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Catalytic Transformation of Biomass Derivatives to Value-Added Chemicals and Fuels in Continuous Flow Microreactors

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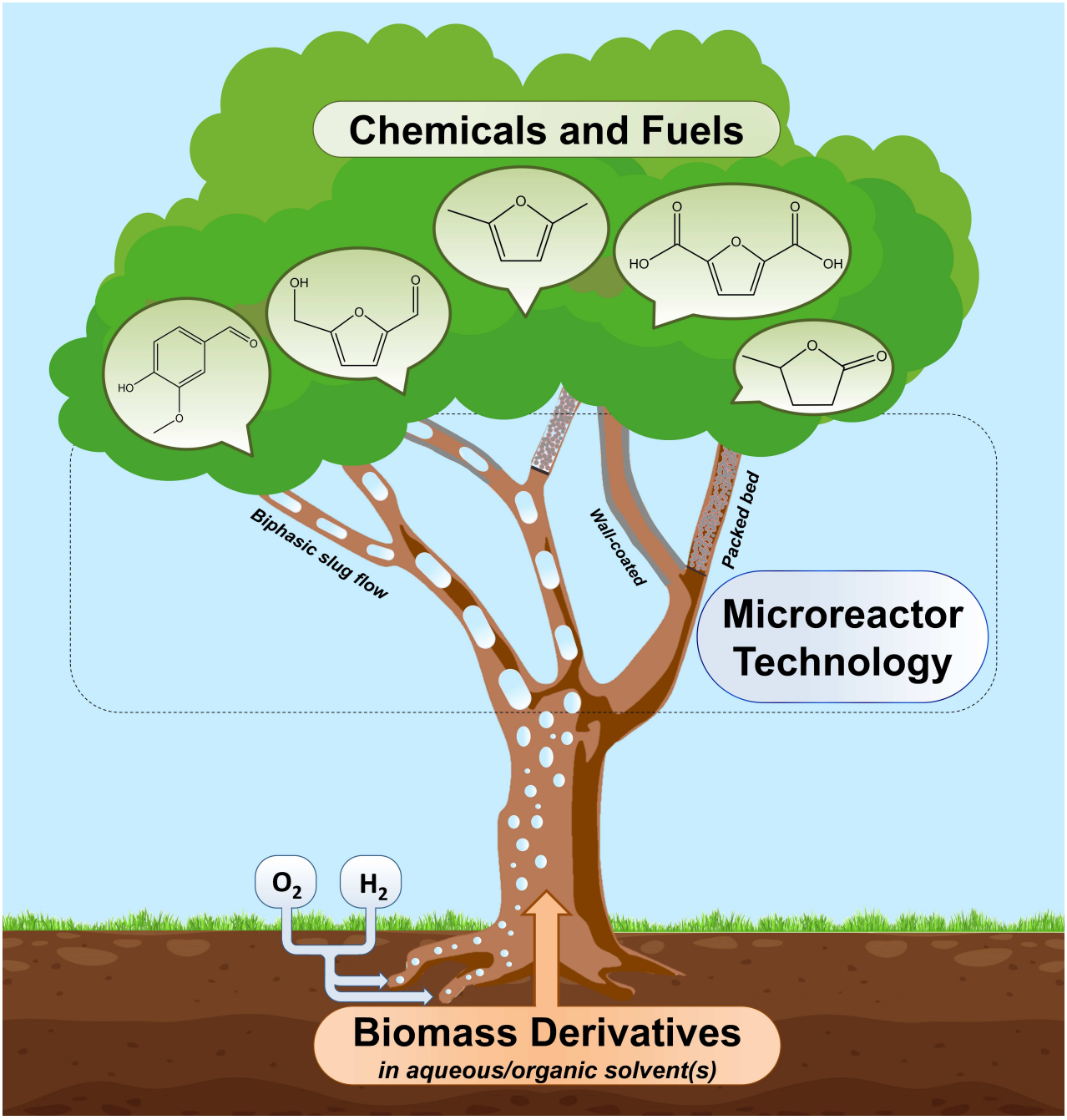

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Biomass as a renewable and abundantly available carbon source is a promising alternative to fossil resources for the production of chemicals and fuels. The development of biobased chemistry, along with catalyst design, has received much research attention over recent years. However, dedicated reactor concepts for the conversion of biomass and its derivatives are a relatively new research field. Continuous flow microreactors are a promising tool for process intensification, especially for reactions in multiphase systems. In this work, the potential of microreactors for the catalytic conversion of biomass derivatives to value-added chemicals and fuels is critically reviewed. Emphases are laid on the biphasic synthesis of furans from sugars, oxidation and hydrogenation of biomass derivatives. Microreactor processing has been shown capable of improving the efficiency of many biobased reactions, due to the transport intensification and a fine control over the process. Microreactors are expected to contribute in accelerating the technological development of biomass conversion and have a promising potential for industrial application in this area.

1. Introduction

1.1. Biomass to Chemicals and Fuels

The worldwide depletion of fossil resources has led to an increase in the demand of renewable and sustainable alternatives for the production of fuels, chemicals and energy. Although solar, wind, hydropower and geothermal power are all sources of renewable energy, biomass is the only largely accessible renewable source of carbon that is essential for the production of fuels and chemicals. Current industrial routes are almost entirely based on petroleum and other fossil resources.[1,2] CO_2 produced by the combustion or decomposition of biomass (derivatives) can result in the regrowth of new biomass by photosynthesis, leading to a complete carbon cycle and a reduction in greenhouse gas emissions. For the production of fuels (e.g., gasoline), it might not be possible to fully replace petroleum resources by biomass due to its limited availability. However, the current biomass reserves are plenty to supply virtually all raw materials required for the present chemical industry.[3]

The use of biomass for producing chemicals and fuels should not compete with the food production, neither by the direct use of edible biomass nor by cultivation on lands that can be used for agricultural purposes (i.e. indirect land use). Furthermore, it should not contribute to deforestation or have other negative ecological impacts. The most promising source of biomass for producing (bulk) chemicals and fuels is typically indigestible biological waste such as lignocellulose, an abundantly available byproduct from agricultural (e.g., corn stover, sugarcane bagasse, straw) and forestry industries (e.g., saw and paper mill discards).[3] Lignocellulose is present as microfibrils in the cell walls of plants and trees. It consists mainly of polysaccharides (ca. 20–30 wt% hemicellulose and 35–50 wt% cellulose) and ca. 10–25 wt% lignin (a highly cross-linked polymer made up of substituted phenols) (Figure 1).

Cellulose can be depolymerized to C_6 monosaccharide sugars (e.g., glucose and fructose) and disaccharides (e.g., sucrose). Hemicellulose can be depolymerized to C_5 sugars (e.g., arabinose, galactose and xylose) and the deconstruction of lignin can generate valuable aromatic compounds (e.g., phenols, phenolics and aromatic hydrocarbons). Other forms of biomass with potential for producing value-added chemicals and fuels are lipids (i.e. triglycerides and fatty acids from plant oils),[4,5] carbohydrates from starches, amino acids from proteins,[6,7] and wood derivatives such as terpenes, terpenoids and rosins.[8,9]

1.1.1. Biomass Conversion Methods

The majority of biomass sources consists of complex polymeric structures (e.g., polysaccharides and lignin) and need to be depolymerized or deconstructed in order to be further processed and used as chemicals or fuels. Many reviews described different chemical routes for the conversion of biomass (e.g., lignocellulose, triglycerides and terpenes) towards value-added chemicals or fuels.[10–14] Carbohydrates (e.g., cellulose, hemicellulose and starch derivatives) have higher oxygen content than petroleum, resulting in an excess of functional groups. While for petroleum it is necessary to add functionality, for carbohydrates it is essential to decrease this in a controlled fashion in order to selectively produce the target chemicals or fuels.[15] This requires alternative conversion methods and (more selective) catalysts. Similarly for the conversion of lignin, selective catalysts or harsh processing conditions are needed for its transformation to value-added products. Methods for biomass conversion to fuels and chemicals can be classified in three main categories: thermochemical, biochemical or chemocatalytic conversion (Table 1).

Thermochemical conversion is typically performed under harsh operating conditions, where biomass is thermally decomposed under high temperatures and pressures. Most commonly this is done by gasification for producing syngas (a gaseous mixture of H_2 and CO),[16,17] anaerobic pyrolysis to well-processable liquid bio-oils,[18] or liquefaction to bio-oils by hydrothermal upgrading (HTU).[19,20] Syngas derived from biomass can be typically converted to methanol,[21] or by Fischer-Tropsch synthesis to olefins,[22] which can function as biofuels or

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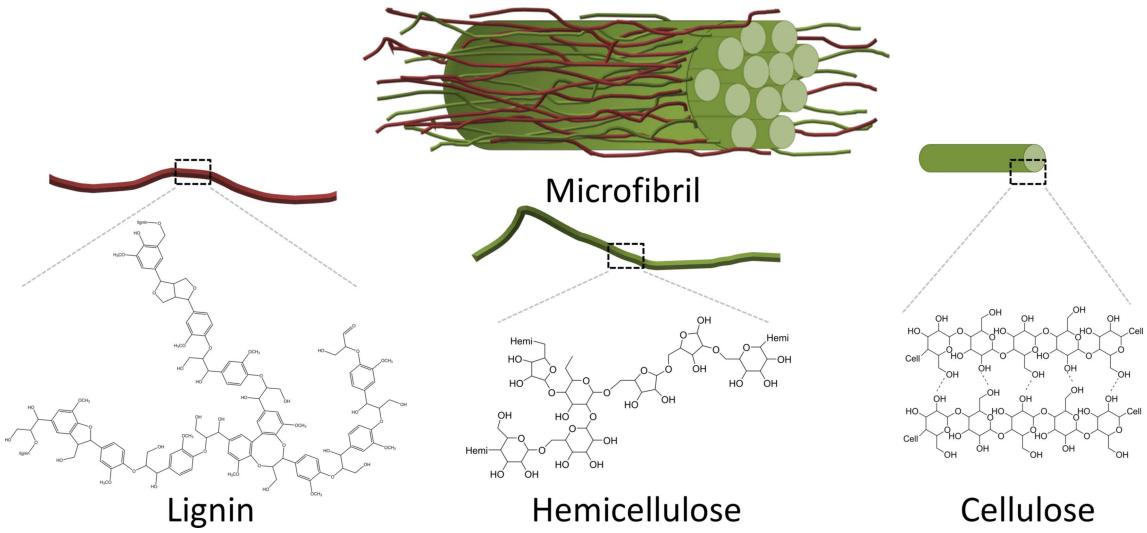

Figure 1. Main components in lignocellulose.

biobased drop-in chemicals in the petrochemical industry. Thermochemical biomass conversion is favorable for bulk processing of recalcitrant biomass sources, as no preceding separation procedures or expensive catalysts are required. Downside is that these operations are costly due to high temperatures required. Furthermore, by thermochemical treatment, the structure of biomass is considerably or completely destroyed and its original functional groups are not utilized effectively.

A biochemical method that can cope with recalcitrant (lignocellulosic) sugar streams under mild reaction conditions (50–70 °C) is fermentation by anaerobic digestion. In the fermentation process, yeast and bacteria consume sugars in the absence of oxygen to produce biobased acids,[23] biogas (e.g., CH_4, H_2),[24] or a mixture of acetone, butanol and ethanol (ABE),[25] depending on the type of bio-organisms and reaction conditions used. ABE and biogas are considered as the promising biofuels and can be an important feedstock for the (bio)catalytic production of (biobased) commodity chemicals. Combined hydrolysis of lignocellulosic biomass followed by fermentation of sugars derived thereof can form bioethanol, a promising biofuel.[26]

Arne Hommes graduated with degrees in chemical engineering (BSc and MSc) from the University of Groningen in the Netherlands in 2014. Currently he is pursuing a Ph.D. degree at the same university under the supervision of Dr. Jun Yue and Prof. Hero Jan Heeres in the green chemical reaction engineering group. His research is focused on the multiphase mass transfer characteristics in continuous flow microreactors and the use of microreactors for carrying out multiphase reactions, in particular the conversion of biomass derivatives to value-added chemicals and fuels. Typical reactions in his current research include the aerobic oxidation and hydrogenation of lignocellulosic biomass derivatives and the production of biodiesel from plant oils.

Hero Jan Heeres received a Ph.D. degree in catalysis from the University of Groningen in 1990. From 1990 to 1991, he performed a postdoc at the University of Oxford on asymmetric catalysis. From 1991 to 1999, he was employed at Shell Research B.V. and worked on a range of applied catalysis topics. He joined the department of chemical engineering at the University of Groningen in 1999 as an assistant professor. In 2003, he was appointed as a full professor in green chemical reaction engineering. His current research interests concern acid- and metal-based catalytic biomass conversions, with an emphasis on biofuels (pyrolysis oil upgrading), platform chemicals and performance materials.

Jun Yue earned his Ph.D. degree in Process Engineering from Université de Savoie in France in 2008. His Ph.D. work was focused on gas-liquid microreactors, supported by a joint PhD program with Dalian Institute of Chemical Physics, Chinese Academy of Sciences in China. Between September 2009 and July 2014, he worked as a postdoc at Eindhoven University of Technology in the Netherlands, where his research on microreactors has been extended to cover liquid-liquid and gas-liquid-liquid systems. Since August 2014, he has been appointed as an assistant professor at the University of Groningen. His current research interests mainly include the development of novel reactor concepts in general and their uses combined with precision catalysis for the synthesis of green fuels, chemicals and materials in particular.

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Table 1. Summary of biomass conversion methods.

Conversion method	Biomass source	Product	Reference
Thermochemical			
Gasification	Mixed	Syngas (CO/H_2)	[16]
Pyrolysis	Mixed	Bio-oil	[18]
Hydrothermal upgrading	Bio-oil	Biofuels	[19,20]
Biochemical			
Fermentation by anaerobic digestion	Carbohydrates	Chemicals (acids)	[23]
		Biogas (CH_4 or H_2)	[24]
		Acetone-butanol-ethanol (ABE)	[25]
		Bioethanol	[26]
Enzymatic transformation	Lignocellulose derivatives	Chemicals/fuels	[27]
Enzymatic (trans) esterification	Lipids	Biodiesel	[28]
Chemocatalytic			
Hydrogenation	Carbohydrates	Chemicals/fuels	[30,31]
Oxidation	Carbohydrates	Chemicals/fuels	[32]
Transesterification	Lipids	Biodiesel	[33–35]

For the targeted production of specific products from biomass sources, more selective processes are required. Enzymes, whether homogeneous or immobilized on a solid support, are highly selective catalysts that can be operated under mild reaction conditions.[27] Enzymes (lipases) allow greener biodiesel synthesis by transesterification of triglycerides, using lower reaction temperatures and requiring less pretreatment/washing steps than the conventional alkali-catalyzed process.[28] Hydrolysis of polysaccharides is commonly performed enzymatically (e.g., using (hemi)cellulase) for the selective production of monosaccharides (e.g., glucose, fructose and xylose).[29] Downside is that enzymes are still expensive and often have a lower catalytic activity and stability than inorganic catalysts.

Chemocatalytic biomass conversion, using homogeneous or heterogeneous inorganic catalysts, is considered more economically feasible than enzymes, as they are cheap, effective and can be operated under relatively mild conditions with high selectivity and stability. Hence, the chemocatalytic conversion of biomass (derivatives) has been researched extensively over the past decade.[14,36,37] The majority of catalytic transformation of biomass and its derivatives (e.g., by oxidation, hydrogenation, hydrolysis and dehydration) reported were performed with heterogeneous catalysts, although homogeneous catalysts also seemed promising.[38] Homogeneous catalysts are cheap and stable, but additional separation procedures are usually required to retrieve/dispose them from the reaction product. Chemocatalytic transformation of biomass over solid catalysts (e.g., micro- and mesoporous materials, metal oxides, supported metals, zeolites, ion-exchanged resins) has been well described.[39,40] Heterogeneously catalyzed biomass conversion allows greener processing as the solid catalyst can be easily recycled and reused. Besides that, there is less chance of fouling or corrosion as with homogeneous (acid) catalysts. In this area, specific reaction types for the transformation of biomass (derivatives) to valued-added chemicals and fuels have been reviewed (e.g., hydrogenation,[30,31] oxidation,[32] and transesterification of triglycerides from biobased lipids for biodiesel synthesis[33–35]).

The most suitable conversion method depends on the chemical composition of biomass feedstocks and the desired target chemical(s) or fuel(s). A facility where chemicals, fuels and energy are produced from biomass feedstocks is often referred to as a biorefinery. Such facility includes several integrated processes with different unit and refining operations. For a fully circular and efficient biorefinery, different conversion methods need to be applied and integrated together.[41–43] In this respect, inorganic catalysts can be combined with thermochemical conversion, such as catalytic pyrolysis for producing BTX (benzene, toluene, xylene)[44] or biofuels,[45] catalytic gasification,[46] and catalytic upgrading of lignin-derived bio-oils.[47] Also enzymes and inorganic catalysts can be combined for one-pot catalytic transformations of biomass (derivatives) to value-added products.[48]

1.1.2. Biobased Platform Chemicals

The above-mentioned biomass conversion methods give rise to biobased drop-in chemicals to be incorporated in conventional petrochemical processes or completely new biobased platform chemicals for producing the target fuels, chemicals and materials derived thereof. Particularly, these biobased platform chemicals can be converted catalytically (e.g., by hydrolysis, dehydration, oxidation, hydrogenation and (trans)esterification) to a great variety of potential precursors for the production of pharmaceuticals, cosmetics, food additives, biobased polymers and many other components (Table 2).

Table 2. Selected literature on the synthesis, uses and transformation of value-added biobased chemicals.

Biobased chemical	Reference
Lactic acid	[53]
Succinic acid[a]	[54,55]
3-Hydroxypropionic acid (3-HPA)[a]	[56]
Itaconic acid[a]	[57]
3-Hydroxybutyrolactone (3-HBL)[a]	[58]
Sugars (glucose, xylose)	[59]
Polyols (glycol, xylitol, sorbitol)[a]	[60]
Isosorbide	[61]
5-Hydroxymethylfurfural (HMF)	[62]
Glucaric acid[a]	[63]
Furfural	[64]
Levulinic acid (LA)[a]	[65]
γ-Valerolactone (GVL)	[66]
2,5-Furandicarboxylic acid (FDCA)[a]	[67,68]
Vanillin	[69]
Glycerol [a]	[70]
Glutamic acid [a]	[71]
Lysine	[72]

[a] Top biobased platform chemicals according to DoE,[49] with additional value-added biobased chemicals selected by others.[50,51]

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In an extensive survey by the US Department of Energy (DoE), 12 most promising chemical building blocks derived from carbohydrates were defined (i.e., 1,4-diacids (succinic, fumaric and malic acids), 2,5-furandicarboxylic acid (FDCA), 3-hydroxypropionic acid (3-HPA), aspartic acid, glucaric acid, glutamic acid, itaconic acid, levulinic acid (LA), 3-hydroxybutyrolactone (3-HBL), glycerol, sorbitol and xylitol/arabinitol), which can potentially replace those platform chemicals from the petrochemical industry used today.[49] Over the years this list has been expanded to include more biomass derivatives (e.g., 5-hydroxymethylfurfural (HMF), furfural, lactic acid and many more).[50,51]

The fermentation of sugars derived from polysaccharides can produce several valuable biobased acids (e.g., lactic acid, succinic acid, fumaric acid, itaconic acid and 3-HPA).[52] Lactic acid is a precursor for the synthesis of ethyl lactate (biodegradable solvent), acrylic acid (building block for plastics, coatings, adhesives, etc.), pyruvic acid (intermediate for pharmaceuticals, food additives, cosmetics, etc.) and polylactic acid (PLA; a biodegradable polyester).[53] Succinic acid can be converted by amination to 2-pyrrolidone (pharmaceutical building block) or hydrogenation to 1,4-butanediol (solvent and polymer building block) via butyrolactone, and react with alcohols to succinate esters (food additives).[54,55] Transformation of other biobased acids (e.g., fumaric, malic and itaconic acids, 3-HPA) can result in comparable derivatives as in the case of succinic acid (e.g., dialcohols, esters or pyrrolidones) that are used for similar industrial applications.[56,57] Microbial conversion of sugars can produce 3-HBL, a valuable chiral building block for the pharmaceutical industry.[58]

