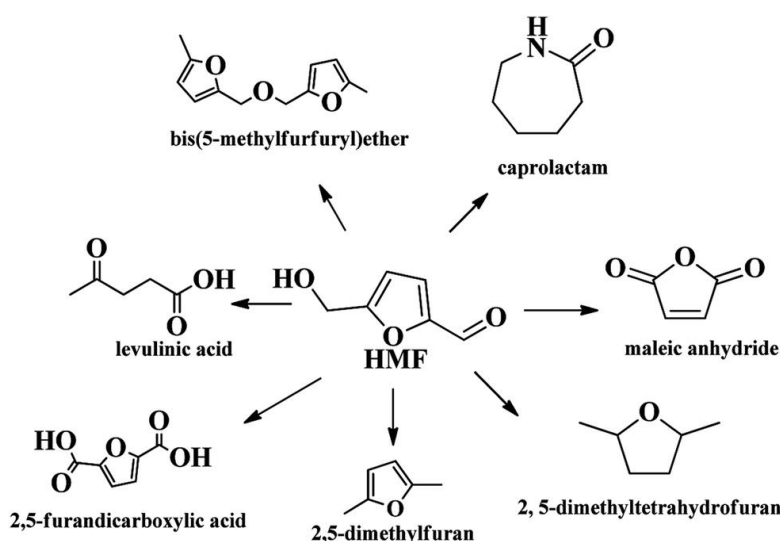# PREPARATION OF ADDED-VALUE MOLECULES DERIVED FROM 5-HMF BY REDUCTION OR OXIDATION USING CONTINUOUS FLOW SYNTHESIS

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ABSTRACT

The use of biomass as a carbon source in order to create platform molecules that serve as a shuttle for the synthesis of high value-added products and thus abandoning the use of fossil resources is a reality. Molecules such as 5-hydroxymethylfurfural contain a great application potential, since it can lead to the formation of numerous products of interest in numerous sectors, such as polymers or biofuels. In turn, the manufacture of HMF from continuous flow technologies for the scaling-up of the production to an industrial level could be made possible, despite the challenges that still need to be overcome in terms of production and scalability. However, it is a promising path that, combined with the right technology or strategy that makes separation and purification economically viable processes, can be disruptive.

ACKNOWLEDGEMENTS

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Este año que estamos viviendo, tan complicado y desagradable para todos, no empaña el hecho de que haya sido satisfactorio académicamente, logrando despertar en mí la ilusión de seguir queriendo aprender sobre la química sostenible. Esto ha sido gracias a cada uno de los profesores que se han preocupado por enseñarnos todo lo que sabían acerca de la materia que impartían. Gracias a muchos de ellos por desplazarse desde otros lugares de España para enseñar y transmitir conocimiento. Por ello, quiero agradecer a cada uno de ellos, y en especial a los profesores de mi Universitat Jaume I, del departamento donde he estado, sobre todo a mi tutor y al coordinador del máster. Un máster que, para mí, ha sido muy enriquecedor.

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CHAPTER 1: INTRODUCTION

1.1 Introduction to Hydroxymethylfurfural (HMF)

These last few years has grown the concern about finding new synthetic routes to produce fuels and chemicals considerably, to make routes more sustainable and environmentally friendly. The fact is that approximately the 86% of fuels and 96% of chemicals in the world are produced in a non-renewable way. They come from fossil resources such as coal, petroleum and natural gas.[1]

It is true that the world has become oil dependent in terms of chemicals and energy source with the pass of the time. Also, nowadays, countries that are experimenting a huge development such as China or India, demand an incredible amount of fossil resources, and this fact has contributed greatly to putting this serious problem in the spotlight. We need to find new methods that provide a solution to the problem. The decrease in resources will require the development of new and sustainable sources for fuels and bulk chemicals.

The global warming concern is another problem that is added to this list. The production of greenhouse gases is something that must be under control. For this reason, the use of renewable energies such as water, wind, solar, ocean and geothermal energies is the possible way to solve this issue. But, in order to synthesize chemicals and products like the ones we have currently producing, we need an alternative source of raw materials not based on fossil sources. In this regards, biomass has emerged as a suitable renewable feedstock, taking advantage of the conversion of the cellulosic part of biomass and/or cellulose-derived substrates to produce chemicals.[2]

In any case, the progressive replacement of oil with biomass implies a series of challenges in terms of processing approaches since both resources are chemically opposed (figure 1). Petroleum is composed of a series of hydrocarbons as opposed to highly functionalized biomass feedstocks, which typically comprise highly oxygenated compounds introduced, in some cases, into complex polymeric structures. As a result, the highly optimized catalytic approaches developed in the past 50 years in the petrochemical industry cannot be directly engineered to process biomass raw materials. For example, while in the petrochemical industry the production of hydrocarbon fuels (diesel, gasoline, and jet fuel) is a relatively simple process that involves the separation of hydrocarbons (fractional distillation) and subsequent catalytic improvement (control of molecular weight and structure), the conversion of biomass to fuels is typically associated with deep chemical changes and multi-step processing.[3] Also, the particular composition of the biomass plays an important role on the design of catalysts. Typical petroleum catalysts designed to withstand high temperatures and

hydrophobic environments may not be effective under the new conditions required to process biomass.
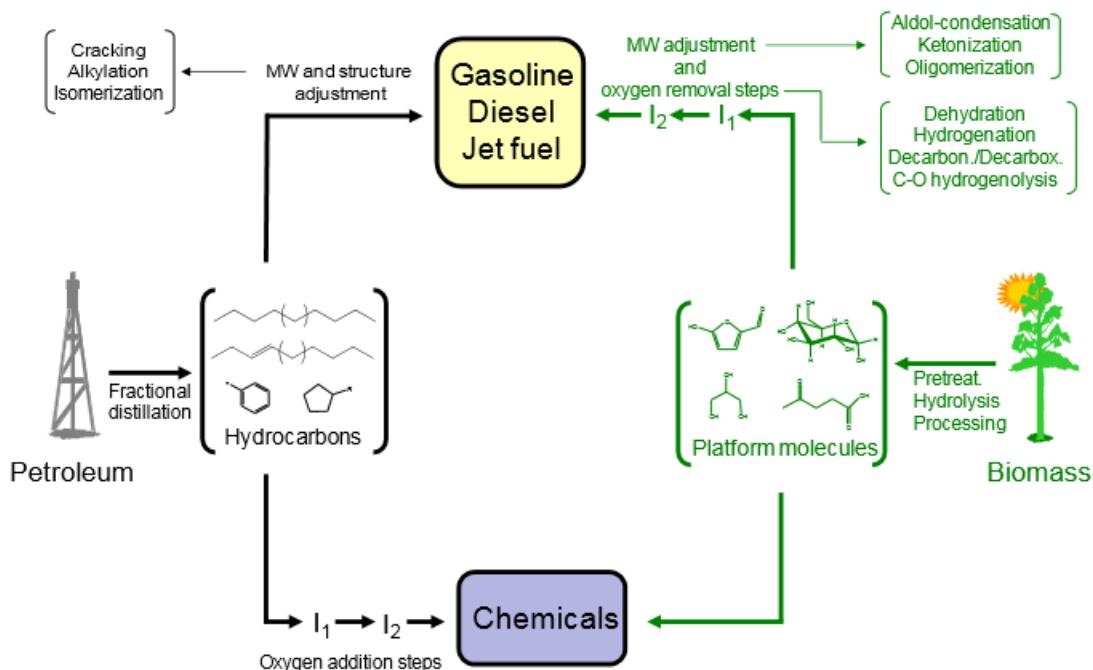
Figure 1. Differences between the processing of oil and biomass with chemical products and liquid fuels. Adapted from ref [3].

The high level of structural and chemical complexity of biomass is an important issue when viewing new processes. A possible solution to overcome the complexity of the biomass is its conversion into simpler fractions that are more easily handled and allow an easier way to work in the subsequent processes. This approach, similar with the one used in the petrochemical industry, adequately facilitates the simultaneous production of fuels, chemicals, and energy in a single facility called a biorefinery. As an important part of this concept of biorefinery, it has recently been identified that a small group of molecules derived from biomass is especially relevant according to a series of indicators. These important biomass derivatives, the so-called platform molecules or building blocks, are relatively simple compounds that contain multiple functionalities in their structures (e.g. carbonyl, carboxyl, hydroxyl groups, double bonds, etc.) that are suitable for a range of chemical transformations into valuable compounds. Platform molecules are carefully selected on the basis of a number of factors including the availability of commercial technologies for their production and their platform potential for the simultaneous production of fuels and chemicals in biorefineries. Relevant examples of platform molecules include sugars (glucose, xylose, fructose ...), polyols (glycerol, sorbitol ...), furans (HMF, furfural...), acids (lactic, levulinic...) and alcohols (ethanol).[4]

Control of chemical reactivity is also an important factor when operating with biomass derivatives. The multiple functionalities of many of these compounds generally lead to high (sometimes uncontrolled) reactivity. Furthermore, many of these molecules have a natural tendency to decompose with temperature. [4]

The biomass possesses a range of excellent merits such as abundance, cheap, diverse and widespread. It is the sole carbon-based renewable resource in the nature giving us the possibility of extracting from it the raw materials needed to produce added-value products (fuels, platform chemicals, polymers, materials and pharmaceuticals). This is, at the end, the core of the chemical industry and conduces us to the concept of biorefinery in order to provide a solution for sustainable development, where renewable feedstocks as biomass or food waste are upgraded to yield fuels and commodity chemicals by means of chemical and biological conversion technologies.

As previously introduced, one of these interesting products that we can produce using the biomass are the platform molecules. This is an increasingly more popular strategy to replace building blocks derived from petrochemicals. Nevertheless, the main drawback is that the use of them is limited due to their high prices and the low-tonnage productions compared with the results that fossil resources provide to the industry in economic terms. However, this is something normal because it needs time, work and dedication to develop suitable industrial processes able to meet the market's needs in terms of cost and production scale. For this reason, the great interest for bio-based platform molecules, especially in the polymer chemistry field, has generated intense efforts for improving their manufacture processes, increasing, consequently, their availability due to higher scale industrial production and lower cost. Subsequently, this improvement in the availability of this kind of compounds has also opened the gate to apply these bio-based building blocks in different strategies towards the production of fine chemicals.

