal dehydration, by employing an α-TiO_2 at 200 °C (Watanabe et al., 2005a,b). The main disadvantage with these catalysts seems to be the high temperature needed in order for the reaction to proceed without limited selectivity and conversion rates. Highly acidic cation-exchange resins such as those derivatized with sulfonic acid groups are also effective catalysts, providing the acidity of mineral acids together with the advantages of the heterogeneous catalysts (Rigal et al., 1981). These, often polystyrene based resins, can only tolerate temperatures up to around 130 °C, which reduces the range of their application. However this temperature range seems to be sufficient to overcome the activation energy barrier, when simultaneously applying the effect of microwave heating (Qi et al., 2008).

4.1.2. *Modified aqueous media and two-phase systems*

Phase modifiers have within the last couple of years proved very effective in promoting the conversion of fructose to HMF. Polar organic solvents that are miscible with water are added in order to increase the rate of the reaction to HMF and reduce the rate of the rehydration process forming by-products (Van

Dam et al., 1986). Commonly employed aqueous phase modifiers are acetone, DMSO and polyethylene glycol (PEG) (Qi et al., 2008; Chheda et al., 2007; Van Dam et al., 1986). A further modification of the aqueous phase system is the introduction of a second immiscible phase to create a two-phase reaction system. An organic phase extracts the HMF from the aqueous phase as it is produced and consequently reduces the formation of rehydration and polymeric by-products. Even with an initial concentration of fructose as high as 50 wt%, remarkable results with selectivity of 77% and a conversion of 90% at 180 °C with HCl as the catalyst have been reported. In comparison similar conditions in water resulted only in a selectivity of 28% and a conversion of 51% (Román-Leshkov et al., 2006).

4.1.3. *Non-aqueous organic solvents*

Until now, the best results for the dehydration of fructose to HMF have been made in high-boiling organic solvents. The low concentration of water prevents the rehydration of HMF to levulinic acid and formic acid. Iodine catalyzes the dehydration of the fructose part of sucrose in anhydrous DMF at 100 °C. Glucose is unaffected under the same conditions (Bonner et al., 1960). High selectivity has also been obtained when using PEG-600 as a solvent together with catalytic HCl. With the acid present a 1:1 solution of fructose and PEG-600 can be obtained at 85 °C (Kuster and Laurens, 1977). The first really high yields were reported by Nakamura and Morikawa (1980) using a strongly acidic ion-exchange resin as the catalyst in DMSO at 80 °C. These conditions gave a yield of 90% after 8 h. The rate of the reaction was strongly affected by the type of resin used (Nakamura and Morikawa, 1980). Quantitative yields, without the use of a catalyst, were reported soon after in DMSO at 100 °C for 16 h (Brown et al., 1982). Good results were also obtained during an investigation of the optimum fructose concentration in DMSO. With 8.5 molar equivalents of DMSO with respect to fructose, a yield of 92% was obtained at 150 °C without any catalyst after 2 h (Musau and Munavu, 1987).

None of the above examples are suitable for production on a large-scale. High-boiling aprotic solvents such as DMSO, DMF and NMP are all miscible with water as well as many other common organic solvents. This makes separation of the desired products very difficult. Furthermore, both DMF and NMP are considered to be teratogenic.

4.1.4. *Supercritical/subcritical solvents*

Since the best results for the dehydration of hexoses to HMF have been in high-boiling organic solvents, the use of low-boiling solvents in their sub- or supercritical state would be an interesting alternative. Subcritical water has emerged in recent years as a feasible alternative to organic solvents at larger scale. Its unique intrinsic acidic and basic properties, makes it particularly interesting as a reaction medium for the dehydration of carbohydrates. When glucose is dehydrated in pure subcritical water, HMF is formed with greater selectivity than when using sulfuric acid or sodium hydroxide as catalysts under the same pressures and temperatures (Simkovic et al., 1987). Watanabe et al. (2005a) explored the use of different TiO_2 and ZrO_2 catalysts in highly compressed water. The anatase-TiO_2 catalyst showed both basic and acidic properties and catalyzed the conversion of glucose to HMF. Yields were only about 20%, but the selectivity was more than 90%. The basic properties of the catalyst were thought to catalyze the isomerization of glucose to fructose, whereas the acidic properties were thought to catalyze the dehydration (Watanabe et al., 2005b). Yields of up to 50% were obtained when using fructose as the starting sugar and different zirconium phosphates as catalysts in subcritical water. No rehydration products were observed, yet the highest selectivity was not more than 61%. By-products were humins and furaldehyde (Asghari and Yoshida, 2006). Interesting results have recently been reported on the catalytic effect of H_3PO_4, H_2SO_4 and HCl in the direct conversion of glucose to HMF in water at 523 K. It was concluded that the weakest acid, H_3PO_4, was the best catalyst for the conversion of glucose into HMF and the strongest acid, HCl, was the best catalyst for the conversion of HMF to levulinic acid. The best yield for HMF was 40% (Takeuchi et al., 2008). More extensive studies on the kinetics of the dehydration of D-glucose and D-fructose in sub- and supercritical water have been made as well as the behavior of HMF under similar conditions (Kabyemela et al., 1999; Asghari and Yoshida, 2007; Chuntanapum et al., 2008).

Nevertheless, the overall results from sub- and supercritical water have so far been unsatisfactory in terms of yields. Bicker et al. (2003) explored other low-boiling solvents such as acetone, methanol and acetic acid. An acetone/water mixture at 180 °C and 20 MPa gave 99% conversion of fructose and a selectivity of 77% to HMF. This excellent result was explained by the structural similarities between acetone and DMSO, which would promote the furanoid form of fructose and hence favor the formation of HMF. The authors also propose a continuous process for the reaction (Bicker et al., 2003, 2005).

4.1.5. *Ionic liquids*

Another attractive alternative to high-boiling organic solvents is the use of ionic liquids. Their unique physical properties such as negligible vapor pressure and non-flammability make them particularly suitable as solvents for large-scale production. There is a possibility to design and functionalize the ions of the ionic liquid, giving them ability to work both as solvent and reagent for certain reactions. There are several examples of ionic liquids that have the ability to solubilize natural polymers such as cellulose, starch and chitin. This opens an excellent opportunity to convert crude biomass into fine chemicals (Liu et al., 2005; El Seoud et al., 2007).

The first dehydrations of fructose and glucose with the help of ionic liquids date back 25 years. Fructose was dehydrated in the presence of pyridinium chloride to HMF in high purity with 70% yield. The corresponding result for glucose was only 5% (Fayet and Gelas, 1983). In 1-butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-methylimidazolium hexafluorophosphate, yields up to 80% from fructose were obtained using DMSO as a co-solvent and Amberlyst-15 resin as the catalyst. The DMSO helped to solubilize the starting fructose and the reaction was faster than in DMSO alone. Performing the reaction in 1-butyl-3-methylimidazolium tetrafluoroborate alone gave a yield of 50% within 3 h (Lansalot-Matras and Moreau, 2003). The best results so far from fructose were made by using the acidic 1-H-3-methylimidazolium chloride as reaction medium. This acted both as solvent and catalyst giving a yield of 92% after 15–45 min at 90 °C. There was no sign of HMF decomposition and glucose remained completely unreacted (Moreau et al., 2006). Recently remarkably good results were found using the ionic liquid 1-ethyl-3-methylimidazolium chloride together with $CrCl_2$, giving a total yield of 70% HMF directly from glucose and virtually no levulinic acid. The authors propose that the actual catalytic specie is the $CrCl_3^-$ ion formed together with the solvent

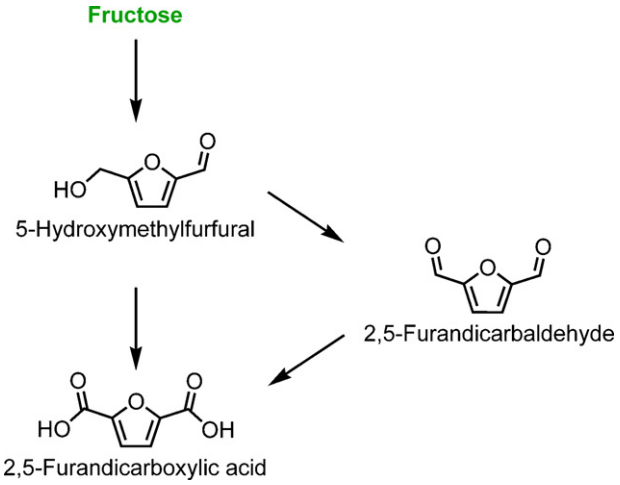

Fig. 2 – Oxidation of HMF to DFF and FDA.

and that it catalyzes the isomerization of β-glucopyranose to fructofuranose, which is subsequently dehydrated to HMF (Zhao et al., 2007). Bao et al. (2008) concluded that ionic liquids with a Lewis acid moiety were more efficient than those with a Brønsted acid counterpart when dehydrating fructose. These ionic liquids were also successfully immobilized on silica, giving a yield of up to 70% from fructose to HMF and completely retained their catalytic activity after five reaction cycles (Bao et al., 2008).

4.2. *Case 2: HMF oxidation to 2,5-diformylfuran and FDA*

FDA has been identified by the U.S. Department of Energy (DOE) biomass program as one of the 12 chemicals that in the future can be used as a feedstock from biomass in biorefineries (Werpy and Petersen, 2004). Due to the presence of the two carboxylic acid groups, FDA is considered to be a biorenewable building block to form polymers from biomass and therefore become an alternative to terephthalic, isophthalic and adipic acids, which are all produced from fossil fuels. Sugars in the form of mono- and disaccharides are easily available from biomass. The hexose type monosaccharides such as glucose and fructose can be catalytically dehydrated into HMF (Corma et al., 2007; Gallezot, 2007; Moreau et al., 2004). HMF can then be oxidized into FDA using a variety of routes and reaction types with stochiometric amount of oxidants. Most of them are described in a review by Lewkowski (2001), including electrochemical oxidation, use of barium and potassium permanganates, nitric acid and chromium trioxide. In this section we will focus on the recently reported catalytic routes for the oxidation of HMF into FDA.

4.2.1. *Oxidation of HMF to DFF*

Though production of FDA from HMF has been of great interest recently, there are few papers on catalytic aerobic oxidation of HMF. In the catalytic route to form FDA the partially oxidized intermediate 2,5-diformylfuran (DFF) is often observed (Fig. 2).

The dialdehyde is a useful product to form other derivatives, and a number of studies have reported on the selective formation of DFF. Thus, Halliday et al. (2003) reported oxidation of HMF to DFF using an in situ reaction protocol where HMF was directly generated from fructose and not isolated. Hence, using ion-exchange resins and, then, VOP-type catalysts the authors obtained DFF with a maximum yield of 45% based on fructose (Halliday et al., 2003). Carlini et al. (2005) reported that HMF, as a starting reagent or produced one pot from fructose, was oxidized to the corresponding dialdehyde in water with methylisobutylketone (MIBK), as well as pure organic solvents, with vanadyl phosphate (VPO) based catalysts (Zr, Nb, Cr, Fe modified) as such or using a TiO_2 support at 75–200 °C and 1 MPa. However, the reported yields were low ($H_2$0:MIBK = 0:30–5:30, HMF conversion 3–10%, selectivity to DFF 100–60%, respectively). Considering the oxidation as a stand-alone reaction and changing the solvents to less polar ones (benzene, toluene) better conversion rates and selectivity were obtained, and using MIBK as a solvent lead to 98% conversion with 50% selectivity. However, in DMF the results are even better (at 150 °C) giving 84% conversion and 97% selectivity.

4.2.2. *Oxidation of HMF to FDA*

The above-described DFF may either be used as a valuable by-product or as an intermediate for obtaining FDA. On the other hand, catalytic reactions leading to the formation of FDA are also reported.

Partenheimer and Grushin (2000) obtained DFF from HMF using metal bromide catalysts (Co/Mn/Zr/Br). The reactions were carried out in acetic acid at atmospheric pressure and also at 70 bar; the yields were 57% and 63% with the conversion of HMF 98% and 92%, respectively. Cobalt as a catalyst was also used by Ribeiro and Schuchardt (2003). Using cobalt acetylacetonate as a bi-functional acidic and redox catalyst encapsulated in silica in an autoclave at 160 °C, they obtained FDA, from fructose via HMF formation, with 99% selectivity to FDA at 72% conversion of fructose. By in situ oxidation of HMF to FDA starting from fructose, Kröger et al. (2000) described a way of producing FDA via acid-catalyzed formation and subsequent oxidation of HMF in a MIBK/water mixture using solid acids for fructose transformation and PtBi-catalyst encapsulated in silicone and swollen in MIBK. The reaction was carried out in a reactor divided with a PTFE-membrane in order to prevent the oxidation of fructose. However, though in principle the integration process has been described, the yields remain quite low. The resulting yield of FDA was 25% based on fructose. In the oxidation of HMF to FDA the use of noble metals was first studied by Vinke et al. (1991). Here, mainly Pd, Pt, Ru supported on different carriers were used as the aerobic oxidation catalysts. Although all the noble metals revealed catalytic activities, only Pt supported on Al_2O_3 remained stable and active and gave quantitative yields of FDA. The reactions were carried out in water at pH 9 using a reaction temperature of 60 °C and a partial oxygen pressure of 0.2.

4.2.3. *Oxidation of HMF to FDA derivatives*

A new approach to the oxidation of HMF has been reported recently by Taarning et al. (2008) using methanol as both solvent and reagent. They performed a reaction with a gold nanoparticle catalyst in an autoclave at 130 °C and 4 bars of dioxygen, and obtaining FDA with 98% yield (according to GC analysis) and 60% isolated yield after sublimation.

5. Process technology

Table 3 indicates some of the key features of possible routes for the conversion of fructose to HMF. A number of observations can be made:

Table 3 – Key features of possible routes for the conversion of fructose to HMF.

Mode of operation[a]	Catalyst[b]	Temp.	Fructose concentration	Solvent media[c]	Highest yield	Reference
B	Hetero.	80 °C	3–4% (w/w)	Water, MIBK	41%	Carlini et al. (2005)
B	Homo.	170 °C	10% (w/w)	Water, DMSO, MIBK, 2-butanol, DCM	87%	Chheda et al. (2007)
B	Homo.	90 °C	3–50% (w/w)	$HMIM^+Cl^-$	92%	Moreau et al. (2006)
B	Hetero.	165 °C	10% (w/w)	Water, MIBK	69%	Moreau et al. (1996)
B	Hetero.	80 °C	6% (w/w)	Water	42%	Carlini et al. (2004)
			3% (w/w)		59%	
B	Homo.	180 °C	30% (w/w)	Water, DMSO, PVP, MIBK, 2-butanol	76%	Román-Leshkov et al. (2006)
			50% (w/w)		71%	
B	Hetero.	90 °C	10% (w/w)	Water, DMSO, PVP, MIBK, 2-butanol	59%	Román-Leshkov et al. (2006)
			30% (w/w)		54%	
B	Hetero.	110 °C	6–10% (w/w)	Water	31%	Carlini et al. (1999)
B		100 °C	6–10% (w/w)	Water, MIBK	74%	
C		85 °C	10–20% (w/w)	Water	26%	
B	Hetero.	100 °C	6% (w/w)	Water	85%	Benvenuti et al. (2000)
C	Hetero.	165 °C	0.5–3.5% (w/w)	Water, MIBK	–	Rivalier et al. (1995)

[a] Process is continuous (C) or batch (B).
[b] Catalyst is homogenous (homo.) or heterogenous (hetero.).
[c] Solent media are: methylisobutylketone (MIBK), dimethyl sulfoxide (DMSO), poly(1-vinyl-2-pyrrolidinone) (PVP), dicholormethane (DCM), and 1-H-3-methyl imidazolium chloride ($HMIM^+Cl^-$).

- Catalyst type
  A variety of catalysts like mineral and organic acids, salts, and solid acid catalysts such as ion-exchange resins and zeolites have been used in the dehydration reaction. The homogeneous acid-catalyzed processes are frequently associated with low selectivity (30–50%) for HMF at a relatively high conversion (50–70%) (Carlini et al., 1999). Moreover, problems related to separation and recycling of the mineral acid as well as of plant corrosion are expected. Thus, recent research has been based on heterogeneous acid catalysts which have considerable potential for industrial application (Carlini et al., 1999).
- Mode of operation
  The dehydration process has mostly been studied in batch operated reactors. Few researchers have examined a continuous process. One exception is the work reported by Kuster and Laurens (1977), who developed a continuous homogeneous catalyzed process for dehydration of fructose to HMF by using a tube reactor with polyethyleneglycol-600 as the solvent. Dehydration of fructose in a continuous stirred tank reactor with phosphoric acid and MIBK as a solvent was also reported by Kuster and van der Steen (1977).
- Media
  The dehydration of hexoses and pentoses has been studied in water, organic solvents, biphasic systems, ionic liquids, and near- and supercritical water. The most convenient solvent for dehydration of fructose to HMF is water. However, water is the reactant in the reverse reaction. Moreover, with the presence of water, HMF decomposes to levulinic acid, formic acid and humins. Organic solvents are thus introduced to improve the dehydration reaction by shifting the equilibrium and suppressing HMF hydrolysis. Relatively high yields were reported for the use of DMSO with ion-exchange catalysts (Nakamura and Morikawa, 1980; Rigal and Gaset, 1985) and quantitative yields of HMF were also reported by heating fructose in the absence of catalyst (Brown et al., 1982; Musau and Munavu, 1987). In spite of the advantages of using DMSO, the difficulties of separation limit its application. Moreover, possible toxic sulfur containing by-products from decomposition of DMSO may cause a risk to health and the environment (Moreau et al., 2004). A biphasic reactor system has been developed to suppress HMF degradation by using organic solvent to separate HMF immediately from the reaction medium as it forms. Consequently some work has been carried out to find the proper extraction solvent. Amongst the solvents reported, MIBK is the most commonly used solvent for extraction of HMF. Due to its relatively low-boiling point, it is relatively easy to separate HMF from MIBK. In general, poor HMF partitioning in the organic solvents leads to the use of large amounts of solvent. Purification of the diluted HMF product thus causes large energy expenditure in the subsequent process (Chheda et al., 2007).

5.1. *New technology*

Román-Leshkov et al. (2006) developed a cost-effective method to produce HMF using a biphasic batch reactor system with phase modifiers. They obtained D-fructose to HMF in high yields (>80%) at high fructose concentrations (10–50 wt%) and delivered the product in a separation-friendly solvent. In the biphasic reactor system, DMSO and/or poly(1-vinyl-2-pyrrolidinone) (PVP) were added as modifiers to suppress the formation of dehydration by-products in the aqueous phase with HCl as the acid catalyst. The product was continuously extracted into an organic phase MIBK modified with 2-butanol to enhance partitioning from the reactive aqueous solution. In this study, they reported an improvement in selectivity from 60 to 75% by adding small amounts of aqueous phase modifiers (such as DMSO and PVP) in the biphasic reactor system. Additionally, by optimizing the partitioning of HMF product into the organic phase, the process not only minimized the degradation of HMF in the aqueous phase, but also achieved efficient product recovery.

Zhao et al. (2007) used a metal chloride catalyst in an ionic liquid for the dehydration of HMF. In this reaction, the only water present in the system was from the dehydration of fructose to HMF reaction, which indicated that the conditions for HMF degradation to levulinic and formic acids were not met. By using this metal chloride in ionic liquid, the reaction could take place at reduced temperature, 80 °C for fructose dehy-

dration, and 100 °C for glucose. 90% yield was achieved from fructose and 70% yield from glucose.

Bicker et al. (2003) reported the use of benign solvents such as acetone, methanol or acetic acid in a sustainable process outline. They reported the dehydration of D-fructose to HMF in sub- and supercritical acetone/water mixtures. The use of this reaction media resulted in higher yields of HMF (77% selectivity, 99% conversion). No solid impurities (humins) were formed. The authors also claimed the potential for a technical process based on this low-boiling point solvent, whereby a price for HMF of about 2 Euro/kg could be achieved if fructose was available at a price of around 0.5 Euro/kg.

However all these new technology approaches for making HMF from fructose have been carried out at a small scale. On a larger scale Rapp has reported yields of ~2.5 kg HMF from aqueous dehydration of fructose (Rapp, 1987). The production of HMF, close to a kg scale, has also been reported using DMSO as the reaction media (M'Bazoa et al., 1990). Nevertheless since high selectivity is crucial for implementing this reaction on an industrial scale, the recent research has been highly focused on alternative routes for improving the selectivity of the dehydration reaction.

5.2. *Process implementation, integration and scale-up*

In order to comply with the demands of efficient and specific conversions of the chemical reactants in a biorefinery with a minimum of economic cost, a special focus on process implementation, integration and scale-up must be paid. The development of combined biological and chemical catalytic reactions without intermediate recovery steps has the potential to become an important future direction for carrying out sustainable organic syntheses (Hailes et al., 2007).

The synthesis of a variety of important chemical building blocks involves multistep reactions often catalyzed by a chemical or biological catalyst. In many cases, the optimal operating conditions are rather different for the individual steps of such synthesis reactions. However, it could prove favorable if such reaction steps are combined or integrated, allowing them to occur concurrently, in proximity to one another, and at or close to their respective optimal operating conditions. Also from an engineering point of view, integration of unit operations could contribute to among other things simpler design, less equipment and less piping (Koolen, 1998). Furthermore, integration could reduce operating time and costs as well as consumption of chemicals and use of energy (Bruggink et al., 2003). An important aspect of process integration is the different working condition for the individual reactions. When the aim is to match different reactions involving enzymes, important factors such as enzyme stabilities, reaction rates, reaction media (e.g. pH, temperature, pressure) and reactor design must be considered. Tools to aid integration of different processes include reactor compartmentalization (Fournier et al., 1996; Byers et al., 1993; de Jong et al., 2008; Chen et al., 1997), medium engineering (Bao et al., 2008; Zhao et al., 2007), ISPR (Freeman et al., 1993; Woodley et al., 2008), optimized reactor designs (Stankiewicz and Moulijn, 2003) and multifunctional catalysts (Bruggink et al., 2003).

The conversion of glucose to FDA involves three steps, each with different optimal physical and chemical parameters like pH, temperature and pressure. Furthermore, the catalysts are of different nature with a bio-catalyst (enzyme) in the isomerization of glucose to fructose and a number of potential chemical catalysts of both heterogeneous and homogeneous nature in the following dehydration and oxidation reactions. While the potential for integration exists, it is only via an economic evaluation that such options can be further considered. A valuable process implementation tool to achieve both qualitative and quantitative understanding of the reaction processes and their potential for improvement is mathematical modeling. A good model should facilitate knowledge and understanding of the chemical reactions and include in a quantitative manner the most important physical and chemical governing parameters. As more is understood about the alternative synthetic routes to FDA, the appropriate modeling tools will also need to be developed.

6. Future outlook

With the implementation of biorefineries and increased interest in biofuel it is clear that the associated sugar-based chemistry will provide a rich variety of chemical products as building blocks for higher value molecules. The extent to which this happens depends on two factors. First the economics of the biorefinery will act as a driver in many cases to provide a means to develop higher value products alongside fuel. Ultimately the value of each product tree will need to be evaluated alongside the associated cost of implementing additional technology. Secondly it is clear that new technology and improved catalytic methods are required to produce high value building blocks such as FDA. Some of the more promising routes lie in new media such as ionic liquids but it is also clear that far higher selectivities are required. In this respect enzyme based catalysis will have a particular and likely expanding role in the future development of biorefinery technology. Finally, the implementation of new technology for biorefineries must be evaluated within the context of green chemistry and the necessary environmental requirements. For example the selection of organic solvents and catalysts must adhere to the criteria for sustainable processing. This is essential in order to ensure that new processes use sustainable processing methods as well as making use of sustainable resources.

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Synthesis of 5-(Hydroxymethyl)furfural in Ionic Liquids: Paving the Way to Renewable Chemicals

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The synthesis of 5-(hydroxymethyl)furfural (HMF) in ionic liquids is a field that has grown rapidly in recent years. Unique dissolving properties for crude biomass in combination with a high selectivity for HMF formation from hexose sugars make ionic liquids attractive reaction media for the production of chemicals from renewable resources. A wide range of new catalytic systems that are unique for the transformation of glucose and fructose to HMF in ionic liquids has been found. However, literature examples of scale-up and process development are still scarce, and future research needs to complement the new chemistry with studies on larger scales in order to find economically and environmentally feasible processes for HMF production in ionic liquids. This Minireview surveys important progress made in catalyst development for the synthesis of HMF in ionic liquids, and proposes future research directions in process technology.

Introduction

As fossil resources for chemicals and fuels are becoming depleted, the search for new pathways from renewable feedstocks has intensified. One compound that has been under particular scrutiny as a future platform chemical is 5-(hydroxymethyl)furfural (HMF), a six-carbon furan ring obtained from the triple dehydration of hexose sugars.[1,2] HMF has been covered extensively in several reviews,[3–5] and is primarily considered a starting material for other chemicals with important applications, such as monomers for plastics,[6] solvents, or fuels (Scheme 1).[7]

During the past ten years, chemical applications with ionic liquids (ILs) have received increased attention, resulting in an exponential increase in the number of papers published. ILs are normally defined as salts that are liquid below 100 °C and exhibit unique characteristics, such as a negligible vapor pressure, nonflammability, high thermostability, and close to infinite structural variation.[8] Moreover, ILs have remarkable solubilizing ability, which enables large natural polymers such as cellulose to be dissolved at high concentrations.[9-13] Chloride-based ILs have an exceptionally high capacity for dissolving carbohydrates since the extensive hydrogen bonding network that constitutes the structure of the solid carbohydrate is disrupted.[8] One IL in particular that has been widely recognized for its ability to dissolve cellulose is 1-butyl-3-methylimidazolium chloride ([BMIm]Cl), which can dissolve as much as 25% crystalline cellulose by weight.[9] This liquid also possesses the ability to completely dissolve significant amounts of crude biomass, such as banana pulp,[12] poplar, eucalyptus, pine, and oak.[13] Furthermore, the addition of mineral acids to [BMIm]Cl enables the efficient hydrolysis of cellulose to its monomeric constituent glucose.[14,15] Apart from chloride, ILs that incorporate the dicyanamide anion also exhibit very high capacities for carbohydrate dissolution.[10]

The combination of ILs and HMF production has become an important field in its own right, since ILs benefit the selectivity of the conversion of hexoses to HMF and opens up the possibility of one-pot reactions directly from crude biomass. Under aqueous conditions, the selectivity of the reaction is hampered by the irreversible hydrolysis of HMF to formic acid and levulinic acid.[16,17] High yields can be obtained in high-boiling solvents such as DMSO, but suffer from difficult product recovery.[18–20] Another important side reaction in the dehydration of hexoses is the formation of polymers known as humins. These species are formed from different intermediates in the reaction and their rate of formation increases as the concentration of the reacting sugar increases.[21,17] Humin formation remains a problem for HMF synthesis in ILs, but can be significantly reduced as the selectivity towards HMF is very high in many reaction systems.