Monosaccharide sugars (e.g., glucose, xylose and arabinose), obtained from hydrolysis of (hemi)cellulose,[59] can be hydrogenated for the production of sugar alcohols or polyols (e.g., sorbitol, xylitol and arabinitol, respectively), used as food additives (e.g. sweetener).[60] The dehydration of sorbitol produces isosorbide, a building block for the production of fuels, solvents, plasticizers and pharmaceutical compounds.[61] The oxidation of glucose leads to gluconic acid and/or glucaric acid. Gluconic acid is used as an additive in food, pharmaceutical, paper and concrete industries.[73] Glucaric acid is used in the production of detergents, pharmaceuticals and polymers.[63] Glucose can be isomerized to other C_6-sugar configurations (e.g., fructose).[74] Both glucose and fructose can be dehydrated to HMF, a promising biobased furan building block.[62] Similarly, the dehydration of xylose can produce furfural.[64] During the dehydration of sugars to furans, LA can be generated as a side product by the furan rehydration. LA is considered a valuable biobased acid,[65] it can be hydrogenated to γ-valerolactone (GVL), a promising fuel additive and non-toxic solvent.[66] The esterification of LA with (biobased) alcohols can produce alkyl (e.g., methyl, ethyl or butyl) levulinate, used as solvents and (biofuel) additives.[75] HMF is considered as a platform chemical of its own,[62] its oxidation can produce e.g., 2,5-diformylfuran (DFF) and FDCA. DFF is used for the production of phenolic resins, pharmaceuticals, ligands and as a polymer building block for polypinacols and polyvinyls.[76] FDCA has applications in the pharmaceutical industry and is a monomer for polyethylene furanoate (PEF),[67,68] a biobased alternative for polyethylene terephthalate (PET) used in the production of e.g., plastic drinking bottles.[77] Hydrogenolysis of HMF can produce e.g., 2,5-dimethylfuran (DMF),[78] a high energy density liquid fuel or 2,5-(bis)hydroxymethylfurfural (BHMF), a monomer for biobased polyesters.[79] Furfural can be hydrogenated to furfuryl alcohol (monomer for furan resins),[80] 2-methylfuran (potential biofuel),[81] and/or 2-methyltetrahydrofuran (MeTHF), a non-toxic solvent.[82]

In the processing of lignocellulose, the pretreatment procedure and biomass feedstocks have a great influence on lignin composition. For instance, Kraft lignin is formed as a byproduct during sulfuric acid treatment of lignocellulose from Softwood in the pulp and paper industry. This lignin can be converted to energy by combustion, to syngas by gasification, converted by pyrolysis to a pyrolytic bio-oil and (subsequently) hydrotreated to biofuels and aromatics. Novel methods have gained interests recently to obtain more pure forms of lignin that are easier to process.[83] The production of target chemicals from lignin has gained increased research interests in recent years.[84–88] Top value-added chemicals derived from (pyrolytic) lignin are mainly aromatic components (e.g., BTX),[89] phenol and a variety of lignin monomer molecules (e.g., propylphenol, eugenol, syringol, aryl ethers or alkylated methyl aryl ethers).[90] The oxidation of these monomers leads to syringaldehyde (aroma, fragrance), vanillin (used for biopolymers and in the flavor and fragrance industry), and vanillic acid (flavoring agent).[69]

Biomass-derived lipids (e.g., triglycerides and fatty acids from plant oils, waste cooking oils or animal fats) are considered as a promising source for generating valuable products.[4,5] Triglycerides and free fatty acid acids (e.g., oleic, linoleic, palmitic and stearic acids) present in lipids can be converted into fatty acid alkyl esters (biodiesel) by the (trans)esterification with a (biobased) alcohol (e.g., methanol, ethanol or butanol) using inorganic,[33–35] or enzymatic catalysts.[28] Biodiesel is considered as a promising biofuel that can partly replace conventional diesel for transportation purposes. During biodiesel synthesis, glycerol is produced as an abundantly available side product and is therefore a relatively cheap biobased building block for the synthesis of a variety of chemicals.[70,91–94] Glycerol can be converted to 1,2-propanediol (for producing polyester resins, cosmetics, etc. and as a deicing fluid) or 1,3-propanediol (used for e.g., composites, adhesives, laminates, coatings) by hydrogenolysis.[95,96] It can also react with CO (by carbonylation) or CO_2 (by carboxylation) to glycerol carbonate (a solvent and monomer for polyesters, polycarbonates, etc.),[97] or be oxidized to C_3 aldehydes (such as the trioses glyceraldehyde (GLA) and dihydroxyacetone (DHA)) which can be further oxidized to C_3 acids (i.e., hydroxypyruvic acid, glyceric acid and tartronic acid) and/or C_2 acids (i.e., glycolic acid and oxalic acid).[98]

Amino acids derived from proteins may have potential to be used as platform chemicals. Cost-effective methods for the isolation of amino acids from protein biomass sources are still not readily available. However, much research is done and it is expected that feasible methodologies will be developed in the

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near future.[6,7] Glutamic acid, obtained by the hydrolysis of plant and animal proteins, can potentially be used for the production of *N*-methylpyrrolidone, *N*-vinylpyrrolidone, acrylonitrile or succinonitrile, that are currently produced from petroleum-based components.[71] Similarly, *L*-lysine is considered as another protein-based platform chemical,[72] as it can be converted to a number of industrial monomers (amongst others caprolactam, a monomer for nylon).[99]

Wood derivatives, like terpenes (e.g., pinene, limonene, carene, camphene, citral),[8] terpenoids,[9] and rosins, are derived from essential oils present in plants and trees. These are applied as fragrances in perfumery and in (alternative) medicine. Their derivatives (e.g., obtained by hydrogenation, oxidation, epoxidation and isomerization) have received interests in food, cosmetics, pharmaceutical and biotechnology industries.

1.1.3. Catalyst Development for Biomass Conversion

Many biomass conversion routes described above are performed chemocatalytically using inorganic catalysts. Hence, the catalyst development specifically for the transformation of biomass and its derivatives to value-added chemicals and fuels has been researched extensively over the past decades.[14,36–40] Homogeneous acid catalysts are widely used for the hydrolytic decomposition of polysaccharides to monosaccharides and the dehydration of sugars to furans. However, heterogeneous Brønsted and Lewis acid catalysts (e.g., metal-substituted zeolites, surface-modified metal oxides and cation-exchange resins) have also been used for these reactions.[39] Most heterogeneous catalysts can be easily recovered by filtration or centrifugation after reaction without a considerable loss in the catalytic activity. Liquid phase hydrogenations and oxidations are commonly performed with heterogeneous catalysts. Supported noble metal (e.g., Ru, Pd and Pt) catalysts exhibit high hydrogenation activity. Particularly, Ru catalysts seem promising for the hydrogenation of a wide variety of biomass compounds (e.g., levulinic acid, succinic acid, glucose, HMF) as they are capable of performing hydrogenations in the liquid phase under relatively low temperatures. Ru has a higher catalytic activity than other metals (Pd and Pt) at the same loading.[30,100,101] Au catalysts seem promising for the fast and selective oxidation of biomass derivatives. They can effectively convert alcohols to aldehydes and carboxylic acids by liquid phase oxidation using molecular O_2 as the oxidant, making them a promising catalyst to convert (lignocellulosic) biomass feedstocks that often have a high oxygen content.[102,103] Moreover, bimetallic catalysts exhibit promising activities in biomass transformation (e.g., dehydration, hydrogenation and oxidation). The synergistic effect by combining two metals within a single catalyst can result in a significantly improved catalytic performance compared to their monometallic equivalent.[104]

One challenge in designing catalysts for biomass transformation is to selectively remove the abundant functional groups or break specific bonds in the biomass-derived feedstock. For heterogeneous catalysts, the porosity and nanostructure are important features which determine the accessibility of catalytic sites and with that, the reaction mechanism and selectivity. Development in porous and nanoscale catalysts (e.g., microporous zeolites, mesoporous silicas, and nanostructured metals and metal oxides) in this area has thus received much attention lately.[105,106] Another challenge particularly relevant to (industrial scale) biomass transformation, is dealing with impurities in the feedstock, depending on the biomass source and the pretreatment method. The effect of these impurities (e.g., sulfur, minerals and salts) on the catalytic performance has already been studied to some extent,[107] and catalysts with a high tolerance should thus be developed for a selective biomass conversion.

1.2. Reactor Engineering Aspects for Biomass Conversion

Despite the extensive research on conversion methodologies (including chemistry and catalyst development), dedicated reactor engineering concepts for the transformation of biomass (and its derivatives) to value-added chemicals and fuels are not widely examined yet. Many biomass transformations are performed in multiphase (e.g., liquid-liquid or gas-liquid) systems with homogeneous or heterogeneous catalysts, where a proper reactor design is essential for its optimal performance. Greener and more efficient processes need to be developed in order to make the production of chemicals from biomass a feasible alternative to petroleum.[40,108–111] In this respect, continuous flow processing is essential. Flow operation is more desirable than batch operation for the high-throughput production of chemicals as it generates less waste and requires less off-time (necessary for start-up and maintenance). Above that, steady state processing in flow allows a fine product tuning and can decrease deviations in the product properties and composition. In order to obtain value-added products, the crude biomass usually needs to be transformed into a liquid state by deconstructing/depolymerization to make it soluble in water or other solvents. The use of flow reactors for biomass conversion to value-added chemicals has been reviewed recently,[112] as well as specifically for the valorization of glycerol.[113]

Traditional continuous flow reactors used in the chemical industry include typically continuous stirred tank reactors (CSTR), tubular, or catalytic reactors (e.g., heterogeneous packed beds, slurry reactors with solid catalysts dispersed in the liquid phase, and monolithic reactors with a catalytically active inner wall).[114] Many newly developed process intensification methods (e.g., reactive distillation, centrifugal reactors, microreactors, reactors assisted by ultrasonic or microwave irradiation) are rarely used in the industry to this date or at least is not a common practice yet.[115]

1.2.1. Process Intensification for Biomass Conversion

The rise of an alternative biobased chemical industry gives opportunities for the implementation of novel processing methods. Smart processing methodologies within the context

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of process intensification (PI) are required for cost-effective catalytic processes, which can be similarly adapted to biomass conversion processes. As such, several novel continuous flow reactor concepts (e.g., centrifugal contactor separator devices, spinning disk reactors and microreactors) and other PI methods (e.g., the use of alternative forms and sources of energy, supercritical fluids and process integration) have already been applied for the conversion of biomass. Such conversion is often performed by multiphase processes (e.g., liquid-liquid production of biodiesel by transesterification,[116,117] reaction-extraction coupling in a liquid-liquid biphasic system,[118] gas-liquid aerobic oxidation[32] and hydrogenation[30,31]). Thus, these processes have great potential to be significantly improved by intensification methods that provide efficient multiphase contact and/or process coupling.[119]

Biodiesel synthesis, using either homogeneous or heterogeneous (enzymatic) catalysts, has been intensified using continuous centrifugal contactor separator (CCCS) devices,[120–125] where chemical reaction (in the annular zone) is combined with separation (in the inner centrifuge). Due to the strong shear force generated by centrifugal forces in the CCCS, liquid-liquid mixing is enhanced considerably, accelerating reactions with fast kinetics that are limited by mass transfer. Besides this, the recovery of acetic acid from an aqueous pyrolysis oil by reactive extraction has been successfully applied in a CCCS device.[126] Another intensified reactor configuration for multiphase (gas-liquid or liquid-liquid) catalytic biomass transformation is the spinning disc reactor, consisting of a rotating disc around which fluids are fed. By the centrifugal forces high mass/heat transfer rates are obtained.[127] It has been used in biodiesel synthesis.[128,129] Enhanced heat/mass transfer can be also obtained in continuous flow microreactors that consist of reaction channels with diameters on the order of ca. 1 mm or below.[130–132] Due to their versatility and flexibility, microreactors are particularly considered as a promising process intensification tool. Many reactions have potential for intensification in microreactors,[133] and they hold great promises for improving (certain types of) biomass transformations.[134] Typically, microreactors have been used for single liquid phase and biphasic (gas-liquid or liquid-liquid) catalytic transformation of biomass derivatives to valuable products using homogeneous or heterogeneous catalysts (e.g., the (biphasic) synthesis of furans from sugars,[135–144] (aerobic) oxidation,[144–149] and hydrogenation of biomass derivatives[144,150–153]). Furthermore, biodiesel synthesis by the (trans)esterification of triglycerides and fatty acids derived from plant oils, waste cooking oils and animal fats has been extensively studied in microreactors using inorganic[154–156] or enzymatic catalysts.[157]

Microwave-assisted chemical synthesis or separation processes benefit from enhanced temperature regulation and better heat distribution.[158] It has been applied to biomass transformation processes,[159] such as biodiesel synthesis,[160] biomass pyrolysis,[161] and the sugar dehydration to furans (e.g., HMF and furfural).[162] These reactions could be performed more rapidly and selectively under microwave processing. Cavitational effects by ultrasonic-assisted processing can enhance mass transfer rate of multiphase (liquid-liquid) processes, fractionate recalcitrant (lignocellulosic) biomass structures and reduce (heterogeneous) catalyst deactivation. This requires lower reaction temperatures, less solvent and catalyst to be used. It has already been applied in biodiesel synthesis,[163] the production of bioethanol from lignocellulosic biomass,[164] and various other (bio)catalytic transformations of biomass to fuels and chemicals.[165]

Process intensification and reaction engineering concepts for biomass refining using supercritical fluids (e.g., water, CO_2) have been explored as well.[166] These allow the optimized performance of biomass separations (i.e. extraction) and transformations (e.g., the hydrogenation of LA to GVL in supercritical CO_2) by induced phase separation for a more selective product retrieval.[167]

When it comes to process integration, integrated heat exchange designs can significantly reduce the energy consumption of (thermochemical) biomass transformation processes (e.g., gasification to syngas,[168,169] bioethanol production from lignocellulosic biomass).[170] Moreover, catalytic reactive distillation, which combines a liquid phase reaction with immediate distillative separation in one unit, has been applied for biodiesel production,[171] the dehydration of glycerol to acetol,[172] and the acid catalyzed upgrading of pyrolysis oil using a high boiling alcohol.[173]

Apart from a proper reactor design, the optimization of downstream operations is equally important in a biorefinery. As such, separation processes required for product workup (e.g., extraction, distillation) could benefit similarly from the aforementioned process intensification principles. This has already been shown in the supercritical extraction of lignin oxidation products,[174,175] and reactive extraction of lactic acid (e.g., obtained from fermentation broths) using microreactors.[176] Herein the extraction rate was much faster than in conventional operations (resulting in smaller volumes required) by the enhanced mass transfer in microreactors.

Many downstream processes require the product to be retrieved from a solvent. Thus, the choice of solvent for performing a certain biomass transformation should be considered carefully. The use of water as a solvent is generally considered green as it is non-toxic and has a low environmental impact. However, to recover organic products from water may require energy intensive separation procedures (e.g., extraction, stripping or distillation), in view of the process economics and/or the environmental aspects with waste water disposal.[177] In this respect, certain organic solvents that require less energy in distillation (due to their lower boiling point), may be favored in some cases from a reactor engineering point of view. Furthermore, the use of organic solvents can facilitate the processing of certain types of biomass, such as lignin (derivatives) and cellulose, that are poorly soluble in water.[178]

1.2.2. Microreactors

Microreactors have typically capillary- or chip/plate-based configurations, with an internal channel (hydraulic) diameter (d_C) between around 0.1–3 mm.[130–132] Although there are differ-

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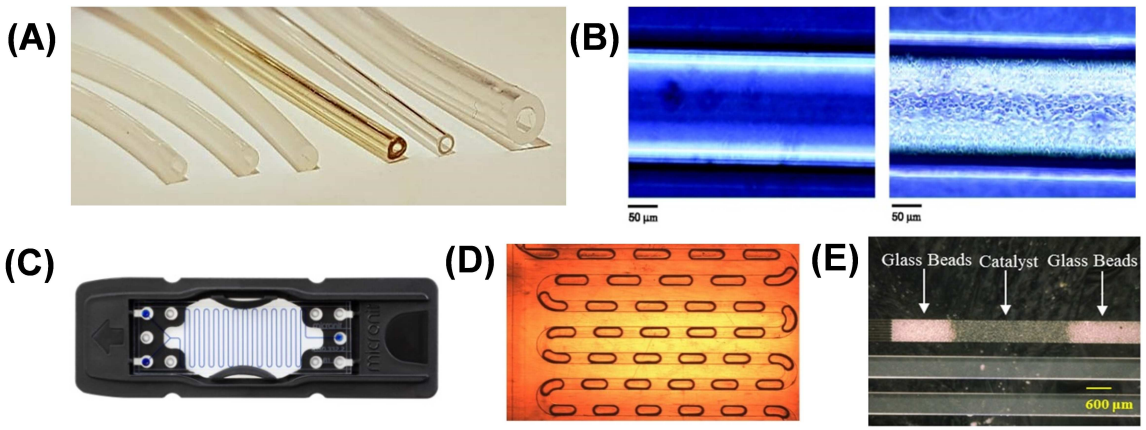

Figure 2. Photos of typical types of microreactors used in the conversion of biomass derivatives. (A) Capillary microreactors of different materials and diameters. From left to right: PTFE (d_c = 1, 0.8 and 0.5 mm), PPSU (d_c = 0.75 mm), glass (d_c = 0.9 mm), PFA (d_c = 1.6 mm, outer diameter is 3.2 mm) capillaries. (B) Fused silica capillary microreactor (d_c = 0.2 mm) for carrying out gas-liquid-solid (hydrogenation) reactions. Empty channel (left) and wall-coated with Pd catalyst (right). Reproduced with permission of ref.[181] Copyright 2004 American Association for the Advancement of Science. (C) Glass chip-based microreactor with an inlet mixer that can be used for biphasic gas-liquid or liquid-liquid reactions (www.micronit.com). (D) A chip-based microreactor made of transparent polyaryl sulfone (PASF). The figure depicts a gas-liquid slug flow profile in the microreactor. Adapted with permission of ref.[182] Copyright 2015 Elsevier. (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. Reproduced with permission of ref.[183] Copyright 2016 Elsevier.

ent definitions regarding at which maximum size a reactor can be still called a microreactor, the exact size range can be relaxed (e.g., expanding to maximum a few millimeters in diameter), provided that the enhanced heat and mass transfer and unique flow characteristics due to miniaturization are still met.[179,180] Microreactors carry out chemical reactions in a continuous flow mode. They are usually made of hydrophilic (e.g., fused silica, glass, polyphenylsulfone (PPSU or Radel®) or stainless steel) or hydrophobic (e.g., polytetrafluoroethylene (PTFE or Teflon®), polyether ether ketone (PEEK), perfluoroalkoxy alkane (PFA)) materials. Typical types of microreactor configurations that have been used in the transformation of biomass derivatives to value-added chemicals and fuels, are depicted in Figure 2.

Due to their small channel size, microreactors have considerably higher surface area to volume ratios as compared to conventional (large scale) reactors. This leads to fundamental advantages such as enhanced mass transfer and excellent temperature uniformity. Multiphase flow in microreactors can achieve interfacial areas on the order of 10,000 m^2/m^3 with an overall volumetric liquid phase mass transfer coefficient (k_La) between 1–10 s^{-1}, considerably higher than in the conventional multiphase reactors.[184] Reactions limited by mass transfer (which is usually the case for highly exothermic reactions or multiphase reactions), can thus be intensified by flow processing in microreactors.[131–133,180,185,186] Given the low amount of reagents handled in a microreactor and a fast heat removal for exothermic reactions, highly explosive reactions (e.g., using O_2 or H_2 under high temperatures and pressures) can be performed without significant safety risks. For reactions in the explosive regime, there is a critical size (quenching distance) below which the flame propagation is suppressed, so that due to the small sizes of microreactors explosions may be prevented.[187]

Microreactors are capable of performing experiments rapidly in terms of reaction time and reactor configuration, making them particularly suitable for studies that require an extensive amount of experimental data (e.g., reaction kinetics or catalyst screening). The precise process control in microreactors allows kinetic data to be obtained more reliably.[188,189] Furthermore, they can be integrated with analytical equipment for on-line and high-throughput data acquisition.[190,191] The small microreactor size renders flow in the laminar regime under which regular (multiphase) flow patterns can be generated (Figure 3). Besides a single phase gas or liquid flow (Figure 3A), multiphase gas-liquid or liquid-liquid slug flow can be generated that features a uniform passage of droplets/bubbles and liquid slug (Figure 3B). The advantage of this well-defined flow is that mass transfer characteristics can be predicted more accurately, making it especially attractive to gain quantitative insights into reactions limited by mass transfer from one phase to the other and for its further optimization.[176,192,193] Slug flow microreactors are thus very promising for carrying out homogeneously catalyzed gas-liquid or liquid-liquid reactions. Also due to the mass transfer enhancement, operations under relatively mild reaction conditions (low gas pressures and temperatures) are possible to obtain a desired reaction rate.