Biomass is made up of carbohydrates, lignin, fatty acids, lipids, proteins, and others. Among these components, carbohydrates are the most interesting ones, because they form the largest natural source of carbon by far. However, they present a drawback as a feedstock, which is the richness of oxygen in their molecular structures. In order to alleviate that problem, there are three ways to reduce the oxygen content in carbohydrates. The first option is the removal of small and highly oxidized carbon molecules, such as CO_2, formaldehyde, and formic acid. By using the fermentative conversion of carbohydrates into ethanol, butanol and CO_2 is a great actuation example.[5] The second option is hydrogenolysis. It consists in the removal of oxygen from the molecule by forming water at the expense of one molecule of hydrogen for each oxygen atom. The third option is the elimination

of water. A clear example is the dehydration of carbohydrates into a wide variety of interesting compounds. Among these compounds, we can find furans and levulinic acid.[5]

Inside the group of these dehydrated products, furan compounds, have especially high potential to produce chemicals and fuels. Particularly, our main object of study is the molecule called 5-hydroxymethylfurfural (5-HMF), which is accessible from fructose, glucose, sucrose, inulin, and cellulose, using acid catalysts.[6] This compound is a platform chemical, which means that it works as a bridge, connecting the lignocellulosic biomass and important biochemicals. It is important to highlight that lignocellulose, which is a very abundant material, includes important polymers, where cellulose and hemicellulose possess high importance, because they are formed by monomers of glucose, among others, and they can be used as a carbon source in fermentation processes for the production of ethanol.

There is a wide range of methods for the synthesis of HMF to be used as platform chemical. It can be obtained typically from fructose but also from glucose *via* isomerization to fructose, as well from cellulose by direct hydrolysis and dehydration. Cellulose is formed by anhydro-D-glucopyranose units linked by β-1→4-glycosidic bonds. So, in order to release the sugar monomers, the hydrolytic degradation is necessary. The hydrolytic degradation must be under control to prevent monosaccharides from reacting at the high temperatures used to avoid the formation of oligosaccharides.

Alternatively, hemicellulose, which can also be used as raw material, is a polymer formed by different sugar units such as glucose, galactose, mannose, xylose and arabinose, and it does not form crystalline regions, being more prone to hydrolysis.

It should be also mentioned that depending on the type of sugar there is a determined rate of hydration, and decreases following the next order: xylose > mannose > glucose. For that reason, hemicellulose is hydrolyzed faster than cellulose.[7] The glucose is a very attractive source because it is cheaper than pure fructose.

HMF is very useful, it is more than a simple intermediate to produce the biofuel dimethylfuran (DMF) and other molecules. As it is shown at Figure 2, HMF has a great relevance for the production of important molecules such as levulinic acid, 2,5-furandicarboxylic acid (FDA), 2,5-diformylfuran (DFF), 2,5-bis(hydroxymethyl)furan (BHMF) and 5-hydroxy-4-keto-2-pentenoic acid (HKPA), among others. Besides, HMF stands out among the platform chemicals for several reasons: Its structure has retained all six carbon atoms that were present in the hexoses and high selectivities have been reported for its preparation as well, in particular from fructose, which

compares favorably with other platform chemicals, such as levulinic acid or bioethanol.[5] Also, the characteristics of HMF makes it a molecule susceptible to a large number of synthetic transformations due to the functional groups it contains. However, the topic of HMF chemistry and its chemical transformations, will be addressed later.
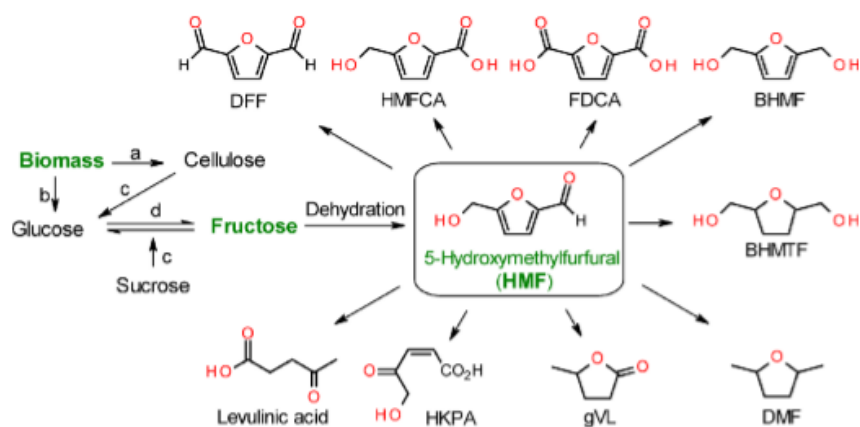
"Steps in the production pathway: (a) pretreatment; (b) pretreatment and hydrolysis; (c) hydrolysis; (d) isomerization. Derivatives: diformylfuran (DFF), 5-hydroxymethylfuran-2-carboxylic acid (HMFCA), 2,5-furandicarboxylic acid (FDCA), 2,5-bis(hydroxymethyl)furan (BHMF), 4-hydroxy-2-ketopentanoic acid (HKPA), γ-valerolactone (gVL), 2,5-bishydroxymethyl)tetrahydrofuran (BHMTF), and 2,5-dimethylfuran (DMF).

Figure 2. 5-HMF as a platform chemical, coming from biomass to its conversion to building blocks. Adapted from ref [8].

Table 1 shows an overview of the physical and chemical properties of HMF.

Table 1. Chemical and physical properties of HMF. Adapted from ref [5].

CAS Registry number	67-47-0
EC-No	200-654-9
Chemical Abstracts name	5-(hydroxymethyl)-2-furancarboxaldehyde
synonyms	5-(hydroxymethyl)-2-furaldehyde, HMF, 5-(hydroxymethyl)-2-furancarbonal, 5-(hydroxymethyl)-2-furfural, 5-hydroxymethyl-2-formylfuran, 5-oxymethylfurfurole, hydroxymethyl furfuraldehyde
molecular formula	$C_6H_6O_3$
Smiles	C1=C(OC(=C1)C=O)CO
molecular weight	126.11
description	yellow powder;[8] odor of chamomile flowers[9]
boiling point	110 °C at 0.02 mmHg,[9] 114–116 °C at 1 hPa[8]
melting point	31.5 °C,[9] 28–34 °C[8]
solubility	freely soluble in water, methanol, ethanol, acetone, ethyl acetate, dimethylformamide; soluble in ether, benzene, chloroform; less soluble in carbon tetrachloride; sparingly soluble in petroleum ether[9]
density	1.243 at 25 °C[8]
refractive index	1.5627 at 18 °C[9]
flash point	79 °C, closed cup[8]
UV absorption maximum	283 nm

Despite of the great properties of HMF and its usefulness, it presents some challenges and problems that must be addressed for it to be used. The side reactions and the isolation are the key factors that must be improved in this field. HMF can be derived from hexoses, particularly it is

preferred from hexoketose D-fructose. The formation of HMF from fructose usually leads to the presence of side reactions, such as isomerization, fragmentation, and condensate formation.[9] Nevertheless, if we compare the yield of HMF starting from D-fructose, it is observed that it is higher than the one obtained from D-glucose under the same conditions. However, since D-glucose is cheaper, several studies have been carried out using glucose as a starting material in the HMF synthesis.[5]
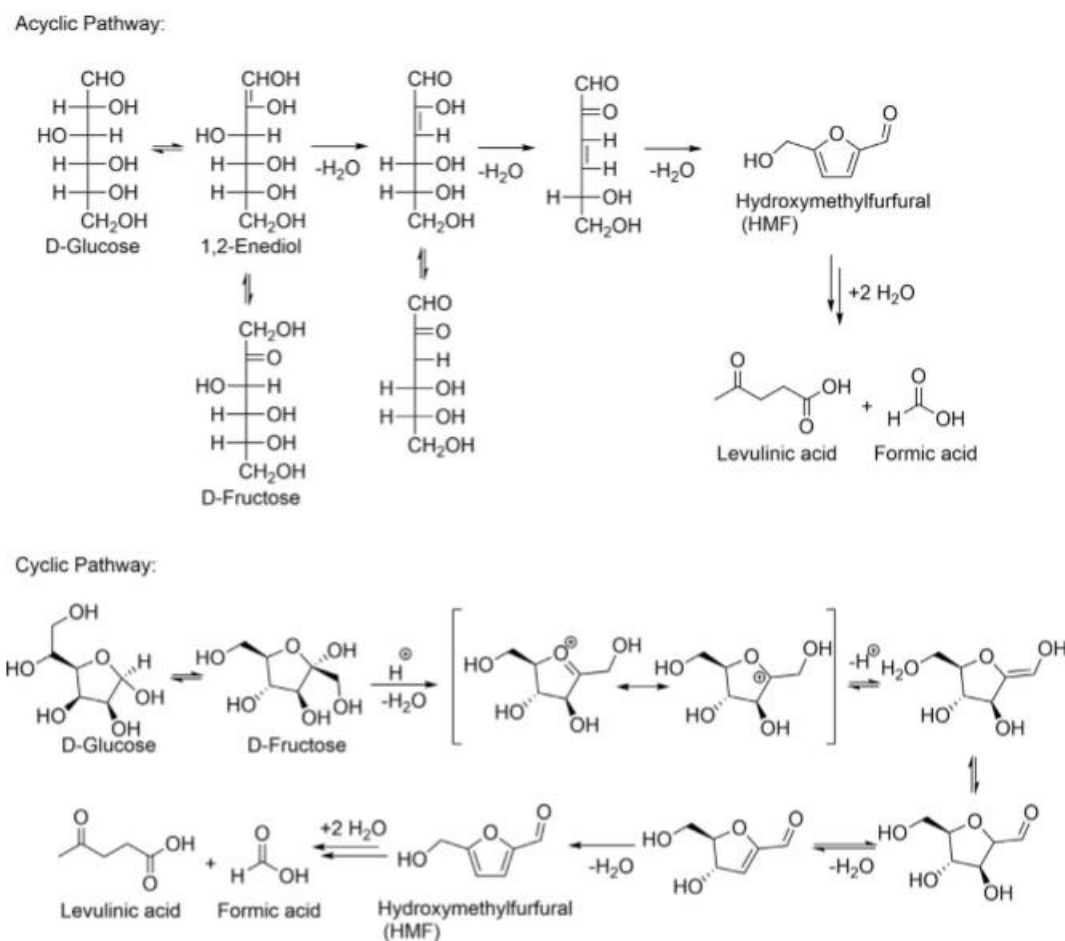
Figure 3. Proposed mechanisms of HMF formation from hexoses. Adapted from ref [10].

The isomerization of glucose to fructose seems to be a required step in the synthesis of HMF from glucose, making an efficient isomerization catalyst necessary. In fact, catalytic systems, particularly bifunctional systems, have been experimented an increase on their research, as this reaction requires the simultaneous use of a base to catalyze the isomerization of the glucose to fructose and an acid to catalyze the dehydration of the fructose This is due to glucose-fructose isomerization is best base-catalyzed and the following dehydration of fructose is acid-catalyzed, taking importance bifunctional catalysts.[11]

Rehydration reaction takes place when HMF reacts with two water molecules in aqueous mixtures, forming levulinic acid and formic acid (Figure 3). This degradation decreases the overall HMF yield, making it necessary to perform purification processes, which translates into an increase in cost. In non-aqueous systems, the rehydration of HMF is suppressed. Besides of the dehydration, condensation reactions occur immediately, forming a black tarry by-product which is based in a complex furanic oligomer called humins. The appearance of this substance is totally undesired because it lowers the efficiency of the dehydration process, renders purification and decoloration difficult, and decreases catalyst efficiency. The pursuit of new ways for humins valorization in order to turn those drawbacks into an advantage is one of the challenges of HMF synthesis.[12]

On the other hand, the presence of condensation products causes a big deal when we talk about separation and purification of HMF. In fact, the thermal lability that HMF present under long-term heating in both alkaline and acidic conditions, causes several difficulties for its recovery. This circumstance makes the separation of HMF from the reaction mixture by distillation a great challenge. Additionally, the storage of HMF is difficult because of its relative instability and sensitivity towards acids, alkalines, and oxygen even under mild conditions. The decomposition of HMF takes place leading to the formation of dimers and larger oligomers.[10]

These obstacles make the separation and purification of HMF one of the most important challenges in the scale-up of HMF production.