This Minireview surveys what has been investigated to date in producing HMF from various carbohydrates in IL media, alongside a section on the implications and challenges that are associated with process development of these reactions. A certain focus is set on the future possibilities for environmentally and economically feasible processes using IL reaction media.

Dehydration of Carbohydrates

Carbohydrates constitute 75% of the world's renewable biomass and cellulose, a glucose polymer, is the most abundant.[22] The dehydration of fructose and glucose serve as

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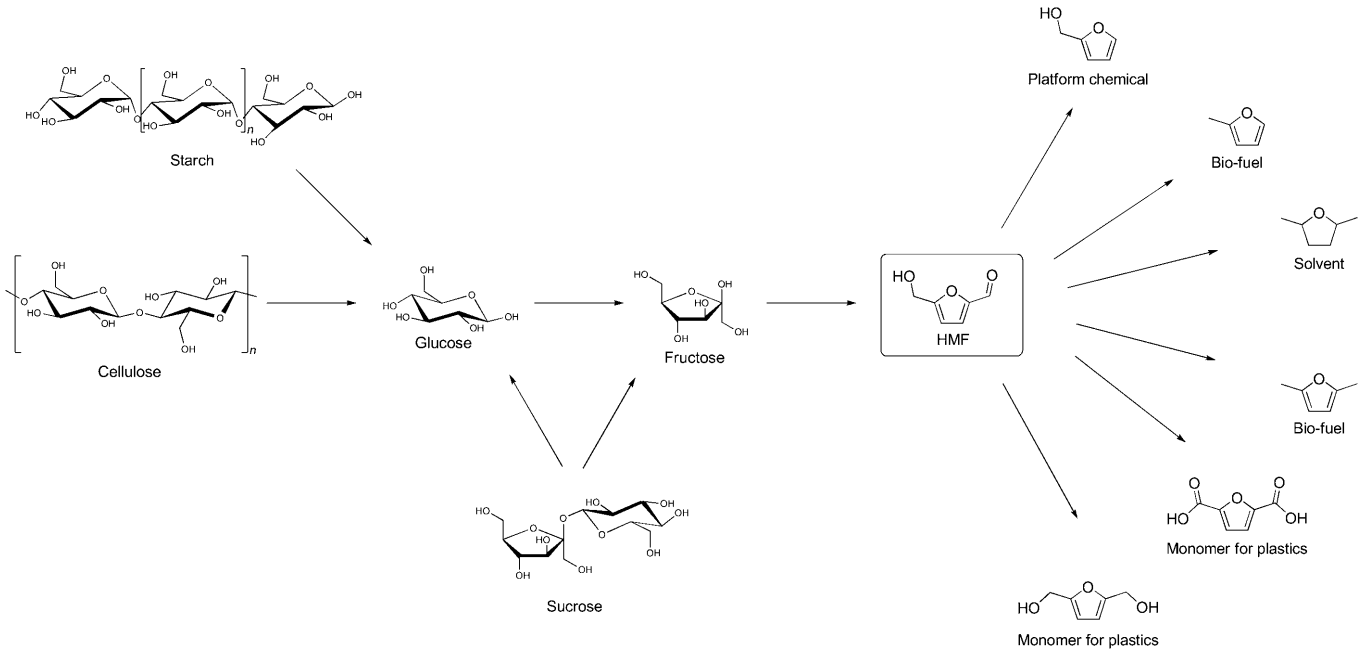


Scheme 1. The synthesis of HMF from carbohydrates and its further derivatization to important chemicals.

model reactions for biomass-derived carbohydrates since the conversion to HMF always involves these sugars in the final reaction sequence. The most noteworthy results in carbohydrate conversion to HMF in ILs are summarized in Table 1.

Table 1. A selection of systems for dehydration of various carbohydrates to HMF in different ionic liquids with or without catalyst.

Entry	Carbohydrate	Solvent	Catalyst	Catalyst amount [mol%]	T [°C]	t [h]	HMF yield [mol%]	Ref.
1	fructose	[MIm]Cl	–	–	90	0.75	92	[40]
2	fructose	[choline]Cl/citric acid	–	–	80	1	91	[50]
3	fructose	[BMIm]Cl	$CrCl_3$	9	100	6	96	[53]
4	fructose	[BMIm]Cl	WCl_6	10	50	4	63	[54]
5	fructose	[BMIm]Cl	HCl	8	23	24	72	[47]
6	glucose	[EMIm]Cl	$CrCl_2$	6	80	3	70	[52]
7	glucose	[BMIm]Cl	$CrCl_3$	9	100	6	81	[53]
8	glucose	[BMIm]Cl	$CrCl_3$	2	n.a.[a]	0.0167	91	[56]
9	glucose	[EMIm][BF_4]	$SnCl_4$	10	100	3	61	[63]
10	glucose	[EMIm]Cl/CH_3CN (5:2)	12-MPA[b]	1	120	3	97	[64]
11	sucrose	[choline]Cl	$CrCl_2$	10	100	0.5	62	[51]
12	sucrose	[EMIm][BF_4]	$SnCl_4$	10	100	3	65	[63]
13	sucrose	[BMIm]Cl/MIBK	$CrCl_3$	14	100	4	100	[42]
14	starch	[EMIm][BF_4]	$SnCl_4$	10	100	3	47	[63]
15	starch	[OMIm]Cl	$CrCl_2$	20[c]	120	1	73[c]	[75]
16	cellulose	DMA/LiCl/[EMIm]Cl	$CrCr_3$; HCl	25; 10	140	2	54	[55]
17	cellulose	[BMIm]Cl	$CrCl_3$	6	n.a.[a]	0.05	62	[72]
18	corn stover	DMA/LiCl/[EMIm]Cl	$CrCl_3$; HCl	10; 10	140	2	48	[55]
19	pine wood	[BMIm]Cl	$CrCl_3$	6	n.a.[a]	0.05	52	[72]
20	inulin	[BMIm][HSO_4]/[BMIm]Cl	Amberlyst 15	75[d]	80	1	82	[78]

[a] Microwave irradiation (400 W); [b] 12-molybdophosphoric acid; [c] wt%; [d] calculated from number of acid equivalents per kilogram catalyst.

Fructose

Dehydration of fructose to HMF has been extensively investigated in aqueous solutions[7,23–34] and organic solvents[18–20,35–37] throughout the 20th century. The first reported example of fructose conversion to HMF in ILs is a somewhat overlooked publication from the early 1980s.[38] Fructose was converted to HMF in pyridinium- and ammonium-based ILs with halides, trifluoroacetate, and tosylate as anions. The best results were obtained with tetraethylammonium bromide, which afforded HMF in 75% yield. This work did not have any immediate impact on the further development of HMF production in salt solutions and it was not until the beginning of the next millennium that carbohydrate conversion in ILs became a hot topic when Lansalot-Matras and Moreau[39] showed that dehydration of fructose in 1-butyl-3-imidazolium-based ILs with $[BF_4]^-$ or $[PF_6]^-$ as anions could be achieved with excellent yields up to 87% using Amberlyst 15 as a heterogeneous acid catalyst and DMSO as cosolvent. They followed up this work by performing dehydration in methylimidazolium chloride ([MIm]Cl), which provided a yield

of 92% in the neat IL without any additives.[40] Their work prompted intensified activity on the topic and in the years that followed several examples on the dehydration of fructose and other carbohydrates in IL media were demonstrated. The difference in reactivity using a Brønsted acidic or a Lewis acidic IL as catalyst in DMSO was investigated by Bao et al.[41] They found that the Lewis acidic liquid showed a higher efficiency, as well as a higher stability for HMF when left for a longer time in the DMSO/IL mixture. However, when the temperature was increased from 80 to 160 °C, the Brønsted acidic IL afforded a slightly higher yield. The employment of Brønsted acidic ILs for the dehydration of fructose has been exploited further in recent studies, both as neat ILs[42,43] and as additives.[44,45] In addition, there have been examples in which addition of a Brønsted acidic to a non-acidic IL markedly promoted the reaction rate of fructose dehydration.[46–48] The use of polyimidazolium salts (PIMS) that were acidified with HCl as catalysts gave yields of 79–84% of HMF from fructose in [BMIm]Cl at 80–100 °C and could be reused 11 times without any detected deactivation.[49]

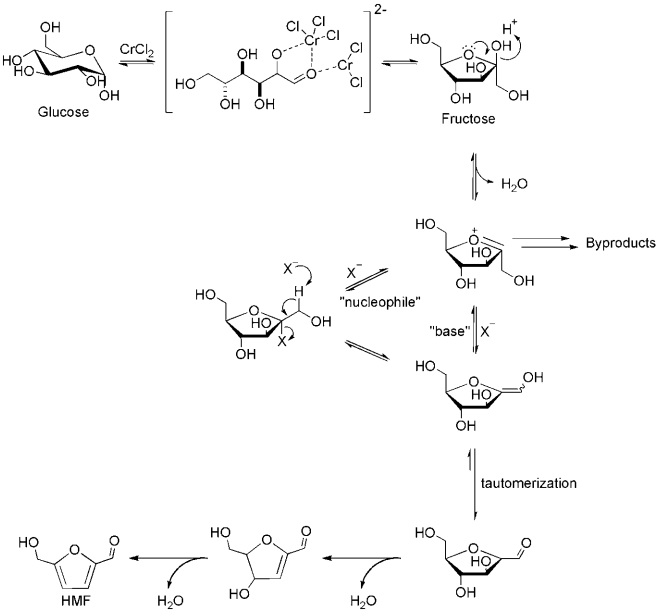
Even though the dehydration of fructose to HMF has been dominated by imidazolium-based ILs, there are some noteworthy exceptions. Making a eutectic mixture of choline chloride and citric acid resulted in a promising catalytic system, which, together with continuous extraction with ethyl acetate, afforded an HMF yield of 91%.[50] The main advantage of this procedure was not only the excellent yield but also the fact that all chemical components involved could be made from renewable sources, even though their main origin today is petrochemical. Choline chloride was further explored by Ilgen et al.[51] to make highly concentrated mixtures of fructose (up to 50 wt%), which resulted in solutions that were liquid below 100 °C, far below the normal melting point of pure choline chloride, which is 300 °C. These mixtures could furnish HMF yields from fructose up to 67% by the addition of *p*-TsOH as catalyst. By increasing the concentration even further, Li et al.[48] managed to dissolve 67 wt% fructose in [BMIm]Cl and with the addition of HCl as catalyst obtained a yield of HMF of 51%.

Chromium chloride is a catalyst that primarily promotes the dehydration of glucose to HMF.[52] Nevertheless, the use of chromium(II) or chromium(III) chloride together with N-heterocyclic carbene (NHC) ligands resulted in HMF yields of up to 96% in [BMIm]Cl.[53]

The examples above have all required temperatures of 80 °C or more to attain full, or nearly full, conversion. However, recent work has shown that the dehydration of fructose to HMF can be achieved with close to full conversion at ambient temperature using [BMIm]Cl as solvent together with WCl_6 as catalyst.[54] The yield was enhanced further when using continuous extraction with THF. In a very recent publication, Lai and Zhang[47] argued that the catalytic effect was present even in the absence of metals. Adding concentrated aqueous HCl to a mixture of [BMIm]Cl and fructose afforded a low-viscosity liquid at ambient temperature which, after 24 h, resulted in an HMF yield of 72%.

Glucose

The conditions by which fructose is converted into HMF are normally ineffective on glucose.[39] A major breakthrough came in 2007 when Zhao et al.[52] published their pioneering work showing that chromium(II) chloride had a remarkable effect on the dehydration of glucose in 1-ethyl-3-methylimidazolium chloride ([EMIm]Cl) leading to an HMF yield of 70%. A number of other transition metal chlorides were also used as catalysts, but they only provided HMF yields below 10%. A higher catalytic effect was ascribed to $CrCl_2$ than to $CrCl_3$, something which has been questioned in later studies. Nevertheless, their work prompted an intense search to further exploit the chromium system as well as finding other catalysts for the direct conversion of glucose to HMF. Binder and Raines[55] made an extensive study on glucose dehydration in dimethylacetamide (DMA) with the addition of halide salts. Adding 10 wt% LiCl or LiBr along with $CrCl_2$, $CrCl_3$, or $CrBr_3$ resulted in HMF yields up to 80%. A putative mechanism was further put forward in which the vital role of the halide ion was made evident (Scheme 2). They did not find a significant activity difference



Scheme 2. Proposed mechanism for glucose dehydration catalyzed by chromium chloride.[29,52,55,57]

between Cr^{II}- and Cr^{III}-based catalysts, which indicated that the oxidation state of the chromium was not decisive. Yong et al.[53] attained an HMF yield of 81% by the use of a NHC–chromium system in [BMIm]Cl, which also exhibited no significant difference between the two oxidation states of chromium. The highest reported yield for HMF from glucose with $CrCl_3$ was made in [BMIm]Cl under microwave heating.[56] The catalyst loading was low (2 mol%) in comparison to other studies and the maximum yield was reached after 1 min.

The chromium-based catalysts have to date only exhibited superb performances in imidazolium-based ILs. Attempts in

other mixtures have yet to give comparable results; for example, a eutectic mixture of glucose and choline chloride resulted in an HMF yield of 45% with Cr^{II} and 31% with Cr^{III}.[51] This is also the only work besides the original work in the group of Zhang[52] that displayed a difference in catalytic performance between the two chromium species. The mechanism of the chromium-catalyzed conversion of glucose to HMF was thoroughly investigated using density functional theory (DFT) calculations by Pidko et al.[57] The study concluded that the dimer complex of $CrCl_2$ lowered the energy for the transition state of the isomerization of glucose to fructose. The transition state was taken to be the hydride shift as in the enzyme catalyzed isomerization with glucose isomerase[58] and the $CrCl_2$ catalyzed conversion of xylose to furfural.[59] A detailed mechanism of glucose dehydration via fructose is shown in Scheme 2. Another mechanism for the isomerization of glucose to fructose can also be envisioned. It is well known that glucose can be isomerized to fructose under basic conditions in aqueous solutions, something that has been employed in supercritical water and organic solvents where both a solid acid catalyst and a basic catalyst have been used simultaneously.[30,31,60,61]

Lanthanide(III) salts have also been investigated as catalysts for the conversion of glucose to HMF.[62] The use of the strongest Lewis acid $Yt(OTf)_3$ resulted in the highest HMF yield of 24% and the catalytic effect increased with increasing atom number in the lanthanide series. An increase in yield was also observed when the chain length of the alkyl groups on the imidazolium cation increased, that is, 1-octyl-3-imidazolium chloride ([OMIm]Cl) had a significantly higher yield than [EMIm]Cl. This phenomenon has not been observed with other catalyst systems where [EMIm]Cl has been superior or equivalent to other methylimidazolium chlorides.[52]

Even though the best yields for the conversion of glucose to HMF have been obtained with chloride- or other halide-containing ILs, a study in 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm][BF_4]) showed that $SnCl_4$ could function as a catalyst for glucose dehydration, with an HMF yield of 61%.[63] Interestingly, both the yield and the selectivity for HMF were higher in [EMIm][BF_4] than both [BMIm]Cl and DMSO when $SnCl_4$ was employed as a catalyst.

The best catalytic system for glucose dehydration hitherto was demonstrated in a very recent publication using 12-molybdophosphoric acid (12-MPA) in [EMIm]Cl with acetonitrile as cosolvent, which offered virtually quantitative yield of HMF.[64] The yield was significantly enhanced by addition of acetonitrile and [BMIm]Cl was equivalent to [EMIm]Cl in performance, whereas 1-butyl-3-methylpyridinium chloride ([BMPy]Cl) and 1-butyl-2,3-dimethylimidazolium chloride ([BDMIm]Cl) induced a lower catalytic effect.

To date, only one example of nonmetal-catalyzed dehydration of glucose to HMF has been reported. In this work, boric acid was utilized as a promoter in [EMIm]Cl, which resulted in an HMF yield of 43%.[65] A supporting NMR spectroscopic study with glucose-2-d_1 confirmed that the conversion of glucose to fructose proceeded via an ene-diol mechanism as opposed the chromium catalyzed isomerization.

The synthesis of HMF from hexoses other than fructose and glucose has very few examples in the literature. An interesting exception is the conversion of red seaweed to HMF via the hexose 3,6-anhydrogalactose in several ILs where choline hydrogensulfate ([choline][HSO_4]) proved to be best with regard to sugar yields as well as HMF formation.[66]

Sucrose

Sucrose consists of one fructose and one glucose moiety linked together by a glycosidic bond. This bond is easily hydrolyzed upon heating in ILs whereby the single units of fructose and glucose are exposed to further reaction.[40] Early work by Fayet and Gelas[38] explored the dehydration of sucrose in pyridinium-based ILs resulting in an HMF yield of 30%. Since no other catalyst was present, it is reasonable to believe that the fructose unit was easily converted to HMF whereas the glucose remained unreacted. This was confirmed later when sucrose in [MIm]Cl underwent nearly quantitative conversion to HMF and glucose.[40] Tong et al.[45] made use of a *N*-methylmorpholinium methylsulfonate ([NMM][CH_3SO_3])/DMSO/LiBr system, by which they attained a HMF yield of 48%.

High-concentration solutions of sucrose and choline chloride (50 wt%) together with chromium chloride catalysts resulted in even higher HMF yields.[51] Notably, a significant difference between $CrCl_2$ and $CrCl_3$ was observed, with HMF yields of 62% and 43%, respectively. Chromium chloride was also used as a catalyst in the investigation by Chun et al.[67] using HCl/[OMIm]Cl/EtOAc mixtures, in which the best results were obtained with a sucrose concentration of 50 wt% and an HCl concentration of 0.3 M. Outstanding results were reported by Lima et al.,[42] who claimed quantitative HMF yield when using a [BMIm]Cl/MIBK/$CrCl_3$ system (MIBK: methyl *iso*-butyl ketone), which is surprising since their results for fructose and glucose alone were only 88% and 79%, respectively, under the same reaction conditions.

Good results were further attained in the $SnCl_4$/[EMIm][BF_4] system where 17 wt% solution of sucrose was converted to HMF with a yield of 65%.[63]

Starch and cellulose

The main advantage of using ILs as media for biomass conversion to HMF is, as mentioned above, the possibility to dissolve carbohydrate polymers and subsequently form HMF and its derivatives in one-pot reactions.[9,13] The first prerequisite for successful dehydration of cellulose or starch is that the polymer is easily depolymerized. It has been established that the addition of an acid catalyst to a [BMIm]Cl solution of cellulose enhances the hydrolysis of the glycosidic linkages between the monomers and that the depolymerization is first-order with respect to catalyst concentration.[68,69] The use of Amberlyst 15 DRY (i.e., containing less than 1.5% water) resulted in an ion exchange of the imidazolium cation on the surface of the solid catalyst that released protons into the solution and made the catalyst work homogenously.[69] An extensive study by Sievers et al.[15] explored the hydrolysis and chemical conversion of

pine wood in [BMIm]Cl. Adding a catalytic amount of trifluoroacetic acid to a solution of pine wood in [BMIm]Cl enabled complete hydrolysis of the carbohydrate fraction to water-soluble sugars at 120 °C, which is relatively mild. Efficient depolymerization has also been achieved with hydrogen gas together with ruthenium and platinum catalysts[70] and $FeCl_2$ in 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogensulfate.[71]

The second prerequisite for achieving a successful reaction of starch or cellulose to form HMF is that the catalytic system can transform glucose into HMF. Several studies that have dealt with glucose dehydration also involved attempts at direct conversion of cellulose to HMF. Binder and Raines[55] expanded their study on fructose and glucose dehydration in DMA/LiCl/[EMIm]Cl with cellulose and untreated corn stover, which were reacted with chromium(II/III) chloride as catalyst to afford HMF in 54% and 48% molar yield, respectively. The addition of [EMIm]Cl to the DMA/LiCl solution markedly enhanced the yield. The HMF yield from cellulose was increased further to 62% from chemical cellulose and 52% from pine wood by the use of $CrCl_3$ in [BMIm]Cl with microwave irradiation.[72] Extraordinary results were obtained by Zhang et al.[73] when using $CrCl_2$ and [EMIm]Cl, yielding 89% of HMF from crystalline cellulose. Remarkably, they used 20 wt% solution even though the highest reported [EMIm]Cl solution of cellulose is 15.8 wt%.[74] They used NMR spectroscopy as measurement of conversion, a less sensitive analysis method than the normally employed HPLC method.

Few examples on the conversion of starch to HMF in ionic media have been reported. Hu et al.[63] employed the $SnCl_4$/[EMIm][BF_4] system, by which an impressive HMF yield of 47% from starch was obtained. A more extensive study was made by Chun et al.[75] on the conversion of several different starch sources in 1-octyl-3-methylimidazolium chloride ([OMIm]Cl) with $CrCl_2$ as catalyst. The starch was initially dissolved in HCl before the addition of IL and catalyst. In this case, ethyl acetate was also present as an extraction medium. The HMF yields were reported as a weight percentage of the initial dry substance and of which tapioca starch gave the highest yield of 73 wt%.

Inulin

The production of HMF from inulin in ionic liquids has not been as extensively studied as cellulose, since inulin is far less abundant in nature. It is nonetheless interesting as an alternative feedstock since it is a fructose polymer and indigestible by humans and thus does not compete with food production.[76]

The eutectic mixture of choline chloride and organic acids introduced for fructose dehydration[50] was further explored for the direct conversion of inulin to HMF.[77] A yield of 64% was obtained with a mixture of choline chloride and oxalic acid, which unlike the conversion of fructose to HMF was more efficient than the choline chloride/citric acid mixture and showed a significantly higher solubility for inulin. In principal, there is no advantage in using a system efficient for glucose dehydration for inulin conversion which was made evident when Hu et al.[63] employed their $SnCl_4$/[EMIm][BF_4] system on inulin, obtaining a moderate 40% yield, even lower than that obtained for starch using the same conditions. An efficient system was developed by Qi et al.[78] using first [BMIm][HSO_4] as depolymerization liquid followed by the addition of [BMIm]Cl and acidic resin for fructose dehydration. The system yielded 82% of HMF from inulin and is the highest reported to date. An interesting system using [BMIM]Cl/glycerol carbonate in a 10:90 ratio together with a wet Amberlyst 70 acidic resin resulted in a yield of 60%.[79] A major part of the ionic liquid was substituted with glycerol carbonate to reduce the cost and environmental impact of the process.

Process Technology and Scale-Up

To date, the application of ILs for the conversion of carbohydrates into HMF has been limited to the laboratory, using small-scale apparatus. While the availability of some ILs is still limited, the incentive for scale-up will be obvious if conversions such as those to synthesize HMF can be made to operate in an economic fashion. Hence, we postulate here possible processes for scale-up in an attempt to highlight some of the future research required in the field. Potential economic and scalable processes can be divided into two types, dependent upon whether the reaction is carried out in biphasic or single-phase media. Both types of processes will require effective product recovery and IL recovery and recycling in order to keep the cost contribution from the IL to a minimum. Organic solvent used for extraction will also need to be recycled to minimize its cost contribution.

Biphasic process

The biphasic process is characterized by the dissolution of the feedstock in the IL such that the reaction can be carried out in a second reactor vessel with the addition of an immiscible organic solvent and the catalyst (homogeneous or heterogeneous). Agitation in the vessel is of key importance to enable adequate mass transfer by creation of a dispersion of one phase in the other. This is particularly critical given the viscosity and density of the IL relative to the immiscible organic solvent phase. Unlike conventional biphasic reactions with an aqueous phase and a water-immiscible organic solvent the values in the IL biphasic reactor show a considerable difference in viscosity and density. Thus, it is likely that power inputs greater than 5 $W L^{-1}$ will therefore be required, which will also limit the individual vessel size. Nevertheless, if the mixing is too vigorous then a stable emulsion may be formed, which will be difficult to separate in the subsequent settler unit. Following the settler the solvent phase is distilled to separate HMF and the solvent recycled. The IL is stripped of water and recycled. A potential flowsheet is shown in Figure 1.

Hu et al.[50] reported using a biphasic reactor for dehydration of fructose in [choline]Cl/citric acid with ethyl acetate as an extraction solvent. A reaction yield of HMF of 86% was attained, whereas using a single-phase system only gave 78%. The yield could be further improved to 92% by using continuous extraction. Another example of a biphasic process is that by Benoit

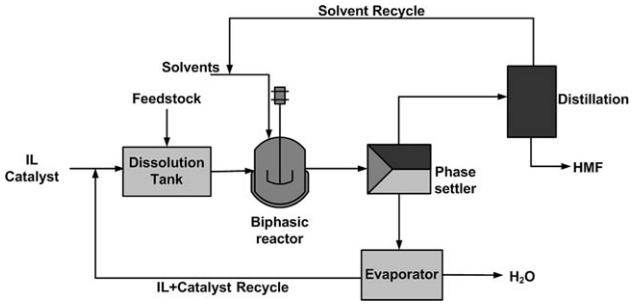


Figure 1. Potential process flow-sheet for biphasic reactor system.

et al.,[79] who significantly reduced the viscosity by making a single-phase mixture of [BMIm]Cl and glycerol (65:35), which in turn formed a two-phase system with MIBK from which HMF could be extracted.