Microreactors open a number of opportunities for heterogeneously catalyzed (multiphase) reactions as well.[179,180,194,195] Solid catalysts can be incorporated by either coating the inner wall of the microchannel with a thin (ca. 1–10 µm) catalytically active layer (Figures 2B, 3C and 3D), or by packing the microchannel with catalyst particles forming a packed bed configuration (Figures 2, 3E and 3F).[180,194,195] Wall-coated microreactors have the advantage that the same (multiphase) flow pattern as in empty ones (e.g., slug flow) can be maintained (Figure 3D). Packed bed microreactors have the advantages of high catalyst loading capacity and the ease of catalyst

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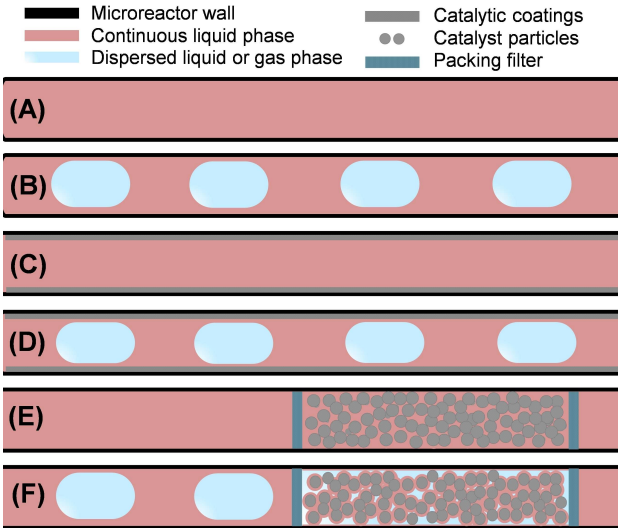

Figure 3. Schematics of typical microreactor configurations and flows therein used for catalytic conversion of biomass derivatives. (A), (C) and (E) represent single-phase liquid flow through an empty microreactor, a microreactor with coated catalysts on the wall and a microreactor with packed catalyst particles, respectively. (B), (D) and (F) represent similar configurations, except with the presence of a gas-liquid or liquid-liquid slug flow, where in (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 (if present).

incorporation (e.g., by gravitational or vacuum filling); commercially produced or homemade catalysts can be directly used and tested for performance and stability. Catalysts should have a particle diameter well below the microchannel diameter in order to form an effective packing structure and a good reactant flow distribution over the bed, and can be retained by filters (Figures 3E and 3F) or inert particles (e.g., glass beads; Figure 2E). However, multiphase flow patterns are altered by the presence of the packed particles and become rather complex. For instance, when introducing an upstream gas-liquid slug flow, liquid-dominated slug flow could be observed in the packed bed, which is characterized by a liquid flow through the particle interstitial voids and most of the catalyst bed, with elongated bubbles moving through the voids (Figure 3F).[180] Moreover, the flow maldistribution might occur (e.g., due to wall-channeling, wettability difference between particles and the microreactor wall),[196] which may adversely affect mass transfer and reaction performance.

1.3. Scope of this Review

Flow processing in microreactors results in significant transport intensification and improved process control as compared to (large-scale) conventional reactors, thus considerably increasing the rate of reactions that are especially limited by mass transfer from one phase to the other and/or heat transfer in the system. This makes them particularly interesting for multiphase (e.g., aerobic oxidation or hydrogenation) reactions that are commonly performed to produce value-added chemicals and fuels from biomass derivatives. Microreactors are easily scaled up by numbering-up, where multiple microreactors are simply stacked in a reactor bundle allowing them to achieve a high-throughput production without need to modify reactor configurations.[197] This makes microreactors attractive for industrial applications, 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 (e.g. due to harvest time/location). Continuous flow microreactors already find their commercial uses in the production of pharmaceuticals and fine chemicals.[198–200] Besides industrial applications, microreactor technology offers numerous advantages for research in the laboratory over conventional batch flasks.[192,201–204] This could contribute in accelerating technological developments in the field of biomass conversion.

Several reviews have focused on specific biomass conversion methodologies (Table 1), on the synthesis, uses and transformations of specific biobased platform chemicals (Table 2), and on reactor engineering or process intensification aspects of biomass transformations (Table 3). The use of continuous flow reactors for the (bio)catalytic conversion of biomass derivatives to value-added chemicals has been partly summarized in the literature.[112,134] However, to the best of the authors' knowledge, a comprehensive and critical review on the latest development in the catalytic conversion of biomass derivatives to value-added chemicals and fuels using continuous flow microreactors has not been published to this date, which will be addressed in this review.

In this review, the potential of microreactors for intensifying different types of biomass transformation is discussed, including the advantages they have on the specific reaction (e.g., better process control for increased selectivity or yield, safer and easier processing). The main focus of this review is on multiphase

Table 3. Selected reviews on process intensification and engineering aspects for biomass conversion.

PI or reactor type	Biomass type and product	Conversion method	Reference
Process intensification (general)	Lignocellulosic biomass	Catalytic	[109]
	Biodiesel synthesis	Catalytic	[116, 117]
Tubular reactors	Lignocellulosic biomass	Catalytic	[112]
	Glycerol conversion	Catalytic	[113]
Microreactors	Lignocellulosic biomass for biomaterials	(Bio)catalytic	[134]
	Biodiesel synthesis	(Bio)catalytic	[154–157]
Microwave-assisted	Bio-waste to chemicals and fuels	Catalytic	[159]
	Biodiesel synthesis	Catalytic	[160]
	Mixed biomass to bio-oil	Thermal (pyrolysis)	[161]
Ultrasonic	Biofuels synthesis	Thermal/catalytic	[165]
Supercritical fluids	Biomass to chemicals, fuels or energy	Thermal/catalytic	[166]
Integrated heat exchange designs	Mixed biomass to syngas	Thermal (gasification)	[168, 169]

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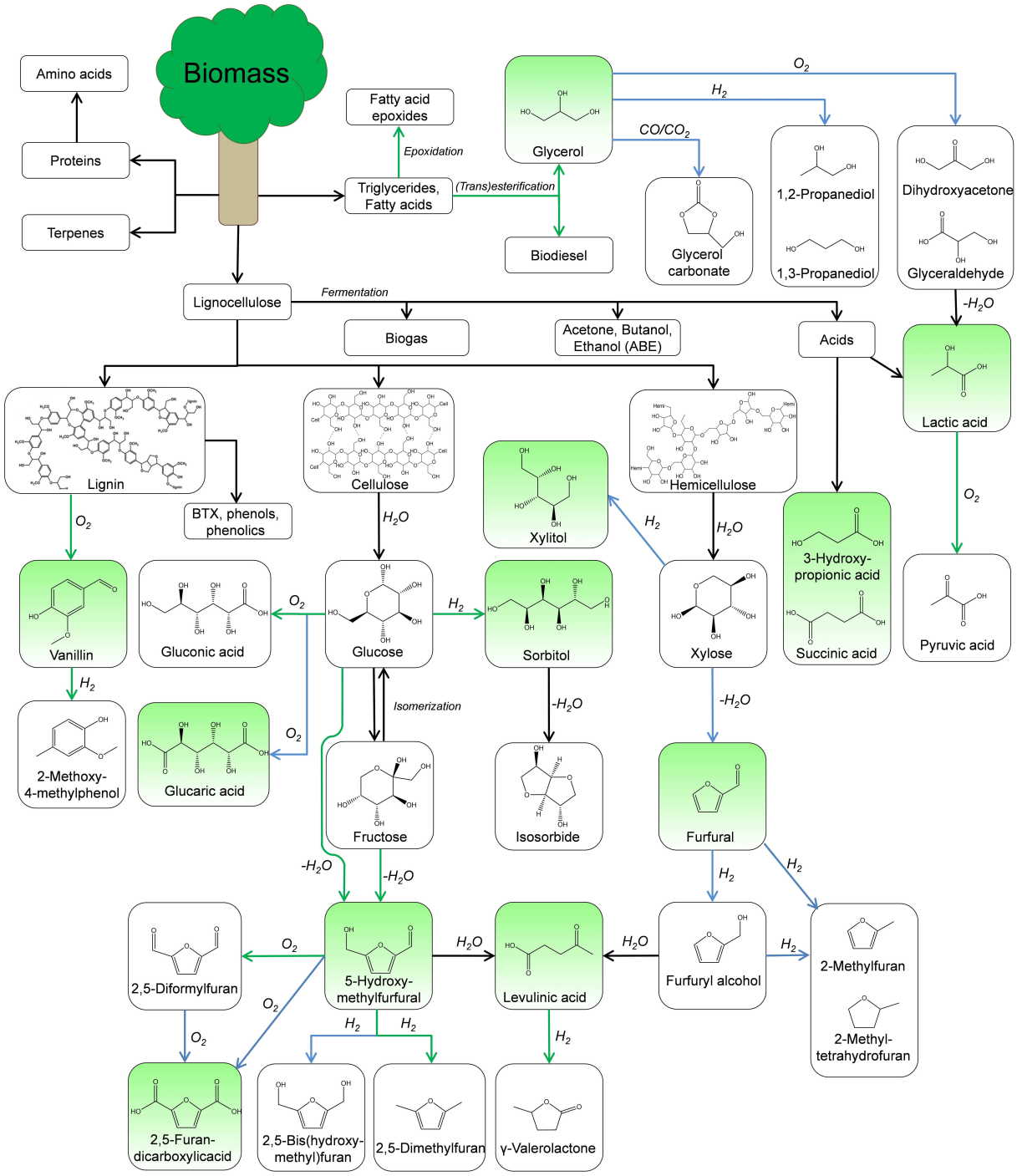

Figure 4. Platform chemicals derived from biomass with selected reaction pathways. Green boxes indicate the most promising biobased platform chemicals. Green lines represent reactions that have been performed in microreactors. Blue lines represent reactions that could potentially be intensified and benefit from microreactor processing.

systems using homogeneous catalysts (i.e. gas-liquid and liquid-liquid systems) and heterogeneous catalysts (i.e. liquid-solid, liquid-liquid-solid and gas-liquid-solid systems). Above that, future prospects for the application of microreactors in this emerging area are discussed. Examples dealt with include the synthesis of furans for sugars, aerobic oxidation and hydrogenation of biomass derivatives, as well as several other reaction types (i.e., esterification, epoxidation, hydrolysis and etherification). A schematic overview on the current state of the art, as well as the future potential on the transformation of biomass derivatives to value-added chemicals and fuels in microreactors, is presented in Figure 4.

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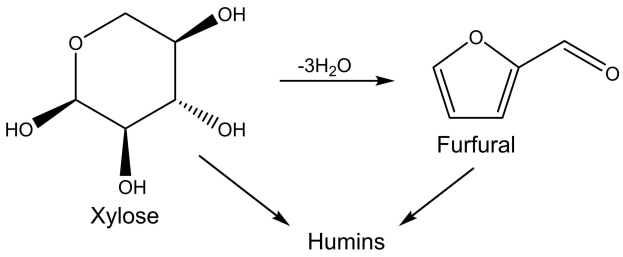
2. Biomass Conversion in Microreactors

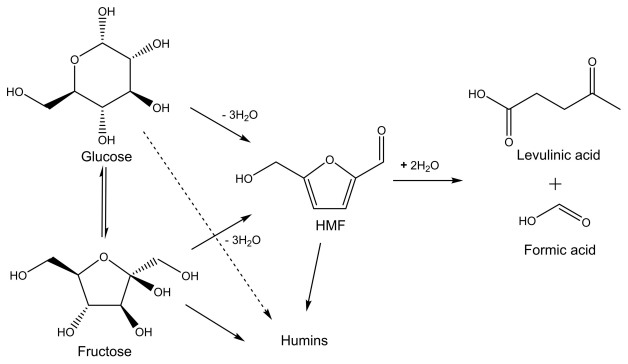
The state of the art is divided based on mainly three different reaction types: i) the catalytic dehydration of sugars to produce furans using homogeneous or heterogeneous catalysts, ii) liquid phase oxidation of biomass derivatives using molecular O_2 or other oxygen sources over homogeneous or heterogeneous catalysts, and iii) liquid phase hydrogenation of biomass derivatives. Finally, several other (e.g., esterification, epoxidation, hydrolysis, etherification) catalytic transformations of biomass derivatives in microreactors are discussed.



Scheme 2. Dehydration of xylose to furfural with the formation of humins as a typical byproduct.

2.1. Synthesis of Furans by Sugar Dehydration

Biobased furans (e.g., HMF and furfural) are considered as important building blocks as they can be converted to a variety of promising biobased chemicals (e.g., FDCA, DMF).[62,64] HMF is synthesized by the dehydration of C_6-sugars, usually fructose. It can also be produced from glucose, either directly or via the isomerization to fructose (Scheme 1). HMF can rehydrate to



Scheme 1. Dehydration of glucose and fructose to HMF with its subsequent rehydration to levulinic acid and formic acid, accompanied by the formation of humins as a typical byproduct.

levulinic acid (LA) and formic acid. Besides that, complex carbohydrate structures are formed by the condensation of sugars with furans resulting in polymers containing furan groups that are poorly soluble in water (i.e. humins).[205] Similarly, the dehydration of C_5-sugars (i.e., xylose) leads to the formation of furfural (Scheme 2).

The dehydration of fructose or xylose is often performed with homogeneous mineral acid catalysts (e.g., HCl, H_2SO_4 and H_3PO_4), and in the case of glucose conversion to HMF also a Lewis acid (e.g., metal chlorides such as $AlCl_3$ or $CrCl_3$) is required.[206–208] The reaction is typically performed at elevated temperatures in a range of 140–250 °C, depending on the sugar type. The dehydration of fructose and xylose has a faster kinetic rate than that of glucose, thus requiring lower temperature operation. Recent development has shown that heterogeneous solid acid catalysts (e.g., ion-exchange resins, immobilized acids, metal oxides) have potential for furan production as they offer better selectivity under relatively mild reaction conditions, although these generally have a lower catalytic activity and thus require longer reaction times.[209] The synthesis of furans by the dehydration of monosaccharides has been widely applied in continuous flow microreactors, together with some work in milli-reactors (with lateral channel dimensions typically on the order of several millimeters, e.g., >3 mm) (Table 4).

2.1.1. Homogeneously Catalyzed HMF Synthesis in a Single Phase System

The first reported HMF synthesis in flow was performed in a single phase homogeneous 0.01 M H_3PO_4 catalyzed aqueous system at high temperatures. 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.[210]

In a glass chip-based microreactor ($d_C = 1.2$ mm), the single phase HCl-catalyzed dehydration of fructose was performed in water (Figure 3A; Table 4, entry 1).[135] The microreactor contained passive mixing geometries along the whole channel to ensure a close to uniform residence time for the desired product yield. The microreactor was capable of handling viscous (50 wt%) fructose solutions and allowed to quickly identify the optimal processing conditions (185 °C and 17 bar) by flow experiments, which resulted in 75% selectivity and 54% yield towards HMF at 71% fructose conversion after 1 min. In a small-scale batch reactor it took 3 min to obtain 50% fructose conversion and 51% HMF yield at 180 °C.[118] The relatively high HMF yield and selectivity obtained in the microreactor was attributed to intensified mass and heat transfer that aided in reducing byproduct formation.

In this flow mode, a direct contact of the reactive phase with the microreactor wall could lead to deposition of insoluble humins, potentially causing reactor clogging. Also the presence of a highly acidic reaction mixture could lead to corrosion of the microreactor.[210] Furthermore, an efficient contact between reactants and catalysts is important since homogeneous liquid phase reactions operated in a single phase laminar flow often result in relatively slow diffusive mixing and a broad residence time distribution that could have a negative influence on the reaction performance.

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Table 4. Dehydration of sugars for the production of furans in continuous flow (micro)reactors.

Entry	System[a]	Substrate	Product	Catalyst	Reactor[b]	Reaction conditions[c]	Results and advantages of flow operation	Reference
1	L	Fructose	HMF	HCl	Glass chip (d_C = 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	[135]
2	L–L	Fructose	HMF	HCl	Glass chip (d_C = 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	[135]
3	L–L	Fructose	HMF	HCl	PEEK capillary (d_C = 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	[136,137]
4	L–L	Fructose	HMF	HCl	PEEK capillary (d_C = 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	[138]
5	L–L	Fructose	HMF	H_2SO_4	PFA capillary (d_C = 1 mm, L = 7.6 m), assisted by microwave heating	Aqueous phase: 0.05 M H_2SO_4, 100 g/L fructose and 120 g/L gluconic acid in water; Organic phase: 2-methyltetrahydrofuran; Slug flow operation, aq:org 1:4; 150 °C, 10 bar	85–89% HMF yield obtained in 10 min	[139]
6	L–L	Fructose and glucose	HMF	H_3PO_4	Stainless steel capillary (d_C = 1 mm, L = 9 m)	Aqueous phase: 2.3% H_3PO_4 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	[140]
7	L–L	Fructose and sucrose	CMF or HMF	HCl	PFA capillary (d_C = 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)	[141]
8	L–L	Fructose, glucose, sucrose and HFCS	CMF	HCl	PFA capillary (d_C = 1 mm, L = 12.7 m)	Aqueous phase: 32–37% HCl and 100 g/L substrate in water; Organic phase: toluene, DCM or DCE; No flow pattern given, aq:org 3:2–2:3; 100 °C, 10 bar	74% CMF yield from fructose (DCE as extraction solvent) in 1 min; 34% CMF yield from sucrose and 66.7% yield from HFCS (DCM as extraction solvent) in 1.5 min	[142]
9	L–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 contin-	93% yield and 93% selectivity of HMF in 4 min; Nearly 100% HMF extraction efficiency obtained by the enhanced mass transfer from small aqueous droplets	[216]

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Table 4. continued

Entry	System[a]	Substrate	Product	Catalyst	Reactor[b]	Reaction conditions[c]	Results and advantages of flow operation	Reference
						uous organic phase, aq:org 1:2; 180 °C, 30 bar		
10	L–S	Fructose	HMF	Immobilized H_2SO_4 on 3-MPTMS	Wall-coated fused silica capillary (d_C = 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	[144]
11	L–S	Fructose	HMF	Amberlyst-15	Packed bed (d_C = 1.65 mm, L_{bed} = 0.3 m, d_p = 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	[143]
12	L–S	Fructose	HMF (derivatives) and EL	Amberlyst-15	Packed bed HPLC column (d_C = 4.6 mm, L_{bed} = 0.25 m, d_p = 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	[227]
13	L–S	Fructose	HMF and *i*-PMF	Amberlyst-15	Packed bed glass column (d_C = 10 mm, L_{bed} = 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;	[228]
14	L–S	Fructose	HMF	Lewatit K2420	Packed bed stainless steel reactor (d_C = 9.5 mm, L_{bed} = 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	[229]
15	L–L–S	Xylose	Furfural	Phosphated tantalum oxide	Packed bed zirconium reactor (d_C = 8 mm, L_{bed} = 0.06 m, d_p = 20–40 mesh)	Aqueous phase: 100 g/L xylose in water; Organic phase: 1-butanol; No flow pattern given, aq:org 2:3; 100–220 °C, 20 bar	96% xylose conversion and 59% furfural yield in 60 min ; High catalyst stability over 80 h on stream	[230]
16	L–L–S	Xylose and xylan	Furfural	GaUSY and Amberlyst-36	Packed stainless steel reactor (d_C = 4.6 mm, d_p = 0.18–0.25, 0.25–0.36 or 0.6–0.7 mm)	Aqueous phase: 5% xylose or 2.5% xylan in water; Organic phase: MIBK, toluene or DCE; Slug flow before entering packed bed, aq:org 1:9 or 1:4; 120–140 °C, 25 bar	69% furfural yield from xylan or 72% furfural yield from xylose in 13.6 min at 130 °C in water/MIBK (10/90 vol %); Highest furfural yield reported directly from hemicellulose	[231]
17	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	[235]
18	L–L–S	Different sugars and water-soluble starch	HMF	TiO_2	Packed bed stainless steel reactor (d_C = 10 mm, L_{bed} = 0.15 m, d_p = 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	[236]

[a] L represent a single liquid phase, L–L a biphasic liquid-liquid system, L–S a single phase liquid reaction over solid catalysts and L–L–S a biphasic liquid-liquid system with a solid catalyst, [b] d_C, d_p, L, L_{bed} appeared in the column represent the inner reactor diameter, catalyst particle diameter, reactor length and catalyst bed length, respectively. Entries 1–11 describe microreactor operations and entries 12–18 milli-reactor operations, [c] Aq:org represents the aqueous to organic volumetric flow ratio.