CHAPTER 2: THE CONTINUOUS FLOW SYNTHESIS

2.1. Introduction to Continuous Flow Synthesis

Flow chemistry has been used for decades in the chemical industry. Lately, the pharmaceutical and pure chemical industries have increasingly been adopting this technology. Inherent enhanced safety, improved product quality, cost effectiveness, and overall production flexibility are factors driving the increasing use of continuous flow chemistry.

Flow chemistry (also known as continuous process or flow-through chemistry) begins with two or more streams of different reagents pumped at specified flow rates into a single cabinet, tube, or microreactor wherein the reaction occurs. Then, the flux containing the resulting compound is collected at the outlet. The solution may also be directed to adjacent flow reactor cycles to generate the final product. Only small amounts of material are required, which greatly improves process safety. Consequently, the inherent design of the continuous flow technology allows us for the use of reaction conditions that could not be safely replicated by using batch reactions. The result is a product with higher quality, less impurities and a minor duration of the reaction cycle.

Generally, flow chemistry equipment consists of pumps that transport reagents, solutions, and solvents to reaction cycles that introduce small volumes of reagents. These are introduced into a mixing-tube connector wherein the reagent-containing flows are combined and transferred to a coil reactor to offer reaction residence time. The reaction mixture can be introduced into a column reactor containing solid reagents, catalysts or absorbents. An online back pressure regulator is responsible for monitoring the system, while online pressure and analysis are often used to provide feedback on reaction performance. Additionally, in-situ spectroscopy can provide real-time data to proactively improve the reaction. For example, in-situ FTIR spectroscopy data can be used to mitigate the imperfect flow effect and control the rate of reagent addition to improve the mixing profile.[13]

In recent years, the number and types of reactions carried out with continuous flow chemistry has increased significantly, especially in pharmaceuticals, pure chemicals, sustainable chemistry, catalytic reactions and polymer materials. This growth is mainly attributed to scaling-up problem observed in batch reactions. These includes potentially dangerous reactions such as hydrogenation reactions, oxidations, halogenations, nitrations, diazotations, Grignard reactions or reactions using toxic gases.[14]

Reactions using reagents that may be hazardous to human health are most safely handled using flow chemistry. Another growing use in flow-through chemistry is the control of stereochemistry, as reaction variables can be more carefully adjusted to control epimerization.

Flow chemistry is useful for reactions where raw materials are in limited supply and where small-scale reactions are preferable. When it is combined with Process Analytical Technology (PAT), flow chemistry enables chemical reactions to be quickly analyzed, optimized and scaled-up. By using continuous real-time analysis, researchers can monitor steady state conditions, troubleshoot problems in the process, and finally identify reactive intermediates. When flow chemistry is analyzed with ATR-FTIR, each functional group of a particular substance has a unique fingerprint that can be tracked over time to obtain a continuous measurement of component concentration such as process conditions or a function. This allows you to track the time and the necessary conditions to reach and maintain a stable state.[13]

New processing approaches are required to control reactivity in biomass derivatives thereby directing the conversion to the desired products. In this regard, continuous flow processing has several significant and inherent advantages for biomass processing as compared to batch reactor technologies.

2.1.1. Continuous Flow Synthesis Linked with Green Chemistry

These last few years, the term sustainable or green has gained popularity and it is usually associated to good practices. A term that is in the order of business nowadays, however, in the chemical field it is a concept that was born in the end of the last century. For example, in 1970 born the Environmental Protection Agency, an organism of the United States federal government charged with protecting human health and protecting the environment: air, water and soil. This agency enacted the Toxic Substances Control Act (TSCA) in 1976, among others, to regulate trade and protect public health and the environment. Back then, health experts already knew that certain chemicals could cause serious health impacts, including cancer, birth defects and damage to the reproductive system. Events of this nature were, among others, those that laid that first stone towards the study and development of the concept of sustainability. Between 1980 and 2000 came out different publications that supposed the emergence of sustainability, among them, the concept of Triple Bottom Line was born, which refers to the results of a company measured in economic, environmental and social terms.[15] The sustainable development is based in three factors:
- Economic prosperity: Equitable distribution of wealth today and in the future.

- Environmental quality: Ensure its longevity.

- Social justice: Respect the values of different cultures and how its future develops.

These three factors are interdependent and interrelated and partially in conflict as it can be observed in Figure 4.
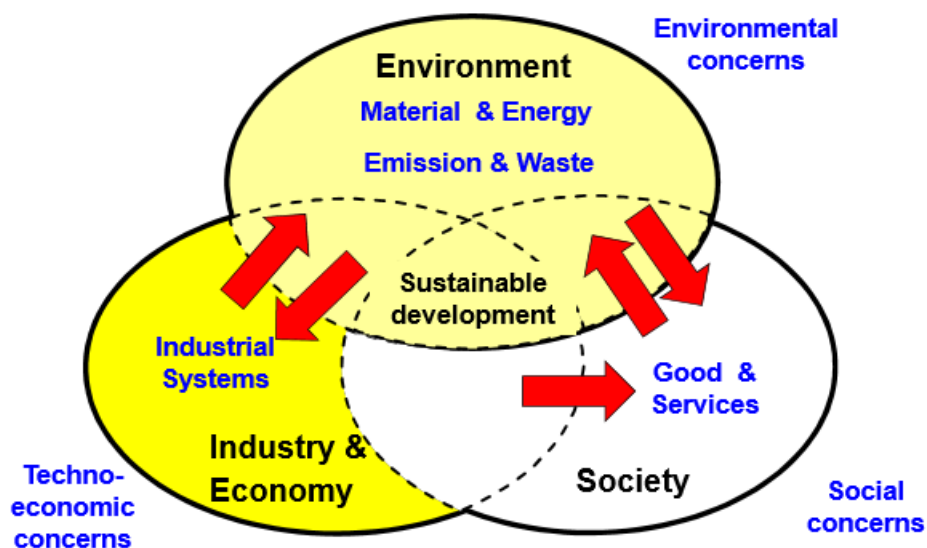
Figure 4. Concept of Triple Bottom Line. It can be observed the correlation between every factor. Adapted from ref [16].

These events lead to the publication, by two pioneering authors in this field like Paul Anastas and John Warner, of the book which would represent a before and after for green chemistry in 1998, called "Green Chemistry: Theory and Practice". In this book, the 12 basic principles (Figure 5) of the green chemistry were postulated, being the first guidance towards sustainable methodologies.[17] What makes this publication special is not only the synthetic procedure itself, but the whole lifetime of the product and side products.

Figure 5. Summary of the 12 principles postulated by Anastas and Warner and their correlation.

Starting from the Pollution Prevention Act, a great attention must be paid to waste production and not only evaluate a process by using the yield and selectivity parameters. It is true that other metrics are needed to summarize better all the features of a synthetic procedure. One of the simplest and most effective is the Environmental factor (E-factor) introduced by Sheldon. This parameter measures the ratio between the kilograms of waste produced per kilograms of desired product and gives the immediate idea of how elegant and complex chemistry may result in a highly environmentally costly process. This value links perfectly with the atom economy and the 12 Principles in order of being key driving factors for the definition of sustainable chemical processes. Nevertheless, these green tools are not the only way to achieve and evaluate the efficiency of a process. The improvement in technical advancements and the innovation in each of the branches of science are also the key to define novel routes to access modern efficient chemistry. [18]

In terms of efficiency, the assays tested by flow chemistry in mini o microreactors, are generally more effective than standard batch protocols and offer much higher throughput per unit volume and per unit time. Despite, for the development of synthetic approaches to fine chemicals and pharmaceuticals the chemistry was based on batch processes as no flow equipment on the laboratory scale was available until very recently.[19] As it happened and happens for green chemistry, where the initial synthetic strategy often requires to be completely redesigned to solve sustainability issues, also happens in the case of flow chemistry, processes often need to be modified in order to incorporate or adapt to a new emerging technology that implies a global improvement of the same.

Flow chemistry opens the gate to a great opportunity to identify a new and efficient strategy that can develop the greening chemical production needed. For this reason, green chemistry and flow

chemistry are likely to be ideal partners for accessing novel chemical spaces and define highly efficient synthetic tools.[18]

2.1.2. Benefits of Working in Flow

As previously highlighted, the advantages of working in flow are many. Therefore, we are facing a very promising technology for the future, since today, it is difficult to scale up. However, although this technology needs further development to meet all the expectations about it, we are going to highlight what benefits the implementation of this technique provides.

Compared to batch production, flow processes present important differences related to the production time and yield. In batch production, reaction time is determined by how long a vessel is held at a given temperature while in the flow regime the volume of the reactor and the bulk flow rate are crucial parameters. Stoichiometry in flow reactors is defined by the concentration of reactants and their flow rate. In batch processes, this is defined by the concentration of chemical reagents and their volumetric ratio. On the other hand, the production reaction time under batch conditions is calculated by how long a container is kept at a given temperature. In contrast, continuous processes, the reactor volume and bulk flow rate determine the production rate.

Currently, the availability of commercially miniaturized flow systems has made it possible to address and guarantee important points in the common laboratory such as simple automation, reproducibility, safety and process reliability due to constant reaction parameters (efficient mixing, temperature, time, amount of reagents and solvent, etc.). It has been shown that when pressure resistant microstructured flow reactors are employed, the reaction temperature can be well above the boiling point of the solvent to supercritical conditions. A given reaction can be accelerated and the production rate of a flow device can be increased by submitting higher flow rates.[20]

Also, there is a huge difference between batch and flow processes when multi-step reactions must be performed. Setting a linear arrangement of several microstructured flow reactors, a continuous multi-step process can be designed. In this way, reagents can be introduced into the reagent stream anywhere in the flow system allowing them to react at the right time. Moreover, flow chemistry can be combined with packed-bed materials that are chemically functionalized with catalysts, reagents or with solid-phase scavengers in order to remove or deactivate impurities and unwanted products, chromatographic separation or liquid/liquid extraction. Other important fields of application in flow chemistry are the combination with photochemical reactions as well as continuous synthesis using hazardous gases such as ozone, CO, or NO as reactants.