Single-phase process

The single-phase process is characterized by the dissolution of the feedstock in the IL (either neat[38,40,47,51–54,56,62,63,65] or in the presence of a cosolvent such as DMSO[39,41,55,64]) such that the reaction can be carried out in a second reactor vessel with the addition of the catalyst. If the catalyst is heterogeneous, the stirred reactor with a filter can be used since a packed bed is likely to lead to a high pressure drop, given the viscosity of the IL (even with a cosolvent). However, only few studies have mentioned heterogeneous catalysts such as ion-exchange resins[80] or Amberlyst[39] and there appear few advantages. Attention should be given to the use of solid acid catalysts, such as Amberlyst, which may exhibit proton exchange with ionic liquid cation resulting in a much more corrosive reaction mixture than expected.[69,79,81] Regardless of the form of the catalyst, the product would be extracted from the IL by an immiscible organic solvent, such as ethyl acetate,[50] toluene,[39] or diethyl ether,[40] in a subsequent step. Thereafter, the IL would be stripped of water and recycled. Investigations on the effect of humins present in the reaction mixture after IL recycling is needed alongside, if necessary, a good procedure for the separation of humins and IL. The extraction-settler unit needs to be carefully designed as discussed in the section describing the biphasic process. A potential flow-sheet is shown in Figure 2.

If a high HMF selectivity can be maintained at full feedstock conversion, another alternative for product recovery is to use

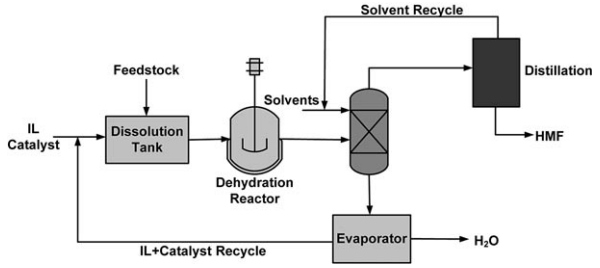


Figure 2. Potential process flow-sheet for single phase reaction system.

distillation of HMF from the IL. The reaction mixture needs to be first sent to an evaporator to remove water formed in the reaction prior to distillation. A potential process flow-sheet based on this option is shown in Figure 3. Although distillation of HMF from IL has not been reported, this option should be possible due to the low vapor pressure of ILs.

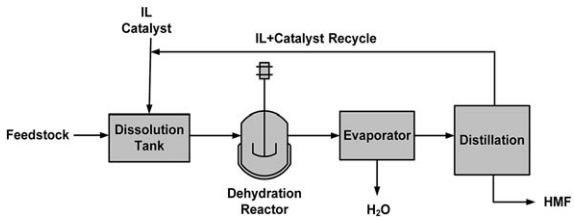


Figure 3. Alternative process flow-sheet for single phase reaction system.

Li et al.[56] suggested a continuous reaction–distillation process for their [BMIm]Cl/$CrCl_3$ system with microwave heating, but have yet to present this idea in practice. The prerequisite for this type of process is that it requires full conversion of feedstocks and can only be applied to reaction media with neat ILs. Qi et al.[82] studied the effect of recycling a [BMIm]Cl/$CrCl_3$ system for the dehydration of glucose, for which five cycles could be performed without loss of activity. After extracting the wet [BMIm]Cl with ethyl acetate, the IL was dried for 24 h.

IL mixtures with DMSO cannot be applied, since removal of DMSO from HMF is very difficult and requires special treatment.[19,83]

Process scale-up

The suggested biphasic and single-phase IL-based processes use conventional process plant and have the advantage of much smaller solvent inventories than non-IL-based processes. Additionally, they provide the important potential for one-pot operation from the feedstock. Clearly, the feedstock choice will also affect the HMF yield and separation requirements downstream and a relatively simple process can be envisioned. However, critical to economic operation is that both processes are dependent upon solvent and IL recycling. From the perspective of design, the biphasic reactor (or liquid–liquid extractor) needs careful consideration. Given the potential market size for HMF, it is clear that continuous operation will be required. Mixer–settler units lend themselves to such an operational mode but, by definition, will operate at less than full conversion to ensure the reaction is completed in an adequate time. Potentially, some of the ILs may be corrosive so suitable materials will be required for construction of parts of the plant in contact with the IL.

Depending on the process, the purity of HMF will vary. HMF obtained from a biphasic process will, depending on the selectivity of the reaction and the purity of the ionic liquid, contain impurities that could make it less valuable as a commodity chemical. A purification step might therefore be necessary.

Low-temperature recrystallization or sublimation are the most obvious choices, considering the melting and boiling points of HMF. The required purity profile of HMF is completely dependent on its application and, since it is primarily considered to be a platform chemical, purification might in some cases not be necessary prior to derivatization.

The use of green eutectic solvents and glycerol as cosolvent are examples of future competing technologies to IL processes. The advantage of an IL-based process over these is the possibility for high-concentration solutions of cellulose in some ILs, making a one-pot process from crude biomass more feasible.

Outlook

The rapidly growing field of HMF production in ILs from carbohydrates holds great promise for the future. The field is nonetheless in its infancy and a number of issues need to be investigated in detail in the continuous search for realistic large-scale processes. Future research should target an economic analysis of the potential processes outlined herein. In addition, some specific subjects concerning the chemistry and process engineering should be addressed as follows:

- A thorough investigation of the influence of both the cation and the anion of the IL on the reaction outcome and an extensive screening of different ILs are needed to ascertain whether the liquids presented herein are superior in performance.
- The mechanism of glucose dehydration needs to be investigated further for optimized performance and the interaction between the ILs and catalysts should be examined.
- Adequate dissolution and reaction kinetics of the feedstock in the IL and further studies with crude biomass as a feedstock for more realistic conditions.
- Even though there are several excellent papers and reviews on physicochemical properties of ILs,[84,85] more specific property data of the relevant ILs in connection with catalysts and substrates are required, for example, stability, as well as density and viscosity.
- Adequate dispersion of the IL and the immiscible organic solvent (power input and mixing studies will be required at a variety of scales), as well as phase separation of the IL and immiscible solvent following intimate contact and removal of water from the IL prior to recycling (the loss on each cycle of IL will require particular attention) need to be investigated. For continuous operation, an understanding of the conversion–kinetic trade-off, which is necessary for continuous stirred tank reactor (CSTR) operation, requires further studies.

It is our belief that a future cost-effective and environmentally acceptable process of HMF production in ionic liquids should be possible if the points listed above are pursued and thoroughly investigated.

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Keywords: 5-hydroxymethylfurfural · biomass · carbohydrates · ionic liquids · renewable chemicals

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TITLE: A METHOD OF PRODUCING HYDROXYMETHYLFURFURAL

FIELD OF THE INVENTION

The present invention relates to a method of producing 5-hydroxymethylfurfural.

BACKGROUND OF THE INVENTION

Many chemical compounds needed for various industries have for many years been derived from the petrochemical industry. However, due to increases in the price of crude oil and a general awareness of replacing petrochemicals with renewable resources there has been and still is a wish to base the production of chemical compounds on renewable resources.

5-hydroxymethylfurfural (HMF) is an example of such a compound because it is derived from dehydration of sugars making it derivable from renewable biomass resources. HMF can for example be converted to 2,5-dimethylfuran by hydrogenolysis of C-O bonds over a copper-ruthenium (CuRu) catalyst (Roman-Leshkov Y et al., Nature, 2007, **447** (7147), 982-U5), which is a liquid biofuel or to 2,5-furandicarboxylic acid by oxidation (Boisen A et al., Chemical Engineering Research and Design, 2009, **87**(9), 1318-1327). The latter compound, 2,5-furandicarboxylic acid, can be used as a replacement of terephthalic acid in the production of polyesters such as polyethyleneterephthalate (PET) and polybutyleneterephthalate (PBT).

US 2008/0033188 discloses a catalytic process for converting sugars to furan derivatives, e.g. 5-hydroxymethylfurfural, using a biphasic reactor containing a reactive aqueous phase and an organic extracting phase.

Román-Leshkov Y and Dumesic JA, 2009, Top Catal, 52; 297-303 discloses similar subject-matter as US 2008/0033188.

US 2009/0030215 discloses a method of producing HMF by mixing or agitating an aqueous solution of fructose and inorganic acid catalyst with a water immiscible organic solvent to form an emulsion of the aqueous and organic phases.

US 7,317,116 discloses an method for utilizing an industrially convenient fructose source for a dehydration reaction converting a carbohydrate to a furan derivative.

Huang R et al., 2010, Chem. Comm., **46**, 1115-1117 discloses integrating enzymatic and acid catalysis to convert glucose into 5-hydroxymethylfurfural.

In the industrial manufacture of high-fructose corn syrup, glucose is often converted into fructose by a process catalyzed by the enzyme xylose isomerase (E.C. 5.3.1.5) which for these

reasons is usually called a “glucose isomerase”.

Glucose can be isomerized to fructose in a reversible reaction. Under industrial conditions, the equilibrium is close to 50% fructose. To avoid excessive reaction times, the conversion is normally stopped at a yield of about 45% fructose.

Glucose isomerase is one of the relatively few enzymes that are used industrially in an immobilized form. One reason for immobilization is to minimize the reaction time in order to prevent degradation of fructose to organic acids and carbonyl compounds that inactivate the enzyme.

The substrate to the GI-columns is highly purified to avoid clogging of the bed and destabilization of the enzyme. The recommended conductivity is < 50 µS/ cm.

A description of the most commonly used glucose isomerases is given in table 1 below. The description is based on literature and information from the manufactures and do not necessarily have to be a description of the exact methods used.

Table 1

Manufacturer	Trade name	Enzyme source	Immobilization method
Novozymes A/S	Sweetzyme IT	*S.murinus*	Crosslinking of cell material with glutaraldehyde, extruded
Genencor International	GENSWEET	*S.rubigonosus*	The enzyme is cross linked with or without cellular debris using PEI (polyethylene imine) and glutaraldehyde. Granular particles are formed by extrusion/marumerization.
Godo Shusei	AGI-S-600	*S.griseofuseus*	Chitosan-treated glutaraldehyde crosslinked cells, granulated.

Another way of producing fructose is by hydrolysis of sucrose to obtain a composition comprising glucose and fructose in a 50:50 ratio.

SUMMARY OF THE INVENTION

The invention provides a first method for producing 5-hydroxymethylfurfural comprising

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0-10.

In one embodiment step i) may alternatively be

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt, and wherein the reaction medium does not comprise an acidic catalyst or does not comprise a strong acid.

The invention also provides a second method of producing 5-hydroxymethylfurfural comprising

I) Subjecting a composition comprising glucose to an enzymatic reaction catalyzed by glucose isomerase

II) Subjecting the composition obtained in step I) to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt.

The invention also provides a third method of producing 5-hydroxymethylfurfural comprising

A) subjecting a composition comprising fructose and glucose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt,

B) removing glucose from the reactor in step A), and

C) converting the glucose obtained in step B) to

a) hydroxymethylfurfural, or

b) fructose by an enzymatic reaction catalyzed by glucose isomerase.

Furthermore, the present invention also relates to the use of 5-hydroxymethylfurfural obtained by a method according to the present invention.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows a schematic drawing of the process wherein some of the relevant steps are indicated. GI indicates an immobilized glucose isomerase reactor, G and F indicates glucose and fructose, respectively.

Fig. 2 shows the effect the choice of salt in the aqueous phase of the reaction medium has on the conversion of sugars, the HMF yield and the HMF selectivity all expressed as percentages. This figure is an illustration of some of the data obtained in example 11.

Fig. 3 shows the activity of immobilized glucose isomerase (Sweetzyme™) as a function of time with a standard substrate containing 45w/w% glucose syrup. This figure is an illustration of some of the data obtained in example 12.

Fig. 4 shows the activity of immobilized glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing a high concentration of NaCl. This figure is an illustration of some of the data obtained in example 12.

Fig. 5 shows the activity of immobilized glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing a high concentration of $MgCl_2$,

$6H_2O$. This figure is an illustration of some of the data obtained in example 12.

Fig. 6 shows the activity of immobilized glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing a high concentration of KCl. This figure is an illustration of some of the data obtained in example 12.

Fig. 7 shows the activity of immobilized glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing a high concentration of Na_2SO_4, 10 H_2O. This figure is an illustration of some of the data obtained in example 12.

Fig. 8 shows the activity of immobilized glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing a high concentration of $MgSO_4$. This figure is an illustration of some of the data obtained in example 12.

Fig. 9 shows the conversion of glucose to fructose by glucose isomerase (Sweetzyme™) as a function of time with a standard 45w/w% glucose syrup substrate. This figure is an illustration of some of the data obtained in example 13.

Fig. 10 shows the conversion of glucose to fructose by glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing 0.01% HMF. This figure is an illustration of some of the data obtained in example 13.

Fig. 11 shows the conversion of glucose to fructose by glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing 0.1% HMF. This figure is an illustration of some of the data obtained in example 13.

Fig. 12 shows the conversion of glucose to fructose by glucose isomerase (Sweetzyme™) as a function of time with a modified 45w/w% glucose syrup substrate containing 1% HMF. This figure is an illustration of some of the data obtained in example 13.

Fig. 13 shows the activity of glucose isomerase (Sweetzyme™) as a function of HMF concentration.

DEFINTIONS AND ABBREVIATIONS

The terms “5-hydroxymethylfurfural”, “hydroxymethylfurfural” and “HMF” may be used interchangeably in the context of the present invention. The IUPAC term of HMF is 5-(hydroxymethyl)-2-furaldehyde and it may also be used in the present context.

The term “enzymatic reaction” refers in the context of the present invention to a chemical reaction catalyzed by an enzyme, where “chemical reaction” refers to the general understanding of this term as a process of transforming one or more chemical substances into one or more other chemical substances.

The term “glucose isomerase” refers in the context of the present invention to an enzyme of E.C. 5.3.1.5 which is capable of catalysing the transformation of D-xylose to D-xylulose. Such enzymes are generally used in the high corn syrup industry to convert glucose into fructose. In the context of the present invention glucose isomerase may be abbreviated to “GI” which is in-

tended to encompass any glucose isomerase, e.g. independent of whether it is immobilized or not. As the currently available glucose isomerases are typically immobilized the term “IGI” may also be used which in the context of the present invention is intended to mean “immobilized glucose isomerase”.

The term “saccharide” refers in the context of the present invention to its well known meaning as an organic compound with the general formula $C_m(H_2O)_n$ also known as a carbohydrate. Thus the term “saccharide” includes monosaccharides, disaccharides, oligosaccharides and polysaccharides.

The term “HFCS” refers in the context of the present invention to High Fructose Corn Syrup.

DETAILED DESCRIPTION OF THE INVENTION

Methods of the present invention

The present invention relates to methods of producing 5-hydroxymethylfurfural (HMF) by dehydration of fructose and/or glucose. In the following slightly different methods are described which however all relate to the same general concept of producing HMF from fructose and/or glucose. These methods may also be seen as different steps of an overall method which may comprise the steps of each of the methods.

Although, the methods are described individually below the steps of each method may be combined with steps from any of the other methods and the embodiments and examples given with respect to one method may also be used in any of the other methods.

<u>First method of the present invention</u>

Step i)

A first aspect of the present invention relates to a method of producing 5-hydroxymethylfurfural comprising

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0-10.

Step i) results in dehydration of fructose to 5-hydroxymethylfurfural. The inventors of the present invention have surprisingly found that salt alone is capable of catalysing this dehydration of fructose to HMF. It is therefore not necessary to add an acidic catalyst to the aqueous phase of the reaction medium which has previously been used to catalyze dehydration of fructose to HMF. This has of course the advantage of avoiding handling of strong acids in the manufacturing process. Other advantages are described below, e.g. in relation to steps iii) and iv).

Hence in another embodiment the above mentioned step i) may optionally be

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, wherein said aqueous phase comprises a salt, and wherein the reaction medium does not comprise an acidic catalyst or does not comprise a strong acid.

The solubility of fructose in the aqueous phase of the reaction medium is much higher than in the organic phase of the reaction medium so the concentration of fructose will generally be much higher in the aqueous phase than in the organic phase of the reaction medium. The dehydration of fructose to 5-hydroxymethylfurfural mainly takes place in the aqueous phase. Some of the HMF may diffuse into the organic phase. This division of HMF between the organic phase and the aqueous phase may described by the partition coefficient, R, where R=(concentration of HMF in organic phase)/(concentration of HMF in aqueous phase). The identity of the organic solvent and the concentration of salt in the aqueous phase affect the value of R. However, in the context of the present invention R may typically be at least 0.8 ($R \geq 0.8$), such as at least 0.9 ($R \geq 0.9$), or at least 1 ($R \geq 1$), or at least 1.1 ($R \geq 1.1$), or at least 1.2 ($R \geq 1.2$), or at least 1.3 ($R \geq 1.3$), or at least 1.4 ($R \geq 1.4$), in particular R may be at least 1.5 ($R \geq 1.5$) or R may be at least 2 ($R \geq 2$).

Once fructose has been dehydrated into HMF, HMF can undergo rehydration thereby producing levulinic acid and/or formic acid. The diffusion of HMF from the aqueous phase into the organic phase is an advantage in order to protect HMF from rehydration.

The presence of salt in the aqueous phase also has the further advantage of decreasing the solubility of HMF in the aqueous phase whereby the equilibrium between HMF in the aqueous phase versus HMF in the organic phase is further shifted towards HMF in the organic phase.

The physical parameters of step i), such as the period of time the reaction takes place, the temperature and the pressure each affect the yield and selectivity of HMF. However, these parameters also affect each other. Thus for example at high temperature the same yield of HMF may be obtained in a shorter period of time than at lower temperatures. Thus the examples of relevant reaction times, temperatures and pressures given in the following does not exclude other examples and they may be combined depending on for example some of the other reaction parameters.

For example step i) described above may be carried out for a period of between 1 second to 20 hours, such as between 1 second to 15 hours, or between 1 second to 10 hours, or between 15 seconds to 20 hours, or between 15 seconds to 15 hours, or between 15 seconds to 10 hours, or between 30 seconds to 20 hours, or between 30 seconds to 15 hours, or between 30 seconds to 10 hours, or between 45 seconds to 20 hours, or between 45 seconds to 15 hours, or between 45 seconds to 10 hours, or between 1 minute to 20 hours, or between 1 minute to 15

hours, or between 1 minute to 10 hours, or between 1 minute to 8 hours, or between 1 minute to 6 hours, or between 30 minutes to 8 hours, or between 30 minutes to 6 hours, or between 30 minutes to 5 hours, or between 45 minutes to 4.5 hours, such as between 40 minutes to 80 minutes, such as for 1 hour, or between 1 to 2 hours, such as for 1.5 hours, or between 100 minutes to 140 minutes, such as for 2 hours, or between 130 minutes to 170 minutes, such as for 2.5 hours, 160 minutes to minutes, such as for 3 hours, or between 190 minutes to 230 minutes, such as for 3.5 hours, or between 220 minutes to 260 minutes, such as for 4 hours, or between 1.5 hours to 4.5 hours.

Furthermore, step i) may be carried out at a temperature in the range of 70-300°C, such as between 70-280°C, or between 70-260°C, or between 70-250°C, or between 80-280°C, or between 80-260°C, or between 80-250°C, or between 90-280°C, or between 90-260°C, or between 90-250°C, or between 110-190°C, or between 110-180°C, or between 110-170°C, or between 110-160°C, or between 120-190°C, or between 120-180°C, or between 120-170°C, or between 120-160°C, or between 125-190°C, or between 125-180°C, or between 125-170°C, or between 125-160°C or between 130-190°C, or between 130-180°C, or between 130-170°C or between 130-160°C, or between 130-150°C, such as between 135-145°C, or between 140-160°C, such as between 145-155°C, or between 150-170°C, such as between 155-165°C.

Typically step i) may be carried out at a pressure ranging between 1 and 200 atm.

In one embodiment step i) may be carried out as a continuous process. In the context of the present invention the term “continuous process” refers to a process which it is not taking place within any defined period of time. The product of such processes is generally also removed continuously from the process. Batch processes are in contrast to continuous processes typically carried out for a specified period of time after which the product is removed from the process. Thus it is more relevant to characterise continuous processes by a mean residence time. In the context of the present invention the mean residence time may in particular be in the range of 0.5 to 2 hours. Generally the shorter residence time the better.

The process of step i) takes place in a reactor. In the context of the present invention the term “reactor” refers in principle to any type of container suitable for carrying out the dehydration of fructose and/or glucose to HMF. Examples of suitable containers are well known to a person skilled in the art and include both those suitable for industrial production and those suitable for lab scale processes.

Fructose is on an industrial scale often manufactured by conversion of glucose to fructose which due to the chemical equilibrium of this conversion typically results in a composition comprising approximately 45w/w% fructose and 55w/w% glucose.

Another way of obtaining a composition comprising fructose and glucose is by hydrolysis of sucrose which results in a mixture of fructose and glucose in a 50:50 ratio also called inverted sugar syrup. The hydrolysis of sucrose to fructose and glucose may for example be catalyzed by invertase (E.C. 3.2.1.26). This combination of fructose and glucose may then be used in step

i) of the method. In general compositions comprising high amounts of fructose; e.g. at least 40%w/w fructose, such as HFCS or invert syrup may be used directly in step i) of the process without first subjecting the composition to an enzymatic reaction catalyzed by glucose isomerase, i.e. step -i).

These compositions may be further purified with respect to fructose to yield a composition comprising from around 55 w/w% to 95w/w% fructose and from around 45w/w% or less glucose. Thus in one embodiment of step i) the composition comprising fructose may further comprise glucose.

Steps –i) and –ii)

If a composition comprising fructose and glucose is used in step i) the first method of the present invention may in particular comprise a further step preceding step i), e.g. step -i) subjecting a composition comprising glucose to an enzymatic reaction catalyzed by glucose isomerase. Examples of methods of such enzymatic catalyzed reactions include but are not limited to those described in Bholand SH et al., Microbiological Reviews, 1996, **60**(2), 280-300 and Pedersen S, Bioprocess Technology, 1993, **16**, 185-208.

Step –i) may be performed similarly to step iv) b) as described below with the exception that the starting material for the two steps are different.

In another embodiment, step i) may be preceded by another step –ii) hydrolysis of sucrose.

Thus the first method of the present invention may relate to a method of producing 5-hydroxymethylfurfural comprising the steps

-i) and i) or –ii) and i).

With respect to step –i) the embodiments and examples described below in relation to step iv) b) may also be used in step –i).

Step ii)

In one embodiment the first method of the present invention may further comprise a step of

ii) Removing 5-hydroxymethylfurfural from the reactor in step i).

The advantage of removing 5-hydroxymethylfurfural (HMF) from the reactor in step i) is that the HMF is protected from rehydration into levulinic acid and formic acid.

Step ii) may in particular also be carried out as a continuous process. The advantage of carrying out the process as a continuous process is by continuously removing HMF from the reactor in step i) it is possible to have a continuous production of HMF in step i). If the method is carried out continuously a composition comprising fructose may also be continuously fed into the process prior to step i).

Carrying out the method continuously may in particular be relevant for industrial production of HMF.

If the method of the present invention is performed as a so called batch process meaning that

after a certain period of time the process is stopped HMF may simply be removed from the reactor by removing the organic phase of the reaction medium from the reactor.

For continuous processes, the HMF may be removed from the reactor by including a loop into the process in which the organic phase of the reaction medium in step i) is recycled. This recycling step may in particular include a step of removal of HMF from the organic phase. Thus in practice the recycling loop involves continuously removing part of the organic phase from the reaction medium in step i), removing HMF from the organic phase which has been removed from the reactor, and then recycling the remaining part of the organic phase into the reactor in step i).

Methods of removing HMF from the organic phase includes known methods for removing HMF from an organic medium and may for example be performed by back extraction, evaporation of solvent, thin film evaporation, wiped film evaporation, chromatography, distillation, adsorption to an inert adsorbent, counter current extraction or any other means of product recovery that is known to a person skilled in the art.

Steps iii) and iv)

If the composition of step i) comprises fructose and glucose then the glucose may in particular be converted to either HMF or fructose. Although, glucose may be converted to HMF directly in the reactor, such as described in examples 3 and 4, the glucose may in a particular embodiment be removed from the reactor prior to converting it to HMF or fructose. Thus the process may in this embodiment further comprise the steps of

iii) Removing glucose from the reactor in step i), and

iv) Converting the glucose obtained in step iii) to

a) Hydroxymethylfurfural

b) Fructose by an enzymatic reaction catalyzed by a glucose isomerase.

Steps iii) and iv) may be carried out in combination with step i), steps –i) and i), steps –ii) and i) or in combination with steps i) and ii), steps –i), and i), steps –i), i) and ii), steps –ii) and i) or steps –ii), i) and ii).

Any of steps i), ii), iii), and iv) or any combination thereof may be carried out in an inert atmosphere such as in an argon or nitrogen atmosphere**.** The advantage of an inert atmosphere is generally that it reduces oxidation and thereby avoids production of too many unwanted side-products.

If step i) and/or the whole process is non-continuous the fructose used in step i) is converted to HMF in step i) and extracted into the organic phase of the reaction medium in step i). In contrast to this most of the glucose present in the composition comprising fructose and glucose is left unreacted in the aqueous phase of the reaction medium. Thus if step i) and/or the whole process is non-continuous step iii); i.e. removing glucose from the reactor instep i) may simply be carried out by removing the aqueous phase of the reaction medium.

If step i) and/or the whole process are continuous methods step iii) may generally be performed by continuously removing part of the aqueous phase from the reactor. Such methods are well known for a person skilled in the art.

Step iv) a) converting the glucose obtained in step iii) to 5-hydroxymethylfurfural may be analogous to the process of converting fructose to HMF; e.g. it may similarly to step i) be carried out by subjecting the glucose to a process in a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt. However, the conditions which are optimal for converting fructose to HMF are not necessarily all the same as those which are optimal for converting glucose to HMF. Hence in the following those conditions of step iv) a) which may differ from those of step i) are described.