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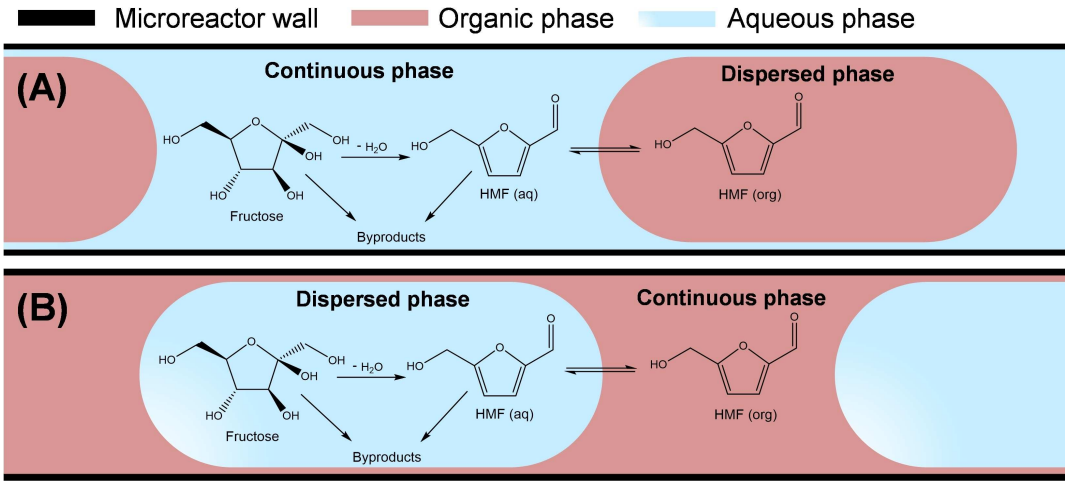

Figure 5. Biphasic slug flow microreactor system for HMF synthesis via the dehydration of sugars (fructose as an example) in an aqueous phase, followed by in-situ extraction to a non-reactive organic phase. In the aqueous phase, byproducts are formed (e.g., levulinic acid, formic acid and humins). (A) Operation in a microreactor of hydrophilic material. (B) Operation in a microreactor of hydrophobic material.

2.1.2. Homogeneously Catalyzed Furan Synthesis in a Biphasic System

Multiphase slug flow operation results in enhanced internal circulation and improves convective mixing in the microreactor.[211–214] Hence, the use of a biphasic aqueous-organic system for homogeneously catalyzed synthesis of furans (e.g., HMF and furfural) has potential for obtaining high furan selectivity and yield. The addition of an organic solvent to an otherwise aqueous reactive phase containing the homogeneous catalyst, functions as a non-reactive extraction phase into which the formed furan is transferred from the aqueous phase, therewith suppressing its rehydration to levulinic acid and polymerization to form humins. With this, 60% HMF yield at 91% fructose conversion could be obtained from the homogeneous acid (0.25 M HCl) catalyzed dehydration of 30 wt% fructose after 2.5–3 min at 180 °C in a biphasic aqueous-organic (2:3 volume ratio) batch system.[118] Methyl isobutyl ketone (MIBK) was used here as a promising organic solvent, because of its low cost, low boiling point (facilitating HMF retrieval after the reaction by distillation) and the relatively high solubility of HMF in this solvent.[215]

By operating such a biphasic system in a microreactor under slug flow operation (Figures 2D, 3B and 5), the superior mixing for an efficient reaction in the aqueous phase is ensured and the extraction rate of HMF towards the non-reactive organic phase is accelerated by the enhanced mass transfer inside droplets/slugs and across the interface (due to internal circulation and high interfacial area available), thus reducing the occurrence of side reactions and increasing the yield and selectivity towards HMF. Many works have been done on the use of continuous flow microreactors for the homogeneous synthesis of HMF in a biphasic system (Table 4, entries 2–9).[135–142,216]

A glass chip-based microreactor was used for the biphasic synthesis of HMF by dehydration of fructose using a mixture of MIBK and 2-butanol as the organic solvent (70/30 wt%) and HCl as the catalyst in the aqueous phase (Table 4, entry 2).[135] The enhanced liquid-liquid mass transfer in the microreactor allowed a fast removal of HMF from the aqueous reactive phase, preventing the formation of byproducts even more than in batch. After 1 min at 185 °C the biphasic microreactor provided higher HMF yield (85%) and selectivity (82%) than after 1 min in single phase operation (being 54% and 75%, respectively). Another potential benefit of performing biphasic HMF synthesis in a microreactor is the prevention of humin deposition on the microreactor wall when the reaction takes place in the droplet. Which phase is dispersed or continuous is determined by the wall wettability properties. With a hydrophilic wall (e.g., glass, stainless steel or fused silica), the aqueous phase is the continuous phase and the organic phase the droplet, giving rise to humin (formed in the aqueous phase) deposition on the wall (Figure 5A). Thus, the configuration described above (Table 4, entry 2) is not preferred and it is more favorable to use hydrophobic microreactor materials (e.g., PFA, PEEK, PTFE). This way, the aqueous droplet is dispersed in a continuous organic phase and does not directly contact the microreactor wall, thus avoiding wall deposition of humins (Figure 5B). Furthermore, by preventing a direct contact of the acid solution with the wall, the occurrence of corrosion is reduced.

Several researchers performed the biphasic dehydration of fructose to HMF using MIBK as the organic solvent in hydrophobic PEEK capillary microreactors (Table 4, entries 3–4),[136–138] which is a preferred wall material to prevent humin deposition on the reactor wall. The increase in the extraction rate under a biphasic slug flow operation gave higher HMF yield (88.5%) and selectivity (91.1%) as compared to those in batch, after 3 min reaction time using 0.025 M HCl as catalyst. From simulation studies, it was concluded that the extraction rate of HMF to the organic phase was enhanced by internal circulation vortexes in the MIBK slugs.[137] Furthermore, relatively high

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organic to aqueous flow ratios resulted in a higher yield and selectivity towards HMF by shifting the distribution equilibrium towards the organic phase.[137,138] However, the need to add high amounts of organic solvent is industrially unfavorable, as it results in a lower space-time yield and a more energy intensive product retrieval. A different approach is to use an organic solvent in which the solubility of HMF is higher.

An alternative green organic solvent is MeTHF. It can be derived from biomass by the hydrogenation of furfural,[82] and due to its low boiling point it can facilitate HMF retrieval by distillation.[217] The H_2SO_4 catalyzed synthesis of HMF from fructose was performed in the presence of gluconic acid in a biphasic water-MeTHF system in a PFA capillary microreactor ($d_C = 1.0$ mm) (Table 4, entry 5).[139] The fructose/gluconic acid substrate mixture was enzymatically synthesized in previous reaction steps by hydrolysis of sucrose to fructose and glucose, after which glucose was selectively oxidized to gluconic acid. HMF yields of 85–89% were obtained in 10 min at 150 °C and 10 bar, the presence of gluconic acid did not affect the dehydration reaction performance. The high HMF yields obtained are partly due to the higher partition coefficient of HMF in the MeTHF-water system (on the order of 2 times higher than in the MIBK-water system).[217] Furthermore, a better temperature distribution was achieved in the microreactor by assisted microwave heating as compared to the oil bath used in a batch setup. This, combined with the enhanced extraction rate, resulted in higher HMF yields in the microreactor than in the batch setup (76%).

Another study used phosphate-buffered saline (PBS) in the aqueous phase (for an accurate pH control to ensure the best catalyst activity) and 2-*sec*-butyl phenol (2BP) as the extractive phase (Table 4, entry 6).[140] Reaction performance was compared between a conventional batch operation and a stainless steel microreactor ($d_C = 1.0$ mm) operated under slug flow. High HMF yields from both fructose (81% in 12 min) and glucose (76% in 47 min) were achieved in the microreactor under 180 °C, whereas it took 5–10 times longer in the batch reactor to reach the same yield under otherwise the same conditions. The higher reaction rate could be mainly due to the better heat transfer in the microreactor versus the slow heating rate in batch. The heating time, which took approximately 5 min in the batch reactor to reach the reaction temperature, was included in the reaction time. Even though the direct glucose dehydration is kinetically much slower than for fructose, still considerable HMF yields could be obtained at a sufficiently long residence time in the microreactor. This is because glucose tends to react more easily with HMF than fructose to form humins, making the dehydration of glucose even more attractive in a microreactor as the fast extractive removal of HMF reduces byproduct formation. Also, HMF is highly soluble in 2BP which further contributed to a reduction of byproduct formation.[218]

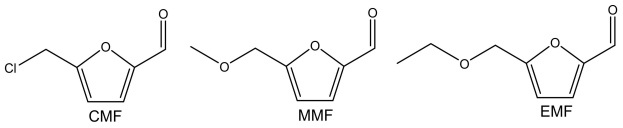

Figure 6. Chemical structures of alternative furans that can be obtained by the dehydration of sugars: 5-chloromethylfurfural (CMF), 5-methoxymethylfurfural (MMF) and 5-ethoxymethylfurfural (EMF).

To further suppress the byproduct formation during the synthesis of HMF under acidic conditions, fructose could be alternatively converted to 5-chloromethylfurfural (CMF) (Figure 6). CMF is more stable in acidic media than HMF, thus less likely undergoes rehydration facilitating its isolation.[219] CMF can be hydrolyzed to HMF or used as a platform chemical directly, as it can produce the same products as HMF (e.g., FDCA by oxidation, DMF by hydrogenation, etc.).

The biphasic synthesis of CMF has been performed in PFA capillary microreactors ($d_C = 1.0$ mm) operated under slug flow, using dichloromethane (DCM) or 1,2-dichloroethane (DCE) as the extracting organic solvent (Table 4, entries 7–8).[141,142] The non-corrosive microreactor material allowed the use of highly concentrated acid solutions. High CMF yields were obtained from fructose after 1 min (61% at 100 °C in the water-DCM system) and from sucrose after 15 min reaction time (74% at 130 °C in the water-DCE system). The reaction towards CMF proceeded much faster as compared to the synthesis of HMF, probably because a highly acidic (37% HCl) reaction medium was used (Table 4, entry 7).[141] The dehydration of fructose resulted in higher CMF yields when using DCE (74%) as the organic solvent compared to toluene (60%) and MIBK (47%) after 1 min reaction time at 100 °C and 10 bar (Table 4, entry 8).[142] This was most likely due to the higher partition coefficient of CMF in DCE, which resulted in more extraction of CMF from the aqueous phase and thus less byproduct formation. Furthermore, the synthesis of CMF was performed from sucrose and high fructose corn syrup (HFCS) as a commercially available fructose feedstock, produced by the enzymatic depolymerization of corn starch.[142] CMF yield of 34% could be obtained from sucrose and 66.7% from HFCS after 1.5 min using DCM as the extractive solvent at 100 °C. The large difference in yield here is because sucrose as a dimer consists of one glucose and one fructose moiety, and the majority of the less reactive glucose remained unreacted.

With the use of microreactors operated under slug flow, high HMF yields can be obtained in biphasic aqueous-organic systems without the need of unattractive solvents (e.g., DMSO that has a high boiling point) as used in the selective HMF production in single phase. Although the extraction rate is increased in the microreactor, it does not affect the equilibrium concentration of HMF over the two phases (determined by its partition coefficient). Once a considerable amount of HMF is formed (e.g., at the late stage of the reaction), the rehydration of HMF to levulinic acid will occur faster than the production of HMF, which may result in a back extraction of HMF from the organic to aqueous phase and a corresponding decrease in the HMF yield and selectivity. An approach to limit the back extraction of HMF is by performing the biphasic dehydration in a membrane dispersion microreactor (Figure 7; Table 4, entry 9).[216] Using this type of microreactor, the aqueous phase of fructose saturated with HCl catalyst was dispersed in the non-reactive organic (MIBK) phase through a stainless steel

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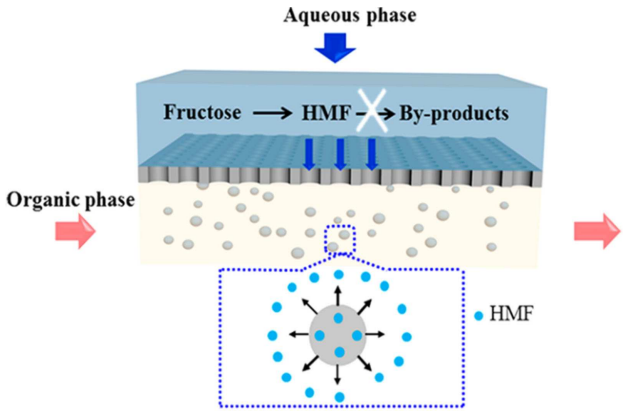

Figure 7. Graphical presentation of the synthesis of HMF by the dehydration of fructose in an aqueous phase, followed by its rapid extraction to an organic phase through tiny droplets in dripping flow generated by a membrane dispersion microreactor. Reproduced with permission of ref.[216] Copyright 2018 ACS Publications.

sintering membrane (3×1×0.6 mm) with tiny (5 μm) pores, placed between a mixing chamber and a cross-flow channel (10×1×0.6 mm). Very small aqueous droplets were generated by the membrane that dripped into the continuous organic phase in the mixing chamber. This, along with the high organic to aqueous volumetric ratio used, led to an extraction efficiency of nearly 100%.[220] A high HMF yield and selectivity (both 93%) was achieved after 4 min at 180 °C and 30 bar.

In short, biphasic microreactor systems are capable of producing HMF selectively in high yields under continuous flow operation (Table 4, entries 2–9). Although the literature has also shown that a good performance could be achieved in batch reactors, e.g., still 91% fructose conversion and 60% HMF yield could be obtained in 2.5–3 min,[118] it should be noted that these batch experiments were performed in lab-scale setups (reactor volume on the order of 10 mL). For scale up to industrial or pilot scale, batch operation tends to suffer from long heating times and poor mass and heat transfer that will negatively affect the HMF yield. Whereas in microreactors, scale-up does not negatively affect reaction conditions as long as the effective (e.g., slug) flow patterns are maintained across different channels by a proper multiphase flow distribution.[221–223]

2.1.3. Heterogeneously Catalyzed Furan Synthesis

Heterogeneous catalysts have several advantages over homogeneous catalysts for the synthesis of furans from sugars. It allows for more sustainable processing as the solid catalyst can be easily recycled and reused (e.g., in a packed bed reactor configuration), so no additional (energy-intensive) separation steps would be required for retrieval of the catalysts from the product stream. Furthermore, there is no equipment corrosion as is the case with homogeneous acid catalysts. Specifically for the sugar dehydration, an advantage is that the solid catalyst properties can be adjusted to the desired reaction performance. The conversion of glucose to HMF, for instance, requires Lewis acidity for the isomerization of glucose to fructose and Brønsted acidity for the subsequent fructose dehydration to HMF. Bifunctional heterogeneous catalysts may give design opportunities for increased furan selectivity, e.g., by a fine and facile tuning of Lewis/Brønsted acid ratio on the catalyst surface and choice of catalysts (including the support) to facilitate the transport of reactant and the formed furan.[224,225]

Only few researchers described the heterogeneously catalyzed synthesis of furans in microreactors (Table 4, entries 10–11).[143,144] A fused silica capillary microreactor, coated with an immobilized H_2SO_4 catalyst, was utilized for catalyzing the single liquid phase synthesis of HMF from fructose in DMSO (Figure 3C; Table 4, entry 10).[144] The coating was applied by modifying the inner surface of the capillary (d_C = 0.15 mm) with 3-mercaptopropyltrimethoxysilane (3-MPTMS) and subsequently oxidizing it with hydrogen peroxide to form H_2SO_4. The fructose conversion and HMF yield (both up to 99%) could be achieved after 6 min at 150 °C, showing a much higher efficiency in the microreactor than in a conventional batch process (where it took 2 h to reach the same conversion with a lower selectivity). The high reaction rates in the microreactor were mainly attributed to the efficient mixing and isothermal conditions, plus the high catalytic surface area per reactor volume.

A packed bed microreactor (d_C = 1.65 mm) was used for the single phase dehydration of fructose to HMF in a mixture of DMSO and 1,4-dioxane over a solid Amberlyst-15 catalyst (Figure 3E; Table 4, entry 11).[143] Amberlysts as heterogeneous catalysts are known for their good activity in dehydration reactions (e.g., fructose to HMF and xylose to furfural).[226] In the microreactor, both internal and external mass transfer limitations could be eliminated by increasing the liquid velocity and decreasing the catalyst particle size (therewith increasing the catalyst surface area per reactor volume). An HMF yield of 92% could be obtained after 3 min at relatively mild conditions (110 °C and 1 bar). Furthermore, the catalyst showed high stability without a significant activity loss after 96 h operation time. Compared with a batch slurry reactor operated under similar reaction conditions, the space-time yield (based on the solvent volume) in the microreactor was 75 times higher.

Several researches focused on the heterogeneously catalyzed dehydration of fructose to HMF (derivatives) in single phase operation (Table 4, entries 12–14),[227–229] or xylose to furfural in biphasic flow (Table 4, entries 15–16)[230,231] using milli-scale packed bed reactors (d_C = 4–10 mm). These milli-reactors could be easily transferred into microreactor configurations and thus give valuable insights in the potential of the latter for the heterogeneous synthesis of furans from sugars. In a packed bed HPLC column (d_C = 4.6 mm) the dehydration of fructose to HMF was performed in the presence of formic acid in ethanol using an Amberlyst-15 catalyst (Table 4, entry 12).[227] In 41.5 min at 110 °C and 1 bar, 89% of fructose was converted to HMF derivatives (mainly EMF) and ethyl levulinate (EL), a value-added chemical used in the fragrance and flavoring industry or as a (biodiesel) fuel diluent.[232,233] No HMF condensation products (i.e. humins) were found. The same

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Amberlyst-15 catalyst was used for the dehydration of fructose to HMF in a packed bed glass column ($d_C = 10$ mm) in a mixture of isopropanol (*i*-PrOH) and DMSO (Table 4, entry 13).[228] Fructose was fully converted to HMF (at 95% yield) and isopropoxymethylfurfural (*i*-PMF) (at 5% yield) under 120 °C and 5 bar after 11.2 min reaction time without humin formation. In an alternative single phase system of water in hexafluoroisopropanol (HFIP), the dehydration of fructose to HMF was executed using a stainless steel packed bed reactor ($d_C = 9.5$ mm) with Lewatit K2420 (an acidic ion exchanger consisting of sulfonic acid on cross-linked polystyrene) as catalyst (Table 4, entry 14).[229] In 20 min residence time, a full fructose conversion with 76% HMF yield was obtained at 100 °C and 20 bar. HFIP is a low boiling point solvent and hence facilitates the distillative retrieval of HMF after its production.[234] The synthesis of furfural from xylose has been performed in a biphasic water-butanol packed bed milli-reactor made of zirconium ($d_C = 8$ mm) (Table 4, entry 15).[230] The reaction was catalyzed over water-tolerant H_3PO_4 modified hydrated tantalum oxide catalysts. Such modification was done to increase the acid density of the catalyst and consequently its reactivity. In this reactor, a 59% furfural yield with a 96% xylose conversion was obtained under the optimized conditions (180 °C and 20 bar) after 60 min, versus a 48% furfural yield after 3 h at 160 °C in a batch autoclave. The higher performance in the flow reactor was likely due to the higher extraction efficiency by an enhanced liquid-liquid mass transfer. No catalyst deactivation was observed over 80 h operation in flow, indicating a high catalyst stability.

Besides the dehydration of monosaccharides (e.g., fructose, glucose and xylose), the direct conversion of polysaccharides in solution (e.g., hemicellulose, starch or pretreated cellulose) to furans has been performed in milli-scale packed bed reactors (Table 4, entries 16–18).[231,235,236] The conversion of xylan (hemicellulose from beech wood) to furfural was performed in a biphasic aqueous-organic system under slug flow operation before entering the stainless steel packed bed milli-reactor ($d_C = 4.6$ mm) (Figure 3F; Table 4, entry 16).[231] MIBK, toluene or DCE was used as the organic solvent. The reaction was catalyzed by a physical mixture of a Lewis acid gallium containing USY zeolite for the isomerization of xylose to xylulose and a Brønsted acid ion-exchanged resin (Amberlyst-36) for hemicellulose hydrolysis and xylulose dehydration to furfural. The large liquid-liquid interfacial area generated in the reactor resulted in a fast extraction of furfural to the organic phase, minimizing the formation of humins. The biphasic aqueous-organic system in the microreactor not only allowed process intensification, but also resulted in an increased product selectivity by promoting catalytic performance. Contact between the solid GaUSY catalyst and water was diminished by the presence of the continuous organic phase, which suppressed metal leaching to the aqueous phase and allowed for a stable operation of at least 24 h on stream. Under the optimal conditions (130 °C and 25 bar), a 69% furfural yield was obtained from xylan after 13.6 min in the case of a water/MIBK (10/90 vol%) biphasic system. At the same reaction conditions using xylose as the substrate, a 72% furfural yield was obtained, showing that xylan could be converted to furfural with almost the same efficiency. Besides, this is the highest reported yield in the literature for hemicellulose processing over a heterogeneous catalytic system. The synthesis of HMF from water-soluble cellulose-based oligomers in a biphasic system with MIBK/N-methyl-2-pyrrolidone (NMP) as the organic solvent mixture (75/25 vol%) was performed in a U-shaped stainless steel packed bed milli-reactor (outer diameter: 6.35 mm) with phosphated TiO_2 nanoparticles as the catalyst (Table 4, entry 17).[235] The oligomers were produced by acid impregnation of microcrystalline (solid) cellulose during ball milling.[237] From these oligomers a 53% HMF yield was obtained in 3.2 min at 220 °C and 60 bar. The presence of NMP in the reaction mixture enhanced the catalytic performance and suppressed the formation of humins. The phosphated TiO_2 catalyst could be recycled for four runs without a loss of catalytic activity. In a stainless steel milli-reactor ($d_C = 10$ mm), HMF was synthesized from a variety of carbohydrate feedstocks (i.e., fructose, glucose, sucrose, corn syrup, honey and water-soluble starch) (Table 4, entry 18).[236] The reactor was packed with TiO_2 catalyst particles ($d_p = 80$ μm) and MIBK or *n*-butanol was used as the organic solvent. TiO_2 catalysts allowed relatively fast synthesis of HMF from glucose (29% HMF yield in 2 min under 180 °C and 34 bar). Furthermore, it was possible to convert water-soluble starch directly in flow to HMF (15% HMF yield in 2 min under 180 °C and 69 bar). Due to its chemical and thermal stability, the catalyst can be regenerated easily by combustion (i.e. in the case of char formation), allowing it to be reused almost indefinitely.

