

Carbohydrates derived platform molecules with an emphasis on the production of 5chloromethylfurfural from starch

By

Cora Sofía Lecona Vargas

Department of Bioresource Engineering Faculty of Agricultural and Environmental Sciences Macdonald Campus, McGill University, Montreal Ste-Anne-de-Bellevue, Quebec, Canada

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Abstract

The conception of biorefineries to address our needs in fuels, fine chemicals, and polymers production is of interest due to the need to decrease environmental pollution, improve or valorize biomass utilization, and decrease our dependence on petroleum. The carbohydrates found in biomass can be transformed into platform chemicals that serve as intermediates for the production of several product types, including fuels, polymers, drugs, and so forth. The purpose of this thesis was to design a green catalytic system for the production of platform chemicals such as 5-hydroxymethylfurfural (5-HMF) and 5-chloromethylfurfural (5-CMF) from starch. The selected starting material, starch, is widely available and can be found in common food wastes.

An overview of carbohydrate-based biorefineries for the production of 5-HMF is given, including pre-treatment methods for lignocellulosic feedstock and a description of the synthetic routes for 5-HMF starting from carbohydrates, including the use of novel systems such as ionic liquids and deep eutectic solvents. The further transformation of 5-HMF into valuable chemicals such as 2,5-furandicarboxylic acid (FDCA) by the use of metal-catalyzed systems and electro-catalytic systems is also discussed. The review also covers the separation techniques for platform chemicals produced in biorefineries, which is critical for the future scale-up of these novel processes.

As part of this work, a low transition temperature mixture composed of choline chloride, citric acid and boric acid was prepared. This catalytic system was found to be suitable for the synthesis of 5-chloromethylfurfural and 5-hydroxymethylfurfural from starch. The synthesis was conducted in a biphasic system using dichloromethane as the extracting solvent into a closed high pressure vessel. The system was optimized using the response surface methodology and it was found that at 100 °C and 90 min of reaction time, up to 17 mol% of 5-HMF and 13 mol% of 5-CMF was produced. At the optimized conditions (120 °C and 135 min) up to 33 mol% of 5-CMF was obtained, with less than 1 mol% 5-HMF. The 5-CMF presented some advantages over 5-HMF due to its hydrophobicity that facilitates its extraction from the reaction medium. Moreover, it was shown that the low transition temperature mixture used in this study could be reused for at least five times. This work opens a new alternative for the synthesis of 5-CMF in eutectic solvents without the use of either HCl or metal chlorides.

Résumé

La création de bioraffineries pour répondre à nos besoins en production de carburants, de produits chimiques fins et de polymères est de plus en plus étudiée afin de réduire la pollution de l'environnement, d'améliorer ou de valoriser l'utilisation de la biomasse et de réduire notre dépendance au pétrole. Les glucides présents dans la biomasse peuvent être transformés en produits chimiques de type plate-forme qui servent d'intermédiaires pour la production de plusieurs types de produits, notamment des carburants, des polymères, des médicaments, etc. L'objectif de ce mémoire était de concevoir un système catalytique vert pour la production de 5-hydroxyméthylfurfural (5-HMF) et de 5-chlorométhylfurfural (5-CMF), deux plateformes chimiques prometteuses. Le matériau de départ sélectionné était l'amidon, qui est largement disponible et peut être trouvé dans les déchets alimentaires courants.

Un aperçu des bioraffineries à base d'hydrates de carbone pour la production de 5-HMF qui inclue les méthodes de prétraitement pour les matières premières lignocellulosiques ainsi qu'une description des voies de synthèse du 5-HMF à partir d'hydrates de carbone de façon conventionnelle mais aussi de par l'utilisation de nouveaux systèmes tels que les liquides ioniques et les solvants eutectiques a fait l'objet d'une revue de la littérature. La transformation ultérieure du 5-HMF en produits chimiques de haute valeur tel que l'acide 2,5-furandicarboxylique (FDCA) par l'utilisation de systèmes catalysés par des métaux et de systèmes électro-catalytiques est également discutée. Cette revue couvre également l'un des sujets les moins discutés dans la littérature actuelle, à savoir les techniques de séparation des produits chimiques de type plate-forme produits dans les bioraffineries, ce qui est essentiel pour la future mise à l'échelle de ce nouveau procédé.