In short, we could summarize the most important advantages that this technology offers us by addressing the following points:

-Minimization of reaction time. Flow chemistry joins to the group of different techniques that chemists have been performing during the history to speed up reactions and optimize them such as microwave, sonication and ultrasounds, but in a different way. This time, taking advantage of the technological innovation that flow chemistry can bring us, enabling the use of unconventional reaction conditions that can accelerate the desired process, it can lead us to more selective and efficient processes paving the route to a greener access to desired molecules.[21]

-Optimization of the screening time. Microreactor technology contributes to the optimization of the reaction conditions and especially in the scaling stage in order to minimize the amount of starting material used, thanks to the small volume reaction capacity, and the time necessary for its processing, achieving the best reaction conditions exploiting automation. Thus, it enables the testing of hundreds of reactions per day.[22]

-Waste minimization. Following the principles of green chemistry, point number five warns of the need to eliminate the use of solvents or to minimize them as much as possible. Generally, the largest contribution to waste is due to the solvents used for running the reaction, for the isolation and purification of the products. Solvents used in many different chemical syntheses are volatile which means that its dispersion in the environment is usually unavoidable. There are other modern alternatives such as supercritical fluids, ionic liquids, bio-based solvents and water, anyway, a careful evaluation of the beneficial effects must be performed before considering them "green" in any process. Flow may be the most efficient tool to reach the highest chemical and environmental efficiency. In fact, to minimize waste, reactants should be used in equimolar amounts combined with the minimal quantity of other solvents and heterogeneous catalyst, being able to recover and reuse them easily.[23]

-Safety improvement. Working in flow ensures that we are creating safe chemistry, resulting in an improvement of the efficiency of a process, may be economical, chemical or both. The adoption of flow techniques is so beneficial in order to manipulate reactive reagents, in the chemical exploitation of unstable intermediates or in the controlling of toxic materials. Subsequently, flow approach can become a strategic tool to optimize safety of a process conducted on larger scale. The minimization of side reactions and, therefore, the formation of undesired and potentially toxic by-products which may be only well separated by tedious and costly procedures, as well as, the generation of extremely difficult to handle reagents and operational risk under high pressure or

autoclave conditions, requiring great safety precautions, make flow chemistry the right solution to deal with these problems.[18]

      -Process intensification and easy scale-up. Continuous flow technology and the process intensification research are very often related, in fact, it is one of the main goals to achieve today. Intensification of a process can be achieved thanks to faster reaction times and higher productivity evaluated as the grams produced per hour per reactor volume or also combining many microrreactors in parallel at the same time. Nevertheless, recently, in the development of scale up processes by flow technology, investigations are also directed on the evaluation of cost, environmental issues and Life Cycle Assessment to better evaluate the actual sustainability of the scaling up process.[24,25]

      -Energy and cost efficiency. Performing reactions in flow conditions is an ideal approach to address energy savings and cost efficiency because under these conditions it is generally possible to define an easy scale-up, to avoid isolation of reactive intermediates, to improve heat/mass transfer and possibly to combine an *in line* purification.[18]

2.2. Applications of HMF in Continuous Flow Synthesis

      Over the last twenty-five years, the number of publications containing key words flow chemistry and hydroxymethylfurfural have grown gradually as seen in Figure 6.

(a)

Key word: Flow chemistry

Number of publications

Year of publication
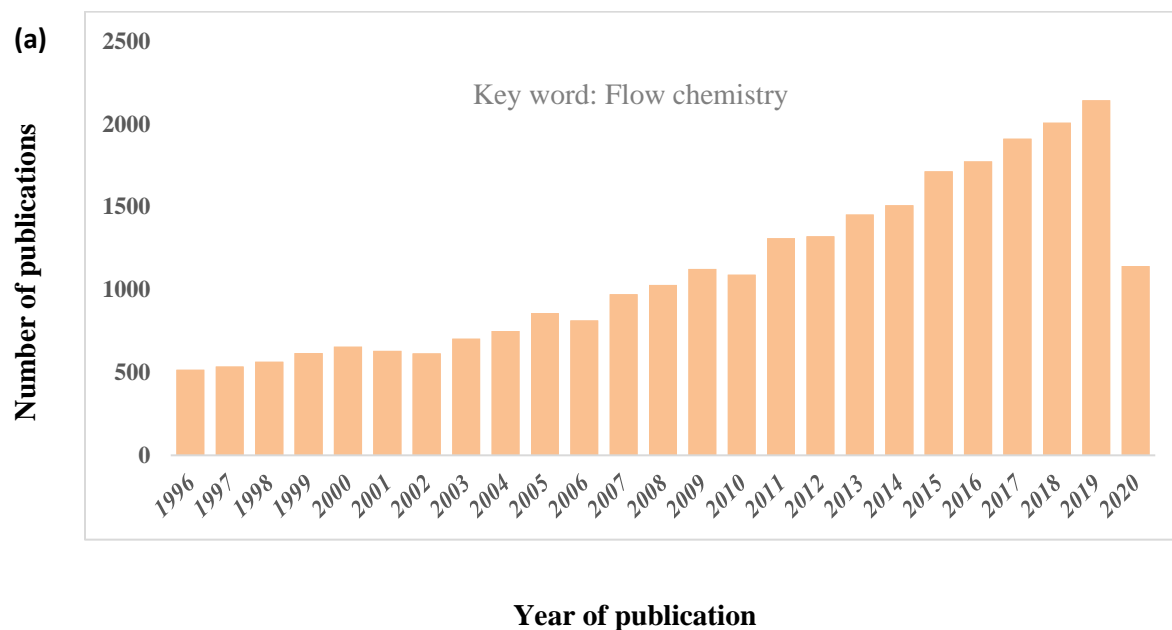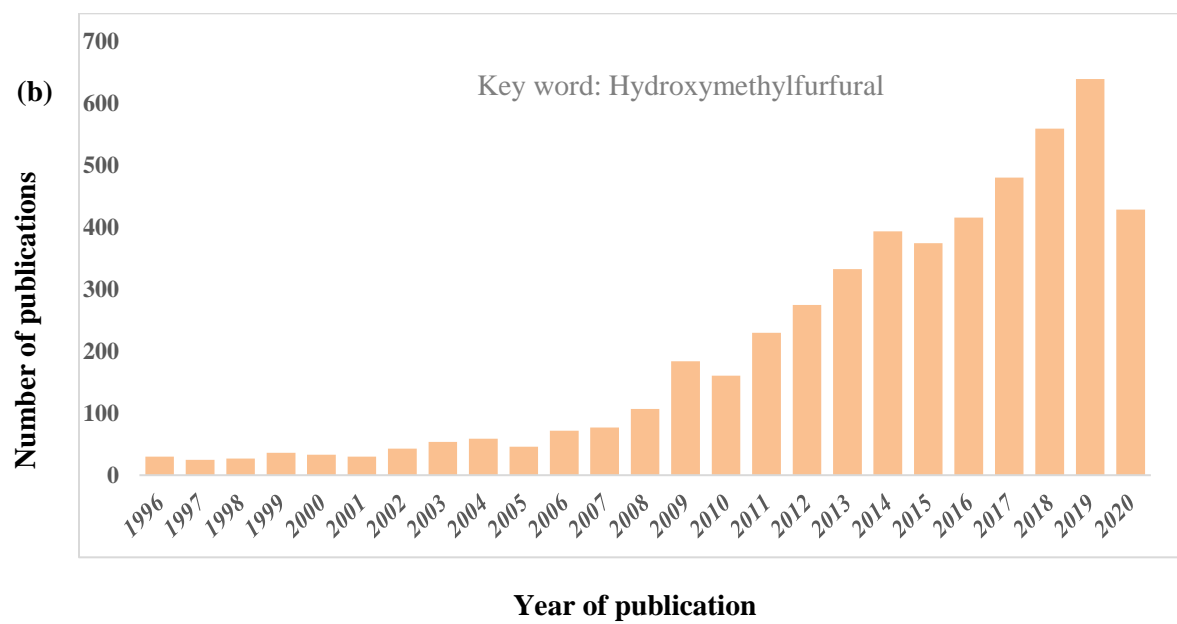
Figure 6. Evolution of the flow chemistry and hydroxymethylfurfural publications during the last 25 years. Data: Web of Science

Therefore, many biomass transformations are performed in multiphase systems employing homogeneous or heterogeneous catalysts. This fact makes the development of a suitable reactor a key step to obtain optimal performance. Continuous flow processing is essential to make the production of chemicals from biomass a feasible alternative to petroleum, becoming the processes greener and more efficient. In this way, steady-state processing in flow allows fine product tuning and can decrease deviations in the product properties and composition, which is a great opportunity to take advantage of this characteristic that this technology gives us to obtain products with high added value, since the raw biomass needs to pass to a liquid state to make it soluble in water or other solvents and thus be able to transform it.[26]

Improved heat/mass transfer can be obtained from continuous flow microreactors. These consist of reaction channels with diameters of the order of approx. 1 mm or less. Due to their versatility and flexibility, microreactors are considered a promising process intensification tool. Furthermore, many reactions have sufficient potential to be intensified in microreactors and certain biomass transformations can even be improved.[27]

Normally, microreactors have been used for the catalytic transformation in single and biphasic liquid phase (gas-liquid or liquid-liquid) of biomass derivatives into valuable products using homogeneous or heterogeneous catalysts.

Microreactors have different kind of configurations, it can be found having a capillary- or

chip/plate-based configurations, with an internal channel (hydraulic) diameter (d_c) between 0.1-3 mm, as it can be observed in Figure 7. By using this technology, chemical reactions are carried out in a continuous flow mode.
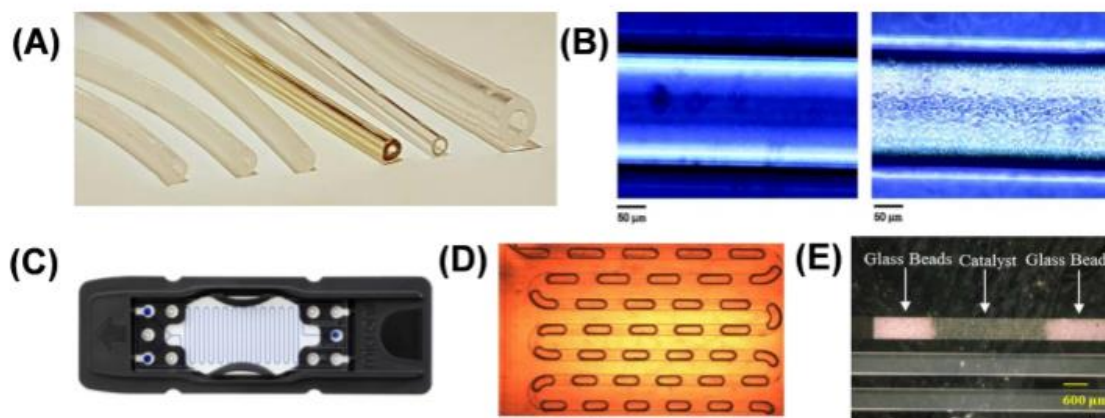
Figure 7. Typical types of microreactors used in the conversion of biomass derivatives to value-added chemicals and fuels. (a) Capillary microreactors of different materials and diameters. (b) Fused silica capillary microreactor for carrying out gas-liquid-solid (hydrogenation) reactions. Empty channel (left) and wall-coated with Pd catalyst (right). (c) Glass chip-based microreactor with an inlet mixer that can be used for biphasic gas-liquid or liquid-liquid reactions. (d) A chip-based microreactor made of transparent polyaryl sulfone (PASF). It is observed a gas-liquid slug flow profile in the microreactor. (e) Silicon/glass chip-based packed bed microreactor with solid catalysts trapped in the reaction channel by inert glass beads for use in the gas-liquid-solid (oxidation) reactions. Adapted from ref [28].