It is noted that the use of a biphasic aqueous-organic system in the heterogeneously catalyzed furan synthesis could prevent blockages of catalysts' active sites by the formation of solid byproducts (e.g., humins). By regular flushing with the organic solvent, humins deposited on the catalyst surface can be removed effectively, preventing catalyst deactivation.[238]

2.1.4. Opportunities

Continuous flow microreactors offer distinct advantages for the synthesis of furans from sugars. The high surface area to volume ratio achieved in microreactors increases heat and mass transfer rates, thus improving the sugar conversion, the furan selectivity and yield in a biphasic system. Microreactors have shown to be able to produce HMF and CMF from C_6 sugars (i.e. fructose and glucose) and disaccharides (sucrose) with high yield and selectivity. The use of alternative C_5 sugars (e.g., xylose) and polysaccharides (e.g., xylan, water-soluble starch and cello-oligomers) for the production of furfural and/or HMF has already been shown in packed bed milli-reactors and the obvious opportunities lie ahead for further intensification in microreactors. However, issues in the solubility of complex polysaccharides in common solvents (e.g., water) may arise and these sugars need to be pretreated (e.g., by acid impregnation) in order to be processed in a liquid phase in flow. A possible way of processing these poorly soluble components in microreactors is by the use of ionic liquids as solvent.[239,240] Ionic liquids are capable of dissolving biobased chemicals with highly

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crystalline structures that are insoluble in water (e.g., cellulose) and have already been widely utilized for the acid catalyzed synthesis of furans from these sugar sources in batch reactors.[241–249]

To assess whether microreactor operation is suitable for HMF (or other furans) production on the pilot or industrial scale other crude sugar sources need to be tested in order to make sure that microreactors are capable of dealing with impurities in the feedstock. In most studies dealing with HMF synthesis in microreactors highly purified sugar feedstocks were used, which is not or less economically feasible for industrial applications. Organic impurities in the sugar feedstock (e.g., lignin and epidermal tissues) that inhibit conversion of polysaccharides, can be effectively removed by pretreating with an alkali or oxidant.[37,250] Inorganic impurities (e.g., Si, Ca and Na), however, cannot be completely removed by pretreatment as they are incorporated in the lignocellulosic framework. The effect of these impurities in crude sugar feedstocks on the heterogeneous catalyst performance should thus be thoroughly investigated in order to make solid conclusions on the applicability of these catalysts in the industry.[107] Similarly, for homogeneously catalyzed furan synthesis, the presence of impurities may complicate catalyst recycling. Furthermore, some (insoluble) impurities are always present in biomass (e.g., dust and sand) depending on the harvest time/location, fertilization and pretreatment method.[251] Solids already present in the biomass feedstock (dust, dirt, salts and organics) or formed during the reaction process (humins), might cause clogging when interacting with the microreactor wall. This may be overcome by using a biphasic system in which the aqueous phase containing the insoluble solid particles is dispersed in a continuous organic phase (Figure 5B).

Many alternative solvents, catalysts and wider process windows (temperature, pressure) can be utilized in microreactors. The dehydration of sugars under elevated temperatures significantly enhances the kinetic rate of furan synthesis, requiring lower residence times and less catalyst amounts. However, when operating this in conventional large scale (batch) reactors, the production of unwanted side products is also accelerated. By coupling the enhanced extraction in microreactors with the enhanced reaction rates under elevated temperatures, the furan selectivity or yield may be increased. In this aspect, kinetics under a wide range of conditions need to be known before process optimization in microreactors is executed.

Alternative homogeneous catalysts that are not strongly acidic might have a potential for the synthesis of furans in microreactors. Lewis acid (e.g., different metal salts, $AlCl_3$, $CrCl_3$, $ZnCl_3$) catalyzed synthesis of HMF can be performed at a relatively low temperature (130 °C).[252] The combination of Lewis and Brønsted acids as homogeneous catalyst has already shown potential for the synthesis of HMF by a direct conversion of glucose-like sugars in batch reactors,[206–208,252–254] and may benefit from the enhanced heat and mass transfer in microreactors. H_3BO_3 (combined with NaCl) is an alternative homogeneous catalyst for the synthesis of HMF. H_3BO_3 is less toxic and less corrosive than commonly used mineral acids (e.g., HCl and H_2SO_4). However, relatively low reaction rates (40–50% HMF yield in 45 min at 150 °C) were obtained with this catalyst in biphasic batch reactors. So the incentive of using a microreactor with this catalyst for biphasic production of HMF might be questionable since an enhancement of the extraction rate would probably contribute less significantly to increased HMF yields.[255]

When choosing a suitable (organic) solvent for the synthesis of furans, partition coefficient, cost, environmental friendliness and the ease of product retrieval need to be evaluated.[217] Recent researches showed the potential of using biomass derivatives as the organic solvent (e.g., GVL).[256] The use of alcoholic solvents (e.g., methanol or ethanol) for the synthesis of HMF ethers (e.g., MMF or EMF; Figure 6) seems promising as they are cheap, potentially biobased and have a low boiling point, facilitating furan retrieval by distillation. Furthermore, the formation of humins is considerably lower when using alcoholic solvents as HMF ethers are less prone to the humin forming condensation reaction with sugars, resulting in a higher selectivity towards the desired furans.[227,228] Above that, HMF ethers have a better storage stability than HMF, which can be advantageous as compared to using HMF as a substrate in the industrial production towards HMF derivatives (e.g., FDCA).[77,257]

2.2. Liquid Phase Oxidation of Biomass Derivatives

Biomass feedstocks (e.g., lignin and polysaccharides) and derivatives (e.g., monosaccharides, HMF and glycerol) can be oxidized to produce value-added alcohols, aldehydes and (carboxylic) acids that can be used for the production of resins, pharmaceuticals, food additives or as monomeric building blocks for the production of biobased polymers (Figure 4).[32] Also oxidative treatment can be performed to deconstruct complex biomass structures (i.e. that of lignin or polysaccharides), making them easier to process. Most commonly, hydrogen peroxide (H_2O_2) or molecular O_2 is used as the oxygen source,[258] together with ozone (O_3) by ozonolysis.[259–261] Biomass oxidation reactions are often performed with inorganic homogeneous (e.g., metal salts) or heterogeneous catalysts (e.g., Au and Ru).

Liquid phase aerobic oxidation reactions, using molecular O_2 as the oxidant (from air or pure O_2), are often limited by mass transfer of O_2 from the gas to the liquid phase. This limitation is partly due to the low oxygen solubility in commonly used solvents and less available gas-liquid interface in conventional oxidation reactors (e.g., bubble columns).[184] Often oxidation reactions are carried out at high pressure conditions to improve mass transfer rate and elevated temperatures to enhance the kinetic rate. The enhanced mass transfer in continuous flow microreactors makes them attractive for carrying out liquid phase oxidation reactions.[262–264] In more detail, enhanced mass transfer of O_2 to the reactive liquid phase can increase the rate of oxidation reactions with fast kinetics (i.e., that tend to be limited by mass transfer). Besides, effective heat transfer in microreactors allows a precise temperature control. Thus, oxidation reactions that are often highly

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exothermic and explosive can be performed without significant safety risks in microreactors (e.g., synthesis with the use of pure O_2 or even under an explosive regime), whereas they tend to pose considerable safety issues in conventional reactors. Furthermore, regular flow patterns (particularly gas-liquid slug flow), combined with improved heat and mass transfer, allows a more precise reaction tuning in microreactors (e.g., in terms of narrowed residence time distribution, uniform reaction temperature, and finely tuned oxygen transport), resulting in an increased selectivity or yield to the desired product. So far, several reports have described the catalytic oxidation of biomass feedstock and its derivatives (e.g., glucose to gluconic acid, HMF to DFF and/or FDCA, lignin to vanillin) in microreactors (Table 5).

2.2.1. Oxidation of Glucose to Gluconic Acid

Gluconic acid is used as an additive in food, pharmaceutical, paper and concrete industries and its production is industrially performed from glucose through a biochemical batch process using microbial biocatalysts.[73] Chemocatalytic production of gluconic acid by oxidation of glucose using solid catalysts is also applied in continuous processes in flow. Heterogeneous Au catalysts have been found effective and stable for the selective liquid phase aerobic oxidation of glucose in CSTRs.[265,266]

Figure 8. Falling film microreactors used for scale-up of enzymatic glucose oxidation to gluconic acid; left: large microreactor with high capacity, right: small microreactor. Reproduced with permission of ref.[145] Copyright 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Microreactors have potential for the aerobic oxidation of glucose as it can significantly increase the reaction rate by the enhancement of oxygen supply.[267] Despite this, to the best of the authors' knowledge, there has been only one publication to this date about the aerobic liquid phase oxidation of glucose in a continuous flow microreactor. The reaction was performed in a falling film microreactor using glucose oxidase as a homogeneous enzymatic catalyst dissolved in the aqueous phase (Table 5, entry 1).[145]

In this reactor system, the reaction took place along three vertical reaction plates (consisting of 16 channels, width × height ($W \times H$) = 1200 × 400 μm; 32 channels, 600 × 200 μm; 64 channels, 300 × 100 μm). In this type of microreactor, a thin liquid film (generated by gravitational force) was in contact with a gas phase, resulting in very high specific surface areas (e.g., 20,000 m^2/m^3),[268] and O_2 saturation of the liquid phase was achieved in 6 s. A liquid-phase volumetric mass transfer coefficient (k_La) on the order of 100 times higher than that of a conventional bubble column could be obtained. By the enhanced mass transfer, the enzyme could be utilized more effectively and the reaction rate was enhanced as compared to batch operation. At 25 °C, 50% glucose conversion was obtained in the microreactor in 25 s, whereas only 27% conversion was reached in a bubble column reactor under similar reaction conditions. Finally, the potential of upscaling the process was shown by using an enlarged plate with a 10-fold increased surface area in which capacities of up to 10 mL min^{-1} (0.1 M glucose) could be processed (Figure 8).

2.2.2. Oxidation of HMF to DFF, FDCA and Other Products

The catalytic oxidation of HMF can produce several value-added biobased chemicals, such as 2,5-furandicarboxylic acid (FDCA), a valuable platform chemical for the production of pharmaceuticals and biobased polymers such as PEF. The formation of FDCA from HMF goes through two intermediate oxidation products: 2,5-diformylfuran (DFF) or 5-hydroxymethylfurancarboxylic acid (HMFCA) depending on the catalyst's preference for alcohol or aldehyde oxidation, and 5-formylfurancarboxylic acid (FFCA) (Scheme 3), which are also valuable chemicals for the production of phenolic resins, pharmaceuticals, ligands or monomers for other biobased plastics.[62]

In the case of using water as solvent for HMF oxidation, the products FFCA and FDCA are poorly soluble, potentially leading to precipitation and possibly clogging in the reactor. In such cases, the synthesis of DFF appears to be more feasible if performed in continuous flow reactors. DFF synthesis is also favorable when using heterogeneous catalysts containing carbon and, to a lesser extent, inorganic catalyst supports which tend to adsorb FFCA and FDCA, therewith blocking catalysts' active sites and reducing the catalytic activity.[269] A continuous flow aerobic HMF oxidation was performed in a packed bed stainless steel milli-reactor (d_C = 7.85 mm; 5% Pt on a variety of inorganic supports as catalyst) in a gas-liquid upflow in the

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Table 5. Catalytic oxidation of biomass derivatives in continuous flow (micro)reactors.

Entry	System[a]	Substrate	Product	Catalyst	Reactor[b]	Reaction conditions	Results and advantages of flow operation	Reference
1	G-L	Glucose	Gluconic acid	Glucose oxidase	Falling film microreactor consisting of 3 vertical plates (16 channels, $W\times H=1200\times400$ μm; 32 channels, 600×200 μm; 64 channels, 300×100 μm)	Liquid phase: 0.1 M glucose and 50–400 U/mL enzyme in phosphate buffer solution, pH = 7; Gas phase: air; 25 °C, 1 bar; Countercurrent flow operation	50% glucose conversion in 25 s vs. 27% conversion in a bubble column reactor; Contact between enzyme solution and O_2 facilitated by large specific interfacial area	[145]
2	G–L–S	HMF	DFF, FDCA	TEMPO on silica	Packed bed PTFE capillary ($d_C=1.65$ mm, $d_p=0.16$–0.24 mm)	Liquid phase: 0.41 M HMF and 5 mol% HNO_3 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	[146]
3	L–S	HMF	HMFCA, FDCA	Nanostructured gold	Wall-coated PET chip ($L\times W\times H=220\times2\times0.15$ 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	[147]
4	G–L–S	HMF	DFF	Fe_3O_4/SiO_2/Mn	Gas permeable PTFE capillary ($d_C=0.61$ mm, $L=0.1$ m, pore size = 110 nm) in wall-coated PTFE capillary ($d_C=1$ 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 wall-coated catalyst for 5 h on stream	[144]
5	G–L–S	Lactic acid	Pyruvic acid	TEMPO on silica	Packed bed PTFE capillary ($d_C=1.65$ mm, $d_p=0.16$–0.24 mm)	Liquid phase: 0.5 M lactic acid and 5 mol% HNO_3 in DCE; Gas phase: O_2; 55 °C, 5 bar; Slug flow before entering the packed bed	98% lactic acid conversion with 98% pyruvic acid selectivity in 15 s	[146]
6	G–L–S	Alkyl lactate	Alkyl pyruvate	$VOCl_3$	Capillary ($d_C=0.5$ or 1.0 mm, $L=0.3$ m)	Liquid phase: 0.2 M alkyl lactate and 0.02 M $VOCl_3$ in acetonitrile; Gas phase: O_2; room temperature, 1 bar; Slug flow operation	30% alkyl pyruvate yield in 2.5 min in microreactor vs. 20 min in batch; Nearly 100% selectivity towards pyruvates	[148]
7	G-L	Softwood Kraft lignin	Vanillin, methyl vanillate	H_2SO_4	Hastelloy capillary ($d_C=1$ mm, $L=2.4$ m)	Liquid phase: 2.5 g/L lignin in methanol/H_2O (80/20 vol %), pH = 1; Gas phase: O_2; 150–250 °C, 32–96 bar; Slug flow operation	40 mg/L vanillin and 10–15 mg/L methyl vanillate produced in 6 min	[149]
8	G–L–S	Glycerol	Glycolic acid, glyceric acid, oxalic acid, tartronic acid, etc.	Au/TiO_2	Packed bed stainless steel reactor ($d_C=4$ mm, $L_{bed}=3$ mm, $d_p=90$–180 μm)	Liquid phase: 0.3 M glycerol and 0.1–0.6 M NaOH in water; Gas phase: O_2; 60 °C, 10 bar;	Selectivity towards oxalic acid and tartronic acid was higher (~15%) than in a batch slurry reactor (<5%);	[272]

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Table 5. continued

Entry	System[a]	Substrate	Product	Catalyst	Reactor[b]	Reaction conditions	Results and advantages of flow operation	Reference
						Upflow, flow pattern not given	Use of small catalyst particles resulted in high pressure drop	

[a] L–S represent a single phase liquid oxidation over a solid catalyst, G–L a biphasic gas-liquid aerobic oxidation (with a homogeneous catalyst) and G–L–S a biphasic gas-liquid aerobic oxidation with a solid catalyst, [b] d_C, d_p, L, W, and H appeared in the column represent the inner reactor diameter, catalyst particle diameter, reactor length, width and height, respectively. Entries 1–7 describe microreactor operations and entry 8 describes a milli-reactor operation.

presence of an aqueous base environment. Under 140 °C and 10 bar O_2, a 100% HMF conversion with ca. 85% FDCA and 15% FFCA yields was obtained in a water/acetic acid (60/40 vol%) solvent at a residence time of 8 min. It was concluded that heterogeneous catalysis of HMF to DFF or FDCA (up to its solubility limit) is technologically feasible.[269] However, it was only possible to successfully convert HMF at very low feed concentrations (<3 wt%) as higher concentrations led to FDCA product precipitation due to its low solubility in water.

A slightly higher inlet concentration of HMF (~5 wt%) was used in its oxidation in a PTFE capillary microreactor (d_C= 1.65 mm) packed with TEMPO on silica as a solid catalyst. O_2 was used as the oxidant and DCE as the liquid solvent with small amounts of HNO_3 as a co-oxidant (Figure 3F; Table 5, entry 2).[146] A gas-liquid slug flow was generated before entering the packed bed. The microreactor processing allowed a flexible synthesis with which the selectivity towards DFF and FDCA could be well tuned. By adjusting the contact time, high yields of DFF (95% in 2 min) or FDCA (~35% in 8 min) could be obtained in the same microreactor system under mild reaction conditions (55 °C and 5 bar O_2). The continuous production of DFF seemed more promising for its superior solubility in DCE as compared to that of FDCA. For contact times higher than 6 min, FDCA (~22% yield in 6 min) starts to crystallize out due to its low solubility in DCE. Thus, the addition of a solvent (mixture) in which FDCA is better soluble is required for its continuous production with higher yields in the microreactor.

The liquid phase oxidation of HMF to HMFCA and FDCA under basic conditions was carried out in a PET chip-based microreactor ($W \times H = 2 \times 0.15$ mm) wall-coated with a nanostructured gold catalyst, using *tert*-butyl hydroperoxide (TBHP) as a homogeneous oxidant in water in the presence of NaOH (Table 5, entry 3).[147] After 50 min in the microreactor, 13.86% HMFCA and 3.76% FDCA yields were obtained under ambient conditions. No FDCA product precipitation issues were mentioned, probably due to the low initial HMF concentration (3 mM) and low product yields (the latter partly caused by the relatively high degree of decomposition (43–56%) of HMF and HMFCA in the presence of the highly reactive TBHP).

A tube-in-tube microreactor was used for the aerobic oxidation of HMF to DFF in DMSO (Figure 9; Table 5, entry 4).[144]

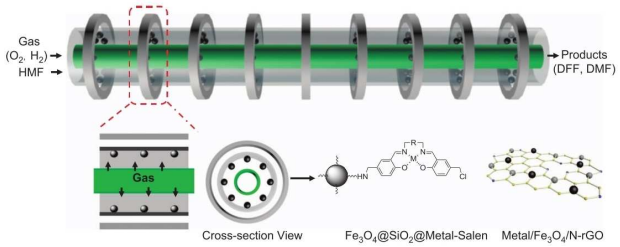
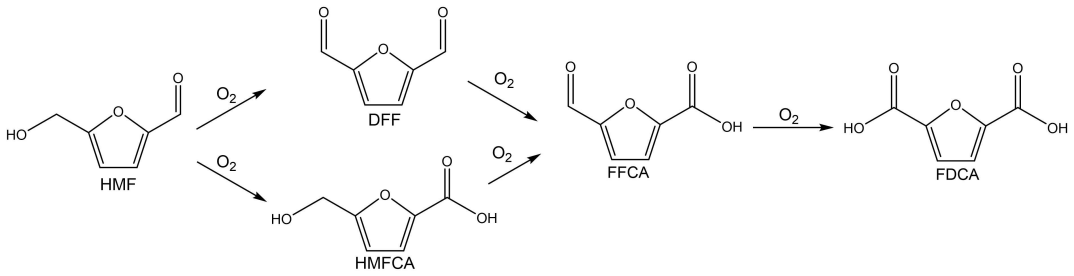


Figure 9. Tube-in-tube microreactor configuration or the solid catalyzed aerobic oxidation of HMF to DFF or hydrogenation of HMF to DMF. A gas permeable PTFE capillary (d_C=0.61 mm) was inserted in a wall-coated PTFE capillary (d_C=1 mm). The gas phase (O_2 or H_2) was fed through the inner capillary and liquid through the outer capillary in co-current flow. Reproduced with permission of ref.[144] Copyright 2015 Springer Nature Publishing AG.

A gas permeable PTFE capillary (d_C=0.61 mm) with narrow pores (110 nm) was inserted in another PTFE capillary (d_C= 1 mm) wall-coated with a magnetic salen-transition metal core-shell catalyst (Fe_3O_4/SiO_2/Mn). The catalyst (immobilized on magnetic nanoparticles) was prepared according to a general



Scheme 3. Oxidation of HMF to FDCA via FFCA and DFF or HMFCA.