Dans le cadre de ce mémoire, un mélange à basse température de transition composé de chlorure de choline, d'acide citrique et d'acide borique a été préparé. Ce système catalytique s'est avéré adapté à la synthèse de 5-chlorométhylfurfural et de 5-hydroxyméthylfurfural à partir d'amidon. La synthèse a été réalisée dans un système biphasique utilisant du dichlorométhane comme solvant d'extraction dans un réacteur fermé à haute pression. Le système a été optimisé en utilisant la méthodologie de surface de réponse et il a été constaté qu'à 100 °C et 90 min de temps de réaction,

jusqu'à 17 % en moles de 5-HMF et 13 % en moles de 5-CMF étaient produits. Dans les conditions optimisées (120 °C et 135 min), jusqu'à 33% en moles de 5-CMF ont été obtenus, avec moins de 1% en moles de 5-HMF. Le 5-CMF a présenté certains avantages par rapport au 5-HMF du fait de son hydrophobicité qui facilite son extraction du milieu réactionnel. De plus, il a été démontré que le mélange à basse température de transition utilisé dans cette étude pouvait être réutilisé au moins cinq fois. Ce travail ouvre une nouvelle alternative pour la synthèse de 5-CMF dans des solvants eutectiques sans l'utilisation de HCl ni de chlorures métalliques.

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Contribution of authors

This thesis is submitted in the form of original papers submitted to peer-reviewed journals. The candidate, Cora Sofía Lecona Vargas, was responsible for designing and conducting the experiments, handling the data analysis, as well as the preparation of the manuscripts and the thesis. Marie-Josée Dumont, supervisor of the candidate, and Valerie Orsat, co-supervisor of the candidate, contributed to all aspects of this research work. They provided assistance, including planning and directing the research, editing and reviewing the thesis and the manuscripts before submission for publication.

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Chapter 1

1.1 General introduction

The emissions of CO_2 from fossil fuels became the dominant source of anthropogenic emissions in the last decades, and they have continued to increase until our days, reaching around 40 billion metric tons of fossil CO_2 emissions per year [1]. However, a vast majority of the industrial activities is based on the petroleum refinery process for the production of transportation fuel, finechemicals, polymers, agrochemicals and even clothes, which shows the strong dependence on this unrenewable resource [2]. For that reason, it is important to switch to more sustainable alternatives, such as the use of biomass in biorefineries.

Both agricultural and food wastes are abundant sources of biomass. Their conversion into valueadded products would prevent their accumulation in landfills, where they contribute to the emission of greenhouse gases [3]. Agricultural and food wastes can contain important amounts of lignocellulose, starch, and free sugars. Those carbohydrates can be transformed into platform chemicals, which are intermediate compounds that due to their chemical structure and functionality can serve as starting materials for the production of high value added molecules, offering flexibility to biorefineries [4].

One of the most researched platform molecules is 5-hydroxymethylfurfural (5-HMF), which is a great candidate due to the high functionality that allows its further transformation. This molecule is obtained from the dehydration of carbohydrates [5]. The analogous molecule, 5-chloromethylfurfural (5-CMF) is emerging as a great platform chemical candidate, with some advantages over 5-HMF. As such, 5-CMF is easier to recover from the reaction medium due to its hydrophobicity, which protects the molecule from degrading into by-products [6].

For the dehydration of carbohydrates, the use of low transition temperature mixtures (LTTMs) such as deep eutectic solvents (DES) has surged as a green alternative over other catalytic systems. This is due to their physicochemical characteristics, such as low vapour pressure, low flammability and high tunability, which allows to design LTTMs as catalysts for different types of reactions [7].

1.2 Study objectives

The general objective of this thesis was to design a green catalytic system for the synthesis of platform molecules such as 5-HMF and 5-CMF, using carbohydrates that can be found in food wastes as starting materials. The selected starting material was starch, which composed of α -(1,4)-linked D-glucose residues.

Specific objectives:

- To prepare deep eutectic solvents (DES) using mixtures of choline chloride and citric acid in combination with other catalysts such as boric acid.
- To synthesize 5-HMF and 5-CMF from starch using the DES previously prepared as solvent and catalyst
- To optimize the synthesis parameters through the response surface methodology in order to maximize the yield of platform chemicals
- To assess the recyclability of the proposed system.

Chapter 2

Carbohydrate-based biorefineries for the production of 5hydroxymethylfurfural and 2,5-furandicarboxylic acid and their separation and purification methods

2.1 Introduction

Fossil fuels contribute largely to greenhouse gas emissions, and their contribution has steadily increased over the years reaching 36.8 Gt of fossil CO₂ emissions in 2018 [1]. Petroleum derivatives are used extensively for transportation, energy, and as raw materials for industrial activities. For example, the chemical industry is based on 6 basic chemicals (ethylene, propylene, olefins, aromatics, xylenes, and methane) to produce a wide range of products. Fossil fuels derived polymers are present in all kinds of containers, adhesives, and toys, amongst others, while fine chemicals are used for the production of pharmaceuticals and everyday life products such as detergents and cosmetics [2]. Therefore, to substitute petrol for a more environmentally friendly resource, new routes of chemical transformation need to be established, from the selected raw biological materials to the final consumer products.