The use of a small channel size leads to fundamental advantages such as enhanced mass transfer and excellent temperature uniformity, the mitigation of safety risks due to the low amount of reagents used, thus being able to carry out exothermic reactions and highly explosive reactions, and more. Also, the possibility of incorporating solid catalysts coating the inner wall of the microchannel with a thin catalytically active layer (Figures 7b, 8c and 8d) or by packing the microchannel with catalyst particles (Figures 7, 8e and 8f) leading to a packed bed configuration is a great application of this kind of reactors shown in Figure 8.[28]
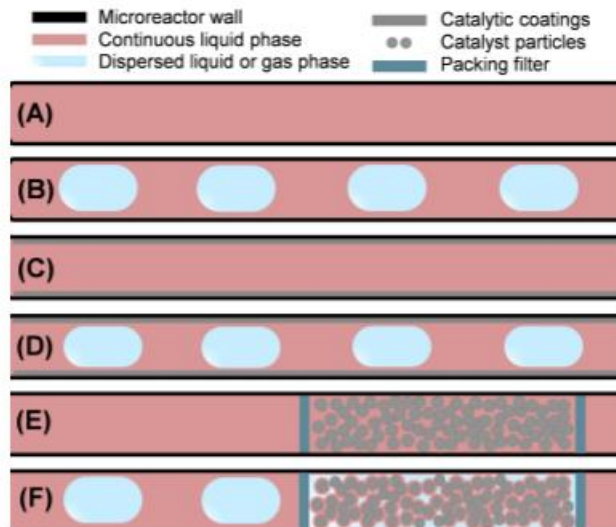
Figure 8. Schematic view of typical microreactors configurations and flows therein used for catalytic conversion of biomass derivatives. (a), (c) and (e) represent single-phase liquid flow through an empty microreactor, a microreactor with coated catalysts on the wall and a microreactor with packed catalyst particles, respectively. (b), (d) and (f) represent similar configurations, except with the presence of a gas-liquid or liquid-liquid slug flow, wherein (f) the upstream slug flow is subject to change when passing the catalyst bed and here the continuous liquid phase is shown to surround the catalyst particles dominantly. In (a)-(c), homogeneous catalysts can be dissolved in the liquid phase or one of the two liquid phases. Adapted from ref [28].

From one hand, wall-coated microreactors have the advantage that the same (multiphase) flow pattern can be maintained (Figure 8d) as in the empty ones (e.g., slug flow). From the other hand, packed bed microreactors have the advantages of a high catalyst loading capacity and incorporation of the catalyst in a simple way (for example, by gravitational or vacuum filling). The particle diameter of the catalyst used must be well below the diameter of the microchannel, in order to obtain an efficient packing structure, as well as a good distribution of the reagent flow over the bed. These can be retained by filters (Figures 8e and 8f) or by inert particles (e.g. glass beads; Figure 7e). However, having introduced packed particles, multiphase flow patterns are altered making them quite complex.[29]

The application of flow processing to microreactors supposes a significant transport intensification and an improvement in terms of process control as compared to conventional reactors (large-scale), increasing the rate of reactions that suffer limitations by mass transfer from one phase to the other and/or heat transfer in the system. This particularity become them very interesting in

order to perform multiphase (e.g. aerobic oxidation or hydrogenation) reactions that are usually related to producing value-added chemicals and fuels from biomass derivatives.

At the same time, the scale-up is possible stacking multiple microreactors in a reactor bundle, achieving a high-throughput production without any reactor modification in their configurations. This fact could become microreactors feasible for industrial applications due to its attractiveness, as their time to market is shortened and allows for modular and flexible processing that is especially attractive for biomass conversion in which the availability of feedstock is irregular. The production of pharmaceuticals and fine chemicals are the main field of commercial use of microreactors. In addition to industrial applications, taking advantage of the own advantages that bring microreactor technology over conventional batch flasks, can lead to an acceleration of technological development in the field of biomass conversion.[30]

The first reported HMF flow synthesis was performed in a single phase homogeneous 0,01 M H_3PO_4-catalyzed aqueous system at high temperatures. The flow set-up used for the acid-catalyzed conversion of carbohydrates to 5-HMF is illustrated in Figure 9.

1- carbohydrate containing vessel
2- plunger pumps
3- carbohydrate solution water
4- pressure meters,
5- reactor (volume 0.25 L)
6- catalyst-containing vessel
7- separator
8- gas cylinder (argon of carbon dioxide)
9- extracted mass receptacle
10- gas discharge line
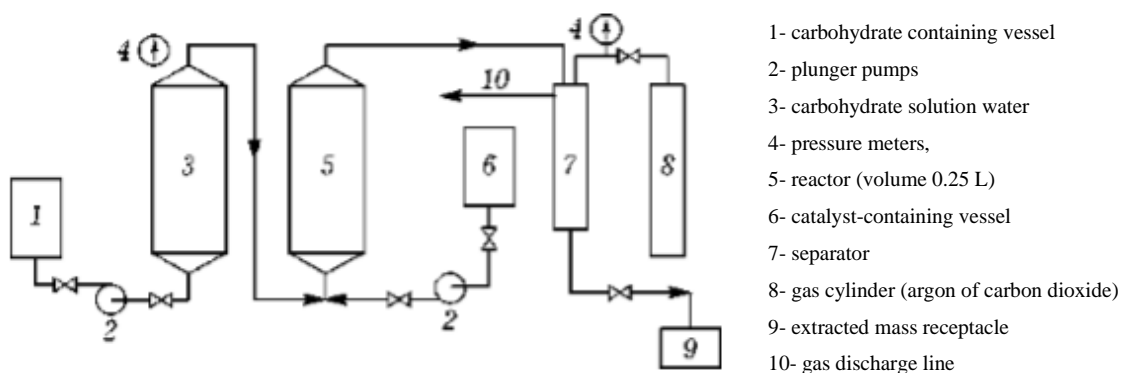
Figure 9. Schematic view of a slow set-up for the acid catalyzed conversion of carbohydrates at high temperatures. Adapted from ref [31].

The kinetics of 5-HMF synthesis were studied from fructose and sucrose at 240°C in water containing acetic and phosphoric acid as catalysts, obtaining the next results (Figure 10):

25
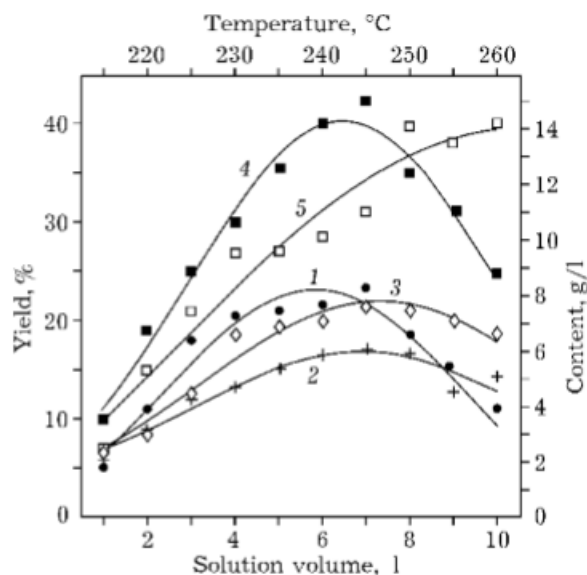
Figure 10. Yield of 5-HMF from fructose (0.25 M) *versus* temperature and phosphoric acid concentration, M: 0 (1), 0.25(2), 0.12 (3), 0.04 (4), 0.01 (5). Adapted from ref [31].

In this last figure, it can be observed the 5-HMF accumulation at the acid catalyzed conversion of fructose depending on phosphoric acid concentration and reaction temperature. At a constant residence time each catalyst concentration provides a particular optimum process temperature, which increases as phosphoric acid concentration decreases. An HMF yield of 40% was achieved after 3 min at 240°C from 0.25 M fructose in water. A meso-scale tubular stainless steel reactor (0.25 L in volume) with a high corrosion resistance was used for handling high temperature under acidic conditions.[31]

Subsequently, Table 2-3 shows several examples of the application of continuous flow by using microreactor technology over three different reaction types related to HMF: i) the catalytic dehydration of sugars to produce furans (HMF) using homogeneous and heterogeneous catalysts (Table 2), ii) liquid phase oxidation of HMF using any oxygen source over homogeneous or heterogeneous catalysts (Table 3), and iii) liquid phase hydrogenation of HMF (Table 3).

Table 2. Dehydration of sugars to produce furans (HMF) in continuous flow microreactors. Adapted from ref [28].