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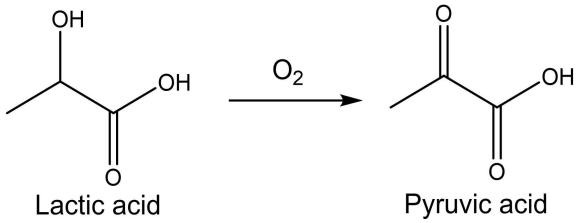
procedure for Mn salen complexes,[270] after which it was fixed at the inner microreactor wall by external magnetic rings. These magnets were placed around the microreactor to fixate the coated catalyst on the microreactor wall and allowed a stable binding up to 5 h on stream without releasing magnetic and catalytic particles into the product stream. Gas molecules in the inner capillary were able to pass through the narrow pores towards the reactive liquid phase in the outer capillary. With this configuration, reaction rates (93% HMF conversion and 84% DFF yield in 60 min) could be significantly increased as compared to conventional bubble column reactors (67% HMF conversion and 42% DFF yield in 16 h) using the same catalyst, due to the enhanced gas-liquid and liquid-solid mass transfer in the microreactor. When coupling the microreactor in series with another upstream microreactor where fructose was converted to HMF (Table 4, entry 10), a direct synthesis of DFF (82% yield) from fructose (92% conversion) in 70 min could be performed in a tandem configuration. In contrast, the enhanced O_2 mass transfer by feeding excessive amounts of oxygen through the inner tube led to the formation of unwanted side products (e.g., over oxidation to CO and CO_2), which resulted in a decreased DFF yield (52% in 60 min). Side reaction occurrence could be suppressed by reducing O_2 transfer through the narrow pores of the permeable PTFE capillary, increasing selectivity towards DFF. This shows the potential of finely tuning gas-liquid mass transfer with gas permeable membranes for enhanced product selectivity/yield.

2.2.3. Oxidation of Lactates to Pyruvates

Lactic acid and its esters (lactates) are biobased chemicals obtained from fermentation and biological processes of biomass. The oxidation of lactic acid can produce pyruvic acid (Scheme 4), a valuable chemical used as an intermediate for the



Scheme 4. Oxidation of lactic acid to pyruvic acid.

production of pharmaceuticals, foods, cosmetics and biobased polymers.[53] An issue in this route is the fast decarboxylation of lactic acid (e.g., to acetaldehyde), thus mild reaction conditions and low amounts of oxidant are required for a selective production of pyruvic acid. By performing the aerobic oxidation of lactic acid in a PTFE capillary microreactor (d_C = 1.65 mm) packed with a TEMPO on silica catalyst, high lactic acid conversion (98%) and selectivity towards pyruvic acid (98%) could be reached in 15 s under 55 °C and 5 bar (Figure 3F; Table 5, entry 5).[146] In the microreactor, the oxygen mass transfer could be regulated accurately by slug flow operation before entering the packed bed, which resulted in a more selective reaction due to the prevention of unwanted side reactions (e.g. decarbonylation).

$VOCl_3$ catalyzed oxidation of different alkyl (i.e. methyl, ethyl, isopropyl, *n*-butyl) lactates to their corresponding pyruvates was conducted in a microreactor (d_C = 0.5 or 1.0 mm).[148] The solid $VOCl_3$ catalyst was mixed as a slurry with the substrate in an acetonitrile solvent. The liquid slurry was mixed with pure O_2 to generate a pseudo gas-liquid slug flow in the microreactor. The pyruvate selectivity was nearly 100% as side reactions were prevented by the enhanced mixing and well-controlled heat/mass transfer in the microreactor (Table 5, entry 6). The increased O_2 mass transfer rate by slug flow processing in the microreactor significantly enhanced the reaction rate as compared to batch operation. At room temperature and atmospheric pressure, it took approximately 2.5 min to achieve 30% pyruvate yield in the microreactor, whereas in a batch reactor it took 20 min to reach the same results under otherwise similar reaction conditions. The reaction rate of this oxidation reaction is dependent on the liquid phase oxygen concentration. The increased O_2 feed towards the liquid phase by the enhanced mass transfer, generated under a gas-liquid slug flow in microreactors, allowed a fast reaction rate under relatively low pressures. This enabled the processing under room temperature, thus reducing energy consumption as compared to the conventional process.

2.2.4. Oxidation of Lignin to Vanillin

The oxidation of lignin can aid in the deconstruction of its complex structure and generate a variety of value-added products such as vanillin (Scheme 5). Vanillin is used in the synthesis of biobased polymers and in the flavor and fragrance industry.[69] However, the mechanism and kinetics of such complex and rigorous oxidation reaction are not widely examined yet. Performing this reaction in a microreactor allows not only to intensify the reaction by enhanced mass transfer, but also to gain mechanistic and kinetic insights thereof thanks to the regular and well-controlled flow conditions. This is particularly important for the selective synthesis of specific oxidation products (among others vanillin), as the over oxidation of the target products to undesired side products can take place. Softwood Kraft lignin, a byproduct obtained from the sulfonate processing of wood chips to pulp for the paper industry, is considered as a promising raw material for the production of aromatic chemicals.[271] The homogeneous H_2SO_4 catalyzed aerobic oxidation of softwood Kraft lignin was performed in a Hastelloy microreactor (d_C = 1 mm) using methanol/water (80/20 vol%) as the solvent (Figure 3B; Table 5, entry 7).[149] The oxidation reaction could be safely operated under acidic (pH = 1) and harsh conditions (150–250 °C and 32–96 bar) in the microreactor. Vanillin and methyl vanillate were produced in relatively high yields in 6 min, as well as other potentially interesting components (e.g., 5-carbomethoxy-vanil-

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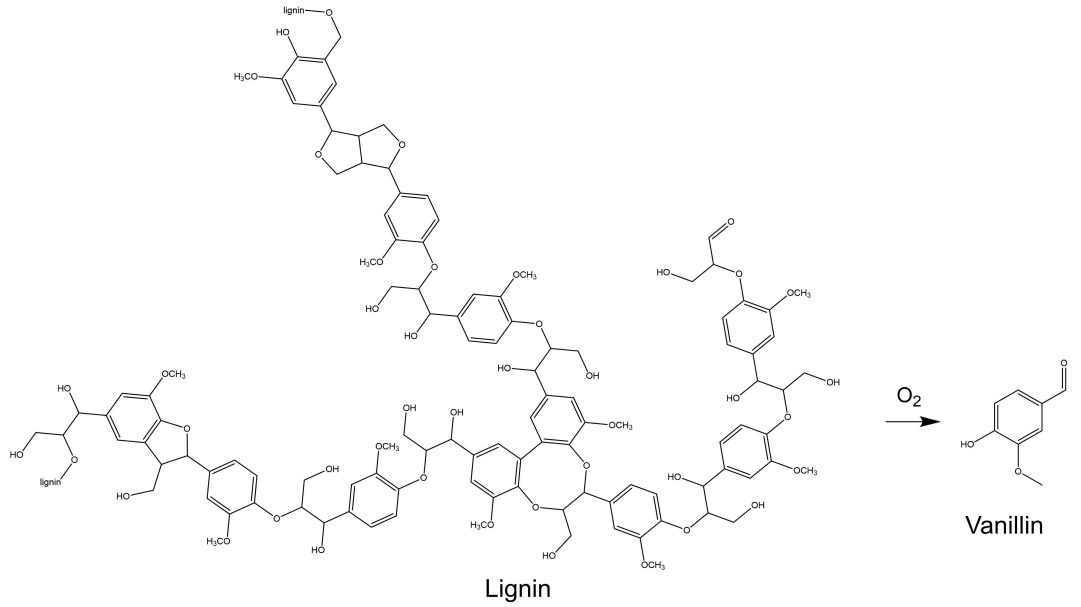
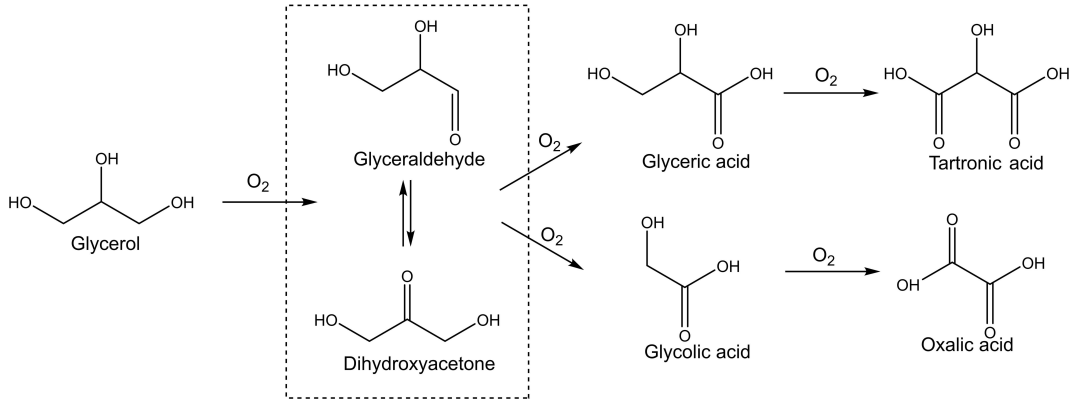


Scheme 5. Oxidation of lignin to vanillin.



Scheme 6. Oxidation of glycerol to C_3 aldehydes (glyceraldehyde and dihydroxyacetone), C_2 acids (glycolic acid and oxalic acid) and C_3 acids (glyceric acid and tartronic acid). Different mechanistic routes for the formation of C_2/C_3 acids have been proposed in the literature and the scheme here is mainly for indicating the most important products observed in the reaction.[98]

lin, methyl 5-carbomethoxy-vannilate, methyl dehydroabietate). Although the reaction rate towards vanillin was not improved in the microreactor as compared to the corresponding batch reactor study, higher vanillin selectivity was obtained. The higher selectivity was most likely due to a better heat transfer in the microreactor, which suppressed the occurrence of lignin degradation reactions that were prevalent in the batch reactor because of the relatively long heating time required therein. From the experimental data in the microreactor, kinetic parameters and activation energies could be derived, which enabled to determine the reaction conditions (250 °C for a few seconds) for a maximum vanillin production. Typically, from a 2.5 g L^{-1} lignin feed, 40 mg L^{-1} vanillin and 10–15 mg L^{-1} methyl vanillate were produced in 6 min.

2.2.5. Oxidation of Glycerol to C_3 Aldehydes and C_2/C_3 Acids

Glycerol, one main byproduct from the production of biodiesel, can be oxidized to produce a variety of C_3 aldehydes and carboxylic acids such as the trioses glyceraldehyde and dihydroxyacetone, which can be further oxidized to C_3 acids (i.e., glyceric acid and tartronic acid) or C_2 acids (i.e., glycolic acid and oxalic acid) (Scheme 6). By performing the heterogeneously catalyzed aerobic oxidation of glycerol in flow,[272–274] high product selectivity could be achieved over a Au/TiO_2 catalyst packed in a milli-reactor ($d_C = 4$ mm) using water as solvent in the presence of base (0.1–0.6 M NaOH) (Table 5, entry 8).[272] The catalyst was prepared by a deposition-precipitation method and subsequently pelletized to bigger particles in order to be incorporated in a packed bed configuration. In this milli-reactor, the selectivity towards secondary oxidation

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products (i.e., oxalic acid and tartronic acid) was higher (~15%) as compared to a batch slurry reactor (<5%) under otherwise similar reaction conditions (60 °C and 10 bar). The gas-solid contact in the milli-reactor was facilitated by the enhanced gas-liquid mass transfer, which resulted in higher O_2 availability at the highly active catalyst surface and thus a more rapid and selective oxidation of glyceric and glycolic acid towards the diacids. However, a significant pressure drop was generated by the small size of the packed catalyst pellets (d_p = 90–180 μm), causing the breakdown of pellets and restricted continuous flow operation to a maximum of 40 h. Thus, it was found that large diameter milli-scale reactors, packed with bigger catalyst particles, were more appropriate to perform this reaction from an industrial point of view despite the slight decrease in mass transfer rate.[273] When it comes to the use of packed bed microreactors for this reaction, pressure drop might be too high especially for the processing of highly concentrated (viscous) glycerol mixtures over packings of small catalyst particle sizes. Hence, alternative configurations (e.g., wall-coated microreactors) could be promising for the continuous flow oxidation of glycerol.

2.2.6. Opportunities

Despite many opportunities for the intensified and selective synthesis of value-added products via the oxidation of biomass derivatives,[32] continuous flow processing in microreactors is still not widely examined yet for such purposes. So far, oxidation of glucose to gluconic acid, HMF to DFF, FFCA and FDCA, lactates to pyruvates and lignin to vanillin have been shown intensified by the enhanced and more controlled heat/mass transfer during flow operation in microreactors, particularly in multiphase gas-liquid flow or in a permeable tube-in-tube microreactor configuration (Table 5).[144–147,149]

The benefits of performing (aerobic) oxidation reactions in microreactors (of non-biomass derivatives) has been reviewed by multiple groups.[262–264] Heterogeneously catalyzed oxidation reactions have been shown to benefit from microreactor operation as compared to larger scale flow reactors. Both wall-coated[275] and packed bed microreactor configurations[183,276,277] have been used for this purpose. Biomass oxidations performed in milli-scale (packed bed) reactors, may benefit similarly in terms of the desired product yield from transport intensification and a precise process control there, as demonstrated in the conversions of HMF to FFCA/FDCA,[269] glycerol to different C_2/C_3 aldehydes and acids,[272–274] glucose to gluconic acid,[278] bio-ethanol to acetic acid,[279] lignin to vanillin,[280] and its derivatives (e.g., vanillyl alcohol to vanillin and piperonyl alcohol to piperonal)[281] (Figure 4). Furthermore, alternative oxidation procedures such as rigorous ozonolysis reactions can be controlled and regulated more effectively in continuous flow microreactors.[282–284] Ozonolysis is a less energy intensive method for the oxidative deconstruction of complex biomass structures (e.g., lignin or polysaccharides) as compared to the catalytic oxidation procedure under elevated temperatures and pressures.[259–261]

The improved safety characteristics in microreactors allow the use of pure O_2 (even under explosive regimes), peroxides or other hazardous reagents, thus the reaction chemistry could be well tuned in a wide range for obtaining the enhanced reaction rate and yields of the target product.[262] The use of molecular O_2 in flow is already performed commercially for the oxidative production of pharmaceutical compounds.[285] Many chemicals derived from biomass oxidation may have applications in the synthesis of novel and existing pharmaceuticals and could therefore be industrially converted using microreactor technology.

Despite the advantageous perspectives of performing oxidation reactions in microreactors, there are several challenges, particularly for the transformation of (certain) biomass derivatives. The use of molecular O_2 for oxidation reactions in microreactors seems more promising for highly selective reactions, as in the occurrence of over oxidation reactions significantly more O_2 is required to achieve the same desired product yield. Side oxidation reactions might lead to the requirement of excessive amounts of O_2 that could negatively affect the desired (e.g., slug) flow profiles in microreactors. In this respect, when high gas to liquid volumetric flow ratios are needed, annular flow processing should be explored to maintain sufficient O_2 availability without negatively affecting gas-liquid interfacial area and mass transfer rate.[286]

Another challenge lies specifically in the precipitation of FDCA that is formed during the oxidation of HMF. FDCA is poorly soluble in water and other commonly used (organic) solvents, which can result in blockage of solid catalysts' active sites (thus reducing the catalytic activity) and reactor clogging (increasing the pressure drop). A possible way to circumvent this in microreactors might be by the addition of an inert carrier phase in which the precipitated FDCA particles are dispersed, preventing them from interacting with the microreactor wall or solid catalysts. A more convenient way is to use solvents in which FDCA has a high solubility. Some research has been done recently on the oxidation of HMF to FDCA using ionic liquids in which FDCA dissolves well,[287,288] however, the application of ionic liquids for industrial production is not economically feasible yet. Of the industrially attractive solvents, FDCA dissolves best in methanol.[289] This makes the MMF pathway by dehydration of sugars in methanol followed by the subsequent oxidation to FDCA in the same solvent a potentially attractive approach for the continuous production of FDCA.[77] Alternative routes that have received industrial interest for the synthesis of FDCA from HMF is via a microbial pathway, or the use of homogeneous metal bromide (Co/Mn/Br) catalysts in an acetic acid solvent.[68]

An alternative method for chemo- or biocatalytic oxidation of biomass (derivatives) is by photocatalysis.[290] In photocatalysis a chemical reaction is performed by exposure of ultraviolet, visible or infrared radiation in the presence of a photocatalyst that absorbs the light and induces the chemical transformation. Photocatalytic reactions can be typically performed under ambient conditions (room temperature and atmospheric pressure), making them less energy intensive. Photocatalysis in microreactors particularly has the benefits of

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accelerated reaction rate (e.g., better light penetration and mass transfer), easy scale-up and milder conditions required as compared to photocatalytic reactions performed in batch reactors.[291] Photocatalytic oxidation has been already conducted in microreactors for the oxygenation of biomass derivatives (e.g., monoterpenes derived from plants and in the singlet-oxygen oxidation of HMF to H^2MF).[292–295] Oxygenated monoterpenes are promising building blocks for the synthesis of pharmaceuticals, flavorants and fragrances.[8] The oxidation of monoterpenes is industrially unfavorable as it requires long residence times and often a low product selectivity is obtained. By performing the oxygenation in slug flow microreactors and in tube-in-tube microreactors using artificial light emitting diode (LED) or natural sunlight, both the product yield and selectivity were enhanced considerably as compared to batch operation.[292] The enhanced gas-liquid mass transfer in microreactors reduced the formation of the activated radicals, accelerating the formation of singlet oxygen, which resulted in a higher reaction selectivity. Particularly using a natural light source instead of artificial LED light makes the continuous flow photooxygenation attractive for industrial scale production.

2.3. Hydrogenation of Biomass Derivatives

Biomass has a high oxygen content as compared to petroleum. By the reductive oxygen removal (hydrodeoxygenation or HDO) of biomass and its derivatives, the amount of functional (alcohol) groups is reduced, which makes them more suitable for the selective production of value-added chemicals or fuels.[15,31] Also, the deconstruction of complex biomass structures (e.g. lignin or polysaccharides) can be performed by C–C bond cleavage (hydrogenolysis), facilitating its processability and valorization.[30] The hydrogenation of biomass and its derivatives has been researched extensively up to this date.[100] Molecular H_2 as an environmentally friendly reducing agent is commonly used for hydrogenation reactions. Biomass derivatives are often present in a liquid phase before being fed to the reactor, resulting in a gas-liquid or in some cases vapor phase (under elevated temperature conditions) hydrogenation system. Another frequently used hydrogen donor is formic acid, a simple acid that can be obtained from biomass by acidic dehydration or oxidation.[296] Industrial scale hydrogenation reactions are typically performed over heterogeneous catalysts in packed bed or slurry reactors.[297] Commonly used catalysts for the hydrogenation of biomass (derivatives) include Raney Nickel (a cheap commercial catalyst) or supported metal catalysts (e.g., Ru, Pt and Pd).[14,30]

Heterogeneously catalyzed gas-liquid hydrogenation reactions are often limited by liquid-solid (L–S) mass transfer.[298] This is why slurry reactors are commonly used, which allows the use of fine catalyst particles resulting in a high ratio of catalytic surface area to reactor volume, accelerating L–S mass transfer and with that, reaction rate.[297] Moreover, gas-liquid mass transfer needs to be well addressed. H_2 typically has a low solubility in liquids (e.g., water, organic solvents), resulting in the requirement of high operating pressures. These mass transfer limitations can be overcome or significantly reduced in microreactors.[298] Small catalyst particles can be incorporated in microreactors in a packed bed configuration that increases the specific catalytic surface area. Above that, packed bed microreactors allow an improved heat management as compared to conventional (large-scale) packed bed reactors.[180] Packed bed microreactors offer an easy and cheap method for catalytic performance testing and kinetic studies in the laboratory. Also by wall-coating of microreactors the specific catalytic surface area can be enhanced considerably and the (precious) catalyst usage can be reduced by an increase in the catalyst effectiveness factor that lowers internal liquid-solid mass transfer limitations. Wall-coated microreactors also have the advantages of the well-defined (e.g., slug) flow pattern as generated in empty microchannels, controlled gas-liquid mass transfer, as without high pressure drop generation as in packed bed (micro)reactors.[180]

Furthermore, microreactors offer a cheap and effective method for high throughput catalyst screening by the fast response and reduced catalyst usage. High pressure hydrogenation reactions can be performed more safely in microreactors, as hot spot formation is (largely) eliminated by the improved temperature control, avoiding thermal runaway.[299] The excellent temperature regulation in microreactors also allows for a more controlled HDO of complex biomass mixtures (e.g., pyrolysis oil or lignin derivatives). Reaction mechanisms and kinetics are not fully known yet of these reactions. By the controlled processing in microreactors, valuable insights thereof may be obtained and used to guide further reaction optimization. Despite these advantages, the study of microreactors for the hydrogenation of biomass derivatives is still limited (Table 6).