The aqueous phase of the reaction medium of step iv) a) may in particular have a pH in the range of 1 to 9, such as a pH in the range of 1 to 8, or in the range of 1 to 7, or in the range of 1 to 6, or in the range of 1 to 5, or in the range of 1 to 4, or in the range of 1.5 to 8, or in the range of 1.5 to 7, or in the range of 1.5 to 6, or in the range of 1.5 to 5, or in the range of 1.5 to 4. .

Furthermore, the reaction medium of step iv) a) may in a particular embodiment comprise an acidic catalyst such as $AlCl_3$. Even though, some of the reaction conditions for step iv) a) may differ from those of step i) the choice of salt, temperature, periods of time etc, described in relation to step i), may also be used in relation to step iv) a).

Examples 3 and 4 describe one way of carrying out a method of the present invention comprising steps i), ii) and iv) a), and steps i) and iv) a), respectively. Thus if the method of the present invention comprises steps i) and iv) a) it may further in one embodiment also comprise a step of cooling between steps i) and iv) a). Furthermore, as shown in examples 3 and 4 it is an advantage to replace the organic phase of the reaction medium in step i) with a new organic phase in the reaction medium of step iv) a) as this increases the yield of HMF. In this context the term "new" refers to fresh meaning that the chemical composition of the organic phase of the reaction medium used in step i) may be the same as that of the organic phase of the reaction medium used in step iv) a).

The present invention describes two different steps of converting glucose to fructose by an enzymatic reaction catalyzed by a glucose isomerase, i.e. steps –i) and iv) b). These two steps are in principle the same step with the exception that the starting material for these steps is different. The starting material for the step preceding step i) may be glucose obtained from generally any suitable source while the glucose used in step iv) b) is obtained from step iii) of the process; i.e. it is removed from the reactor in which fructose is converted to HMF. Thus the composition comprising glucose used in step iv) b) may for example comprise any combination of the following components; HMF, organic solvent from the organic phase of the reaction medium and side-products, such as humins, soluble polymers, levulinic acid and formic acid produced in step i). In the context of the present invention the term "humin" or "humins" refer to insoluble or non-soluble polymers. Some of the components, e.g. the insoluble humins, may block the immobi-

lized glucose isomerase reactor. Thus in a particular embodiment one or more of these compounds may be removed from the composition comprising glucose prior to subjecting it to the glucose isomerase; i.e. step iv) b). Hence the method may further comprise a step between steps iii) and iv) b) comprising removing one or more components. For example the method may in one embodiment comprise a step of removing humins between steps iii) and iv) b). For industrial purposes the non-soluble humins may typically be removed by filtration. The sugars, i.e. glucose and/or fructose, used in the present invention may be obtained by saccharification of starch. In this case the soluble polymers may be recycled in the process by adding them to the step of starch saccharification.

Furthermore, the glucose withdrawn from the reactor in step iii) may be withdrawn as an aqueous solution and it may therefore be relevant to remove some of the water prior to subjecting it to the glucose isomerase in step iv). This may for example be performed by evaporation.

The step of converting glucose to fructose by an enzymatic reaction catalyzed by a glucose isomerase is in the present context not limited to any particular method.

Currently the glucose isomerases used on an industrial scale are immobilised glucose isomerase, in particular glucose isomerase (GI) based on a glutaraldehyde crosslinked cell material, although columns with GI immobilized on ion exchange resins as carrier material are also known. However, the methods of the present invention are not limited to the use of immobilised glucose isomerases. Thus it is foreseen that also non-immobilized glucose isomerase may be used in the present invention.

Examples of suitable glucose isomerases which may be used in the present invention include glucose isomerase from *S.murinus*, *S.rubigonosus* or *S.griseofuseus* which in particular may be immobilized by crosslinking of cell material with glutaraldehyde. Examples of such commercially available immobilized glucose isomerases include but are not limited to Sweetzyme from Novozymes A/S or Gensweet from Genencor International or AGI-S-600 from Godo Shusei.

The process conditions for use of the glucose isomerase to convert glucose to fructose depend on e.g. the starting material and the particular glucose isomerase. Such conditions are well known for a person skilled in the art. For example borate may be present to boost the fructose equilibrium. The inventors of the present invention have surprisingly found that high concentrations of salt stabilize the immobilized glucose isomerase. Thus the inventors of the present invention has found that the functionality of glucose isomerase is not affected under conditions were the conductivity is in the range of 6-25 mS/cm, which is approximately 100 times higher than the conductivity of 50 µS/cm which is generally recommended for glucose isomerase.

As the aqueous phase of the reaction medium in step i) comprises high salt concentrations the composition comprising glucose obtained in step iii) of the present invention also comprises a high concentration of salt. Glucose isomerase are generally used under conditions where the salt concentration is lower than that of the composition comprising glucose obtained in step iii) of the present method. It was therefore a surprise that the inventors of the present invention

found that the high concentration of salt in the composition comprising glucose obtained in step iii) did not affect the functionality of the glucose isomerase in step iv) b) of the method. Typically current recommendations for the use of glucose isomerase is that the conductivity is <50µS/cm, while the inventors of the present invention found that the functionality of glucose isomerase (Sweetzyme™) may be as high as 6-25 mS/cm as shown in example 12. Furthermore it actually appeared that the high salt concentration with NaCl further stabilised the glucose isomerase. In the case with KCl and Na_2SO_4 the glucose isomerase performance was comparable with a normal glucose substrate without the addition of extra salts.

For step iv) b) the starting material is glucose removed from the reactor in step i), which is generally the aqueous phase or part of the aqueous phase of the reaction medium in step i). The aqueous phase of the reaction medium may become acidic due to e.g. levulinic acid and formic acid which may often formed as by-products of the process of dehydration of fructose to HMF. Thus the composition comprising glucose which is removed from the reactor in step iii) may be acidic. Glucose isomerase typically works optimally at a pH in the range of 6-9 thus the pH of the composition comprising glucose obtained in step iii) may in a particular embodiment be adjusted to a pH in the range of 6-9 prior to performing step iv) b). Examples of suitable bases for adjusting the pH include but are not limited to Na_2CO_3 and NaOH. An advantage of the present invention is that the inventors of the present invention have found that it is not necessary to use an acidic catalyst in step i) of the method. This reduces the need to add base to the composition comprising glucose obtained in step iii) of the method prior to subjecting it to glucose isomerase in step iv) b). Furthermore, another advantage of avoiding the acidic catalyst or avoiding using a strong acid as catalyst, in the reaction medium of step i) in this embodiment is that when pH is adjusted to a higher pH it generally also results in an increase of the salt concentration. Although, the inventors of the present invention have found that glucose isomerase functions at higher salt concentrations than previously anticipated too high salt concentrations, such as higher than 25w/w% as indicated in example 12, may still affect the functionality of the glucose isomerase adversely. In this case it would therefore be necessary to remove some of the salt from the composition comprising glucose which is withdrawn from the reactor prior to subjecting it to the glucose isomerase. Thus by avoiding acidic catalysts or avoiding using strong acids as catalysts, in the reaction medium of step i) no or at least less salt has to be removed from the composition comprising glucose obtained in step iii) prior to subjecting it to step iv) b).

Another way of regulating the pH of the composition comprising glucose obtained in step iii) is by extracting acids from the organic phase of the reaction medium into the aqueous phase of the reaction medium.

The fructose obtained from step iv) b) may further be subjected to step i) thereby creating a loop in the method where glucose removed from step i) is converted to fructose in step iv) b) which is then subsequently converted to HMF in step i). Thus the above mentioned process may in a particular embodiment comprise a further step of

v) Subjecting the fructose obtained in step iv) b) to the process of step i).

The advantage of including steps iii), iv) b) and v) in the method of the present invention, i.e. removing glucose from the reactor in step i) and converting it to fructose which is then subsequently re-introduced in step i) is that based on the starting material used in step i) the relative yield of HMF is higher than if e.g. the glucose is not recycled. Furthermore, step iv) b) also has the advantage of creating less unwanted side-products such as humins, than step iv) a) which is the conversion of glucose to HMF.

Embodiments of the first method

Thus a method according to the present invention may comprise the steps of

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0-10.

In another embodiment the method according to the present invention comprises the steps of

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0-10.

ii) Removing 5-hydroxymethylfurfural from the reactor instep i).

In yet another embodiment the method according to the present invention may comprise the steps of

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0-10.

ii) Removing 5-hydroxymethylfurfural from the reactor in step i).

iii) Removing glucose from the reactor in step i), and

iv) Converting the glucose obtained in step iii) to

a) Hydroxymethylfurfural

b) Fructose by an enzymatic reaction catalyzed by a glucose isomerase.

In yet another embodiment the method according to the present invention may comprise the steps of

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0-10.

iii) Removing glucose from the reactor in step i), and

iv) Converting the glucose obtained in step iii) to
   a) Hydroxymethylfurfural
   b) Fructose by an enzymatic reaction catalyzed by a glucose isomerase.

In any of the above mentioned methods step i) may alternatively be

i) Subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase, wherein said aqueous phase comprises a salt, and wherein the reaction medium does not comprise an acidic catalyst or does not comprise a strong acid.

Any of the above described methods may further comprise step –i) or step –ii) as described above.

Furthermore, as also described above those processes comprising step iv) b) may also in a further embodiment comprise the above mentioned step v).

The methods of the present invention may be carried out as continuous processes or as batch processes.

Second method of the present invention

A second aspect of the present invention relates to a method of producing HMF comprising

I) Subjecting a composition comprising glucose to an enzymatic reaction catalyzed by glucose isomerase

II) Subjecting the composition obtained in step I) to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt.

This process may in one embodiment further comprise the steps of

III) Removing glucose from the reactor in step II), and

IV) Converting glucose obtained in step III) to
   a) Hydroxymethylfurfural, or
   b) Fructose by an enzymatic reaction catalyzed by glucose isomerase.

Step I) is the same as the step –i) described above. Thus the embodiments described in relation to the step –i) may apply *mutatis mutandis* to step I).

Step II) is similar to step i) described above with the exception that a pH range is not defined in step II). In a particular embodiment the pH of the aqueous phase of the reaction medium in step II) may be in the range of 1.0 to 10. The embodiments, examples and reaction conditions described in relation to step i) may apply *mutatis mutandis* to step II).

Step III) is similar to step iii) described above and the embodiments, examples and reaction conditions described in relation to step iii) may apply *mutatis mutandis* to step III).

The step of converting glucose to HMF; i.e. step IV) a) may in particular comprise subjecting the

glucose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt. In this embodiment the aqueous phase may in particular have a pH in the range of 1-9.

Step IV) a) is similar to step iv) a) above and the embodiments, examples and reaction conditions described in relation to step iv) a) above may apply *mutatis mutandis* to step IV) a).

Step IV) b) is similar to step iv) b) described above and the embodiments and reaction conditions described in relation to step iv) b) may apply *mutatis mutandis* to step IV) b).

Third method of the present invention

A third aspect of the present invention relates to a method of producing HMF comprising

A) subjecting a composition comprising fructose and glucose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt,

B) removing glucose from the reactor in step A), and

C) converting the glucose obtained in step B) to

a) hydroxymethylfurfural, or

b) fructose by an enzymatic reaction catalyzed by glucose isomerase.

Step A) is similar but not identical to the embodiment of step i) where the composition comprises both glucose and fructose. However, in a particular embodiment the pH of the aqueous phase of the reaction medium in step A) is in the range of 1.0 to 10. Furthermore, all of the embodiments, examples and reaction conditions described in relation to the embodiment of step i) wherein the composition comprises fructose and glucose may apply *mutatis mutandis* to step A).

Step B) is similar to step iii) described above. Hence the embodiments, examples and reaction conditions described in relation to step iii) may apply *mutatis mutandis* to step B).

Step C) a) is similar to step iv) a) described above and the embodiments, examples and reaction conditions described in relation to step iv) a) may apply *mutatis mutandis* to step IV) a).

Step C) b) is similar to step iv) b) described above and the embodiments, examples and reaction conditions described in relation to step iv) b) may apply *mutatis mutandis* to step IV) b).

Equipment useful for carrying out these different steps is well known for a person skilled in the art.

Use of HMF

The HMF produced by any of the above mentioned first, second and third methods may be further processed to obtain another product. Examples of such products include but are not limited to 2,5-furandicarboxylic acid and 2,5-dimethylfuran.

The HMF produced by any of the above mentioned processes may in particular be oxidized to produce 2,5-furandicarboxylic acid. Hence any of the above mentioned methods may comprise a further step of oxidizing the obtained HMF to 2,5-furandicarboxylic acid.

Examples of methods suitable for oxidizing HMF to 2,5-furandicarboxylic acid include but are not limited to those described in US patents US 4,977,283 and US 7,411,078, and US patent application US 2008/0103318.

US 4,977,283 describes a process for the oxidation of 5-hydroxymethylfurfural which comprises oxidizing 5-hydroxymethylfurfural in a aqueous medium with oxygen in the presence of a catalyst which contains at least one metal of the platinum group.

US 7,411,078 describes oxidizing e.g. 5-hydroxymethylfurfural with a metal permanganate in an alkaline environment to produce 2,5-furandicarboxylic acid. Advantageously, the alkaline environment contains at least one of alkali metal hydroxides and alkali earth metal hydroxides, and the oxidation is performed at a temperature of from 1 to 50°C.

US 2008/01003318 describes a method of oxidizing hydroxymethylfurfural (HMF) includes providing a starting material which includes HMF in a solvent comprising water into a reactor. At least one of air and O_2 is provided into the reactor. The starting material is contacted with a catalyst comprising Pt on a support material where the contacting is conducted at a reactor temperature of from about 50°C to about 200°C.

Hence any of the methods of the present invention may comprise as a further step a process of oxidizing HMF to 2,5-furandicarboxylic as described above.

Furthermore, the present invention also relates to the products obtained by any method according to the present invention.

Compositions

The present invention relates to the production of hydroxymethylfurfural by dehydration of fructose and/or glucose.

The methods of the present invention may use different starting materials, i.e. a composition comprising fructose, a composition comprising glucose, or a composition comprising glucose and fructose. As these three compositions may have certain features in common the term “starting material” used in the following refers to all three compositions; i.e. a composition comprising fructose, a composition comprising glucose, and a composition comprising fructose and glucose. Often such industrially produced compositions comprise both glucose and fructose, however the present invention is not limited to such composition as compositions which have been purified with respect to either glucose or fructose can also be used.

The term “composition” is in the context of the present invention to be understood in its broadest context; however it may typically be an aqueous solution.

The compositions used in the present invention as starting materials, i.e. the composition comprising fructose, the composition comprising glucose, and the composition comprising glucose

and fructose, may typically contain a total of at least 20w/w% glucose and fructose, such as a total of 30-90w/w% fructose and glucose, e.g. 40-90w/w% fructose and glucose, or a total of 50-90w/w% fructose and glucose, or a total of 60-90w/w% fructose and glucose, or a total of 70-90w/w% fructose and glucose, or a total of 80-90w/w% fructose and glucose.

As the compositions used as starting materials in the methods of the present invention in many cases may be obtained from natural sources, e.g. biomass, they may also contain other components than fructose and/or glucose including other saccharides. For example the compositions used as starting material in the methods of the present invention may comprise 0-10w/w% oligosaccharides.

The choice of starting material may to some extent affect the combination of steps in a method of the present invention. Furthermore, the compositions comprising glucose, fructose or glucose and fructose, used in the methods of the present invention, may as described above comprise other saccharides than fructose and glucose.

For example if a composition comprises a relative high amount of fructose it may be used directly as a starting material for the dehydration process of fructose to HMF; i.e. in steps i), II) and A) of the methods of the present invention. In this context a “relative high amount of fructose” may typically be a composition wherein at least 40w/w% of the total amount of saccharides in the composition is fructose or that fructose constitutes at least 40w/w% of the total amount of saccharides in the composition.

Thus the compositions used in steps i), II) and A) of the present invention, i.e. a composition comprising fructose, the composition obtained from step I), and a composition comprising glucose and fructose may in a particular embodiment be a composition wherein 40-100w/w% of the total amount of saccharides in the composition is fructose. More particularly 45-100w/w% of the total amount of saccharides may be fructose, or 45-95w/w% of the total amount of saccharides may be fructose, or 50-95w/w% of the total amount of saccharides may be fructose.

Examples of compositions wherein fructose constitutes more than 40w/w% of the total amount of saccharides present in the composition include but are not limited to HFCS (high fructose corn syrup), invert sugar, inulin and compositions which have been purified with respect to fructose.

HFCS typically comprise 40-60w/w% fructose of the total amount of saccharides. Moreover, the ratio of fructose to glucose HFCS is typically between 40:60 and 60:40, such as a ratio between 44:56 and 46:54, more particularly a ratio of 45:55. In some cases the ratio of fructose to glucose in HFCS may be in the range of 53:47 to 59:41, or in the range of 40:60 to 44:56.

Invert sugar also known as inverted sugar syrup, arise from hydrolysis of sucrose and invert sugar therefore typically comprises fructose and glucose in a ratio of approximately between 48:52 and 52:48, such as a ratio between 49:51 and 51:49, more particularly a ratio of 50:50. Thus fructose typically constitute 48-52w/w% of the total amount of saccharides in invert sugar, in particular 49-51w/w% of the total amount of saccharides is fructose, even more particularly

50w/w% of the total amount of saccharides is fructose. Glucose similarly constitute 48-52w/w% of the total amount of saccharides in invert sugar, in particular 49-51w/w% of the total amount of saccharides in invert sugar is glucose, even more particularly 50w/w% of the total amount of saccharides in invert sugar is glucose.

Inulins are polymers that mainly comprises fructose units joined by a β(2→1) glycosidic bond and which typically have a terminal glucose units. Hydrolysis of inulin typically results in a composition wherein approximately 90w/w%, e.g. in the range of 85-95w/w%, of the total amount of saccharides is fructose and approximately 10w/w%, e.g. in the range of 5-15 w/w%, of the total amount of saccharides is glucose.

If on the other hand a composition comprising a relative high concentration of glucose and a relative low concentration of fructose is used as a starting material in a method of the present invention it is an advantage to include a step of increasing the amount of fructose relative to the amount of glucose prior to using it in the dehydration process of steps i), II) and A) of the present inventions. Methods of increasing the amount of fructose in a composition include steps I), –i) and –ii) described above but it may also involve other methods such as purification of fructose. In this context a “relative high concentration of glucose” means a composition wherein 60-100w/w% of the total amount of saccharides is glucose, such as 60-95w/w% of the total amount of saccharides is glucose.

Furthermore, in this context the term “relative low concentration of fructose” means a composition wherein fructose constitutes 40w/w% or less than 40w/w% of the total amount of saccharides, i.e. wherein 0-40w/w% of the total amount of saccharides is fructose.

Examples of such compositions comprising a high concentration of glucose and a low concentration of fructose include but are not limited to glucose obtained from any source of starch, such as but not limited to corn, wheat and potatoes, glucose obtained from cellulosic biomass, e.g. fibres, stovers, wheat, or straw. The glucose may also be obtained from other sources of starch or biomass known to a person skilled in the art.

Glucose obtained from starch typically results in a composition wherein approximately 92-98w/w% of the total amount of saccharides is glucose.

Converting glucose to fructose by an enzymatic reaction catalyzed by glucose isomerase, e.g. steps –i), iv) b), I), IV) b) and C) b) of the present invention typically results in a composition wherein approximately 43-47w/w% of the total amount of saccharides is fructose and approximately 53-57w/w% of the total amount of saccharides is glucose. Thus the ratio of fructose to glucose in these compositions may typically be in range of 43:57 and 47:53, such as in the range of 44:56 and 46:54, or approximately 45:55.

Reaction medium

The processes of converting fructose or glucose to HMF in steps i), II), A), iv) a), IV) a) and C) a) take place in a reaction medium comprising an aqueous phase and an organic phase. Thus

the reaction medium of the present invention comprises two phases which typically may be liquid phases due to the nature of the components involved and the dehydration process. In the context of the present invention the term “phase” refers to the solubility of the aqueous phase in the organic phase and vice versa. Thus in the context of the present invention it means that the solubility of the aqueous phase in the organic phase and vice versa is so low that the reaction medium comprises two distinct phases; i.e. the aqueous phase and the organic phase.

The term “aqueous phase” means in the context of the present invention that the solvent of the aqueous phase is mainly water. In this respect “mainly water” means that 50-100v/v% of the solvent of the aqueous phase is water, e.g. 55-100v/v% of the solvent of the aqueous phase is water, or 60-100v/v% of the solvent of the aqueous phase is water, or 65-100v/v% of the solvent of the aqueous phase is water, or 70-100v/v% of the solvent of the aqueous phase is water, or 75-100v/v% of the solvent of the aqueous phase is water, or 80-100v/v% of the solvent of the aqueous phase is water, or 85-100v/v% of the solvent of the aqueous phase is water, or 90-100v/v% of the solvent of the aqueous phase is water, or 95-100v/v% of the solvent of the aqueous phase is water. Thus the aqueous phase of the reaction medium of the present invention comprises in particular less than 50v/v% other solvents, such as DMSO. Hence the amount of other solvents, including DMSO, than water in the aqueous phase of the reaction medium may in particular be in the range of 0-50v/v%, more particularly in the range of 0-45v/v%, or in the range of 0-40v/v%, or in the range of 0-35v/v%, or in the range of 0-30v/v%, or in the range of 0-25v/v%, or in the range of 0-20v/v%, or in the range of 0-15v/v%, or in the range of 0-10v/v%, or in the range of 0-5v/v%.

It is particularly relevant that the solvent of the aqueous phase is mainly water when step iv) b), IV) b) or C) b) are present in a method of the present invention because other solvents may affect the functionality of the glucose isomerase used in these steps. For example glucose isomerase does not function optimally if DMSO is present. Trace amounts of such unwanted solvents may of course be present. It is just advantageous that the amount of other solvents is not so high that it affects the functionality of the glucose isomerase significantly. The amount of solvent which may be present without significantly affecting the functionality of the glucose isomerase depends on the particular solvent.

The aqueous phase of the reaction medium comprises a salt. In the context of the present invention the term “salt” is to be understood as an ionic compound composed of cations (positively charged ions) and anions (negative ions) so that the product is electrically neutral (without a net charge). These component ions can be inorganic such as chloride (Cl^-), as well as organic such as acetate ($CH3COO^-$) and monoatomic ions such as fluoride (F^-), as well as polyatomic ions such as sulfate (SO_4^{2-}), or monovalent ions, such as Na^+, or divalent ions, such as Mg^{2+}. There are several varieties of salts. Salts that produce hydroxide ions when dissolved in water are basic salts and salts that produce hydronium ions in water are acid salts. Neutral salts are those that are neither acid nor basic salts. Zwitterions contain an anionic center and a cationic

center in the same molecule but are not considered to be salts. Examples include amino acids, many metabolites, peptides and proteins. When salts are dissolved in water, they are called electrolytes, and are able to conduct electricity, a property that is shared with molten salts.

The presence of salt in the aqueous phase decreases the solubility of HMF in the aqueous phase whereby the equilibrium of HMF between the aqueous phase and the organic phase is shifted towards the organic phase. This results in a further shift in the equilibrium of the dehydration process of glucose and/or fructose to HMF in the aqueous phase towards production of more HMF.

The salt present in the aqueous phase may in particular be an inorganic salt, such as a salt selected from the group consisting of but not limited to metal halides, sulphates, sulphides, phosphates, nitrates, acetates and carbonates.

Examples of such salts include but are not limited to sodium chloride (NaCl), magnesium chloride ($MgCl_2$), lithium chloride (LiCl), potassium chloride (KCl), calcium chloride ($CaCl_2$), cesium chloride (CsCl), sodium sulphate (Na_2SO_4), potassium sulphate (K_2SO_4), lithium bromide (LiBr), sodium bromide (NaBr), potassium bromide (KBr), lithium nitrate ($LiNO_3$), sodium nitrate ($NaNO_3$), potassium nitrate (KNO_3) and potassium iodine (KI).

The salt may in particular be a metal halide, such as NaCl, $MgCl_2$, LiCl, KCl, $CaCl_2$, CsCl, LiBr, NaBr, KBr or KI.

The concentration of salt may depend on the choice of salt, however it may for most salts be in the range of 1-20w/w%.

The inventors of the present invention has shown that by combining the salt with a weak acid, such as boric acid, the HMF yield and fructose conversion increased even further. Without being bound by any theory the inventors of the present invention are of the opinion that the combination of the sugars (e.g. fructose or glucose) and salt may affect the acidic effect of boric acid causing it to behave more acidic than without the presence of sugar and salt.

Hence in a particular embodiment the aqueous phase may comprise a weak acid. In the context of the present invention a weak acid is an acid with a pK_a-value which is 1 or higher than 1 (pK_a(weak acid) ≥ 1). Examples of such acids include boric acid ($B(OH)_3$). The amount of weak acid, e.g. boric acid, in the aqueous phase may typically be in the range of 0.1-200 g/L, such as in the range of 5-200 g/L, or in the range of, 10-200 g/L, or in the range of 10-150 g/L, or in the range of 25-150 g/L, or in the range of 50-150 g/L, or in the range of 50-125 g/L, or in the range of 75-125 g/L, such as 100 g/L.

Addition of a weak acid such as boric acid to the reaction medium does not decrease the pH as much as when using a strong acid as a catalyst. Thus the advantages of using salt as catalyst compared to using a strong acid also applies to using a combination of salt and a weak acid, such as boric acid, as a catalyst.