The concept of biorefinery has surfaced in recent years as an option to address those concerns, by the utilization of biomass to transform its constituents into biofuels, biopolymers, high-value products, and fine chemicals as well as the generation of power [8].

The International Energy Agency (IEA) defined biorefining as the "sustainable processing of biomass into a spectrum of marketable biobased products and bioenergy"[9]. This definition takes into account the production of chemical products or materials, as well as fuels or power as a source of energy, which is similar to the traditional refinery concept based on fossil fuels; the main differences with traditional refineries are the use of biomass, which is a renewable resource, and the sustainability of the processes.

The biomass, which is the biogenic matter produced by biological processes [10], can be composed of different biomolecules such as proteins, lipids, carbohydrates, and lignin, among others. Carbohydrates, including starch, cellulose, hemicellulose, and free sugars, can be used to produce the platform chemicals identified in 2004 by the US Department of Energy [11], and those identified in the revised list of Bozell, J.J. and Petersen G. R. (2010)[4]. According to the type of biomass used, biorefineries are classified in generations, where the first generation of biorefineries uses purified feedstock from food sources (such as sugars and vegetable oils), the second generation uses non-food sources (such as agricultural and food wastes), and the third generation uses oil-rich algae as biomass source [12, 13].

Food wastes are defined as the part of biomass which is discarded during one of the stages of the food supply chain, i.e. agriculture and processing, handling and storage, retail market, or during the final consumption [14]. The use and valorization of food wastes fit into the circular economy model of biorefineries, taking into account that 45% of fruits and vegetables are wasted every year along the line of the production-to-consumption [15].

The use of biological feedstocks to produce new materials is related to the concept of bioeconomy. That concept refers to the scenario where the industrial inputs are derived from biological renewable sources [16]. However, this concept does not consider the circularity of the process, where the life cycle of the product is re-defined in a way that the residues are reduced or re-utilized, for example by using the by-products as a resource of another industry. Both terms, circular economy and bioeconomy, can synergize each other, integrating both principles. The integrated concept was called Circular Bioeconomy [16] and refers to the use of biological renewable resources as an industrial raw material, focusing on the reduction of resource consumption and the utilization of by-products. Biorefineries are aligned with that concept as biomass is used for the production of different products in a sustainable circular manner (Fig. 1). Additionally, biorefineries can create employment opportunities, helping not only to fix the environmental concerns, but also the economic and social concerns [17].



Figure 1. Schematic representation of circular biorefining

One of the key platform molecules for the biorefinery industry is 5-hydroxymethylfurfural (HMF), the dehydration product of hexoses. The worldwide market size of HMF was estimated at USD 61 million in 2022, and there is an increasing number of small-scale production plants, mainly established in Europe (AVA Biochem, Robinson Brothers) and China (Sugar Energy, Beijing Lys Chemicals, Xuzhou Ruisai Technology, Wutong Aroma Chemicals) [18]. However, its high production cost hinders its larger scale production, therefore the focus of the current research is on searching for cheaper end-to-end processes using low-cost feedstock [18, 19].

Through the catalytic oxidation of HMF, 2,5-furandicarboxylic acid (FDCA) can be obtained. FDCA can be polymerized with ethylene glycol to produce poly(ethylene furanoate) (PEF), a possible replacement for the polyethylene terephthalate (PET) plastics with superior mechanical properties [20]. That, combined with the biocompatibility and biodegradability of FDCA make it an attractive substitute for petrochemicals. The market size for FDCA was USD 441.5 million in 2020, but it is expected to rapidly grow and reach USD 857.3 million by 2028 due to the regulations on plastic use and carbon emissions [21-23]. Important FDCA market players are Avantium Holdings NV, Synbias, Carbone Scientific, V&V Pharma Industries, Tokyo Chemical Industry, Novamont SPA, among others [21].

Numerous holistic reviews of platform chemicals derived from biomass have been published, such as Takkellapati, S. (2018) [24] and Esposito D. (2015) [25], however, the aim of this review is to introduce the reader to the utilization of carbohydrates from food wastes for the production of valuable chemicals, with focus on HMF and its derived product FDCA. This review also opens a new perspective on the current research towards the development of separation methods that allow the scaling-up of novel synthetic routes for platform molecules. First, the type of biomass and its processing, including pre-treatment methods for lignocellulosic feedstock, are summarized. Then, some synthetic routes for HMF and FDCA are presented, exploring from the traditional use of acids and metals catalysts to the use of green solvents such as ionic liquids and deep eutectic solvents. Finally, the separation and purification methods currently cited in the literature are explored, from the most traditional methods like liquid-to-liquid extraction to the more specialized absorption-based methods.