2.3.1. Hydrogenation of Sugars to Sugar Alcohols

The hydrogenation of sugars for the production of sugar alcohols (e.g., sorbitol, xylitol and arabitol; commonly used as sweeteners/food additives)[60] is commercially performed in three phase slurry or trickle bed reactors using Raney Nickel as a cheap and selective heterogeneous catalyst.[297,300,301] The gas-liquid hydrogenation of glucose to sorbitol has been reported using a washcoated Ru catalyst over γ-Al_2O_3 support in a monolithic loop microreactor (400 cells per square inch (cpsi), corresponding to an average channel diameter below 0.625 mm) operated under slug flow (Figure 3D; Table 6, entry 1).[150] The reaction rate in the microreactor was 1.5–2 times faster than that in a stirred tank slurry reactor. External (gas-liquid) mass transfer limitations were observed in the slurry reactor, while internal (liquid-solid) mass transfer limitations were more prevalent in the microreactor since the gas-liquid slug flow generated in monolithic channels considerably enhanced the external mass transfer. Thus, monolithic catalysts with sufficiently thin catalyst layers (to overcome internal mass transfer limitations), combined with their enhanced gas-liquid mass transfer, might be a promising alternative to suspended powder catalysts for enhancing the overall reaction rate for the hydrogenation of glucose.[150]

The hydrogenation of a mixture of C_5 sugars (*L*-arabinose and *D*-galactose towards arabitol and galactitol, respectively)

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Table 6. Catalytic hydrogenation of biomass derivatives in microreactors.

Entry	System[a]	Substrate	Product	Catalyst	Microreactor[b]	Reaction conditions	Results and advantages of flow operation[c]	Reference
1	G–L–S	Glucose	Sorbitol	Ru/γ-Al_2O_3	Wall-coated cordierite monolith (400 cpsi, average $d_C < 0.625$ mm, $L = 0.05$ m)	Liquid phase: 40 wt% glucose in water; Gas phase: H_2; 100–140 °C, 80 bar; Slug flow operation	Reaction rate in monolith was 1.5–2 times faster than that in a stirred tank slurry reactor; External mass transfer limitations could be diminished	[150]
2	G–L–S	Arabinose and galactose	Arabitol and galactitol	0.5 wt% Ru/C	Packed bed stainless steel capillary ($d_C = 2.4$ mm, $L_{bed} = 0.35$ m, $d_p = 800$–1000 μm)	Liquid phase: 5 g/L arabinose/galactose mixture (molar ratio = 1:5); Gas phase: H_2; 90–150 °C, 30–60 bar; Slug flow before entering the bed, gas holdup = 0.6	External and internal mass transfer limitations could be diminished; 70% arabinose and 70% galactose conversion at 150 °C and 40 bar at 3 mL min^{-1} liquid feed; Fine tuning in microreactor allowed accurate reactor model development	[151]
3	G–L–S	HMF	DMF	Ru/Cu/Fe_3O_4/N-rGO	Gas permeable PTFE capillary ($d_C = 0.61$ mm, $L = 0.1$ m) in wall-coated PTFE capillary ($d_C = 1.2$ mm, $L = 0.1$ m)	Liquid phase: 0.5 M HMF in DMSO; Gas phase: H_2; 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	[144]
4	G–L–S	Pyrolysis oil	Biofuel	Presulfided NiMo/Al_2O_3	Packed bed stainless steel capillary ($d_C = 0.762$ mm, $L_{bed} = 2.5$-18 cm, $d_p = 38$–45 or 75–150 μm)	Liquid phase: pyrolysis oil; Gas phase: H_2; 180–270 °C, 12.4–31 bar; Slug flow before entering the bed	Internal and external mass transfer limitations were negligible; The extent of HDO (64%) and STC (3.19 $g_{H2}\ g_{cat}^{-1} s^{-1}$) were higher than in milli-reactors (10.7%, 0.84 $g_{H2}\ g_{cat}^{-1} s^{-1}$ for $d_C = 3.2$ mm and 10.1%, 0.39 $g_{H2}\ g_{cat}^{-1} s^{-1}$ for $d_C = 6.4$ mm)	[152]
5	G–L–S	4-Propylguaiacol	4-Propylphenol, diverse phenolics	Presulfided NiMo/Al_2O_3	Packed bed stainless steel capillary ($d_C = 0.762$ mm, $L_{bed} = 2.5$-18 cm, $d_p = 38$–45 or 75–150 μm)	Liquid phase: 1.1 M substrate in hexane; Gas phase: H_2; 200–450 °C, 16.5–33 bar; Slug flow before entering the bed	Internal mass and heat transfer limitations were negligible; Fine tuning in microreactor allowed accurate kinetic model development	[153]
6	L–S	Vanillin	2-Methoxy-4-methylphenol	AgPd/g-C_3N_4	Wall-coated stainless steel coiled capillary ($d_C = 0.8$ mm, $L = 10$ m)	Single phase: 0.2 M vanillin and 0.3 M formic acid in water/methanol (90/10 vol%); 40–70 °C, 1 bar	100% vanillin conversion in 50 min	[303]
7	L–S	LA	GVL	AgPd/g-C_3N_4	Wall-coated stainless steel coiled capillary ($d_C = 0.8$ mm, $L = 10$ m)	Single phase: 0.2 M LA and 0.3 M formic acid in water/methanol (90/10 vol%); 70 °C, 1 bar	100% GVL yield in 50 min	[303]

[a] L–S represents a single phase liquid hydrogenation (formic acid as hydrogen source) over solid catalysts. G–L–S represents a biphasic gas-liquid hydrogenation over a solid catalyst, [b] d_C, d_p and L appeared in the column represent the inner reactor diameter, catalyst particle diameter and reactor length, respectively, [c] STC represents the space time consumption of H_2 ($g_{H2}\ g_{cat}^{-1} s^{-1}$) during hydrodeoxygenation (HDO).

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was performed in a microreactor (d_C = 2.4 mm) packed with 0.5 wt% Ru/C catalysts subject to an upstream slug flow (Figure 3F; Table 6, entry 2).[151] Both external and internal mass transfer limitations could be diminished by the enhanced gas-liquid mass transfer in the microreactor and by using sufficiently small (d_p = 80–100 μm) catalyst particles. A conversion of 70% for both arabinose and galactose was obtained at 150 °C and 40 bar at a 3 mL min^{-1} liquid feed (gas holdup = 0.6). Since the external mass transfer resistance could be (almost) entirely diminished in the microreactor, a pseudo-homogeneous reactor model was developed taking into account internal diffusion limitations, which could accurately describe the reaction rate. This model could subsequently be used to identify process conditions for an optimal reactor performance.

2.3.2. Hydrogenolysis of HMF to DMF

Hydrogenolysis of HMF to DMF, a potential biofuel with high energy density,[78] was performed in a tube-in-tube microreactor coated with bimetallic Ru/Cu on Fe_3O_4/N-rGO catalysts (Figure 9; Table 6, entry 3).[144] The microreactor was operated in cocurrent flow with the gas phase (H_2) in the inner permeable PTFE capillary (d_C = 0.61 mm) surrounded by the outer catalytically wall-coated PTFE capillary (d_C = 1.2 mm) through which the reactive liquid phase (HMF in DMSO) was fed. The doped N atoms functioned as a metal aggregation preventer and provided preferable immobilization sites for the metal catalyst. Iron particles were incorporated in the catalytic coating that was kept in place by magnets on the outside of the microreactor, in which the magnetic pull prevented the column coating from leaching out. No significant decrease in the catalyst activity was observed after 2 days of operation. By the efficient heat and mass transfer in the microreactor, 91% DMF yield was obtained after 20 min under relatively mild conditions (8 bar and 150 °C). Also when operating the hydrogenation reaction in a tandem microreactor, where HMF produced from fructose dehydration in a previous microreactor was used as the feedstock (Table 4, entry 10), 90% DMF yield could be obtained in a total reaction time of 26 min under the same reaction conditions. It is worth mentioning that the use of magnets for catalyst immobilization complicates the process scale up and alternative catalyst incorporation strategies may be more suitable for industrial applications.

2.3.3. Hydrodeoxygenation of Pyrolysis Oil to Biofuels

Thermochemical treatment (i.e. fast pyrolysis) of crude biomass mixtures can result in complex bio-liquids (e.g., pyrolysis oil), that are easier to process than crude biomass feedstocks.[18] Pyrolysis oil is a complex mixture that can contain over 400 different chemical compounds (depending on the biomass source), which complicates the selective production of target chemicals.[2] Furthermore, it has a high oxygen content (40–50 wt%) giving it a low heating value and making it unattractive to use directly as a biofuel. Thus, hydrodeoxygenation (HDO) with H_2 gas is a viable strategy to upgrade pyrolysis oil in this respect. HDO reaction performance is often expressed in the extent of HDO (amount of oxygen removed) and space time consumption (STC) of H_2 (amount of H_2 consumed per reaction time and catalyst weight).

HDO of pyrolysis oil was performed in a stainless steel microreactor (d_C = 0.762 mm) under an upstream gas-liquid slug flow profile with presulfided NiMo on Al_2O_3 packed as the catalyst (Table 6, entry 4).[152] Commercially available catalyst particles were modified by grinding and sieving to reduce particle size and facilitate their incorporation into the microreactor by gravitational filling. Due to the small catalyst particles used (d_p = 38–45 μm), both external and internal mass transfer limitations could be diminished under the operating conditions (180–270 °C and 12–31 bar). The extent of HDO (64%) and STC (3.19 g_{H2} $g_{cat}^{-1}s^{-1}$) were higher in the microreactor than in larger diameter packed bed milli-reactors (being, respectively,10.7% and 0.84 g_{H2} $g_{cat}^{-1}s^{-1}$ for d_C = 3.2 mm, 10.1% and 0.39 g_{H2} $g_{cat}^{-1}s^{-1}$ for d_C = 6.4 mm). Considerably lower operating pressures and residence times were required in the microreactor to achieve the same results as compared to milli-reactors, as the H_2 supply rate was still sufficiently high at lower pressures due to the enhanced mass transfer in the microreactor. To gain kinetic and mechanistic insights into this complex reaction, HDO of 4-propylguaiacol (a model compound for lignin derivatives in pyrolysis oil) was performed using the same catalyst and microreactor (Table 6, entry 5).[153] Also here internal mass and heat transfer limitations could be neglected under the conditions used (200–450 °C and 16.5–33 bar), allowing to accurately determine rate expressions in the microreactor for the development of a kinetic model. This model gives further insights in predicting the integral reactor behavior for HDO of lignin fractions in pyrolysis oil and further aids in the reaction optimization therein.

2.3.4. Hydrogenation of Vanillin to 2-Methoxy-4-methylphenol and LA to GVL using Formic Acid as the Hydrogen Source

A process was developed for the heterogeneously catalyzed hydrogenation of vanillin to 2-methoxy-4-methylphenol, a flavoring agent and a potential biofuel,[302] under mild conditions (40–70 °C and ambient pressure). A wall-coated stainless steel coiled capillary (d_C = 0.8 mm) was used to carry out the liquid phase hydrogenation using formic acid as the hydrogen donor (Table 6, entry 6).[303] The microreactor wall was coated with a bimetallic catalyst consisting of silver and palladium nanoparticles supported on graphited carbon nitride (AgPd/g-C_3N_4). The nitrogenous framework of the support strongly attached to the metal nanoparticles, which prevented metal leaching. Full conversion of vanillin was achieved in the microreactor after 50 min at 70 °C. Furthermore, by the microreactor operation, a potential reaction mechanism was proposed. The reaction presumably occurs by the initial adsorption of formic acid on the catalytic surface to a formate species, which subsequently facilitates the hydrogenation of vanillin on the AgPd surface. In the same catalytic microreactor, the upgrading of levulinic acid (LA) to γ-valerolactone (GVL), a fuel additive and promising biobased solvent,[66] was performed with 100% GVL yield after 50 min at 70 °C (Table 6, entry 7).[303] The use

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of formic acid as a hydrogen donor particularly shows high potential in this case, as it is obtained in stoichiometric quantities during the transformation of carbohydrates to LA (Scheme 1).

2.3.5. Opportunities

Studies on the liquid phase hydrogenation of biomass derivatives in continuous flow microreactors remain still limited. Most flow studies on the hydrogenation of biomass derivatives focused on the (heterogeneous) catalyst performance and paid little attention on the (micro)reactor performance and optimization thereof. The majority of heterogeneously catalyzed hydrogenation reactions is limited by internal (liquid-solid) mass transfer and could benefit from the enhanced liquid-solid interfacial area in packed bed or wall-coated microreactors. The controlled heat transfer in microreactors can reduce safety risks for the liquid-phase hydrogenation of biomass derivatives using H_2 as such reactions are highly exothermic. Microreactors have already shown potential for the hydrogenation of glucose and other sugars to sorbitol and other sugar alcohols, HMF to DMF, and the upgrading of pyrolysis oil and lignin derivatives by HDO. Single phase hydrogenation using formic acid as the reducing agent has been applied for the conversion of LA to GVL and vanillin to 2-methoxy-4-methylphenol.

Other hydrogenations in microreactors not detailed in this review include the transformation of bioethanol to ethane in a stainless steel packed bed microreactor chip ($L \times W \times H = 30 \times 1.25 \times 0.03$ mm),[304] 2-methylfuran to 2-methyltetrahydrofuran (MTHF) in a silicon/Pyrex microreactor ($d_C = 0.4$ mm),[276] and 5-methylfurfural to a variety of furans (e.g., 5-methylfurfuryl alcohol, DMF, 2-methylfuran, etc.) in a wall-coated fused silica capillary ($d_C = 250$ μm).[305]

Many other conventional (non-biobased) hydrogenation reactions have been performed using heterogeneous catalysts in wall-coated or packed bed microreactors.[180,181,306–308] In packed bed microreactors the use of small catalyst particles is inevitable, potentially causing high pressure drop. Wall-coated microreactors can maintain enhanced mass transfer without higher pressure drop generation,[180] making them potentially suitable for the processing of highly viscous biomass sources such as in the HDO of glycerol or thick bio-oils.

Several researchers have reported the heterogeneously catalyzed hydrogenation of biomass derivatives by (vapor or liquid phase) processing in larger diameter packed bed (e.g., milli- or meso-) reactors. Interesting reaction candidates include e.g., the reforming of (sugar) alcohols to liquid alkanes,[309,310] the conversion of glycerol to 1,2- and/or 1,3-propanediol,[311–313] furfural to furfuryl alcohol and/or other hydrogenation products (e.g., THFA, 2-methylfuran)[314–317] in the liquid phase. Most of these studies were focused on the catalytic performance or stability, and did not pay considerable attention to the influence of the reactor configuration on the reaction performance. Thus, the process intensification potential has not been well explored and these hydrogenation reactions might benefit similarly from flow operation in microreactors (Figure 4).

2.4. Miscellaneous Catalytic Biomass Transformations

In this chapter, several other catalytic biomass transformations are briefly reviewed, including multiphase (gas-liquid or liquid-liquid) transformations over homogeneous or heterogeneous catalysts, or single phase liquid transformations over heterogeneous catalysts. Thermochemical transformations of biomass in microreactors have been occasionally reported and are not included in this review, for which the readers are referred to the corresponding literatures: pyrolysis (coupled with analytical equipment),[318–320] and the production of syngas by the (catalytic aqueous phase) reforming of carbohydrates[321–323] or glycerol.[324–327] Also the Fischer-Tropsch synthesis of liquid olefins from biomass derived syngas or methane has been reported in microreactors,[328–331] but will not be elaborated in this review.

2.4.1. Esterification

Biphasic liquid-liquid or single liquid phase (trans)esterification reactions can benefit from the enhanced heat and mass transfer in microreactors. This has been extensively shown for the biphasic production of biodiesel by the transesterification of triglycerides from plant oils in several reviews.[154–157] Besides biodiesel synthesis, catalytic esterification of biobased acids (e.g., lactic acid and succinic acid obtained by fermentations) with (biobased) alcohols may also benefit from biphasic processing in microreactors. This esterification could be integrated in a fermentation process by the addition of an alcohol phase containing homogeneous catalysts where the extracted acids are directly converted to value-added products (e.g., alkyl lactates, succinic esters as biodegradable solvents).[10]

Chemocatalytic esterification of biomass derivatives, apart from biodiesel synthesis, has not yet been reported in microreactors to the best of the authors' knowledge. The only reported type of biomass esterification so far was performed biocatalytically using immobilized enzymes in packed bed microreactors. The single liquid phase esterification of caffeic acid (hydroxycinnamic acid), an aromatic acid abundantly present in plants, to alkyl caffeates (i.e., methyl caffeate and caffeic acid phenethyl ester),[332,333] and the synthesis of alkyl levulinates by the esterification of levulinic acid with an alcohol (1-butanol or ethanol) have been reported in packed bed microreactors.[334,335] These reactions could be intensified as compared to batch reactors, mainly due to the increased catalytic surface area and enhanced heat control in the microreactor.

2.4.2. Epoxidation

Epoxidations are usually reactions between an alkene and a peroxide (e.g., H_2O_2, peracid) or O_2. Unsaturated fatty acids from plant oils and esters thereof (biodiesel) can be modified by the epoxidation of their double bond(s) to an oxirane ring. These fatty acid epoxides can be used as a precursor for the

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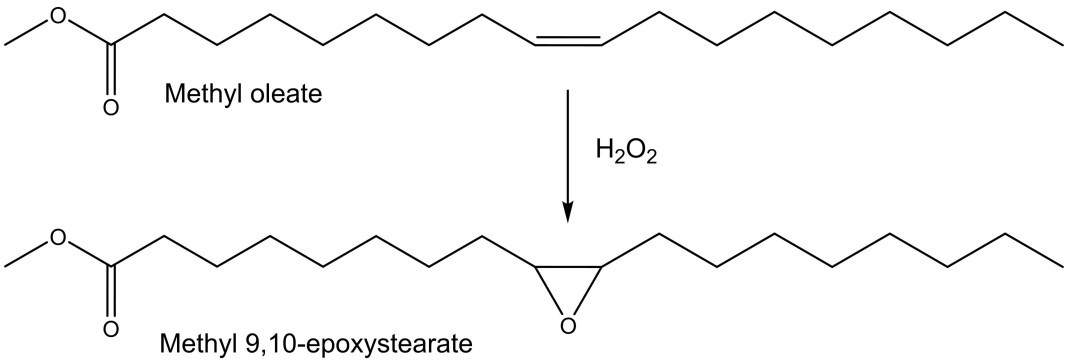


Scheme 7. Epoxidation of methyl oleate to methyl 9,10-epoxystearate.

production of lubricants, stabilizers, pharmaceuticals or fuel additives.[336] The biphasic liquid-liquid epoxidation of fatty acid methyl esters (FAME biodiesel) has been performed in microreactors.[337–339]

The epoxidation of methyl oleate to methyl 9,10-epoxystearate with H_2O_2 as the oxidant and ethylenediaminetetraacetic acid (EDTA) as the stabilizer was performed in a glass capillary microreactor ($d_C = 0.53$ mm) wall-coated with TiO_2 catalyst (Scheme 7).[337] The catalyst coating was applied to the microreactor by filling the glass capillary with a solution of TiO_2 (10 wt%) in ethanol. The ethanol was then removed with heat and vacuum (i.e. static method), after which the capillary was calcinated for 5 h at 300 °C. In the microreactor an epoxide yield of 43.1 % was obtained after 2.7 min, which was about 23 times higher than in a conventional batch reactor after 15 min under similar reaction conditions (60 °C, 1 bar). The reaction rate increase is probably due to the enhanced mixing of the organic and aqueous phases. Despite the improved reactor performance, the wall-coated catalyst configuration showed poor stability as it peeled off after 3 h operation. Improved adhesive properties of the catalytic coating should be thus developed for it to become feasible for long-term industrial operations.

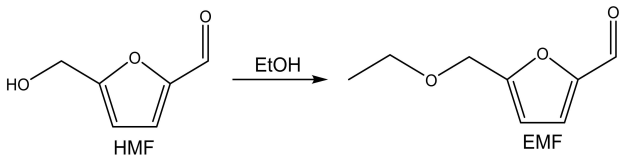
Similarly, the epoxidation of triglycerides from soybean oil benefitted from microreactor processing.[338] A Bayer sandwich reactor consisting of micromixer and capillary microreactor (37 mL in volume) was reported to intensify the process and improve the quality of the epoxidized soybean oil (ESO) product. The maximum epoxy number (an indication of the amount of epoxy groups per triglyceride molecule) could be increased from 6 obtained after a few hours in batch to 7.3 in the microreactor in 6.7 min at 75 °C. Furthermore, microreactor operation allowed continuous oil-water separation based on their gravity difference in a decanter,[340] making it potentially interesting for industrial applications. In a follow-up study, a tandem microreactor system was developed in which the transesterification of soybean oil to fatty acid methyl esters (FAME biodiesel) was coupled in flow with the subsequent immediate epoxidation in a second microreactor. Epoxy numbers up to 5.52 of epoxidized FAME were obtained in 12 min due to the intensified mass transfer in the microreactor.[339] Besides, the successful performance of the tandem reactor configuration shows that microreactors facilitate multistep synthesis in flow.