Entry	System	Substrate	Product	Catalyst	Reactor	Reaction conditions	Results and advantages of flow operation	Ref
1	L	Fructose	HMF	HCl	Glass chip (dC=1.2 mm, L=3 m) with passive mixing element	Single phase: 0.1 M HCl and 10–50 wt% fructose in water; 80–200°C, 1–20 bar	54% HMF yield and 75% selectivity in 1 min at 185°C and 17 bar	
2	L	Fructose	HMF	HCl	Glass chip (dC=1.2 mm, L=3 m) with passive mixing element	Aqueous phase: 0.1 M HCl and 10–50 wt% fructose in water/ DMSO (80/20 wt%); Organic phase: mixture of MIBK/2-butanol (70/ 30 wt%); No flow pattern given, aq:org 2:1–1:5; 185°C and 17 bar	85% yield and 82% selectivity of HMF in 1 min; Biphasic system allowed processing 50 wt% fructose without reactor fouling problem	
3	L	Fructose	HMF	HCl	PEEK capillary (dC=0.5– 0.8 mm, L not specified)	Aqueous phase: 0.025 M HCl and 100 g/L fructose in water; Organic phase: MIBK; Slug flow operation, aq:org 2:1–1:5; 180°C, 100 bar	88.5% yield and 91.1% selectivity of HMF in 3 min	
4	L	Fructose	HMF	HCl	PEEK capillary (dC=1 mm, L=0.7– 5.1 m)	Aqueous phase: 0.25– 2 M HCl and 100 g/L fructose in water; Organic phase: MIBK; Slug flow operation, aq:org 1:9; 120–160°C, 18 bar	Over 90% HMF yield in 40 s at 150°C	
5	L	Fructose	HMF	H_2SO_4	PFA capillary (dC=1 mm, L=7.6 m), assisted by microwave heating	Aqueous phase: 0.05 M H2SO4, 100 g/L fructose and 120 g/L gluconic acid in water; Organic phase: 2methyltetrahydrofuran; Slug flow operation, aq:org 1:4; 150°C, 10 bar	85–89% HMF yield obtained in 10 min	
6	L	Fructose and glucose	HMF	H_3PO_4	Stainless steel capillary (dC=1 mm, L=9 m)	Aqueous phase: 2.3% H3PO4 and 1 wt% fructose or glucose in PBS, pH=2; Organic phase: 2BP; Slug flow operation, aq:org 1:0– 1:4; 170–190°C, 20 bar	80.9% HMF yield from fructose in 12 min and 75.7% yield from glucose in 47 min at 180°C; Faster reaction than batch due to higher extraction efficiency and better heat transfer	
7	L	Fructose and sucrose	CMF or HMF	HCl	PFA capillary (dC=1 mm, L=12.7 m)	Aqueous phase: 32% HCl and 100 g/L fructose or sucrose in water; Organic phase: DCM or DCE; Slug flow operation, aq:org 1:1; 100–130°C, 8 bar	61% CMF yield from fructose in 1 min (100°C, DCM as extraction solvent); 74% CMF yield from sucrose in 15 min (130°C, DCE as extraction solvent)	
8	L	Fructose	HMF	HCl	Cross-flow channel (10×1 ×0.6 mm) and stainless steel sintering membrane (3×1 ×0.3 mm; 5 µm pore size)	Aqueous phase: 0.025 M HCl and 100 g/L fructose in water; Organic phase: MIBK; Bubbly flow of aqueous droplets in continuous organic phase, aq:org 1:2; 180°C, 30 bar	93% yield and 93% selectivity of HMF in 4 min; Nearly 100% HMF extraction efficiency obtained by the enhanced mass transfer from small	

#	Phase	Substrate	Product	Catalyst	Reactor	Conditions	Results
9	L-S	Fructose	HMF	Immsobilized H_2SO_4 on 3-MPTMS	Wall-coated fused silica capillary (dC=0.15 mm, L=0.2 m)	Single phase: 0.5 M fructose in DMSO; 150°C, 1 bar	Up to 99% fructose conversion and 99% HMF yield in 6 min
10	L-S	Fructose	HMF	Amberlyst-15	Packed bed (dC=1.65 mm, Lbed=0.3 m, dp=0.2– 0.7 mm)	Single phase: 0.3 M fructose in 1,4-dioxane/ DMSO (90/10 vol %); 110°C, 1 bar	92% HMF yield in 3 min; Internal mass transfer limitations diminished by using small catalyst particles; No significant catalyst activity loss after 96 h
11	L-S	Fructose	HMF (derivatives) and EL	Amberlyst-15	Packed bed HPLC column (dC=4.6 mm, Lbed=0.25 m, dp=0.3 mm)	Single phase: 0.05 M fructose and 0.5 M formic acid in ethanol; 110°C, 1 bar	89% fructose conversion in 41.5 min; 37% yield towards HMF derivatives (mainly EMF) and 52% yield towards EL; no solid humins formation
12	L-S	Fructose	HMF and *i*-PMF	Amberlyst-15	Packed bed glass column (dC=10 mm, Lbed=0.05 m)	Single phase: 45 g/L fructose in i-PrOH/ DMSO (15/85 vol%); 120°C, 5 bar	95% HMF and 5% i-PMF yields in 11.2 min; i-PrOH solvent improves HMF selectivity;
13	L-S	Fructose	HMF	Lewatit K2420	Packed bed stainless steel reactor (dC=9.5 mm, Lbed=0.15 m)	Single phase: 0.1 M fructose and 12.5– 17.5 vol% water in HFIP; 95–105°C, 20 bar	76% HMF yield in 20 min; Same results obtained in packed bed as batch reactor
14	L-L-S	Cello-oligomers	HMF	Phosphated TiO_2	Packed bed U-shaped stainless steel reactor (outer diameter 6.35 mm)	Aqueous phase: 50 g/L substrate in water; Organic phase: MIBK/ NMP (75/25 vol%); Single premixed stream before entering packed bed, aq:org 1:1; 220°C, 60 bar	Soluble cello-oligomers obtained by acid impregnation of cellulose; 53% HMF yield in 3.2 min from cello-oligomers
15	L-L-S	Different sugars and water-soluble starch	HMF	TiO_2	Packed bed stainless steel reactor (dC=10 mm, Lbed=0.15 m, dp=80 µm)	Aqueous phase: 20– 50 wt% sugar or 5 wt% starch in water; Organic phase: MIBK, n-butanol, or others; No flow pattern given, aq:org 1:10; 180°C, 34– 138 bar	29% HMF yield from glucose with TiO_2 in 2 min at 180°C and 34 bar; 15% HMF yield from water-soluble starch in 2 min under 180°C and 69 bar

Table 3. Catalytic oxidation (entry 1-3) and hydrogenation (entry 4) of biomass derivatives in continuous flow microreactors. Adapted from ref [28]

Entry	System	Substrate	Product	Catalyst	Reactor	Reaction conditions	Results and advantages of flow operation	Reference
1	G-L-S	HMF	DFF, FDCA	TEMPO on silica	Packed bed PTFE capillary (dC=1.65 mm, dp=0.16– 0.24 mm)	Liquid phase: 0.41 M HMF and 5 mol% HNO3 in DCE; Gas phase: O_2; 55°C, 5 bar; Slug flow before entering the packed bed	97% conversion of HMF with 98% DFF selectivity in 2 min; ~35% FDCA yield in 8 min; No catalyst decomposition over 8 h	
2	L-S	HMF	HMFCA, FDCA	Nanostructured gold	Wall-coated PET chip (L×W×H=220×2×0.15 mm)	Single phase: 3 mM HMF, 12 mM NaOH and 70% TBHP in water; Room temperature, 1 bar	13.86% HMFCA and 3.76% FDCA yields in 50 min	
3	G-L-S	HMF	DFF	$Fe_3O_4/SiO_2/Mn$	Gas permeable PTFE capillary (dC=0.61 mm, L=0.1 m, pore size=110 nm) in wall-coated PTFE capillary (dC=1 mm, L=0.1 m)	Liquid phase: 0.5 M HMF in DMSO; Gas phase: O_2; 150°C, 1 bar; Cocurrent flow, gas phase in the inner capillary and liquid phase in the outer capillary	93% HMF conversion and 84% DFF yield in 60 min; 82% DFF yield by direct synthesis from fructose in 70 min in tandem configuration; Stable magnetic binding of wallcoated catalyst for 5 h on stream	
4	G-L-S	HMF	DMF	Ru/Cu/ Fe3O4/N-rGO	Gas permeable PTFE capillary (dC=0.61 mm, L=0.1 m) in wall-coated PTFE capillary (dC=1.2 mm, L=0.1 m)	Liquid phase: 0.5 M HMF in DMSO; Gas phase: H2; 150°C, 8 bar; Cocurrent flow, gas phase in the inner capillary and liquid phase in the outer capillary	91% DMF yield and 100% HMF conversion in 20 min; No significant catalytic activity loss after 2 days of operation	

Based on the three types of reactions shown in the tables, we can affirm that the use of continuous flow systems in reactions performed with HMF, although for now it has to be on a small scale, gives rise to great results of selectivity and performance, giving us significant advantages in terms of efficiency.

CHAPTER 3: SYNTHETIC APPLICATIONS OF HMF

3.1. Purification of HMF

Previously, we discussed the main problems that companies or researchers that work with HMF must deal with. The contribution to the development of its industrial production by patenting various process technologies is a hard work because of the challenges that they have to face in the upscaled HMF production, such as the formation of side-products, solid humins overall, the separation of HMF from the reaction media, and its subsequent purification. The by-product formation depends on the reaction parameters and it directly affects the purification and therefore, the economic efficiency of the HMF production, making it feasible or not.

In order to make a process more efficient and viable in terms of by-products it is better to prevent the formation of these side-products from the beginning. The other possibility is to try to valorize. For example, the formation of levulinic acid during the synthesis of HMF reduces its yield, but it presents only a minor problem because of its high added value as a platform chemical. However, the formation of humins promote a valorization which is a crucial factor to consider the process economically profitable. Also, due to humins chemical structure and its yield dependence during the process, as well as their complex separation process, valorization of humins continues being investigated.

In order to achieve a successful separation and purification of HMF is essential to avoid condensation reactions because they cause most of the problems that appear in this section.

The use of polar aprotic co-solvents such as DMSO, in the transformation of fructose into HMF has resulted in systems with high HMF yields and less by-product formation. Several aspects of the role of DMSO in the conversion to HMF such as the ability to increase the reaction rate in the absence of an acid catalyst are still debated. Nevertheless, synthetic carbohydrate chemistry states that DMSO is an advantageous solvent for water removal reactions in furan and pyran systems. Currently, the proposed role of DMSO in the conversion of fructose is summarized in:[32]

1- DMSO alters the isomer distribution of fructose.
2- DMSO promotes conversion through solvation effects.
3- DMSO reduces HMF susceptibility to nucleophilic attack.
4- DMSO stabilizes HMF in solution.

Despite the use of DMSO or other similar solvents with high boiling points (Tb) reduce the formation of side-products significantly, the problem shows when the recovery of HMF from these

solvents takes place, being a major issue in large-scale production. In order to make purification processes, distillation or extraction are the main ways to achieve it, using, for example, ethyl acetate. This is a key factor, the election of the solvent is essential because it must take into account its boiling point and its affinity to the separate product, which in this case is HMF. Separation and purification can result in a very cost-intensive process economically, requiring large amounts of organic solvents.[10]

The fact of being in an aqueous system or a nonaqueous system differs on the strategy used.

3.1.1. Separation and purification strategies for aqueous systems

In this kind of systems, the path followed to achieve the isolation of HMF is: (1) filtration of solids (humins), (2) neutralization, (3) HMF isolation (solvent extraction or others) and finally (4) HMF purification (vacuum distillation or others).

(1). Filtration: It has been reported the use of a pressure filter, achieving a successful separation of the insoluble products.[33] Also, it exists the possibility of centrifugation, however there is a lack of information in reference to this.

(2). Neutralization: At the moment of using homogeneous acid catalysts, the acid is previously neutralized to a pH of about 5-6[33]. It is usually used $CaCO_3$, but the use of other bases such as K_2CO_3[34] and $Ca(OH)_2$[33] was also reported.