2.2 Types of feedstock and pretreatments for lignocellulosic biomass

According to the Food and Agriculture Organization of the United Nations, food loss and waste can occur in any part of the supply chain, from food suppliers to retailers and consumers. Food loss can be as high as 25 % for roots, tubers and crops, and around 22 % for fruits and vegetables [3]. The residues obtained from fruits and vegetables contain significant quantities of carbohydrates and lignocellulosic biomass (Table 1) which can be used for the production of chemicals and materials.

Carbohydrates are biomolecules of polyhydroxylated aldehydes and ketones which can be "simple" (monosaccharides) or "complex" (disaccharides or polysaccharides). As a consequence of the chiral centers present in all monosaccharides, different stereoisomers exist in nature, in L and D configurations [26]. Starch for example consists of two main macromolecules known as amylose and amylopectin. Those polysaccharides are chains of α -(1,4)-linked D-glucose residues, interconnected through α -(1,6)-glucosidic linkages. It can be found in tubers, legumes and cereals [27-29]. To be considered as a good source of carbohydrates for biorefineries, the biomass used should not compete with food, for instance, carbohydrates can be extracted from unconventional sources such as fruit seeds and peels, often discarded during processing [28]. Good sources of

starch are avocado, mango, and jackfruit seeds as well as potato peels (Table 1). The chemical composition of fruit peels will depend, among other factors, on the maturation stage. For example, in banana and plantain at early stages, the starch content is elevated, but as the fruit is aging, the starch is hydrolyzed into simple sugars [30]. The use of mature peels can be advantageous as simple sugars are easier to extract for example in alcohol or water [31], however the lignin content tends to increase with maturation, interfering during the processing of the biomass [30]. Orange peels are also a good source of starch and present a low lignin content [31].

Food wastes with high sugar content							
Biomass source	Starch	Free	Cellulose	Hemicellulose	Lignin	Reference	
	(%)	sugars	(%)	(%)	(%)		
		(%)					
Mature banana peel	2.6	33.2	15.6	0.4	13.3	[30]	
Silk banana pulp	7.5	22.8 ^a	-	-	-	[32]	
Mature plantain peel	0.1	38.3	6.1	0.3	15.0	[30]	
Orange peel	<1.0	15.0	11.9	14.5	2.2	[31]	
						[33]	
	Agri-fo	ood wastes	with high lig	gnocellulosic con	tent		
Biomass source	Starch	Free	Cellulose	Hemicellulose	Lignin	Reference	
	(%)	sugars	(%)	(%)	(%)		
		(%)					
Banana rachis	-	-	23.0	11.2	10.8	[8]	
Apple pomace	-	2.2	14.3	11.4	29.2	[34]	
Mango peel	-	-	9.2	14.5	4.2	[33]	
Wheat Straw	-	-	35.0-39.0	23.0-30.0	12.0–16.0	[35]	
Barley Straw	-	-	36.0-43.0	24.0-33.0	6.3–9.8	[35]	
Rice Straw	-	-	29.2-34.7	23.0-25.9	17.0–19.0	[35]	
Corn Cobs	-	-	33.7-41.2	31.9-36.0	6.1–15.9	[35]	
Sugarcane Bagasse	-	-	25.0-45.0	28.0-32.0	15.0-25.0	[35]	
Food wastes with high starch content							
Biomass source		Starch (%	()	Sugars (%)	Fiber (%)	Reference	
Potato peel extracts		66.8		1.4	-	[31]	
Avocado seeds		27.5–29.	8	4.6–7.4	7.6–8.6	[28]	
Jackfruit seeds		60.0-80.	0	-	-	[28]	
Mango kernels		58.9–64.	0	-	-	[28]	
Green banana peel		14.0		1.4	36.3	[30]	
Green plantain peel		39.3		4.3	29.7	[30]	