For the process of dehydrating fructose to HMF; i.e. steps i), II) and A) the aqueous phase of the reaction medium may in a particular embodiment have a pH in the range of pH 1.0 to 10,

such as in the range of pH 1.5-10, or in the range of pH 1.6-10, or in the range of pH 1.7-10, or in the range of pH 1.8-10, or in the range of pH 1.9-10, or in the range of pH 2.0-10, or in the range of 2.1-10, or in the range of pH 2.2-10, or in the range of pH 2.3-10, or in the range of pH 2.4-10, or in the range of pH 2.5-10, or in the range of pH 2.6-10, or in the range of pH 2.7-10, or in the range of pH 2.8-10, or in the range of pH 2.9-10, or in the range of pH 3 to 10, or in the range of pH 3 to 9, or in the range of pH 3.5 to 9, or in the range of pH 3 to 8, or in the range of pH 3.5 to 8, or in the range of 4 to 9, or in the range of pH 4 to 8.5, or in the range of pH 4 to 8, or in the range of pH 4.5 to 10, or in the range of pH 4.5 to 9, or in the range of pH 4.5 to 8.5, or in the range of pH 4.5 to 8, or in the range of pH 5 to 10, or in the range of pH 5 to 9, or in the range of pH 5 to 8.5, or in the range of pH 5 to 8, or in the range of pH 5.5 to 10, or in the range of pH 5.5 to 9, or in the range of pH 5.5 to 8.5, or in the range of pH 5.5 to 8, or in the range of pH 6 to 10, or in the range of pH 6 to 9, or in the range of pH 6 to 8.5, or in the range of pH 6 to 8.

For the process of dehydrating glucose to HMF, i.e. steps iv) a), IV) a) and C) a) the pH of the aqueous phase of the reaction medium may in particular be in the range of 1 to 9, such as a pH in the range of 1 to 8, or in the range of 1 to 7, or in the range of 1 to 6, or in the range of 1 to 5, or in the range of 1 to 4, or in the range of 1.5 to 8, or in the range of 1.5 to 7, or in the range of 1.5 to 6, or in the range of 1.5 to 5, or in the range of 1.5 to 4.

The dehydration of glucose and/or fructose to HMF mainly takes place in the aqueous phase of the reaction medium and the process may create by-products. Some of these by-products are acidic and they may therefore cause the pH of the aqueous phase to fall as the dehydration of glucose and/or fructose to HMF takes place. Thus in the context of the present invention the pH range of the aqueous phase of the reaction medium refers to t_0 of the dehydration process in steps i), iv) a), II), IV) a), A and C) b). Thus it is the pH of the aqueous phase of the reaction medium at the point in time where all components are present but prior to any actual dehydration of fructose or glucose to HMF has taken place. For example if the method of the present invention is run as continuous process on an industrial scale the pH of composition comprising fructose, glucose or fructose and glucose may be the same as the pH of the aqueous phase of the reaction medium at t_0 when no acidic catalysts are added to the reaction medium. For example if the starting material, i.e. the composition comprising fructose or fructose and glucose, used for the dehydration of fructose to HMF, i.e. in steps i), II) and A) has been obtained from conversion of glucose to fructose by an enzymatic reaction catalyzed by a glucose isomerase, e.g. in steps –i), iv) b), I), IV) b) or C) b), the pH of the composition obtained from this conversion will typically be in the range of 6.5-7.5. As glucose isomerase currently is used on an industrial basis as columns to which the glucose isomerase is immobilized this means that the pH of the composition leaving the glucose isomerase may typically be in the range of 6.5-7.5. It may of course be possible to adjust the pH of this composition before it enters the dehydration process in steps i), II) or A).

In alternative embodiment the aqueous phase of the reaction medium for the process of dehydrating fructose to HMF; i.e. steps i), II) and A) does not contain an acidic catalyst or does not comprise a strong acid. In the context of the present invention “does not contain an acidic catalyst” means that no acidic catalyst has been added to the reaction medium. The term “does not comprise a strong acid” means that no acids with a pK_a-value below 1 has been added to the reaction medium; i.e. “a strong acid” is in the context of the present invention to be understood as an acid with a pK_a-value which is lower than 1 (pK_a(strong acid)<1). It does not exclude the presence of acidic compounds which may be formed as by-products of the dehydration process. Examples of such acidic catalysts include but are not limited to mineral acids, such as HCl, HNO_3, H_2SO_4, H_3PO_4, sulfonic acid, sulfonic acid resins, zeolites, acid-functionalized Mobil composition materials (MCM’s), sulphated zirconia, heteropolyacids, phosphates such as $NbOPO_4$, vanadium phosphate, solid silica- and silica-alumina, Brøndsted or Lewis acid catalyst. The inventors of the present invention has surprisingly found out that the salt present in the aqueous phase is able to function as catalyst for the dehydration fructose to HMF making it unnecessary to use other catalysts such as acidic catalysts which have previously been used. Hence in a particular embodiment the aqueous phase of the reaction medium in steps i), II) and A) of the present invention does not comprise an acidic catalyst or does not comprise a strong acid.

Although, the inventors of the present invention found out that it is not necessary to use an acidic catalyst for the dehydration of fructose to HMF such catalysts may still be present in the aqueous phase of the reaction for example in small amounts. Thus any of the above mentioned catalysts may be present in the aqueous phase of the reaction medium.

Furthermore, for the process of dehydration of glucose to HMF, i.e. steps iv) a), IV) a) and C) a) it may also be an advantage to include an acidic catalyst, such as $AlCl_3$ to minimize the production of unwanted side-products. The optimal reaction conditions for the dehydration of fructose and glucose, respectively, to HMF are not the same.

The organic phase of the reaction medium comprises an organic solvent and optionally other components.

A suitable organic solvent is preferably a solvent which is non-miscible with the aqueous phase of the reaction medium and which is capable of solubilising HMF at room temperature (25°C) or higher. More preferably the organic solvent is a solvent having a higher solubility for HMF than the solubility of HMF in the aqueous phase, so that HMF is extracted from the aqueous phase into the organic phase.

Examples of such organic solvents include in particular but are not limited to alcohols, ketones, chlorinated alkanes, ethers, acetates or combinations thereof.

In a particular embodiment the organic solvent may be methyl-isobutylketone (MIBK), tetrahydrofuran (THF), 2-BuOH (2-butanol) or any combination of two or more of these organic solvents. Combinations of the organic solvents may for example be MIBK and 2-BuOH, such as in

a ratio of between 5:5 and 9:1 MIBK:2-BuOH, more particularly 7:3 MIBK:2-BuOH. THF is shown to be good at extracting HMF from the aqueous phase and the amount of unwanted side-products is also diminished compared to when other organic solvents are used.

Other examples of useful organic solvents include but are not limited to low molecular weight alcohols, such as fusel oil, isoamyl alcohol, butanol or isopentyl alcohol, straight or branched alcohols, such as pentanol, tertbutyl alcohol or 1-butanol, straight or branced alkanones, such as butanone, pentanone, hexanone, heptanone, diisobutylketone, 3-mehtyl-2-butanone, or 5-methyl-3-heptanone, cycloalkanones, such as cyclobutanone, cylclopentanone or cyclohexanone. Other examples of organic solvents include but are not limited to nitriles, such as benzonitrile, aliphatic and cycloaliphatic ethers, such as dichloroethylether or dimethyl ether, saturated and unsaturated aliphatic or aromatic hydrocarbons, such as furan, or nitroalkanes, such as nitromethane or nitropropane, and halogenated alkanes, such as dichloromethane (DCM), chloromethane, trichloromethane or trichloroethane.

The ratio of the volume of the aqueous phase to the volume of the organic phase may in a particular embodiment be in the range of 1:0.1 to 1:100 (aqueous phase:organic phase or aq:org).

As described above it is an advantage if the solubility of HMF is larger in the organic phase than in the aqueous phase of the reaction medium. This may be described by a parameter called the partition coefficient of the aqueous and organic phase with respect to HMF. In a particular embodiment the partition coefficient for the aqueous and organic phase with respect to HMF is at least 0.8, such as at least 0.9, or at least 1.0, or at least 1.1, or at least 1.2, or at least 1.3, or at least 1.4, or at least 1.5, such as at least 2.

EXAMPLES

Example 1: Selective dehydration of fructose from fructose/glucose mixture

2.5 mL of an aqueous solution of 171 g/L glucose, 123 g/L fructose, 245 g/L sodium chloride and 0.36 g/L hydrogen chloride was added 10 mL MIBK and stirred under a nitrogen atmosphere in a 25 mL sealed glass reactor tube at 140 °C for 1 hour. The organic and aqueous phases of the product were analyzed by HPLC (High Pressure Liquid Chromatography), showing that 49% of the introduced glucose or fructose was converted, leaving 87% of the introduced glucose unconverted. The yield of HMF was 33%, corresponding to a selectivity of 68%.

Example 2: Dehydration of glucose to HMF with aluminum chloride

2.5 mL of an aqueous solution of 245 g/L sodium chloride, 294 g/L glucose and 1.31 g/L aluminum chloride was added 10 mL MIBK and stirred under a nitrogen atmosphere in a 25 mL sealed glass reactor tube at 140°C for 2.5 hours. The organic and aqueous phases of the product were analyzed by HPLC, showing that 85 % of the glucose was converted. The yield of HMF

was 51%, corresponding to a selectivity of 60%.

Example 3: Two step dehydration of fructose/glucose mixture – with solvent exchange

2.5 mL of an aqueous solution of 245 g/L sodium chloride, 171 g/L glucose, 123 g/L fructose and 0.36 g/L hydrogen chloride was added 10 mL MIBK and stirred under a nitrogen atmosphere in a 25 mL sealed glass reactor tube at 140°C for 1 hour. The reaction mixture was cooled and the organic phase was collected. To the aqueous phase was added 10 mL MIBK and 50 µL aqueous solution of 0.5M aluminum chloride. The mixture was stirred under a nitrogen atmosphere in a 25 mL sealed glass reactor tube at 140°C for two to four hours. The aqueous and organic phases were analyzed by HPLC. The results are given in table 1.

Table 1: Results for two step dehydration of HFCS42 with solvent exchange

Reaction time with $AlCl_3$	Conversion of sugars	HMF yield	HMF selectivity
2 hours	70%	51%	72%
4 hours	90%	63%	70%

Example 4: Two step dehydration of fructose/glucose mixture – without solvent exchange

2.5 mL of an aqueous solution of 245 g/L sodium chloride, 171 g/L glucose, 123 g/L fructose and 0.36 g/L hydrogen chloride was added 10 mL MIBK and stirred under a nitrogen atmosphere in a 25 mL sealed glass reactor tube at 140°C for 1 hour. The reaction mixture was cooled and 50 µL aqueous solution of 0.5M aluminum chloride was added. The mixture was stirred under a nitrogen atmosphere in a 25 mL sealed glass reactor tube at 140°C for two to four hours. The aqueous and organic phases were analyzed by HPLC. The results are given in table 2.

Table 2: Results for two step dehydration of HFCS42 without solvent exchange

Reaction time with $AlCl_3$	Conversion of sugars	HMF yield	HMF selectivity
2 hours	72%	50%	70%
4 hours	86%	51%	59%

Example 5: Synthesis and extraction of HMF from fructose at 160°C in a biphasic water/MIBK reactor with NaCl addition

3 ml of aqueous sample phase solution containing 20% (wt/wt) fructose were poured into a 15 ml reactor. NaCl was added to the water phase to give a NaCl concentration of 50 g/L followed by addition of 12 ml MIBK as organic HMF extraction phase.

The reaction mixture was heated to 160°C and run for 120 min, where after samples were taken for HPLC analysis.

The HMF yield was 75%, the selectivity 79% and fructose conversion 94%

Under the same conditions but without addition of NaCl the following results were obtained:

The HMF yield was 39%, the selectivity 86% and the fructose conversion 46%

Example 6: Synthesis and extraction of HMF from fructose at 160°C in a biphasic water/MIBK reactor with NaCl addition

3 ml of aqueous sample phase solution containing 20% (wt/wt) fructose were poured into a 15 ml reactor. 0.2g NaCl was added to the water phase.

5 mg of the sulfated zirconia catalyst where then added to the water phase reaction mixture followed by addition of 12 ml MIBK as organic HMF extraction phase. The reaction mixture was heated to 160°C and run for 240 min, where after samples were taken for HPLC analysis.

The HMF yield was 68% and the selectivity 70%.

Example 7: Synthesis of HMF with glucose/fructose mixture at 150°C

An aqueous solution containing 10 wt% glucose and 10 wt% fructose (3 mL, 0.0022 mol glucose, 0.0023 mol fructose) was mounted in an Ace vial pressure tube (stable to ~20 Bar). Solid NaCl (150 mg, 0.0026 mol) was dissolved in the aqueous phase followed by the addition of MIBK (12 ml) as extracting solvent. The pressure stable tube was sealed and heated to 150°C for 2 h and subsequently allowed cooling to room temperature. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC. The results of the HPLC showed 84 % glucose from glucose, 0.0019 mol; 44 % fructose from fructose, 0.0010 mol; 33 % HMF from fructose, 0.0008 mol; total sugar conversion 33 %; HMF selectivity from fructose 59 %.

Example 8: Synthesis of HMF with glucose/fructose mixture at 160°C

An aqueous solution containing 10 wt% glucose and 10 wt% fructose (3 mL, 0.0022 mol glucose, 0.0023 mol fructose) was mounted in an Ace vial pressure tube (stable to ~20 Bar). Solid NaCl (150 mg, 0.0026 mol) was dissolved in the aqueous phase followed by the addition of MIBK (12 ml) as extracting solvent. The pressure stable tube was sealed and heated to 160°C for 105 min and subsequently allowed cooling to room temperature. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an inter-

nal standard (*i*-PrOH) and analyzed via HPLC. The results of the HPLC showed 80 % glucose from glucose, 0.0018 mol; 4 % fructose from fructose, $9.5 \cdot 10^{-5}$ mol; 64 % HMF from fructose, 0.0015 mol; total sugar conversion 59 %; HMF selectivity from fructose 67 %.

Example 9: Synthesis of HMF with glucose at 150°C (control)

An aqueous solution containing 10 wt% glucose (3 mL, 0.0022 mol) was mounted in an Ace vial pressure tube (stable to ~20 Bar). Solid NaCl (150 mg, 0.0026 mol) was dissolved in the aqueous phase followed by the addition of MIBK (12 ml) as extracting solvent. The pressure stable tube was sealed and heated to 150 °C for 2 h and subsequently allowed cooling to room temperature. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC. The results of the HPLC showed 95-97 % glucose, 0.0021-0.0022 mol; 2 % HMF, $4.5 \cdot 10^{-5}$ mol; total sugar conversion 3-5 %.

Example 10: Synthesis of HMF with fructose at 150°C (control)

An aqueous solution containing 10 wt% fructose (3 mL, 0.0019 mol) was mounted in an Ace vial pressure tube (stable to ~20 Bar). Solid NaCl (150 mg, 0.0026 mol) was dissolved in the aqueous phase followed by the addition of MIBK (12 ml) as extracting solvent. The pressure stable tube was sealed and heated to 150 °C for 2 h and subsequently allowed cooling to room temperature. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC. The results of the HPLC showed 61 % fructose, 0.0012 mol; 29 % HMF, 0.005 mol; total sugar conversion 39 %; HMF selectivity from fructose 73 %.

Anticipations and approximations for the glucose / fructose mixture

The yield of glucose and fructose were calculated according to the initial amount of each present in the sample. Hereby the interconversion of glucose and fructose were neglected. The HMF yield was calculated based on the fructose only. Thereby a small amount arising from glucose was neglected. The amounts of formic acid and levulinic acid were below the detection limit of the HPLC apparatus. Please note that the conversions of fructose and glucose separately do not add up to the total sugar conversion as e.g. 100 % fructose conversion ≈ 50 % total sugar conversion. HMF selectivity's were calculated based on the fructose conversion, due to the assumption above. The remaining products to complete the mass balance were not detected, but were likely to comprise of soluble and insoluble, reversible and irreversible dimers, trimers and polymers of glucose, fructose, HMF and combinations hereof.

Example 11: The effect of various salts

Generally, aqueous solutions containing 30 wt% fructose (3 mL, 0.0058 mol) were mounted in an Ace vial pressure tube (stable to ~20 Bar). Various solid salts (0.0026 mol) were dissolved in the aqueous phase followed by the addition of MIBK (12 ml) as extracting solvent. The pressure stable tube was sealed and heated to 160°C for 2 h and subsequently allowed cooling to room temperature. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC. The results are shown below in table 3 and in figure 2.

The best result with respect to HMF yield was obtained with KCl (98 % fructose conversion, 70 % HMF yield, HMF selectivity 72 %). The best result with respect to HMF selectivity was obtained with KBr (87 % fructose conversion, 64 % HMF yield, HMF selectivity 74 %).

Table 3:

Salt	NaCl	$MgCl_2$	$MgCl_2$	LiCl	NaCl	KCl	Na_2SO_4
Conversion	90.7	99.5	99.9	99.7	98.3	97.6	96.5
HMF yield	46.7	57.5	59.6	66.9	68.1	70.0	41.1
Selectivity	51.5	57.8	59.7	67.1	69.2	71.7	42.6
Mg	150	522	261	109	150	191	365

Table 3 continued:

Salt	K_2SO_4	LiBr	NaBr	KBr	$LiNO_3$	$NaNO_3$	KNO_3	KI
Conversion	100.0	96.6	93.9	86.9	84.0	82.6	71.3	97.0
HMF yield	39.9	64.8	65.3	64.4	36.2	33.8	26.1	60.5
Selectivity	39.9	67.1	69.5	74.1	43.1	40.9	36.6	62.4
Mg	447	223	264	305	177	218	260	426

Salts investigated

$MgCl_2$ with respect to the Mg content, $MgCl_2$ with respect to the chloride content, NaCl, LiCl, KCl, Na_2SO_4 with respect to the sulphate content, K_2SO_4 with respect to the sulphate content, LiBr, NaBr, KBr, $LiNO_3$, $NaNO_3$, KNO_3, KI.

Example 12: Glucose isomerase performance at high salt concentrations

Standard procedure for all columns:

3 gram immobilized glucose isomerase (Sweetzyme™) was loaded in a column heated to 60°C and a substrate flow of 50 gram/hour was applied. The substrate was either normal 45 w/w%

sterile filtered glucose solution containing 1 g/L $MgSO_4 \cdot 7H_2O$ and 0.18 g/L NaS_2O_5 or a modified 45 w/w% glucose syrup with addition of a relative high concentration of a salt. Samples were collected on a regular basis for HPLC analysis and the enzyme activity was calculated according to the following equation (Jorgensen, O.B., et al., Starch-Starke, 1988. **40**(8), 307-313).:

$$A = 0.926\frac{F_w}{w}X_e\frac{DP_1}{100}DSln\frac{X_e - X_i}{X_e - X}$$

where:

A: specific activity of immobilized enzyme (micromol/min/g enzyme) (IGIU/g: Immobilized Glucose Isomerase Units/g)

0.926: unit conversion factor

F_w: Flow rate of syrup (g/h)

w: Weight of enzyme (g)

DP_1: Inlet % of (glucose + fructose) in dry substance (100 at analytical conditions)

DS: Dry substance content (%)

X: Conversion = outlet % fructose/DP_1

X_i: inlet % fructose/DP_1

X_e: X at equilibrium (0.51 at 60°C)

DP_1, X_i and X_e were assumed constant with following values:

DP_1: 99.7

X_i: 0

X_e: 0.5078

The following salt conditions were applied for 6 columns

Column 1:

Normal 45 w/w% sterile filtered glucose solution containing 1 g/L $MgSO_4 \cdot 7H_2O$ and 0.18 g/L NaS_2O_5. Key performance results are presented in table 4 and activity results are listed in table

5 and figure 3 shows a graphical presentation of the course of the activity.

Column 2:

Sodium chloride (NaCl) mixed in standard 45% glucose syrup (as in column 1) to give a final concentration of NaCl of 50 g/l or 0.86M. Key performance results are presented in table 4 and activity results are listed in table 5 and figure 4 shows a graphical presentation of the course of the activity.

Column 3:

Magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) mixed in standard 45% glucose syrup (as in column 1) to give a final concentration of $MgCl_2$ 40.9 g/l or 0.86M with respect to chloride (86.97 g/l $MgCl_2 \cdot 6H_2O$). Key performance results are presented in table 4 and activity results are listed in table 5 and figure 5 shows a graphical presentation of the course of the activity.

Column 4:

Potassium chloride (KCl) mixed in standard 45% glucose syrup (as in column 1) to give a final concentration of KCl of 63.78 g/l or 0.86M. Key performance results are presented in table 4 and activity results are listed in table 5 and figure 6 shows a graphical presentation of the course of the activity.

Column 5:

Sodium sulfate decahydrate ($Na_2SO_4 \cdot 10H_2O$) mixed in standard 45% glucose syrup (as in column 1) to give a final concentration of Na_2SO_4 61.08 g/l or 0.86M with respect to sodium (137.82 g/l $Na_2SO_4 \cdot 10H_2O$). Key performance results are presented in table 4 and activity results are listed in table 5 and figure 7 shows a graphical presentation of the course of the activity.

Column 6:

Magnesium sulfate ($MgSO_4$) mixed in standard 45% glucose syrup (as in column 1) to give a final concentration of $MgSO_4$ of 102.98 g/l or 0.86M. Key performance results are presented in table 4 and activity results are listed in table 5 and figure 8 shows a graphical presentation of the course of the activity.

Table 4: Key performance results for columns 1-6

Column	Salt	Concentration (g/l)	Initial activity (IGIU/g)	Decay rate (IGIU/g/hr)

1	No	-	438.60	0.10
2	NaCl	50.00	423.56	0.06
3	$MgCl_2$	40.90	480.68	0.37
4	KCl	63.78	429.32	0.10
5	Na_2SO_4	61.08	409.18	0.12
6	$MgSO_4$	102.98	401.39	0.34

In conclusion, Sweetzyme™ shows good stability in the presence of NaCl, KCl and Na_2SO_4.

Table 5: Performance in terms of activity results for glucose isomerase for the six columns. Blue shaded regions represent high salt conditions whereas no shading means normal syrup.

Column 1: normal syrup		Column 2: 50 g/l NaCl		Column 3: 40.9 g/l $MgCl_2$	
Time/h	Activity	Time/h	Activity	Time/h	Activity
21.25	437.91	19.25	431.74	18.67	426.24
49.25	441.63	47.25	438.80	46.67	437.70
69.75	444.75	67.75	438.50	67.17	433.67
141.75	431.05	139.75	425.49	139.17	420.99
166.58	448.13	164.58	471.33	164.00	489.74
190.58	421.40	188.58	469.46	188.00	471.38
214.58	412.38	212.58	451.52	212.00	454.69
236.92	426.67	234.92	468.84	234.33	463.15
312.33	417.07	310.33	466.38	309.75	442.52
334.50	412.78	332.50	468.14	331.92	432.66
381.92	394.46	379.92	449.12	379.33	409.54
477.50	381.64	475.50	446.72	474.92	351.70
501.42	377.86	499.42	445.83	498.83	343.55
525.33	370.29	523.33	439.69	522.75	340.36
550.42	376.77	548.42	436.34	547.83	307.44
572.25	364.64	570.25	436.11	569.67	301.06
645.00	369.22	643.00	446.01	642.42	291.22
672.75	357.03	670.75	435.86	670.17	283.93
Column 4: 63.78 g/l KCl		Column 5: 61.08 g/l Na_2SO_4		Column 6: 102.98 g/l $MgSO_4$	
Time/h	Activity	Time/h	Activity	Time/h	Activity
18.17	398.12	17.83	418.97	17.50	412.41
46.17	410.62	45.83	433.23	45.50	420.62
66.67	411.97	66.33	432.90	66.00	419.46

138.67	415.42	138.33	427.76	138.00	428.95
163.50	429.63	163.17	439.97	162.83	436.79
211.50	448.90	187.17	449.17	186.83	452.92
233.83	469.08	211.17	437.81	210.83	465.04
309.25	468.47	233.50	449.65	233.17	424.51
331.42	469.21	308.92	437.45	308.58	370.47
378.83	443.80	331.08	437.38	330.75	366.35
474.42	430.17	378.50	429.47	378.17	324.95
498.33	428.76	474.08	381.79	473.75	306.53
522.25	418.17	498.00	387.83	497.67	298.41
547.33	437.40	521.92	382.13	521.58	299.60
569.17	438.97	547.00	394.91	568.50	310.87
641.92	455.49	568.83	393.80		
669.67	426.01	641.58	376.25		
		669.33	370.35		

Example 13: The effect of HMF on the initial activity of Sweetzyme™

To demonstrate the effect of 5-hydroxymethylfurfural (HMF) on the initial activity of Sweetzyme™ a number of batch experiments with varying amount of HMF were performed.

Standard procedure:

2.5 gram immobilized glucose isomerase (Sweetzyme™) was loaded to a 250 mL square shaped bottles with screw cap. The bottles were placed in an orbital shaker and heated to 60°C. The substrate was either normal 45 w/w% sterile filtered glucose solution containing 1 g/L $MgSO_4 \cdot 7H_2O$ and 0.18 g/L NaS_2O_5 or a modified 45 w/w% glucose syrup with addition of HMF. Samples were collected on a regular basis for HPLC analysis and the enzyme activity was calculated.

The following conditions were applied for 4 bottles. The term conversion is defined as the fructose/glucose ratio.

Bottle 1:

Normal 45w/w% sterile filtered glucose solution containing 1 g/L $MgSO_4 \cdot 7H_2O$ and 0.18 g/L NaS_2O_5. Conversion vs. time is presented in figure 9 and the initial activity is calculated to be 392.

Bottle 2:

HMF is mixed in standard 45% glucose syrup (as in bottle 1) to give a final concentration of HMF of 0.01w/w%. Conversion vs. time is presented in figure 10 and the initial activity is calculated to be 389.

Bottle 3:

HMF is mixed in standard 45% glucose syrup (as in bottle 1) to give a final concentration of HMF of 0.1w/w%. Conversion vs. time is presented in figure 11 and the initial activity is calculated to be 378.

Bottle 4:

HMF is mixed in standard 45% glucose syrup (as in bottle 1) to give a final concentration of HMF of 1w/w%. Conversion vs. time is presented in figure 12 and the initial activity is calculated to be 364.

Figure 13 shows the Sweetzyme™ activity as a function of HMF concentration and it can be seen that the activity is not seriously affected by the presence of HMF.

Example 14: Glucose isomerase performance with substrate containing NaCl and MIBK

3.44 gram immobilized glucose isomerase (Sweetzyme™) was loaded in a column heated to 60℃ and a substrate flow of 50 gram/hour was applied. The substrate was 45 w/w% sterile filtered glucose solution containing 1 g/L $MgSO_4 \cdot 7H_2O$ and 0.18 g/L NaS_2O_5. To the substrate was added NaCl to a final concentration of 50 g/l and around 20 ml MIBK per liter glucose substrate which is enough to saturate the substrate with MIBK.