(3). Isolation: Traditionally, solvent extraction has been the way to isolate HMF from the aqueous phase by usually using ethyl acetate as the solvent of choice. Generally, the ethyl acetate layer is dried after extraction using typical drying agents ($MgSO_4$ or Na_2SO_4). In reactive aqueous-organic systems, it has been studied several organic solvents for in situ solvent extraction from aqueous systems by NaCl at 180°C, and the results are shown in Figure 11, correlating the partitioning coefficient R of HMF, defined as the concentration of HMF in the organic phase divided by the concentration of HMF in the aqueous phase, and the HMF selectivity. The results show a poor relationship between HMF selectivity and the partitioning.

Figure 11. Correlation between HMF selectivity and the partition coefficient (R) with different types of solvent for the dehydration of fructose in saturated NaCl (pH=1 HCl, 180°C). Open symbols correspond to solvents that are partially miscible with water and closed symbols correspond to completely miscible in water without presence of salts at room temperature. Adapted from ref.[5]

In the case of using alcohols as solvents, the HMF yield is reduced due to side reactions (ether formation and acetization). However, alcohols are considered environmentally friendly. This, coupled with the fact that give considerable HMF yields, makes them a good choice as solvents.

The use of water as solvent would be ideal environmentally, but in this case, the formation of side products is so high that this option is not recommended. The formation of solid side-products in the continuous production of HMF in this kind of systems by using mineral acids as catalysts makes it unfeasible for the moment.[10]

For the recovery of HMF from aqueous solutions, Menkhaus et al. reported the use of polyethyleneimine (PEI), a soluble cationic polyelectrolyte.[35] The separation of PEI with absorbed HMF was performed using a membrane filtration (MWCO, 10000 cut-off), followed by a centrifugation step and acidification with diluted sulphuric acid, up to 59% of HMF was recovered. Regarding to the purification process, different techniques has been described. Among this, we find two different purification techniques, distillation and crystallization.

(4). Purification: In order to obtain pure HMF, the distillation under reduced pressure is typically performed. The distillation of crude HMF is considered troublesome due to thermal degradation of HMF associated with the formation of tarry carbonaceous materials. There are patents preventing further degradation of HMF during the distillation. On the one hand, Jones proposed to protect the crude HMF from moisture by degassing at a high vacuum and continuously distilling the HMF at higher temperature under pressure, obtaining a pure HMF yield over 90%. On the other hand, Hunter proposed the use of a falling film evaporator to reduce contact time at elevated

temperatures.[36] Also, the formation of tarry materials and deposits in the still during the distillation can be avoided adding a non-volatile flowing agent like PEG-600.[5] For the HMF crystallization process, it has been reported starting from concentrated HMF fractions in aqueous solution and from a dichloromethane solution. The crude HMF fraction obtained from chromatographic process was concentrated by heating to 80°C under vacuum until its water-content was about 7%. After that, the HMF crystallization was achieved by cooling the HMF fraction in a multistage stirred crystallizer. The mixture was cooled from room temperature to 10°C with a cooling rate of 5°C/h. When the mixture reached 10°C, it was seeded with HMF crystals, continuing cooling until 4°C. The obtaining of HMF crystals was completed, achieving a purity of 97%. Finally, recrystallization was performed in order to obtain a final yield of 99.4% of pure crystalline HMF.[33]

3.1.2. Separation and purification strategies for nonaqueous systems

As it has been highlighted previously, the use of high boiling solvents, such as DMSO, or non-volatile solvents, such as ionic liquids, the non-isolated yields are generally high.

In order to achieve the separation of the HMF from the reaction mixture, numerous methodologies have been proven. For example, M'Bazoa et al. isolated HMF from DMSO solution using dichloromethane (DCM), getting a 96% of HMF extracted with a small fraction of DMSO. Then, the solvent was removed and HMF was purified by crystallization. However, the use of DCM is controversial due to its toxicity and potential harmful to the environment. Also, the use of an intermediate as part of the process to obtain high purity HMF is another way to achieve it. Reichert and co-workers isolated and purified HMF from a reaction mixture obtained by hydrolysis of 5-acetoxymethylfurfural (AMF) to HMF in methanol. Finally, HMF was crystallized from a methyl tert-butyl ether (MTBE) solution by cooling it slowly to 5°C after removal of its impurities and volatiles.[37]

It is difficult to find reports on isolation and purification of HMF from ionic liquid systems. Therefore, the use of ionic liquids in order to develop a green method for HMF production provides an opportunity to use small or no amounts of organic solvents. Nevertheless, due to the high cost of ILs and unresolved separation issues, HMF synthesis in ionic liquids has never been industrialized. The extremely low vapour pressure associated with ILs allows the distillation of volatile products from the medium, but product separation from ionic liquids is compromised for HMF due to the high boiling point and low thermal stability of HMF. This problem on the separation of HMF has been discussed several times by using different techniques to alleviate it, such as thermal distillation under

a high vacuum and a high temperature or the extraction using typical organic solvents. However, these solutions bring several problems with themselves, such as extreme conditions, volatility or toxicity, and these are usually the same issues that ionic liquids aimed to avoid. The wide capacity of ionic liquids to change its properties by combining different types of ions in order to work successfully in different separations can be a promising way to improve this field. Also, the integration of ionic liquids in continuous flow processes is possible by using microreactors technology. In spite of being a promising way to develop new ways or processes it is necessary to alleviate certain limitations, such as its high costs.[38]

3.2. Chemical conversions of HMF

The characteristics in the structure that shows the HMF molecule give it the ability to allow the formation of numerous target molecules.
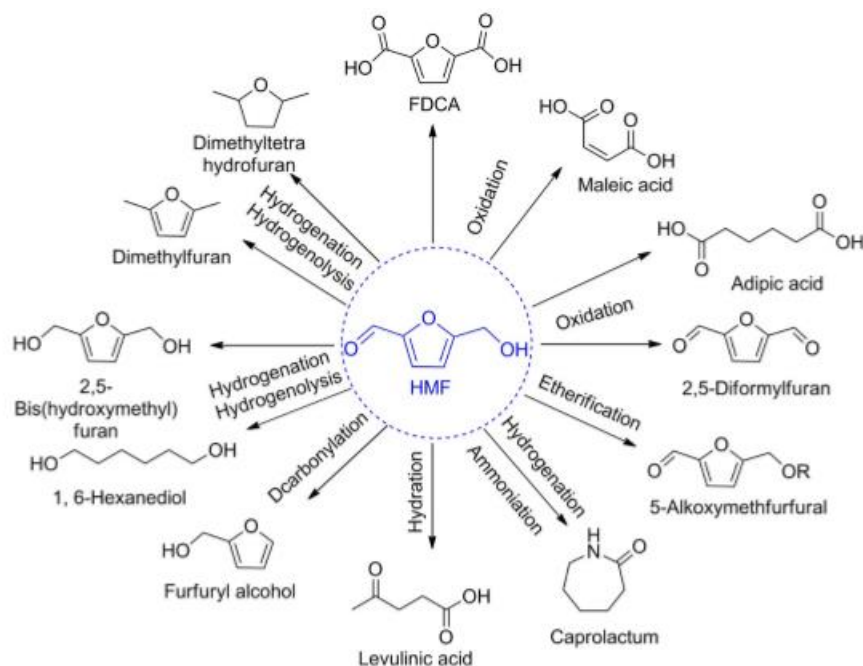

Figure 12. Schematic representation of HMF acting like platform chemical deriving in other target molecules of interest.

Selective oxidation and reduction of the formyl, hydroxyl groups and furan ring; carbonyl and hydroxyl homologation; and whole-skeleton transformations is going to be summarized.
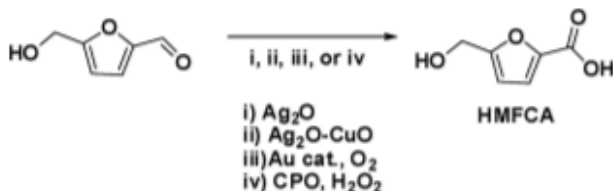
3.2.1. Oxidation

Selective oxidation of HMF can lead to form 5-hydroxymethyl-2-furancarboxylic acid (HMFCA) and 2,5-diformylfuran (DFF). The first one can be obtained if the oxidation is focused on the formyl group and DFF can be obtained if the selective oxidation is performed on the hydroxyl group. Also, if the oxidation involves both groups, formyl and hydroxyl, it is formed 2,5-furandicarboxylic acid (FDA) (Scheme 1). These compounds are very interesting as well as starting materials in order to be transformed or for being chemical building blocks for industry.[39]

HMFCA   DFF   FDA
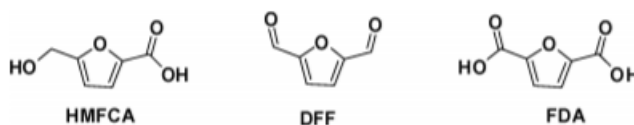
Scheme 1

In the selective oxidation of the formyl group it has been reported several conditions for the transformation of HMF into HMFCA as it can be observed in Scheme 2.[40]

i, ii, iii, or iv   HMFCA

i) Ag$_2$O
ii) Ag$_2$O-CuO
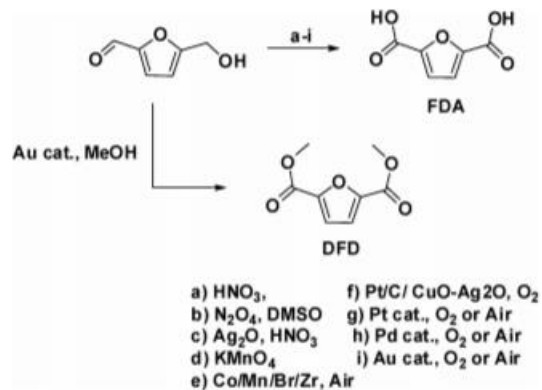iii)Au cat., O$_2$
iv) CPO, H$_2$O$_2$

Scheme 2

The formation of DFF is consequence of the selective oxidation of the hydroxyl group of HMF. This compound is an important monomer for industry. Table 4 shows the different oxidants used in different oxidations of the hydroxyl group of HMF.

Table 4. Examples of oxidation of HMF to DFF using different oxidants.

| Entry	Reaction conditions	Yield (%)
1[125]	Pb(OAc)$_2$, pyridine	37
2[126,127]	CrO$_3$, pyridine	73, 68
3[128]	Ac$_2$O, DMSO	76
4[128]	HNO$_3$, DMSO	31–67
5[128]	N$_2$O$_4$, DMSO	76
6[117]	BaMnO$_4$	93
7[129]	K$_2$Cr$_2$O$_7$, DMSO, ultrasonic irradiation	75
8[179]	TMACC, Al$_2$O$_3$, ultrasonic irradiation	72
9[15,130]	PCC, Al$_2$O$_3$, ultrasonic irradiation	58
10[131]	PCC, CH$_2$Cl$_2$	65
11[132]	[EMIM][OTf], CAN, 100 °C	100
12[122]	CPO/H$_2$O$_2$	^{a}
13[124]	4-Benzoyloxy-TEMPO, Ca(ClO)$_2$	81
14[133]	Dess–Martin periodinane	74

^{a} 89% conversion of HMF and 59% selectivity.