2.4.3. Hydrolysis

Biobased sugars from crude biomass feedstocks are often in the form of polysaccharides or disaccharides. Hydrolysis of these complex sugars towards monosaccharides (e.g., glucose, xylose) is required to increase their processability and facilitate their selective transformation into value-added chemicals.[59] The hydrolysis of sucrose to an equimolar mixture of glucose and fructose has been performed enzymatically with invertase immobilized on silica (30–45 mesh) in a packed bed microreactor ($W \times L \times H = 3 \times 70 \times 1$ mm). A space time yield (STY) of 44.92 g L^{-1} h^{-1} was obtained.[341] The same reaction was carried out where the invertase catalysts was incorporated as a wall-coating in an array of glass capillaries ($d_C = 0.45$ mm) within a polymethylmethacrylate (PMMA) housing.[342] The increased catalytic surface area in the wall-coated microreactors resulted in an enhanced reaction rate (STY = 69.0 g $L^{-1}h^{-1}$).

2.4.4. Etherification

The etherification of HMF with ethanol to 5-ethoxymethylfurfural (EMF), a potential biofuel (Scheme 8), was performed



Scheme 8. Etherification of HMF to EMF.

in a PTFE capillary microreactor ($d_C = 0.5$ mm) wall-coated with Fe_2O_3 on a reduced graphene oxide (rGO) catalyst.[144] The reaction was executed under mild conditions (70 °C and 1 bar),

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diminishing the requirement of using elevated pressures to prevent evaporation of the ethanol (EtOH) solvent. The Fe_2O_3 loading allowed the fixation of rGO catalyst to the inner microreactor wall by magnet rings on the outside of the microreactor. Complete HMF conversion with 99% EMF yield was obtained in 6 min, whereas it took 12 h in a pressurized batch autoclave to obtain 96% HMF conversion and 92% EMF yield at 100 °C with the GO catalyst. The yield increase in the microreactor is mainly due to the higher catalytic surface area to reactor volume and better catalyst performance of rGO than GO.

2.4.5. Opportunities

Other classes of biomass transformation that may benefit from (multiphase) flow processing in microreactors, but have not been described in the literature thus far, are carboxylation/carbonylation using CO or CO_2 and aminations using NH_3.[343] The use of CO/CO_2 for other carboxylations has already been applied in microreactors.[344,345] The synthesis of glycerol carbonate by carboxylation/carbonylation of glycerol with CO or CO_2 in the presence of O_2 or H_2 may benefit from the enhanced heat and multiphase mass transfer in microreactors.[346] Glycerol carbonate is considered a valuable platform chemical as its wide reactivity allows it to be used for a broad range of reaction applications.[97] The carboxylation of glycerol is often considered problematic because of the thermodynamic limitations and safety issues when dealing with CO. By microreactor operation, wider process windows may be possible to overcome these limitations, for instance by a safer and more energy efficient application of microwave heating than in conventional reactors.

Reductive amination of aldehydes and ketones with an amine (e.g. NH_3) and H_2 can be catalyzed by solid catalysts.[347] The amination of (biobased) acids (e.g., succinic acid, itaconic acid, LA or 3-HPA) can produce pyrrolidones that are widely used for the synthesis of polymers, dyes, surfactants, pharmaceuticals and agrochemicals. Furthermore, biobased ketones or aldehydes (e.g., furfural, glyceraldehyde) and carboxylic acids can be converted to value-added amines or pyrrolidones.[348–350] These gas-liquid reductive aminations may benefit from operation in microreactors by overcoming gas-liquid mass transfer limitations and having well-regulated temperature distribution for an intensified and more selective product formation. The single phase reductive amination of biobased aldehydes (i.e., furfural, LA, HMF) with aniline has been applied using Au catalysts in batch and flow reactors.[351] Thus, one step further to (multiphase) microreactor processing seems highly feasible.

3. Challenges and Future Perspectives

Despite the numerous advantages microreactors have to offer for the conversion of biomass derivatives to value-added chemicals and fuels, there are generally several major challenges that need to be well addressed in order to increase the technical and economic feasibilities of the industrial application of microreactor technology in this area.[110]

3.1. Solid Handling

Although the majority of biomass transformations described in this review encompass reactions involving "clean" gas and liquid flows, solids may be present (e.g., as dust or sand) in some biomass feedstocks,[251] or during reactions with product precipitation (e.g., the oxidation of HMF to poorly soluble FDCA) or with complex byproduct formation (e.g., insoluble humins during the dehydration of sugars). Wall interaction of these solids could result in particle accumulation that may cause clogging of the microreactor. Clogging can result in excessive pressure drop and reactor malfunction. Furthermore, active sites of heterogeneous catalysts (if present) can be blocked, reducing the catalytic performance. Catalyst coking can occur when processing biomass at elevated temperatures. Coking is a common problem in large-scale packed bed reactors, where it is handled by periodically performing post-reaction treatments (e.g., flushing, combustion) on the packed bed to regenerate the catalyst.[352] However, this is no longer effective when significant solid amounts have accumulated before the purging is commenced. Several active strategies (e.g., ultrasonic treatment) have been applied to continuous flow containing solid particles in microreactors to reduce the chance of channel blockage.[353–356] Yet this can be energy intensive. Although the chance of clogging is higher in microreactors due to their small internal channel dimensions, the unique multiphase flow profiles (e.g. slug flow) generated in microreactors can actually aid in preventing contact of solid particles with the reactor wall. This can be done by adding an inert carrier liquid as the continuous phase which covers the microreactor wall where the solid particles cannot pass through (Figure 10),[354,357] a method that has already been applied for microfluidic synthesis of solid polymer particles.[358] Solid formation could be handled by slug flow processing when the reaction is performed in the dispersed (droplet) flow, preventing solid particles from contacting the microreactor wall by the presence of the surrounding film of the inert continuous (slug) phase. This strategy is also applicable in the biphasic synthesis of furans in slug flow microreactors where the deposition of humins (present in the reactive aqueous phase) onto the hydrophobic microreactor wall is prevented by the surrounding organic extraction phase (Figure 5B).

3.2. Incorporation of Solid Catalysts

Many catalytic biomass transformations to value-added products are performed with solid catalysts, hence effective strategies for incorporating solid catalysts into microreactors are essential for an optimal reactor performance. Most commonly, catalysts are immobilized in the microreactor by wall coatings or in the form of packed particles.

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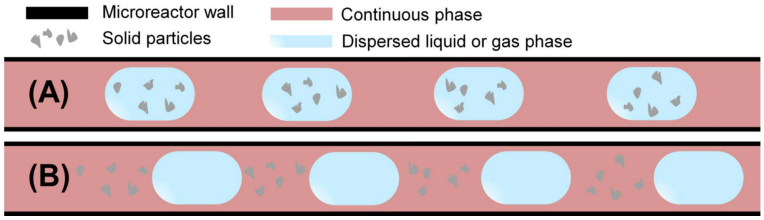

Figure 10. Insoluble solid (e.g., humins, precipitated product, heterogeneous catalyst) particles dispersed in a biphasic slug flow microreactor. (A) Solid particles suspended in the dispersed liquid phase of liquid-liquid slug flow, where a film layer from the continuous phase prevents it from contacting the microreactor wall. (B) Solid particles suspended in the continuous liquid phase of a liquid-liquid or gas-liquid slug flow, where they can contact the microreactor wall.

The immobilization of catalysts to a microreactor wall often requires dedicated coating procedures, depending on the catalyst type, wall material and geometry.[359] Catalyst replacement in the case of deactivation can lead to microreactor damaging or requires somewhat cumbersome or energy intensive removal procedures (particularly by the additional drying and calcination steps). Current coating removal procedures are not yet economically feasible and in order to achieve this, milder procedures need to be developed (e.g., by reducing energy required for drying and calcination).[360] Furthermore, wall-coated microreactors often result in less stable catalyst configurations as they can peel off from the microreactor wall due to poor adhesion, making them prone to leaching. Durability of these wall-coated catalyst configurations have to be increased to reduce maintenance time and costs.

Catalyst particles (either commercially available or those developed in the lab using conventional synthesis approaches) can be easily packed in microreactors (e.g., by gravitational or vacuum filling). High specific catalytic surface areas can be reached by insertion of small diameter particles, offering excellent liquid-solid mass transfer. The disadvantages of these dense packings are that a significant pressure drop is generated over the microreactor (if the catalyst particles are very fine and/or the catalyst bed is long) and it may result in complex, non-ideal multiphase hydrodynamics (e.g., by wall-channeling, wettability issues).[196] Relatively large diameter catalyst particles with highly porous inner structures (e.g., hollow spheres,[361] foam or sponge based),[362] might offer increased catalytic areas without generating exorbitant pressure drop. Furthermore, the incorporation of these in microreactors might be done without the requirement of difficult immobilization procedures (e.g., use of dense packing filters).[363] Hence, the development of such catalysts for transformations of biomass derivatives into value-added chemicals has received recent research interests.[106]

An alternative method for the incorporation of solid catalysts into multiphase microreactors is by dispersing catalyst particles in the liquid droplet or slug (Figure 10).[364,365] This slurry-like slug flow combines the advantage of high interfacial area with the ability to use small catalyst particles (e.g., on the micrometer scale) while maintaining a low pressure drop over the system. In such a configuration, the solid catalysts would have to be recycled after each run, which is not highly favored as effective (in situ) recovery methods of solid catalysts and flow recycling of these in microreactors are yet to be developed. Another downside of this configuration might be the risk of accumulation of solid particles in the microreactor (e.g., in the dead flow zone or corner area), however, this can be overcome by different methods (e.g., ultrasonic treatment or by the addition of an inert carrier phase) as described in Section 3.1. This approach has already been applied in the $VOCl_3$ catalyzed oxidation of lactates to pyruvates (Table 5, entry 6).[148]

3.3. Upscaling of Multiphase Microreactors

In order for microreactors to become attractive for industrial production of (biomass derived) chemicals and fuels, production capacity needs to be increased towards the pilot or industrial scale. Although upscaling of microreactors can be generally performed easily by numbering-up (e.g., pileup of microfluidic chips, bundling/stacking of capillaries, parallelization of microchannels),[197,366] there are some challenges in particular for multiphase flow processing. Selective troubleshooting (e.g., in case of clogging, leakage and catalyst deactivation) for different microreactor channels might be problematic for identifying in which microchannels there is a malfunction. This requires selective solutions for which it is not necessary to abort the entire production. In this respect, online monitoring represents a good option to diagnose malfunction,[190,191] and with the use of modular microreactors, the malfunctioned parts can be detached and replaced without affecting production.[367] Another issue is (multiphase) flow maldistribution across parallel microchannels that might result in a loss of several inherent advantages of flow processing in microreactors. For instance, the fluid residence time over different microchannels can vary due to fabrication imperfections or flow disturbance, negatively affecting the performance of reactions that need to be tuned precisely (i.e. in the selective synthesis of intermediates). Furthermore, maldistribution in gas-liquid or liquid-liquid processing can negatively affect the unique multiphase (e.g. slug) flow profiles across microchannels or even separate the different phases completely.[368] By robust (modular) flow distributor design (e.g., by incorporating high pressure drop channels in the fluid distributor) and applying

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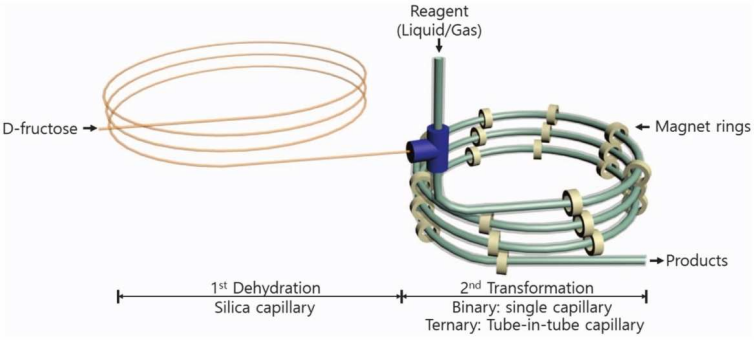

Figure 11. Tandem microreactor for the synthesis of HMF from fructose with the subsequent immediate modification (i.e., decarbonylation, etherification, oxidation or hydrogenolysis) in a second microreactor attached in series. Reproduced with permission of ref.[144] Copyright 2015 Springer Nature Publishing AG.

precise channel fabrication methods, it is possible to generate a uniform multiphase (gas-liquid or liquid-liquid) flow distribution.[221,368,369] The effective scaled-up application of these optimized distribution strategies for (multiphase) catalytic processing may eventually lead to industrially viable intensified transformation of biomass derivatives to value-added chemicals and fuels using microreactor technology.

Scaled-up continuous flow (micro)reactor processes for liquid phase oxidation reactions have already been developed and utilized in commercial processes.[262] This was mostly done by adjusting the characteristic flow reactor dimensions (i.e. channel shape or by the incorporation of mixing elements), in addition to numbering-up of reaction channels.[367,370,371] For instance, Corning glass microreactors with heart-shaped splitters/mixers were commercially used (e.g. for the scaled up flow oxidation of alcohols to aldehydes)[371–373] with increased productivity. Similar microreactor configurations may be equally applied in the upscaling of (oxidative) biomass transformations for industrial processing. Upscaling by the use of increased channel diameters (i.e. milli-reactor configurations) may result in less pressure drop and thus lower operation costs. However, these usually cope with a loss of efficiency and increased safety risks as compared to microreactors, primarily due to the inferior heat and mass transfer obtained therein.

3.4. The "Micro-Biorefinery"

Microreactors allow the development of effective and flexible small-scale production sites. For microreactors, upscaling (by numbering-up) is not necessarily linked to a decrease in the efficiency as is the case for many conventional processing methods. This way, it can bring the process to the biomass source, instead of the other way around. By this, valuable chemicals or fuels can be produced locally in a "micro-biorefinery", making it a possible solution for the logistic issues that are likely to arise from shifting towards a biobased economy.[374]

The majority of studies describing the catalytic conversion of biomass use highly purified biomass feedstocks. The use of pure feedstocks is essential for gaining valuable insights in the reaction mechanisms, kinetics and catalytic performance of these reactions in the laboratory. However, it is unlikely that the use of these purified feedstocks is feasible for industrial processes. Many organic and inorganic impurities in the biomass feedstock can be effectively removed by chemical pretreatment or washing.[37,250] However, some inorganic impurities (e.g., Si, Ca and Na) cannot be easily removed when they are built in the biomass framework. Hence, these partly pretreated feedstocks derived from biomass should be tested in order to perform proper techno-economical evaluations of industrial biomass processing in microreactors. The influence of impurities on the reaction mechanism (e.g., side reactions), catalytic performance (e.g., poisoning, coking or deactivation),[107] multiphase flow properties and reactor performance (e.g., clogging or corrosion) should be properly addressed before industrial processing can be considered in microreactors. Besides that, when aiming for a fully circular micro-biorefinery, not only the use of crude (lignocellulosic) biomass-derived feedstocks is necessary, but also other chemicals that are required in the processes should be retrieved from renewable sources. This includes commodity chemicals (e.g., H_2 from biogas or syngas for hydrogenation, alcohols retrieved from fermentation broths for (trans)esterification), organic solvents obtained by lignocellulosic biomass upgrading (e.g., GVL, MeTHF, etc.),[375] as well as any other chemicals used in biomass transformation processes.

For an integrated micro-biorefinery, in which crude biomass is converted to value-added chemicals and fuels continuously, multiple (micro)reactor operations in which different reactions take place need to be performed in series. Cascade processes combining multiple synthesis and separation steps are possible using configurations constituting of multiple continuous flow microreactors.[376] Cascades of two microreactors (i.e. tandem microreactor) were used for the dehydration of fructose to HMF (Table 4, entry 10), followed by the immediate modification to value-added furan derivatives (i.e., furfuryl alcohol by decarbonylation, EMF by etherification, DFF by aerobic oxidation (Table 5, entry 4) or DMF by hydrogenolysis (Table 6, entry 3) in a second microreactor) (Figure 11).[144]

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Similar tandem systems combining milli- and microreactors for the transformation of biomass derivatives have been scarcely used to this date.[227,339] The integration of (multiple) microreactor processes with other conventional reactors, separations and processing steps needs to be performed in order to assess the applicability of microreactor technology in industrial biorefineries.

These tandem reactions were performed as individual reactions in series, alternatively one-pot reactions could be applied in microreactors by combining two (or more) reaction steps in a single microreactor. One-pot conversion of carbohydrates into furan derivatives (e.g., by dehydration of fructose to HMF followed by oxidation to FDCA or hydrogenolysis to DMF) has already been demonstrated in batch systems.[377] This implicates a possible three-phase (e.g., gas-liquid-liquid) operation in a microreactor in the presence of solid catalysts, where an effective method can be developed for the one-pot catalytic conversion of fructose to HMF by dehydration followed by immediate hydrogenation upon HMF extraction to the organic phase. So far, three-phase (gas-liquid-liquid) flow operation in microreactors is scarcely applied in reaction studies,[378] and thus deserves much research attention.

4. Summarized Outlook

Biomass is considered as a promising renewable alternative for petroleum for the production of chemicals and fuels. The catalytic conversion of biomass (and its derivatives) represents a selective method under relatively mild reaction conditions. Reaction chemistry and catalyst development in biomass conversion processes have been widely examined over the past decades. However, dedicated reactor engineering concepts are not widely examined yet, especially when it comes to multiphase systems. Microreactors are a promising tool for process intensification. The enhanced heat and mass transfer associated with continuous flow processing in microreactors offers great potential for uplifting the performance of many multiphase reactions/systems related to biobased chemicals and fuels synthesis.

Many chemical reactions involving the conversion of biomass derivatives into value-added chemicals and fuels are performed in a multiphase system in the presence of homogeneous or heterogeneous catalysts (e.g., synthesis of furans with its *in situ* extraction, aerobic oxidation, gas-liquid hydrogenation), and can benefit significantly from microreactor processing. Typically, the production of HMF by the acid-catalyzed dehydration of sugars in the aqueous phase, followed by *in situ* HMF extraction to an organic phase could be performed more selectively in microreactors. The enhanced liquid-liquid mass transfer in microreactors accelerated the extractive removal of HMF upon formation and thus reduced the occurrence of side reactions, therewith improving its selectivity and yield. Furthermore, by slug flow processing in the microreactor the formation of solid byproducts (i.e. humins) was reduced and could be handled more effectively (i.e., preventing particle accumulation and reactor clogging due to the reaction confinement in the droplet). Aerobic liquid-phase oxidation (e.g., of glucose to gluconic acid, HMF to DFF/FDCA, lactates to pyruvates, lignin to vanillin) and hydrogenation of biomass derivatives (e.g., sugars to sugar alcohols, HMF to DMF, pyrolysis oil to biofuels) have been investigated to a lesser extent in microreactors, using wall-coated and packed bed catalysts. Aerobic oxidation reactions are often limited by mass transfer of O_2 from the gas to the liquid phase and could therefore be intensified considerably in microreactors. Another advantage is that microreactors allowed for controlled handling of highly exothermic oxidation reactions and were able to safely execute reactions involving explosion risks (e.g., using pure O_2). For hydrogenation reactions, it was possible to effectively perform rapid catalytic screening using (mainly) monolithic or packed bed microreactors. Furthermore, using small catalyst particles in the microreactor allowed an optimized liquid-solid mass transfer and an increase in the reaction rate. The improved temperature distribution by enhanced heat transfer in microreactors makes the conduction of often highly exothermic gas-liquid hydrogenation reactions therein safer and can allow more selective product generation.

There are still several challenges to be overcome before microreactor technology can be effectively applied in commercial biomass conversion processes. Novel procedures for the handling of solids (e.g. insoluble humins) to prevent catalyst coking and microreactor clogging have been successfully shown in the lab and should be tested for scaled up applications. Alternative and more facile incorporation methodologies for heterogeneous catalysts (e.g., other than wall-coated or packed catalysts) that can reduce leaching or high pressure drop generated are under development. Proper fluid distributor designs have been developed for the effective numbering-up of microreactors without losing inherent multiphase flow advantages in microreactors.

The conversion of biomass derivatives in continuous flow microreactors can give important insights in chemistry, catalytic performance and reactor engineering concepts in the research laboratory, further accelerating technological developments in the field. Also from an economic perspective, the local small-scale production of chemicals or fuels in a "micro-biorefinery" could be a solution to the logistic issue that may arise in the transition towards a biobased economy. However, for industrially relevant biomass conversion processes, the integration of microreactors with many other conventional reactors and separations steps needs to be performed in order to make a sound techno-economical evaluation on the application potential of microreactor technology.

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Conflict of Interest

The authors declare no conflict of interest.

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