Samples were collected on a regular basis for HPLC analysis and the enzyme activity was calculated according to the following equation and the results are shown below in table 6 [Jorgensen, O.B., et al., Starch-Starke, 1988. **40**(8), 307-313]:

$$A = 0.926 \frac{F_w}{w} X_e \frac{DP_1}{100} DSin \frac{X_e - X_i}{X_e - X}$$

where:

A: specific activity of immobilized enzyme (micromol/min/g enzyme) (IGIU/g: Immobilized Glucose Isomerase Units/g)

0.926: unit conversion factor

F_w: Flow rate of syrup (g/h)

w: Weight of enzyme (g)

DP_1: Inlet % of (glucose + fructose) in dry substance (100 at analytical conditions)

DS: Dry substance content (%)

X: Conversion = outlet % fructose/DP_1

Xi: inlet % fructose/DP_1

X_e: X at equilibrium (0.51 at 60°C)

DP_1, X_i and X_e were assumed constant with following values:

DP_1: 99.7

X_i: 0

X_e: 0.5078

Table 6: Glucose isomerase activity as a function of time

Time (h)	Activity (IGIU/g)	Substrate
19.83	387.58	Normal syrup
93.58	395.15	Normal syrup
118.83	416.97	Syrup with NaCl and MIBK
140.75	433.99	Syrup with NaCl and MIBK
164.00	435.48	Syrup with NaCl and MIBK
187.33	437.58	Syrup with NaCl and MIBK
283.75	364.90	Syrup with NaCl and MIBK
308.25	378.56	Syrup with NaCl and MIBK
335.67	376.48	Syrup with NaCl and MIBK

After 9 days with the substrate containing NaCl and MIBK, the decay rate is not affected compared to a column with normal syrup.

Example 15: Glucose isomerase performance with substrate containing hydroxymethylfurfural (HMF)

3.11 gram immobilized glucose isomerase (Sweetzyme™) was loaded in a column heated to 60°C and a substrate flow of 50 gram/hour was applied. The substrate was 45 w/w% sterile filtered glucose solution containing 1 g/L $MgSO_4 \cdot 7H_2O$ and 0.18 g/L NaS_2O_5. To the substrate was added hydroxymethylfurfural (HMF) to a final concentration of 0.1 w/w% HMF.

Samples were collected on a regular basis for HPLC analysis and the enzyme activity was calculated according to the following equation and the results are shown below in table 7 [Jorgensen, O.B., et al., Starch-Starke, 1988. **40**(8), 307-313]:

$$A = 0.926 \frac{F_w}{w} X_e \frac{DP_1}{100} DS \ln \frac{X_e - X_i}{X_e - X}$$

where:

A: specific activity of immobilized enzyme (micromol/min/g enzyme) (IGIU/g: Immobilized Glu-

cose Isomerase Units/g)

0.926: unit conversion factor

F_w: Flow rate of syrup (g/h)

w: Weight of enzyme (g)

DP_1: Inlet % of (glucose + fructose) in dry substance (100 at analytical conditions)

DS: Dry substance content (%)

X: Conversion = outlet % fructose/DP_1

X_i: inlet % fructose/DP_1

X_e: X at equilibrium (0.51 at 60°C)

DP_1, X_i and X_e were assumed constant with following values:

DP_1: 99.7

X_i: 0

X_e: 0.5078

Table 7: Glucose isomerase activity as a function of time

Time (h)	Activity (IGIU/g)	Substrate
68.50	376.93	Normal syrup
94.25	360.39	Syrup with 0.1 w/w% HMF
116.25	267.97	Syrup with 0.1 w/w% HMF
139.50	368.20	Syrup with 0.1 w/w% HMF
162.75	359.92	Syrup with 0.1 w/w% HMF
237.25	367.23	Syrup with 0.1 w/w% HMF
259.17	353.51	Syrup with 0.1 w/w% HMF
283.67	363.92	Syrup with 0.1 w/w% HMF
311.08	358.90	Syrup with 0.1 w/w% HMF

After 9 days with the substrate containing HMF, the decay rate is not affected compared to a column with normal syrup.

Example 16: Using a combination of NaCl and boric acid as catalysator

An aqueous solution containing 30 wt% fructose (3 mL, 5.7 mmol) was mounted in an Ace vial pressure tube (stable to ~20 Bar) and solid $B(OH)_3$ (0.3 g, 5 mmol) and/or solid NaCl (0.15 g, 3 mmol) were added to the solution. MIBK was added as extraction solvent so that an organic:aqueous volume ratio of 4:1 was obtained. The tube with the reaction mixture was placed in a preheated oil bath for a specified time under magnetic stirring (420 rpm) at a 150°C (reac-

tion times were measured after a stable oil bath temperature had been reached). After the reaction, the tube was removed from the oil bath and cooled to room temperature before a sample was taken for analysis. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC.

The results are shown below in Table 8.

Table 8: Dehydration of fructose to HMF with salt and/or boric acid in the aqueous phase

Catalyst	HMF yield (%)	Fructose conversion (%)
None	2	3
50 g/L NaCl	5	13
100 g/L $B(OH)_3$	22	39
50 g/L NaCl and 100 g/L $B(OH)_3$	55	83

Example 17: The effect of different salts together with boric acid

An experiment similar to that described in example 16 was carried out using different salts in combination with boric acid.

An aqueous solution containing 30 wt% fructose (3 mL, 5.7 mmol) was mounted in an Ace vial pressure tube (stable to ~20 Bar) and solid $B(OH)_3$ (0.3 g, 5 mmol) and solid salt (3 mmol with respect to the anion) were added to the solution. MIBK was added as extraction solvent so that an organic:aqueous volume ratio of 4:1 was obtained. The tube with the reaction mixture was placed in a preheated oil bath for a specified time under magnetic stirring (420 rpm) at a 150°C for 45 min (reaction times were measured after a stable oil bath temperature had been reached). After the reaction, the tube was removed from the oil bath and cooled to room temperature before a sample was taken for analysis. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC.

The results are shown below in table 9.

The *R* value indicated in table 9 is the HMF distribution obtained between the MIBK phase and the aqueous phase, i.e. $[HMF]_{MIBK}/[HMF]_{aq}$

Table 9: Dehydration of fructose to HMF with different salts and boric acid in the aqueous phase

Salt	Fructose conversion (%)	HMF yield (%)	HMF selectivity (%)	*R* value (MIBK:aq)

LiCl	69	45	66	1.1
LiBr	61	38	62	1.0
$LiNO_3$	49	21	42	0.9
NaCl	70	46	65	1.0
NaBr	60	38	64	0.9
$NaNO_3$	49	20	41	0.9
Na_2SO_4	90	41	45	1.7
KCl	67	44	65	1.0
KBr	63	39	62	0.9
KI	56	35	63	0.7
KNO_3	49	20	40	0.8
K_2SO_4	89	40	46	1.5
MgCl	81	52	65	1.1
$AlCl_3$	100	21	21	1.1
$FeCl_3$	99	36	36	1.1

Example 18: Salt and boric acid as catalysts with different organic extraction solvents

An experiment similar to that described in example 16 was carried out with different organic extraction solvents.

An aqueous solution containing 30 wt% fructose (3 mL, 5.7 mmol) was mounted in an Ace vial pressure tube (stable to ~20 Bar) and solid $B(OH)_3$ (0.3 g, 5 mmol) and NaCl (0.15 g, 3 mmol) were added to the solution. Different organic extraction solvent were added resulting in a organic:aqueous volume ratio of 4:1. The tube with the reaction mixture was placed in a preheated oil bath for a specified time under magnetic stirring (420 rpm) at a 150°C (reaction times were measured after a stable oil bath temperature had been reached). After the reaction, the tube was removed from the oil bath and cooled to room temperature before a sample was taken for analysis. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC.

The results are shown below in table 10.

The *R* value indicated in table 10 is the HMF distribution obtained between the MIBK phase and the aqueous phase, i.e. $[HMF]_{MIBK}/[HMF]_{aq}$.

Table 10: Dehydration of fructose to HMF with different organic extraction solvents

Organic extraction solvent	HMF yield (%)	Fructose conversion (%)	HMF selectivity (%)	R-value

MIBK	46	70	65	1.0
MIBK/2-BuOH; 7:3	50	72	70	1.9
2-BuOH	37	59	63	2.3
THF	34	54	63	3.2
THF/60 min	38	63	60	3.7
THF/75 min	51	75	67	3.6

Example 19: Dehydration of glucose and sucrose to HMF with NaCl and boric acid as catalyst

An experiment similar to that described in example 16 was carried out with the exception that glucose and sucrose were used as substrates for dehydration to HMF.

An aqueous solution containing 30 wt% glucose (3 mL, 5.7 mmol) or sucrose (3 mL, 6.0 mmol) was mounted in an Ace vial pressure tube (stable to ~20 Bar) and solid $B(OH)_3$ (0.3 g, 5 mmol) and NaCl (0.15 g, 3 mmol) were added with the exception that some of the experiments with glucose as substrate no catalyst was included, i.e. no $B(OH)_3$ and NaCl. MIBK was added as organic extraction solvent in an amount resulting in a organic:aqueous volume ratio of 4:1. The tube with the reaction mixture was placed in a preheated oil bath for a specified time under magnetic stirring (420 rpm) at a 150°C for the indicated periods of time (reaction times were measured after a stable oil bath temperature had been reached). After the reaction, the tube was removed from the oil bath and cooled to room temperature before a sample was taken for analysis. A sample of the reaction mixture was collected and filtered through a syringe filter (0.45 µm PTFE), mixed with an internal standard (*i*-PrOH) and analyzed via HPLC.

The results with glucose and sucrose as substrates are shown below in tables 11 and12, respectively.

With sucrose as substrate (the data presented in Table 12) the calculated HMF selectivity is based on the assumption that all the produced HMF comes from conversion of the fructose in sucrose.

Table 11: Dehydration of glucose to HMF with NaCl and/or boric acid in the aqueous phase

Catalyst	Time (min)	Glucose conversion (%)	HMF yield (%)	HMF selectivity (%)
None	45			
NaCl + $B(OH)_3$	45	8	2	25
None	180	13	1	10

NaCl + $B(OH)_3$	180	36	10	27
None	300	24	3	13
NaCl + $B(OH)_3$	300	41	14	34

Table 12: Dehydration of sucrose to HMF with NaCl and/or boric acid in the aqueous phase

Time (min)	Glucose yield (%)	Fructose yield (%)	HMF yield (%)	HMF selectivity (%)
45	45	18	24	75
90	45	8	33	78
105	44	5	36	79
120	43	3	37	79

CLAIMS

1. A method of producing 5-hydroxymethylfurfural comprising

i) subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt and has a pH in the range of 1.0 to 10.

2. A method of producing 5-hydroxymethylfurfural comprising

i) subjecting a composition comprising fructose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt, and wherein the reaction medium does not comprise an acidic catalyst or does not comprise a strong acid.

3. A method according to any of claims 1 and 2, wherein said method further comprises

ii) removing 5-hydroxymethylfurfural from the reactor in step i).

4. A method according to any of claims 1-3, wherein the composition comprising fructose also comprises glucose.

5. A method according to claim 4, wherein said method prior to step i) further comprises

-i) subjecting a composition comprising glucose to an enzymatic reaction catalyzed by glucose isomerase.

6. A method according to any of claims 4 and 5, wherein said method further comprises

iii) Removing glucose from the reactor in step i), and

iv) Converting the glucose obtained in step iii) to

a) Hydroxymethylfurfural

b) Fructose by an enzymatic reaction catalyzed by glucose isomerase.

7. A method of producing 5-hydroxymethylfurfural comprising

I) subjecting a composition comprising glucose to an enzymatic reaction catalyzed by glucose isomerase

II) subjecting the composition obtained in step I) to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt.

8. A method of producing 5-hydroxymethylfurfural comprising

A) subjecting a composition comprising fructose and glucose to a process in a reactor comprising a reaction medium, wherein said reaction medium comprises an aqueous phase and an organic phase and wherein said aqueous phase comprises a salt,

B) removing the glucose from the reactor in step A), and

C) converting the glucose obtained in step B) to

a) hydroxymethylfurfural, or

b) fructose by an enzymatic reaction catalyzed by glucose isomerase.

9. A method according to any of claims 7-8, wherein the aqueous phase of the reaction medium in step II) and A) has a pH in the range of 1.0 to 10.

10. A method according to any of the preceding claims, wherein one or more of the steps are performed continuously.

11. A method according to any of the preceding claims wherein the concentration of salt in the aqueous phase of the reaction medium is in the range of 1-20w/w%.

12. A method according to any of the preceding claims wherein the partition coefficient of the aqueous phase and the organic phase of the reaction medium with respect to 5-hydroxymethylfurfural is at least 1.0.

13. A method comprising converting the HMF obtained from a method according to any of

the preceding claims into 2,5-furandicarboxylic acid (FDA); 2,5-dimethylfuran; 2,5-dimethyltetrahydrofuran; formic acid; levulinic acid; 2,5-bis(hydroxymethyl)furan, 2-methylfuran, 2-hydroxymethylfuran.

14. Use of 2,5-furandicarboxylic acid obtained according to the method of claim 13 for polymer building blocks, plasticizers, hydrogenation to biodiesel, further reaction into furan diamines, furan diols, hydrogenated products.

ABSTRACT

The present invention relates to a method of producing 5-hydroxymethylfurfural by dehydration of fructose and/or glucose.