In the case of performing the oxidation of both groups, the consequence is the formation of FDA (Scheme 3), which is a potential biorenewable replacement monomer for terephthalic acid in polyethylene terephthalate plastics, and has been described as one of the building blocks of the future.[41]

a) HNO₃,
b) N₂O₄, DMSO
c) Ag₂O, HNO₃
d) KMnO₄
e) Co/Mn/Br/Zr, Air

f) Pt/C/ CuO-Ag2O, O₂
g) Pt cat., O₂ or Air
h) Pd cat., O₂ or Air
i) Au cat., O₂ or Air

Scheme 3

The oxidation of the furan ring can be performed as well, under photo-oxygenation conditions, using alcohol as a reaction medium. The oxidation takes place firstable with the formation of an endoperoxide. Then, the attack of an alcohol on the formyl group or on the 5-position of the furan ring is produced, leading respectively to hydroxybutenolide (Scheme 4, route a) as a major product and alkoxybutenolide (Scheme 4, route b) as a minor product. Moreover, Marisa et al. reported the photochemical oxidation of HMF in water providing a possible intermediate or monomer for the chemical industry, the 5-hydroxy-4-keto-2-pentenoic acid (Scheme 5).[42]
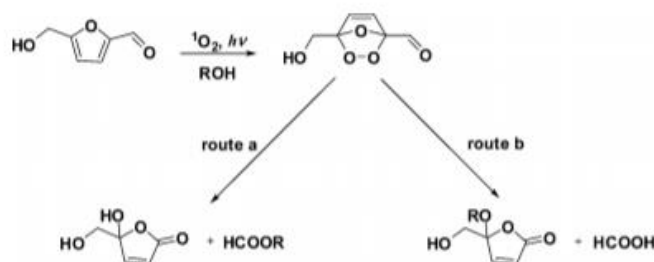
Scheme 4
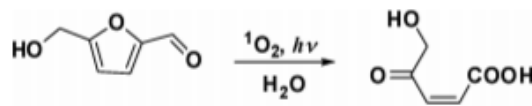
Scheme 5

3.2.2. Reduction

The selective reduction of the HMF can be involved in the furan ring and/or the formyl group (Scheme 6). Thus, the selective reduction of the formyl group leads to the formation of 2,5-bis(hydroxymethyl)furan (BHMF), which is an important chemical building block used in the production of polymers and polyurethane foams.

In order to produce BHMF by reduction of HMF, the use of sodium borohydride reports high yields. Also, it has been studied BHMF synthesis using formalin and aq. NaOH, reporting 76.9% yield.[43] Nickel, copper chromite, platinum oxide, molybdenum oxide and sodium amalgam catalysts were found to be effective for this transformation. The production of BHMF has been studied in aqueous media as well, by using nickel, copper, platinum, palladium or ruthenium as catalysts in the HMF hydrogenation. BHMF was obtained as the main product when copper and platinum catalysts were used. The use of Pt/C, PtO$_2$ or 2CuO·Cr$_2$O$_3$ reported a 100% conversion and selectivity of BHMF, while the use Pd/C[44] or Raney® nickel catalysts in hydrogenation of the furan ring, lead to the formation of 2,5-bis(hydroxymethyl)tetrahydrofuran as the major product in high yield (Scheme 6).[40]

i) NaBH$_4$
ii) formalin, aq. NaOH
iii) Cu or Pt cat., H$_2$

iv) Pd or Ni cat., H$_2$
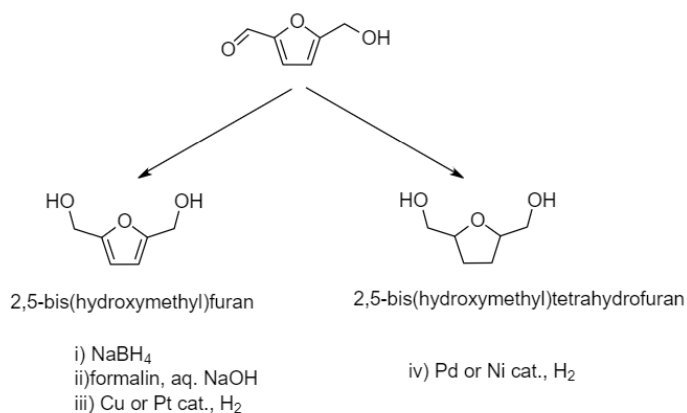
Scheme 6

On the other hand, the formyl and hydroxyl groups can be simultaneously reduced, leading to the formation of 2,5-dimethylfuran (DMF), which has a particular interest due to its high energy content and its potential use as a biofuel.

Several reports have been registered in order to achieve this transformation, for example, DMF synthesis from HMF hydrogenation using Ru-Co/SiO$_2$ as catalyst prepared by sol-gel method is promising, achieving 96% DMF yield (Table 5) and observing the importance of reaction

temperature on the DMF formation phenomenon, reporting the >99.9% DMF yield at 120°C for 8 h and at 140°C for 4 h with 15 bar hydrogen pressure.[45] Other report comprises the use of highly efficient 3% Pd/C catalyst (Table 6), showing almost complete conversion of 5-HMF in 4 h. TON and TOF of 3% Pd/C for 5-HMF hydrogenolysis were found to be 280.42 and 70.10 h^{-1} respectively. The increase in temperature and pressure leads to reach almost total conversion (99%) whereas temperature played predominant role for tuning the selectivity from HMF to DMF.[46]

Table 5. Effect on DMF yield and HMF conversion depending on the catalyst type. Adapted from ref [45].

	Ru/SiO$_2$	Ru-Co/SiO$_2$	Co/SiO$_2$
DMF yield (%)	Not detected	96.0	Not detected
HMF conversion (%)	31.1	100	38.1

Reaction conditions: HMF: 0.5 g, THF: 23 g, naphthalene (internal standard): 0.013 g, 180 °C, 2 h, 15 bar H$_2$

Table 6. Hydrogenolysis of HMF over different catalysts. Adapted from ref [46]

Entry	Catalyst	Conversion (%)	Selectivity (%)				
			DMF	MFAL	MFFR	BHMF	UnK
1	Activated carbon	10	0	2	0	12	86
2	3%Pd/C	99.9	99	0.3	0	0.7	0
3	3%Pt/C	87	70	7	6	15	2
4	3%Ir/C	30	87	4	3	6	0
5	3%Ru/C	88	89	3	2	6	0
6	3%Rh/C	60	84	6	2	2	6
7	3% Pd/Al$_2$O$_3$	53	47	13	16	21	3
8	3%Pd/ZrO$_2$	42	41	10	13	30	6
9	3%Pd/CeO$_2$	25	32	22	18	18	10

Reaction conditions: HMF = 100 mg, IPA = 20 g, catalyst = 10 mg, T = 443 K P = 300 psi, agitation = 1000 rpm, t = 4 h.

3.2.3. Other transformations

Taking advantage of the **formyl group**, many types of reactions can be carried out. Among these, it can be performed the reductive amination in order to obtain products, for example, that can serve as intermediates for further transformations or that can be used in the medical field. Wittig-type reactions, Baylis-Hillman reactions, acetal formations, aldol condensations (synthesis of biologically active compounds and useful intermediates for the synthesis of biofuels) are other examples of reactions that can be carried out benefiting of the formyl group.

The transformations that can suffer the **hydroxyl group** are accompanied by the formation of halides, in order to form useful intermediates for the synthesis of HMF derivatives due to their high reactivity, the formation of ethers, via condensation reaction of HMF with alcohols, giving rise to the formation of ether derivatives, and the hydroxyl group can also undergo esterification reactions, among others.

Apart from oxidation and reduction reactions, the cleavage of the **furan ring** of HMF can take place in acidic conditions in order to perform the hydrolysis.[47] The importance of this process was very relevant, especially when starting directly from biomass due to the formation of levulinic acid as the final product. This compound, together with its derivatives, are important chemical building blocks with various applications such as production fuels, fuel additives and polymers.

Also, the functional groups present in the HMF structure (hydroxyl and aldehyde) provides the molecule with structural motifs for the synthesis of heteromacrocycles, which are of considerable interest due to their biological activity and complexation properties.[40]

CHAPTER 4: OVERALL DISCUSSION AND CONCLUSIONS

It is clear the necessity of new carbon sources that can replace the high dependence that our society have, nowadays, of fossil resources. Biomass stands out among all possibilities as the main source of carbon in a renewable way. From this, numerous platform molecules can be developed, among them, the HMF is the one that attracts our interest. Numerous articles have been reported about the production of HMF from carbohydrates, where it has been shown that the production of HMF from fructose is the least problematic compared to others such as glucose, sucrose or cellulose, since the main drawback of glucose-based carbohydrates resides in the isomerization to fructose, which requires different conditions from the fructose dehydration step. Besides the improvement made in understanding the mechanism and kinetics of the dehydration process, significant challenges still remain in transferring it to and industrial scale. For this reason, more efficient reaction conditions (lower temperature and/or higher carbohydrate initial concentration), higher conversions and HMF selectivity are desirable, all linked with environmentally friendly processes. The high reactivity and multifunctionality is what make HMF a starting material of special interest; it is a primary alcohol, an aromatic aldehyde and a furan ring system simultaneously. In addition, multiple high added-value molecules can be derived from this molecule and that is why there has been a growing interest in its large-scale production. Among other synthetic reactions, oxidation and reduction reactions provide convenient synthetic pathways for the production of chemical building blocks for the polymer industry and biofuels starting from HMF.

Technology improvement is a key factor in order to improve the efficiency of this kind of processes and at the same time remove the limitations that a synthetic method can present. For this reason, continuous flow technology is a useful tool that is directly linked with green chemistry in order to develop sustainable processes. In this case, continuous flow microreactor technology fits perfectly with chemical reactions involving the conversion of biomass derivatives into value-added chemicals and fuels, since microreactors can lead to better selectivity and intensification processes. However, several challenges need to be overcome before microreactor technology can be effectively applied in commercial biomass conversion processes. On a laboratory scale it has been proven the handling of solids (insoluble humins) to prevent catalyst coking and microreactor clogging but must be tested for scaled-up applications. Added to the above, several aspects ranging from the election of the starting material, of the solvent and the catalyst, as well as the recycling of both, to the formation of side-products need to be considered for a good comprehensive evaluation of the

process. Application of ionic liquid solvent systems are showing great promise, however it is necessary to focus on finding efficient ways to address the problems that they present, such as the separation of HMF from the ionic liquids and their recycling eliminating impurities. Moreover, the extraction and purification processes of HMF are a section that is also in the spotlight as well. Finding efficient green ways to achieve that objectives making the process economically viable is the main goal, because of the scaled-up of the process would be achieve only if the pathway is feasible and profitable. Making a combination of all this technology that has been mentioned and trying to benefit from the advantages that each one presents in order to develop new processes or routes that could alleviate the inconveniences that existing processes present is the way to follow and by which we must advance.

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