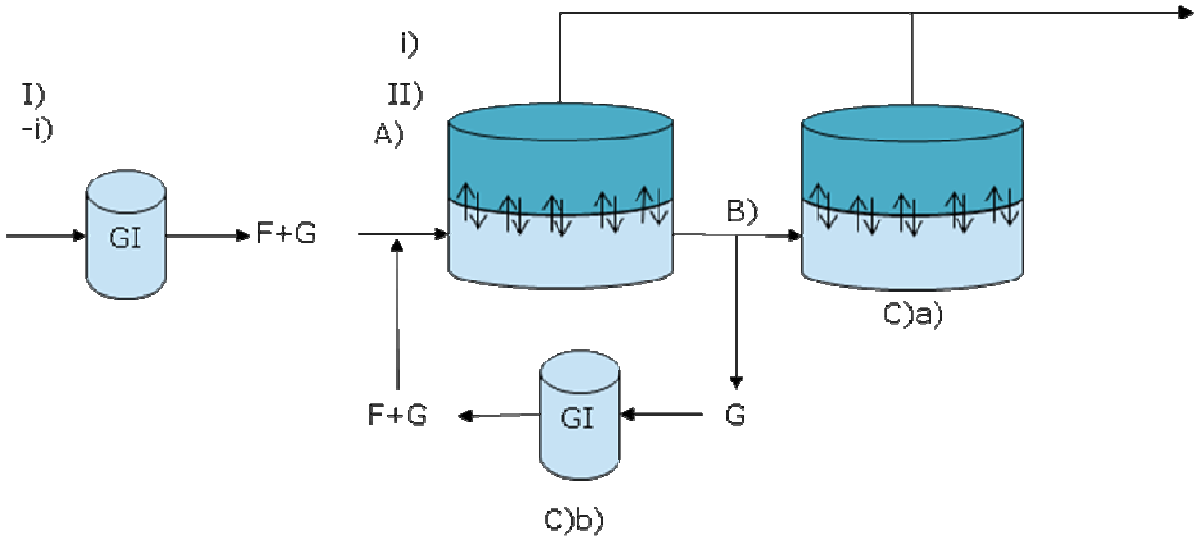


Figure 1

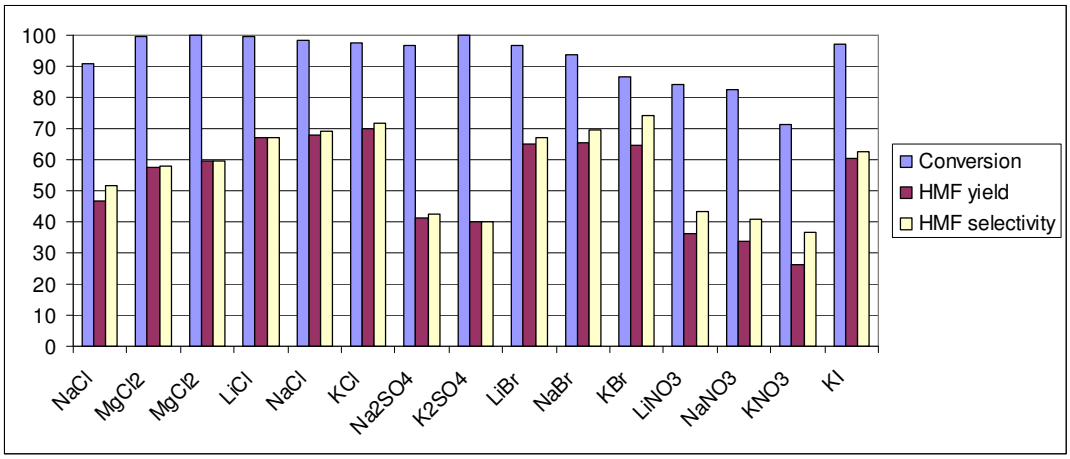


Figure 2

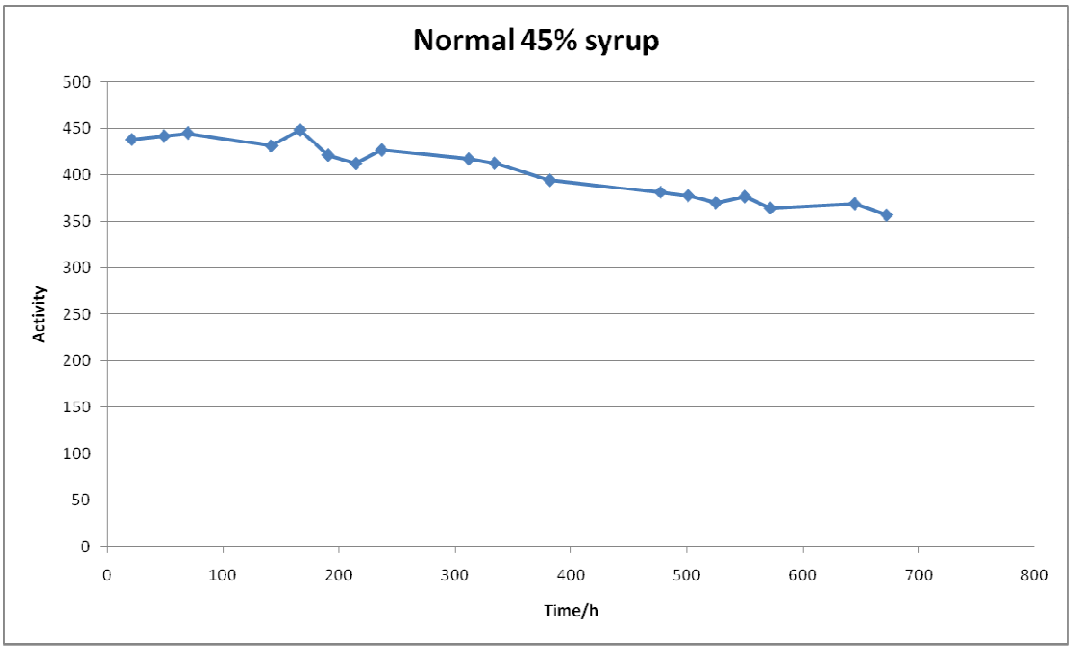


Figure 3

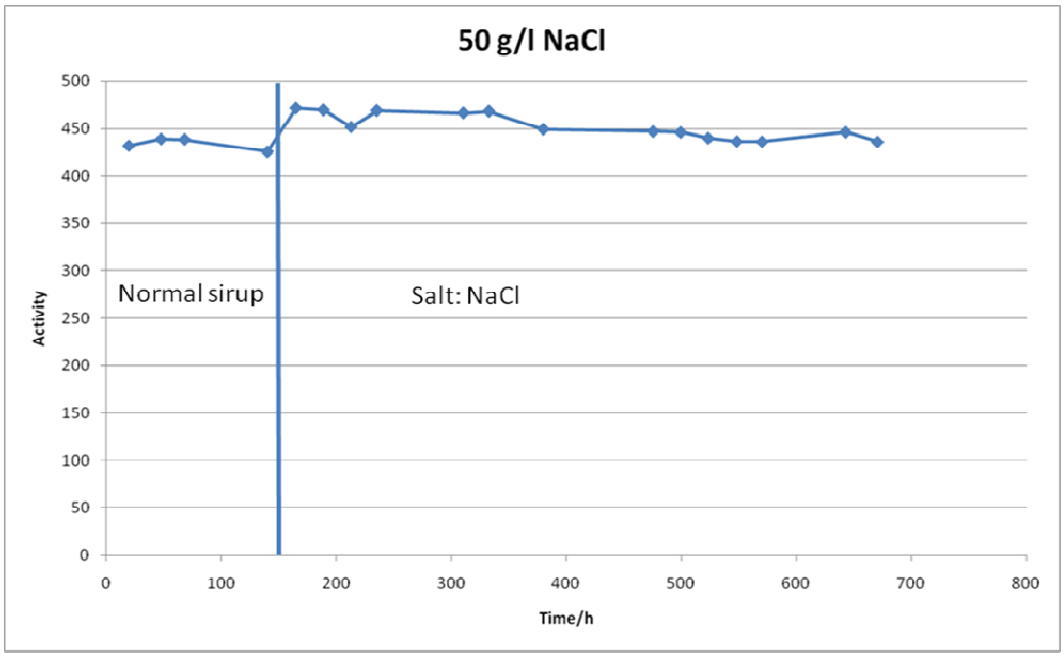


Figure 4

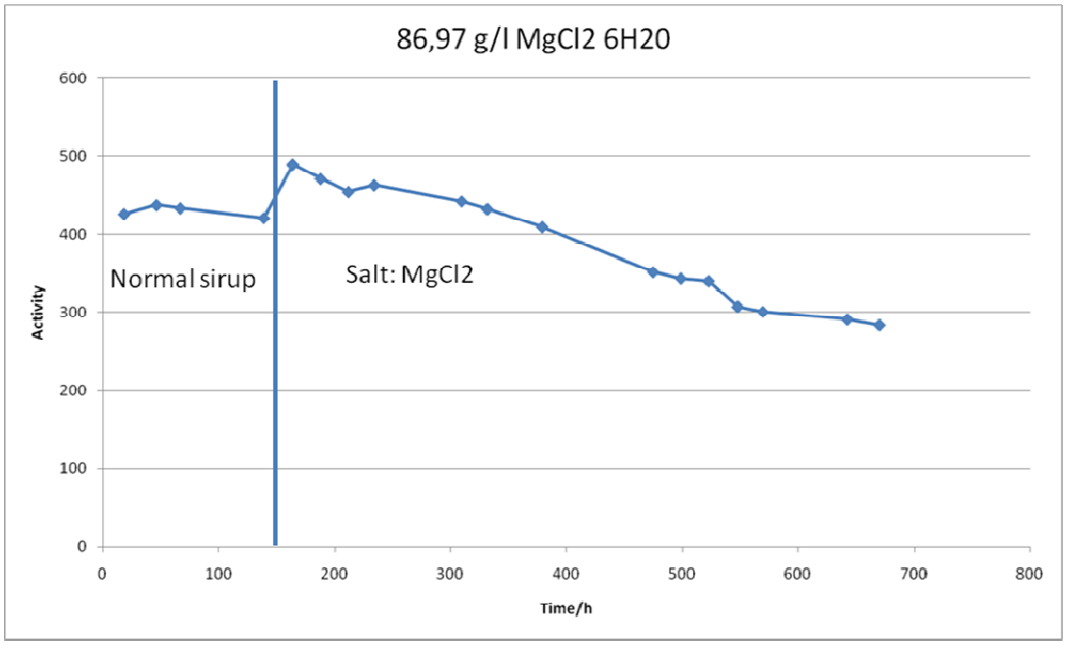


Figure 5

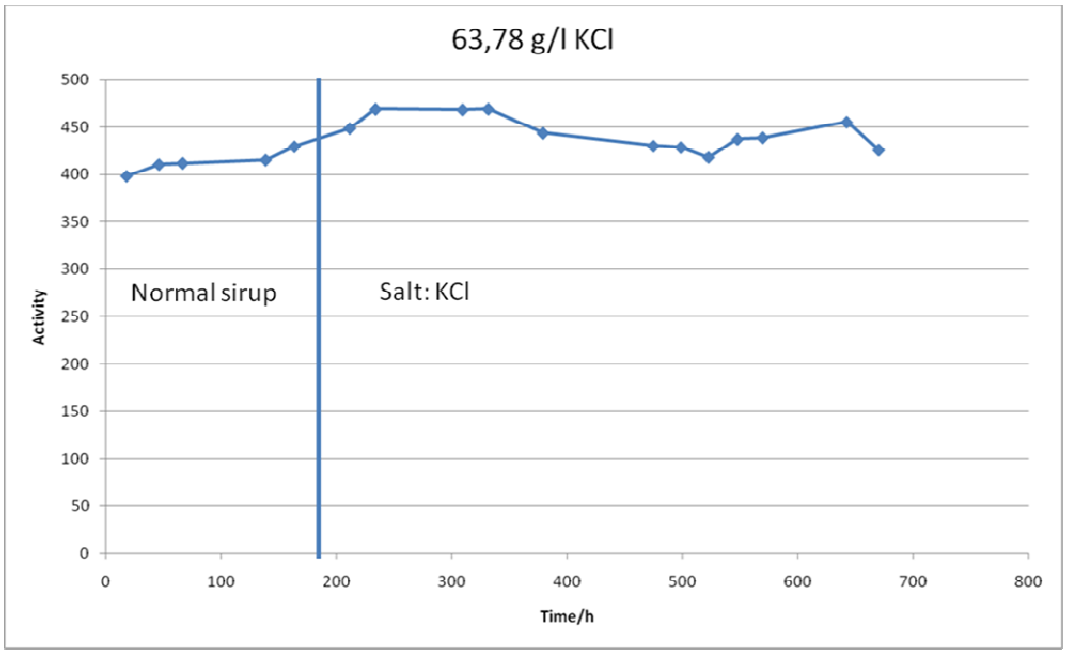


Figure 6

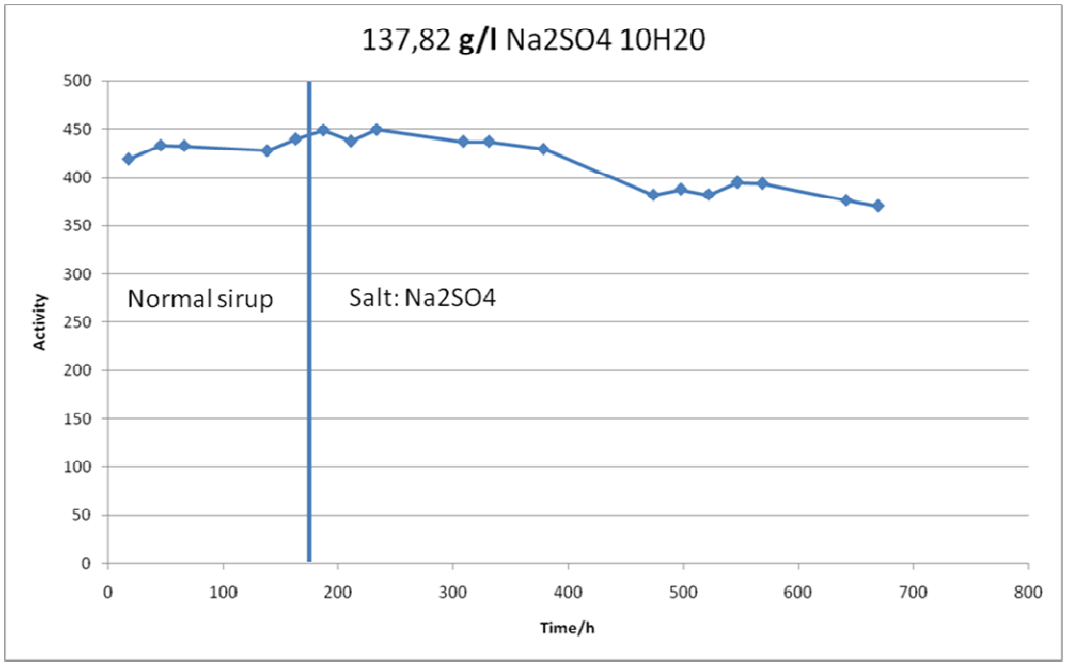


Figure 7

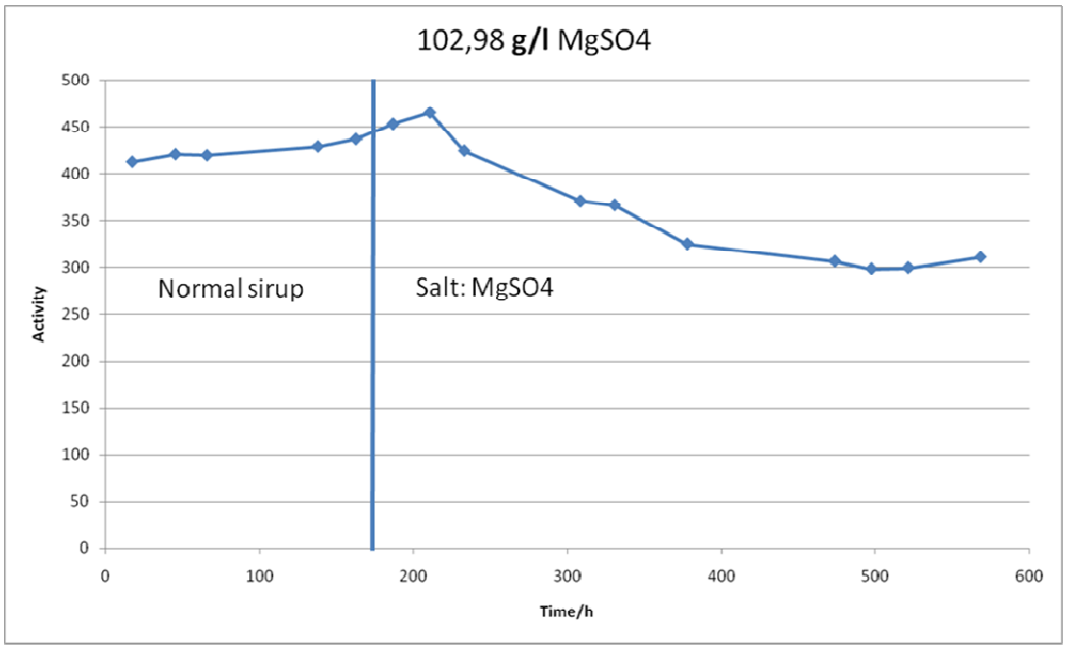
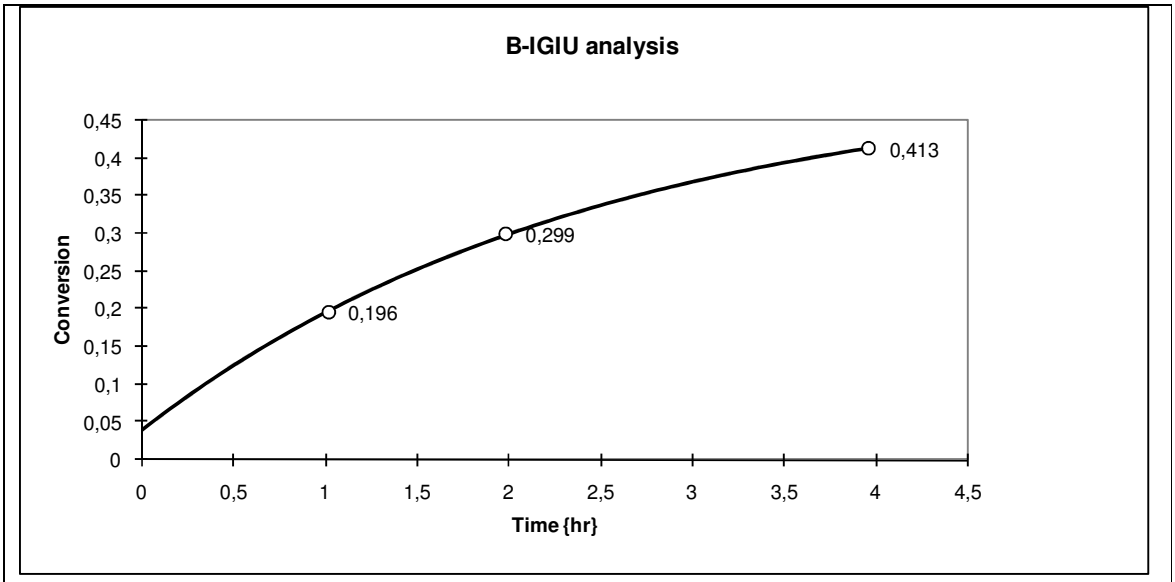


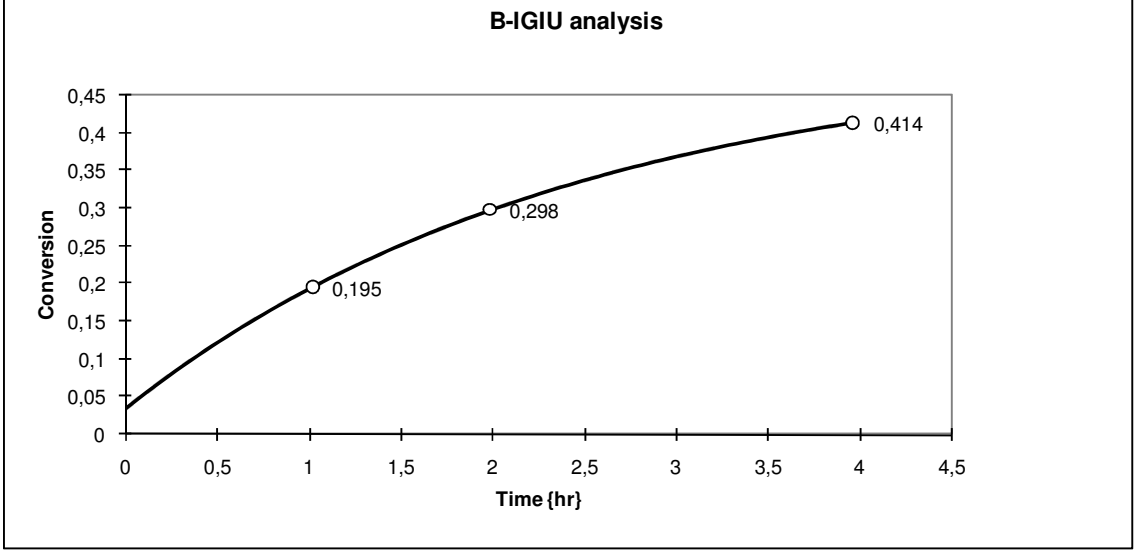
Figure 8



0% HMF

Activity: 392 B-IGIU/g

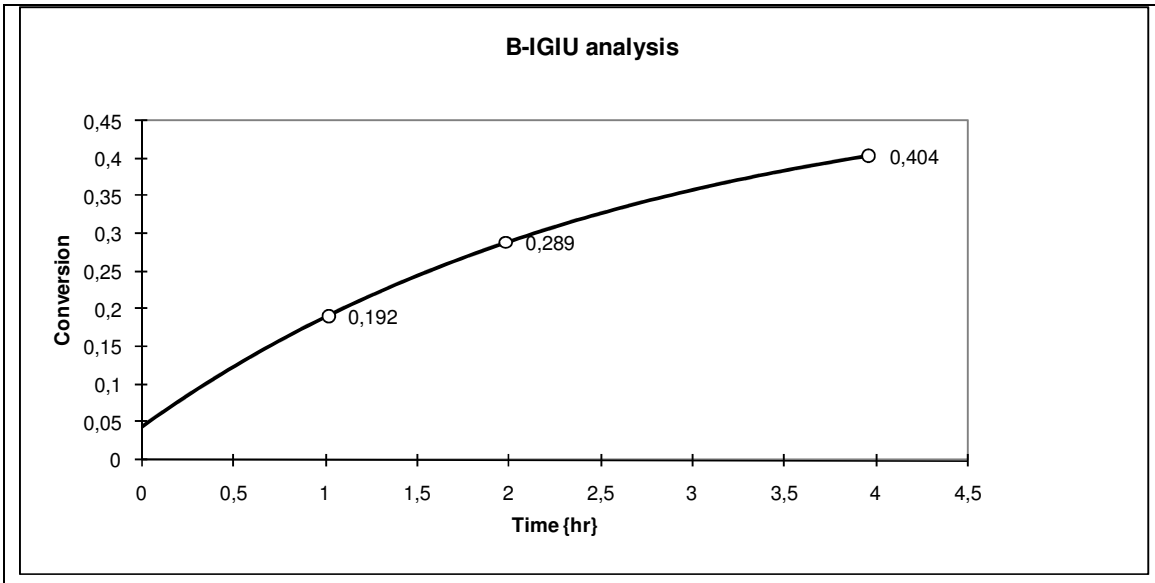
Figure 9



0.01% HMF

Activity: 389 B-IGIU/g

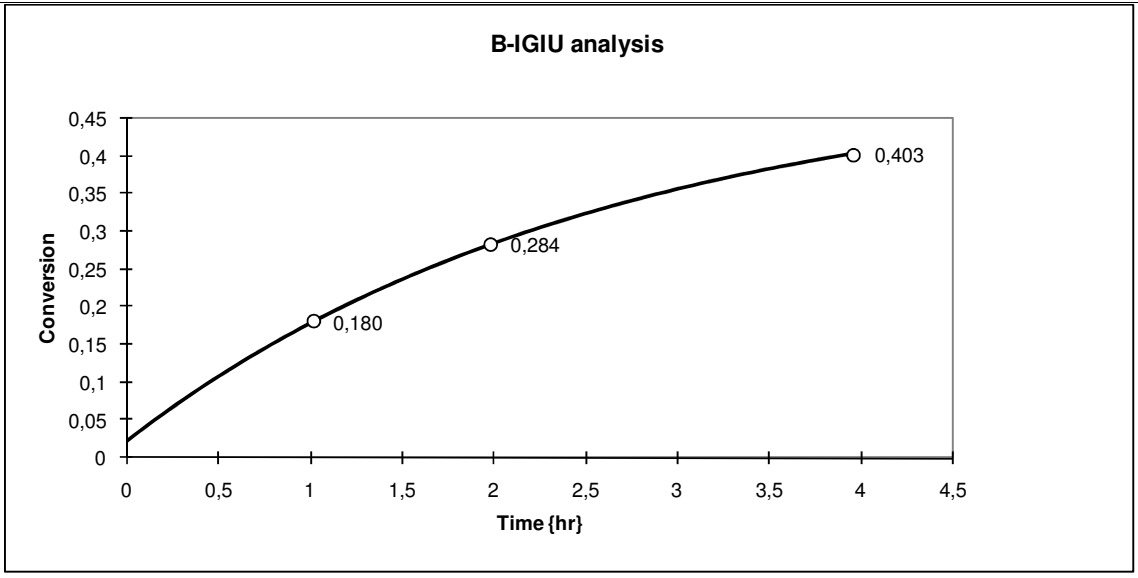
Figure 10



0.1% HMF

Activity: 378 B-IGIU/g

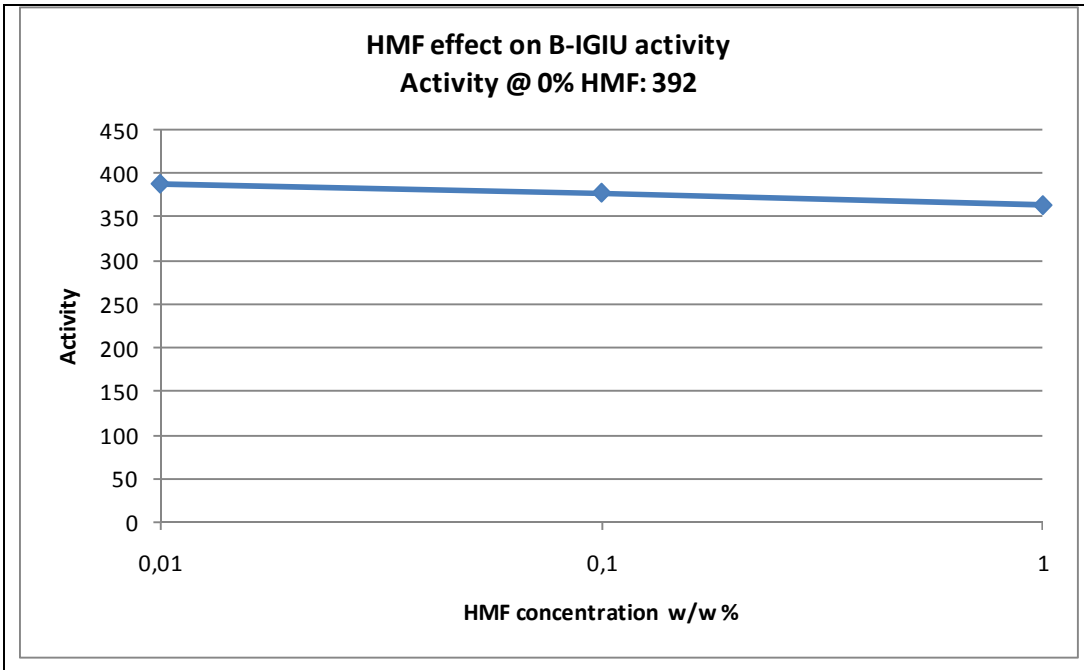
Figure 11



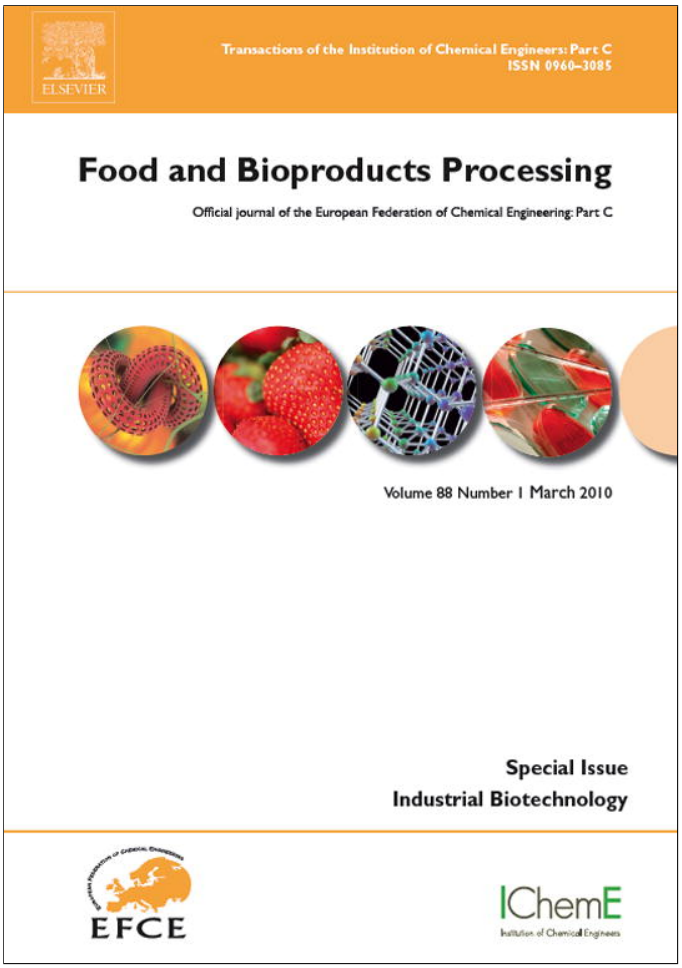
1% HMF

Activity: 364 B-IGIU/g

Figure 12



Activity as a function of HMF concentration



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Process considerations for the scale-up and implementation of biocatalysis

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ABSTRACT

With increasing emphasis on renewable feed-stocks and green chemistry, biocatalytic processes will have an important role in the next generation of industrial processes for chemical production. However, in comparison with conventional industrial chemistry, the use of bioprocesses in general and biocatalysis in particular is a rather young technology. Although significant progress has been made in the implementation of new processes (especially in the pharmaceutical industry) no fixed methods for process design have been established to date. In this paper we present some of the considerations required to scale-up a biocatalytic process and some of the recently developed engineering tools available to assist in this procedure. The tools will have a decisive role in helping to identify bottlenecks in the biocatalytic development process and to justify where to put effort and resources.

Keywords: Biocatalysis; Scale-up; Reactors; Process design

1. Introduction

Today, industrial biotechnology is promoted as a clean, environmentally friendly technology with the potential to transform the chemical industry from petrochemical based oil refineries, using harsh reaction conditions, to the so-called bio-refineries where commodity chemicals can be produced from renewable feed-stocks using mild bioprocesses and thereby contribute to a more sustainable chemical industry (IB-IGT, 2009). Indeed the technology fits very well into the much discussed sustainable chemistry concepts (Jaeger, 2004): the processes are inherently very benign as they are run at moderate temperatures and pressures, using renewable feed-stocks and usually no toxic chemicals in the process.

Industrial biotechnology is already employed in a number of industrial sectors; examples range from animal feed, pulp and paper, leather, detergents, textiles and energy to modifications of starches and fats in the food sector (Kirk et al., 2002), as well as the production of organic and amino acids and vitamins by fermentation (Frazzetto, 2003). However, the focus of the current article is on the use of enzymes (either isolated or immobilised or alternatively contained in 'resting' cells) as catalysts for the synthesis of chemical products—biocatalysis.

Biocatalysts are frequently the preferred choice of catalyst when high selectivity is required. Potentially, introduction of biocatalysis can reduce the total number of processing steps and in particular avoid protection and de-protection steps, leading to a higher atom efficiency (Schmid et al., 2001). Based on published reports reviewing the application of biocatalysis in industry it is clear that the majority of products from industrially implemented biocatalytic processes to date are chiral compounds (Straathof et al., 2002; Schmid et al., 2002; Liese et al., 2006; Pollard and Woodley, 2007). However, biocatalysis is not only interesting for high-value, low-volume, products like chiral pharmaceuticals but also for specialty and effect chemicals, like surfactants, as well as for bulk chemicals and bio-fuels. Indeed the impact of biocatalysis in other industry segments is increasing (for instance recently introduced applications can be found in the manufacture of cosmetic ingredients and polymers).

As the scale of biocatalytic processes increase, more emphasis will be required on the chemical and process engineering considerations, alongside the necessary biotechnological developments. For example, the requirements regarding process intensity and cost reduction are more demanding for high-volume chemicals and bio-fuels, and

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although many different potential processes have been presented in academic literature only a few have made commercial success.

There are several reasons for this:

(1) The biocatalyst is often perceived as too expensive to bring about an economically feasible process.
(2) The development of an optimized biocatalytic process takes a long time and requires many different competencies (as will be shown later).
(3) The probability of success is difficult to estimate.
(4) It is difficult to evaluate the cost of different biocatalytic processes because there is a lack of data on the factors contributing to the total cost.

The development of a biocatalytic procedure at scale is a complex task; it requires broad inter-disciplinary skills and many factors contribute to the final economic competitiveness of the process. Frequently solutions necessitate a compromise between different requirements and therefore good analytical and design tools are required to evaluate the many choices that are presented, to avoid running into dead-ends. In this paper we discuss the considerations required to scale-up and implement biocatalytic processes and describe some of the process engineering tools currently being developed that can be useful in understanding the process to help make rational decisions.

2. Biocatalytic process development

Unlike chemical reaction engineering with as established design paradigm (see Fogler, 2006), to date no procedure for biocatalytic process development has been established. Nevertheless some of the potential steps which should be examined are outlined in the following (Lilly and Woodley, 1996).

2.1. *Reaction characteristics*

A first step in the development of any new reaction scheme is to examine the physical reaction characteristics and determine what constraints these will put on the process. Properties such as reaction thermodynamics and substrate/product solubility and stability under the possible reaction conditions are all important. Estimations of thermodynamic data through computer-based models can assist in finding some of these data.

2.2. *Selection of biocatalyst*

If a reaction has been identified as being a suitable candidate for biocatalysis, the next step is most likely to find an enzyme or enzyme system that is effective for the desired conversion. For some applications, off-the-shelf biocatalysts can be found, but this is most normally not the case. Nature offers a huge diversity of specific enzyme sources and these could be screened for the desired activity. However this could be very time consuming and as many enzyme providers offer screening kits for different types of reactions this would probably be an easier starting point.

When activity for the desired reaction is found, recombinant DNA technology enables the possibility to engineer enzyme functionality (Turner, 2009; Reetz, 2009). The procedure is based on generation of a library of variants that is then screened for the desired properties. The goal is to improve the activity (reaction rate), selectivity and stability of the catalyst. However, a major limitation is that it is generally difficult to simultaneously screen for all of these properties (so-called multi-functional screening) (Burton et al., 2002).

Another critical issue in this step is to effectively manage the almost unlimited number of possible protein variants. Traditional high-throughput screening techniques have limits to the number of variants that can be screened at a reasonable cost. Tools such as ProSAR (Fox and Huisman, 2008) and cluster screening (Vogel, 2007) have been developed to keep the number of screens down.

Recombinant DNA technology tools such as directed evolution have indeed opened up the possible applications and target molecules of biocatalysis and there are several examples where new biocatalytic routes have been established through significant improvement of an existing enzyme via iterative rounds of mutagenesis and screening (Tracewell and Arnold, 2009; Reetz, 2009). To develop a new biocatalyst could be estimated to take about 3–15 months employing a team of skilled scientists (Huisman, 2009). Nevertheless, improvement of the biocatalyst can be essential for many industrial applications. For instance Martin et al. (2007) managed to improve the activity of an aminotransferase by a factor of almost 300, while at the same time improving the stability of the enzyme towards the process conditions, yielding a much more economic process. In another example, Reetz et al. (2006) managed to improve the enantio-selectivity of an epoxide hydrolase from a selectivity factor (E) of around 5–115, by introducing nine mutations to the wild type enzyme.

2.3. *Process development*

Since the chemical industry is under a lot of pressure to reduce processing costs in order to compete in the global market, the performance criteria for a given biocatalytic process are frequently high, and thus the ultimate benchmark for competing technologies will inevitably be cost per kilogram of product. For this reason, both technical and economic indicators should be evaluated when comparing different process options.

The performance of a biocatalytic process is based on a large number of factors. In Fig. 1 a typical biocatalytic process is outlined with some of the most important success factors listed. The efficiency of the fermentation, the form of the biocatalyst, the reaction conditions used, as well as the conditions for downstream product and biocatalyst recovery will strongly influence the performance and the economic sustainability of the process (Burton et al., 2002).

2.4. *Biocatalyst production*

The cost of the whole process is often very dependent on the efficiency of the production of the biocatalyst. A large number of microbial organisms and eukaryotic hosts are available for the production of recombinant protein and different fermentation protocols have been established that allow rapid growth on simple media to produce high cell densities. Combined with the tools to express proteins effectively and in high concentrations, the possibility of obtaining the desired biocatalyst more easily and at a reasonable cost has in recent years increased markedly. Using a fed-batch strategy a cell density of 50–100 g dry cell weight/L with up to 30% by weight being the desired protein can routinely be achieved (Lee, 1996; Vidal

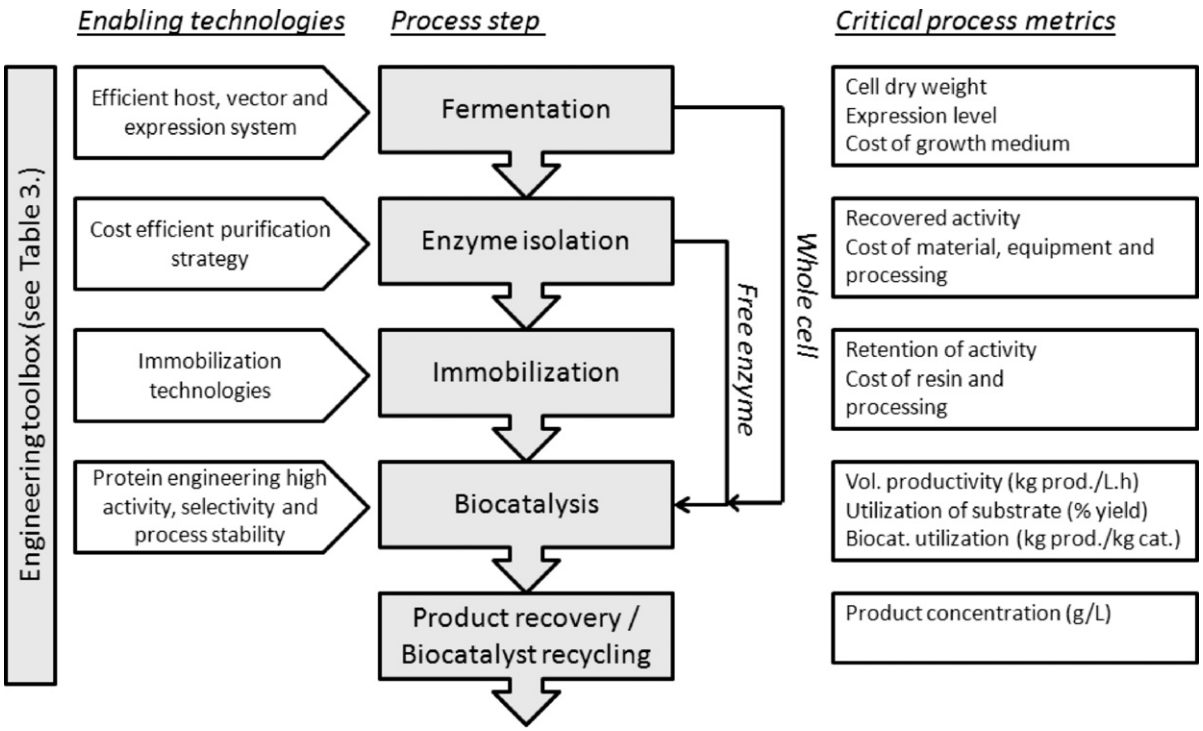

Fig. 1 – Success factors for the economic feasibility of a biocatalytic process.

et al., 2005; Durany et al., 2005). Most commonly submerged fermentation of *Pichia pastoris*, *Escherichia coli* or *Saccharomyces cerevisiae* is used (El-Mansi et al., 2006).

However, to get to the point of an optimised expression system is unfortunately not always straightforward and many choices affect the production efficiency, not only the choice of host but also the choice of vector and inducer system, as well as the medium composition and growth conditions (Thiry and Cingolani, 2002).

2.5. *Biocatalyst form*

Another important consideration in the development process is whether the conversion should be carried out using a whole-cell or an isolated enzyme (Woodley, 2006) and whether the biocatalyst should be immobilized or not. Using whole-cells may improve the stability of the enzymes and it can enable easier regeneration of co-factors *in situ* avoiding the addition of expensive co-factors, such as NAD(P)H. For example NAD+ costs ca 3000 €/kg. Consequently, just adding 1 g NADH per litre to a process with a product concentration of 100 g/L, the addition contributes about 30 €/kg to the product even if no other losses are assumed. This is clearly unrealistic at scale and therefore cofactor recycle, whether in the cell or via a separate recycle scheme, is always required for industrial implementation.

Moreover, whole-cells can be used with minimum preparation, such as a simple drying step. However, whole cells can also produce unwanted side-products, could suffer from mass-transfer limitations and generally have limited compatibility with organic solvents and high concentrations of substrate or product, which can cause problems downstream due to cell lysis. An isolated enzyme process would be easier to implement due to simplicity but the trade-off is higher upstream cost and therefore re-use of the enzyme is often necessary (potentially via immobilisation) to keep costs down. As a rule-of-thumb the crudest possible form of the enzyme acceptable, to maintain product quality, should be used (Pollard and Woodley, 2007).

Immobilisation is often key to improving the operational performance of an enzyme (Sheldon, 2007). Especially for use in a dry media, such as an organic solvent, it is difficult to use biocatalysts without immobilisation or cross-linking since the enzyme molecules (or cells) are prone to aggregation. Other potential benefits are enhanced stability, possibility of use in a packed-bed or fluidised-bed and prevention of protein contamination in the product (Bornscheuer, 2003). Fast and easy separation of the biocatalyst from the reaction medium is sometimes a key factor for enzymatic resolution reactions where the reaction has to be stopped at a certain conversion to preserve the high enantiomeric excess (ee) of the product. Simpler downstream processing and easy biocatalyst recovery for immobilized enzymes also leads to an improved process economy, which may be essential for developing a competitive process.

A general method for immobilization that can be applied to any enzyme is not available and therefore the typical approach used is trial and error. Efficient immobilization protocols should take into account the physiochemical properties of the carrier (or matrix) as well as the enzyme, to obtain the best compromise between stability, activity, handling and cost (see Hanefeld et al., 2009 or Cao et al., 2003 for comprehensive reviews). For large-scale production of the biocatalyst the procedures should be quick, robust, scalable and reproducible and the enzyme should be stable during each step. Also working environment issues such as the handling of cross-linking chemicals and dust-producing materials should be considered (Kirk and Christensen, 2002).

Some examples of industrially used immobilised enzymes used at the multi-tonne scale are: glucose isomerase (on an inorganic carrier) for production of high fructose corn syrup, penicillin G acylase (covalently attached to polyacrylate) for the production of semi-synthetic penicillins, lactase (on an ion exchange resin) for producing low-lactose milk, TL lipase (on

silica) for fat modification and lipase B from *Candida antarctica* (NZ435)(on polyacrylate) for use in resolutions for example in the manufacture of pharmaceutical intermediates.

By selecting the appropriate technique, savings can be made in the added cost of the biocatalyst to the process. A key factor is the selection of an appropriate enzyme loading on the resin (Bosley and Peilow, 1997). Optimal cost effectiveness will depend on the cost of both enzyme and immobilisation matrix and the proportions in which they are mixed. In order to make 1 kg of immobilized enzyme a loading of about 5–10% of protein is normally used. Carrier pricing varies between 20 and 200€/kg and the cost for the enzyme lies in the range of 300–2000 €/kg for standard enzymes such as lipases and proteases (special enzymes can cost from 10 to 50 k€/kg). Because the immobilization process takes up to a few days to finish, a final pricing is between 200 and 1500 €/kg.

It is important to keep in mind that the price of an immobilized enzyme does not say much on its own. For an effective industrial process a productivity of around 10 tons of product per kg of immobilized enzyme is required. This normally requires considerable stability. For example immobilized glucose isomerase used to produce high fructose corn syrup has an operating life-time of about one year. Depending on the number of recycles of the enzyme (up to 200 is usually required) the cost contribution to the produced product varies between a few hundred euro/kg (for pharmaceuticals) down to a few cents/kg (for bulk chemicals), but is most normally in the range of 10–0.1 €/kg (Schoevaart, 2009; Rozzell, 1999).

2.6. *Reactor selection*

There are several reactor types available for enzymatic reactions, all of which offer specific benefits and drawbacks (Balcão et al., 1996; Straathof et al., 2002). The aspects that need to be considered are: cost, space, mass-transfer, kinetics, heating and cooling, ease of operation and reusability of the catalyst (Fernandes et al., 2005; Woodley and Lilly, 1994). The batch process is, due to the simple setup, the equipment flexibility and the ease of operation, the most commonly used reactor set-up. A drawback at large scale is the low volumetric productivity and that immobilised enzyme or cells will be exposed to mechanical stress from the stirring which could lead to the physical loss of the enzyme preparation and thereby contamination of the product and significantly decreased catalytic activity (Hilterhaus et al., 2008; Shimada et al., 2002; Watanabe et al., 2005). Another difficulty is how to deal with the inevitable gradual decline in enzyme activity as the number of re-uses increases (Nielsen et al., 2008); either the reaction conditions (e.g. time or temperature) have to be adjusted or more enzyme must be added to the reactor as the activity decreases. Both of these strategies will naturally only be feasible to a limited extent. The stirred tank can also be used in continuous mode but this is generally not a good idea as the concentration of substrate in the reactor means it makes bad use of the catalyst with Michaelis–Menten kinetics (Woodley and Lilly, 1994).

The packed-bed reactor (PBR) is an alternative set-up for running enzymatic conversions using immobilised biocatalysts (Hills, 2003). The benefits over the stirred tank are generally the lower investment cost and higher volumetric productivity and that it can be run in a continuous mode. The kinetic profile is identical to the batch stirred tank. Possible problems of mechanical shear forces are eliminated (Xu, 2003), and separation of the enzyme from the product is simplified. The shorter residence time in the reactor can also lead to less side reactions. On the other hand, drawbacks of using a PBR could be internal and external mass-transfer limitations, channelling over the bed and high pressure drops over the bed (dependent on the support). Further, adjustments of pH or *in situ* product removal or addition of reactants becomes rather complicated. One way to deal with this problem is by running several PBRs sequentially with intermittent product removal or addition of substrate (Nielsen et al., 2008). Alternatively the packed-bed holding the biocatalyst could be attached to the reactor via a loop (Hills, 2003).

A bubble column or air-lift reactor is a reactor in which the reaction medium is kept mixed and aerated by introduction of air into the bottom of the reactor. This reactor type is mainly applied to facilitate the contact and/or reaction of a liquid and a gaseous phase, but it can also serve a purpose where high viscosity of the reactants make the use of a packed bed impractical (Hilterhaus et al., 2008). The air serves both as a non-abrasive mixer as well as in some cases a medium for removing the water formed in the reaction.

Table 1 – Extra considerations required at scale.

Need for GRAS solvents
Impurity profile of real process feeds
pH control
Addition of substrate(s)
Logistics/process timing

Table 2 – Constraints of scale.

Area/volume reduced for heat transfer
Pressure drop in packed beds
Mixing time in stirred tanks
Risk of contamination
Power/unit volume for mixing

3. Scale-up

The scale-up of all processes, whether biocatalytic or otherwise, is often associated with reduced process performance. However, provided certain considerations are taken into account this should not be a problem. One of the major challenges for industrial (white) biotechnology will be the development of processes on a large scale and thus far, as discussed previously, only a handful of processes have been operated at a truly (greater than 10,000 tons per year) large scale. Successful scale-up of a biocatalytic processes requires a good understanding of the interactions between the biocatalyst and the chemical and physical environment in the reactor. The objective in reactor selection and operation is to control this environment at all scales, such that accurate predictions can be made as scales are changed. However, it is more difficult to control the physical environment during scale-up. Some key considerations are listed in the following section (see also Tables 1 and 2).

3.1. *Key considerations*

3.1.1. *Reactors*

Reactors as they are scaled-up will provide their own challenges. For example as a stirred tank is scaled the mixing time is increased. Indeed in large reactors mixing times of 1–2 min

can be expected. In fact the time constants of all processes are increased with scale and therefore an evaluation of the effect of time-dependent variables on performance is an important prerequisite to scale-up. In addition, the surface area/unit volume is also reduced such that heat transfer via a jacket becomes limiting. Temperature control of biocatalytic reactions at large scale is not normally a problem. However, highly exothermic reactions such as enzymatic phenol polymerization or microbial conversions with actively metabolising cells require efficient cooling. This can be achieved with a cooling jacket on small scale reactors but usually requires additionally the insertion of cooling coils at a larger scale. Likewise for packed-bed reactors this will also be a limitation. In the past, the bed heights that have been used have been limited by the pressure drop across the bed. However, improvements in particle properties are now allowing faster flow rates to be used such that they can be used as differential reactors with rapid recycle. To avoid the problem of pressure drop across the bed, a fluidised bed may be used. However, until recently these have not been operated successfully on a large scale with immobilized biocatalysts. The major problem has been the difficulty of achieving constant linear liquid velocities across the bed which is essential to maintain plug flow. In some cases, companies are now accepting the loss in efficiency in catalyst utilization caused by deviations from plug-flow in large fluidised beds, because of other advantages. Bubble reactors have been built to around 500 m^3 and stirred tanks to around 200 m^3.

3.1.2. *pH control*

Many biocatalytic processes are associated with a pH change (acid production/consumption or alkali production/consumption or combinations thereof). Since the biocatalyst and often also the reactants and products need to be controlled in a tight window of pH, then the control of pH is critical. On a laboratory scale, buffers can be used but this is not possible at larger scales, where acid or alkali will be titrated into the reactor to neutralize the pH change that occurs. Surprisingly perhaps many plants lack the equipment for such metered addition of acid or alkali. The concentration of titrant used is dependent upon the mixing and resultant dilution, but for effective control good mixing is required to avoid 'hot' spots of high or low pH. Poor mixing may cause problems unless some kind of distribution system is used instead of the normal single point addition.

3.1.3. *Risks/contamination*

While biocatalytic processes are safe to operate without risks of explosion or extremes of temperature or pressure, there are other risks. Scale-up implies larger vessels and if microbial contamination leads to a loss of the batch, then a considerable amount of material is lost. This means that the economies of scale are not the same as other industry sectors.

3.1.4. *Logistics*

The increased time constants for the process upon scale-up also have a significant effect on the logistics of the process. At scale decisions about batch operation (the normal mode) need to incorporate the timing of all operations. In recently reported (Baldwin et al., 2008) work we scaled-up a biocatalytic process to 200 L. Decisions about overnight storage of the whole-cell biocatalyst proved critical to reactor operation.

Box 1: Specific problems that can arise on scale-up.

Immobilized enzymes. For immobilized biocatalyst particles suspended in an aqueous reaction medium there is the additional problem of damage to the particles at high agitation speeds with turbine impellers. Other agitators which are better suited to bulk mixing are preferable. Attrition of the particles may cause difficulties in their recovery and re-use.

Oxygen. If oxygen is a substrate for the reaction or is required to maintain the metabolic activity of a microbial catalyst then air, or oxygen, must be supplied. As in aerated agitated fermenters, oxygen transfer rates decrease with scale and may not meet the potential oxygen demand on a large scale.

Two-liquid phase. The presence of two liquid phases in the reactor necessitates good mixing in order to create an adequate dispersion and appropriate interfacial area. The scale-up of liquid–liquid dispersions requires less power input per unit volume than the corresponding gas–liquid systems since organic and aqueous liquid densities are close and interfacial tensions usually relatively low. Nevertheless as scale is increased sufficient additional energy must be supplied to maintain interfacial area. More problematic are regions of poor or excessive mixing where phase separation or emulsification respectively, may occur. Likewise inversion in poorly mixed regions of large scale vessels should be avoided since it may have particularly deleterious effects on the biocatalyst.

3.1.5. *Real process feeds*

Scale-up also implies the use of real process feeds. This will require filtration in any case (which is not required with purified reagents used on a laboratory scale) but may also require precautions against the problems of impurities (some of which may also be toxic to the biocatalyst).

3.1.6. *GRAS solvents*

While a number of scaled biocatalytic processes work with organic solvents or biphasic mixtures or organic solvent and aqueous phase, it is nevertheless the case that most biocatalytic processes operate in an aqueous environment. For scale-up few precautions are required and the operation is therefore considerably simplified. However this also means that the recovery process often requires solvents. For scale-up the list of suitable solvents is limited and they need to be GRAS (Generally Regarded As Safe) approved (Box 1).

4. Engineering tools

In comparison with the development of a conventional chemical process, bioprocess design problems are frequently challenging due to the lack of precedent and, to some extent, the additional complexity from intra-process interactions. Consequently there is a particular need for a systematic design framework which can handle a large range of different design problems and guide the engineer through the whole bioprocess development. Although significant progress has been made, such a framework has yet to be developed and here we suggest some useful engineering tools to assist in bioprocess development to facilitate knowledge-based decision-making.

In the various sectors of the chemical industry, there are different process objectives. For pharmaceutical processes, rapid process development is required to enable effective implementation (Pollard and Woodley, 2007). For fine chemicals, developing a process which ensures a high yield is crucial (Hatti-Kaul et al., 2007). Alternative technologies, such as process intensification techniques and process integration, may be applied to increase the yield, reduce the number of process steps and finally reduce the process cost. In bio-refining, a large number of possible process configurations, feedstock and product combinations result in a highly complex process synthesis problem (Sammons et al., 2007). At the very early stage of process development, a lot of potential catalysts, starting material or technologies, result in a large number of possible process configurations. The challenge is thus to use the limited information at hand to eliminate the least promising configurations and provide a focus for the investment of research and development effort.

Since carrying out experiments is expensive and time consuming, especially when scaling up, process modelling and simulations can allow an efficient evaluation of various process options. In order to model the process, some data are needed, including in particular thermodynamic and other property data for the various components. Many compounds involved in biocatalytic processes are relatively new compared to conventional chemicals, and thus data (including pure property and thermodynamic data) are generally not available. One solution is to use available software models to estimate the required parameters. There are many packages available, which can estimate the pure property data as well as thermodynamic data of a compound through its chemical structure, e.g. the ThermoData Engine from NIST (Diky et al., 2007) and ICAS developed by Gani et al. (1997).

Once the required data has been generated, chemical process design software such as ProII, Aspen or other packages can be used to simulate the alternative process configurations, although depending on the complexity of the process a simple spread sheet could be sufficient. The cost of the materials and energy for producing the same amount of product can then be used to eliminate unattractive process options and identify promising options for further studies. Cost analysis can also be used to identify bottlenecks in the flowsheets (Alvarado-Morales et al., 2009). Information on the cost contribution for the different parts of the process can be used to identify the most costly parts that need improvement.

Design metrics for evaluating process options should not only include profitability measures but also environmental metrics, and other techno-economic metrics (Law et al., 2008). One method available is Life Cycle Assessment (LCA), a standardised methodology (ISO, 1998) used for assessing the environmental impact of a product including the full life cycle from cradle-to-grave as well as the impact during its use-phase (see Fig. 2). One important lesson from the LCA work to date is that it is crucial to identify the step in a product's life cycle that has the highest impact on the environment so that the efforts for improvements can be focused there and to avoid shifting the environmental burden of one phase into another. Recently more research has been directed towards supporting the general view of biocatalysis being a green technology (Hatti-Kaul et al., 2007, Henderson et al., 2008, Petersson et al., 2005, Thum and Oxenbøl, 2008; Kim et al., 2009). For example, Adlercreutz and co-workers (Petersson et al., 2005) found that the main contribution to energy consumption in the enzymatic production of wood coating was

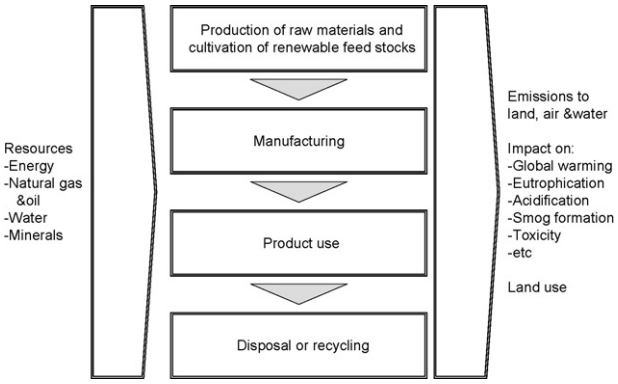

Fig. 2 – Overview of steps included in a life cycle assessment of a chemical product from cradle-to-grave. The emissions from transportation are also included.

not in the actual manufacturing step but rather in the production of the raw materials (crop cultivation). This means that the benefit of biocatalysis does not come from a lower process temperature, but from an improved utilisation of the raw materials, which can be achieved with a high process yield. Although the LCA methodology is straightforward in principle, limited availability of data and decisions for example regarding allocation of environmental impact between products and side-products can make it a time consuming task.

Regime analysis is a useful tool to identify bottlenecks and to assess the potential benefit gained from alleviating these. Key to this is the choice of several process metrics which adequately describe the effect of limiting regimes and simultaneously allow for sensitivity analyses of the varying process conditions. For example in a recent study we have analyzed the key process limitations of the Baeyer–Villiger mono-oxygenase catalysed synthesis of optically pure lactones using regime analysis (Law et al., 2006). In the study, limitations in product concentration, catalyst longevity and reaction rate were quantified and the effect on important process metrics was analysed. In particular, this study was focussed on the way the metrics change with catalyst concentration. By using this assessment, the sensitivity of the metrics to potential changes to process and catalyst were successfully analysed.

Another tool recently studied in our laboratory and by others is 'windows of operation', which graphically illustrates how process constraints impact the performance of a process (Woodley and Titchener-Hooker, 1996). Briefly, the windows of operation are found by evaluating how various process variables, e.g. catalyst concentration or stability, impact key process metrics, e.g. the reaction rate and productivity (Fig. 3). Defining hurdle (or threshold) values for the process metrics, allows identification of process conditions that fulfil these constraints (Law et al., 2008). In this way windows of operation may be used to help understand and optimise biocatalytic processes. The method has been developed and applied in chemo-enzymatic process design (Blayer et al., 1996), pharmaceutical process design and other biocatalytic processes (Law et al., 2008).

Finally, sensitivity and uncertainty analysis are tools that can be applied to investigate the robustness of the process models, quantify the expected extent of variation in the process outcome and identify the source for variations in process performance (Saltelli et al., 2005). Sensitivity analysis can help guide the development of biocatalytic processes,

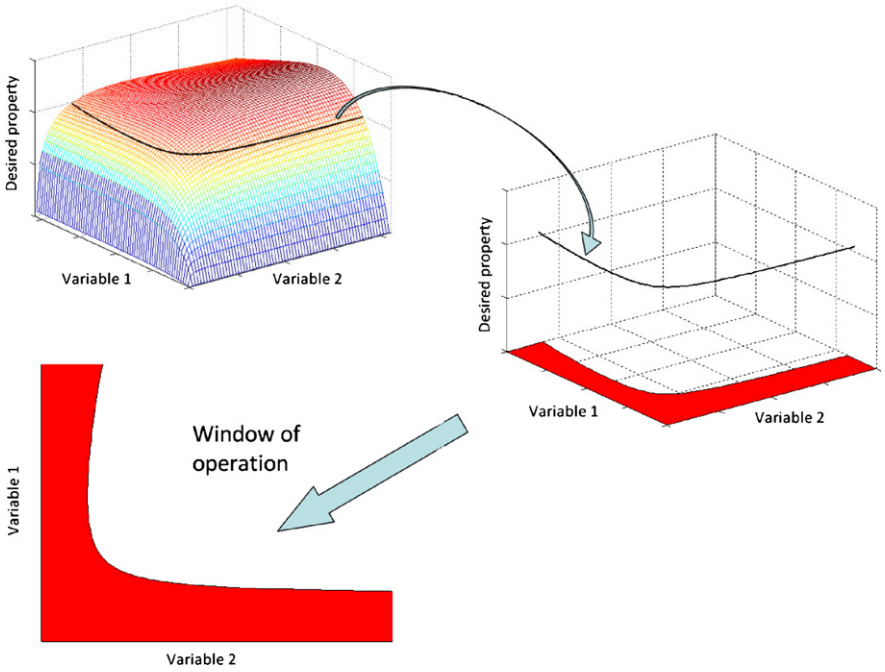

Fig. 3 – Identification of operational windows is a systematic process development approach to help understand and optimize the bioprocess design.

Table 3 – The engineering toolbox.

Engineering tool	Objectives	References
Process modelling and costing	Technical and economical evaluation of promising processes	Sammons et al. (2007) and Marquardt, 2009
Sensitivity and uncertainty analysis	Evaluate model robustness and impact of sources of uncertainty on process performance	Sin et al. (2009), Bühler et al. (2006), Saltelli et al. (2005) and Biwer et al. (2005)
Regime analysis and windows of operation analysis	Determine process constraints, limiting factors and feasible conditions	Law et al. (2006, 2008) and Blayer et al. (1996)
Life cycle assessment	Evaluate the environmental impact of the product and the process	Petersson et al. (2005), Thum and Oxenbøl (2008), Kim et al. (2009) and Henderson et al. (2008)

by relating sources of variation to process performance and evaluating different process scenarios. For example, Schmid and co-workers (Bühler et al., 2006) have used sensitivity analysis to determine that mass-transfer rates in a two-liquid-phase system have little effect on the overall productivity in a biocatalytic oxidation process. Uncertainty analysis on the other hand analyses the propagation of various sources of uncertainties for quantifying the overall uncertainty on the modelled process output (Sin et al., 2009). Cooney and co-workers (Biwer et al., 2005) have applied uncertainty and sensitivity analysis to penicillin V production to obtain a better understanding of production variations and evaluate the most important sources of uncertainty. Such information is of high-value for engineers make decisions, needing to ensure a consistent production and evaluation of potential process improvements (Table 3.).

5. Future perspectives

There is an increasing interest in the use and application of biocatalytic processes at an industrial scale, driven by the need for renewable feed-stocks and also green chemistry requirements. Most industrial biocatalytic processes to day use single step conversions, but future biocatalytic processes will incorporate some new complexities. For example, multi-enzymatic reactors that are already starting to provide solutions to a number of chemical challenges. Likewise chemo-enzymatic reactions will also become more common and bring new challenges for process development. Future processes will also incorporate process intensification techniques which will complicate the process. In particular in situ product removal will require recycle streams (the time-constants for which are highly dependent on scale).

In comparison with conventional industrial chemistry, the use of bioprocesses and biocatalysis is a rather young technology. Although enormous progress has been made in the implementation of new processes (especially in the pharmaceutical industry) no fixed methods for process design have been established to date. In this paper we have presented some of the considerations required to scale-up a biocatalytic process and some of the engineering tools available to assist in this procedure. The tools will have a decisive role in helping to identify bottlenecks in the biocatalytic development process and to justify where to put effort and resources. These analyses should be performed from project inception throughout the life-time of the project and involve environmental as well as economic indicators to achieve a solution where resources are used efficiently.

With the development of more standardized protocols and technology platforms, the development process will be simplified making it easier to implement new processes in a collaborative manner between chemists, biochemists, microbiologists, as well as biochemical and chemical engineers.

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