Table 1. Composition of some agricultural and food wastes

^{a.} Sucrose 7.2 %, Glucose 4.6 %, Fructose 11.0 %

Lignocellulosic biomass is the most abundant type of biomass and can be found as part of the cell walls of plants for instance in common agricultural residues such as wheat, barley and rice straws and in corn cobs. It is mainly composed of cellulose (40-50 %), hemicellulose (25-30 %) and lignin (15-20 %) [36]. Cellulose is a linear polysaccharide composed of anhydro-D-glucose monomers linked by a β -(1,4)-glycosidic bond. Hydrogen bonds are highly present within adjacent hydroxyl groups and between chains. These interactions confer high stability to the molecule and promote the formation of crystalline regions and the arrangement in the form of fibrils [37]. Hemicellulose is a branched polysaccharide composed of pentoses such as xylose and arabinose, and hexoses, such as mannose, galactose and glucose, linked by β -(1,4) glycosidic bonds [38]. Lignin is an aromatic macromolecule, composed of phenylpropyl alcohols [39]. It is a high molecular weight, branched heteropolymer, composed of monomeric units or monolignols such as coniferyl, guaiacyl (G), syringyl (S) and p-hydroxyphenyl (H) units [40]. The three polymers interact via ionic, covalent, hydrogen, and aromatic bonding, thus conforming a very tight and recalcitrant structure [40], as can be expected, due to the strong interactions between the lignocellulosic components, it results challenging to process it, therefore, the first step for the utilization of this type of biomass consist in different kind of pretreatments.

The pretreatments can be classified as physical, chemical, physicochemical and biological (Fig. 2) [41]. The type of pre-treatment chosen depends on the chemical characteristics of the biomass (cellulose/hemicellulose/lignin content), the costs and the desired final products [41].



Figure 2. Types of lignocellulosic biomass pretreatments

2.2.1 Physical pretreatments

Physical pretreatments can be performed by mechanical means as well as the application of electromagnetic or sound waves to facilitate the rupture of lignocellulosic biomass. The mechanical pretreatments can be used alone in low-lignin content biomass, or combined with chemical or biological methods [41]. Depending on the purpose of the pretreatment, the proper equipment needs to be chosen (Table 2) [42].

Equipment	Principle	Advantages	Drawbacks	Energy
Disc mills	Material passes between two rotating discs causing friction and grinding. Discs can contain notches. Size ranges from 300- 200 µm.	Efficient in grinding fibrous materials. Narrow particle size distribution	Small operating volume.	Milling of wood material 4.2 MW h/ton
Attritor and bead mills	Reactor filled with grinding bodies. It has a rotating impeller.	Particles being ground cannot leave the contact zone. When the size of the grinding media is small enough (\leq 300 µm), nanosized particles are obtained.	It is difficult to isolate grinding products when dry grinding. High wear of grinding media elevates cost of operation.	n.d.
Ball mills	Biomass is placed along with grinding bodies in a rotating cylinder. The friction between the cylinder walls and grinding bodies causes the movement of bodies, which start to grind the material.	Good for laboratory-scale research, even at not optimized conditions the material will be ground. In some cases, the particles of the material act as grinding bodies (auto-grinding).	Low production capacity. It generates high frequency mechanical vibrations requiring the equipment to be installed in a separate foundation.	0.4 MW h/ton
Hammer and knife mills	This type of equipment contains one or two discs with grinding elements (hammers or knifes). The material is dispersed to the walls due to	High production capacity. Narrow size distribution.	Reduce particle size only to several millimeters. Mesh size less than 1mm able to resist high mechanical loads are very expensive. Used	1.5- 0.7 MW h/ton

Table 2. Examples	of equipment	used for mechani	cal pretreatment [42].
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centrifugal forces,	only for pre-
where it is	grinding
exposed to	
grinding	
elements.	

A mechanical pretreatment can be considered as mechanochemical when there are chemical effects due to the mechanical forces applied. For example, it has been demonstrated that by ball-milling, the cellulose will not only reduce the particle size, but also the crystallinity and degree of polymerization. By the combination of mechanical treatments with solvents or catalysts, a synergistic effect can be observed. Some examples are the addition of acids or bases during wet ball milling, the addition of a solid catalyst such as metal oxides or resins (mechanocatalytic approach) [43] or even the addition of enzymes during milling (mechanoenzymatic approach)[44]

On the other hand, the radiation-based methods take advantage of both ionizing and non-ionizing waves, modifying the structure of biomass, making easier the depolymerization of cellulose and hemicellulose. For instance, electromagnetic ionizing waves such as gamma rays can be applied to biomass for the formation of radicals and subsequent breakdown of the crystalline regions of cellulose, and the rupture of glycosidic bonds [41, 45]. Microwaves are non-ionizing electromagnetic waves of frequencies ranging from 300 MHz to 300 GHz, which are absorbed by the molecules causing changes in the vibrational energy and heat [46]. The heat generated along with the pressure of the system (thermal effect) cause the disruption of lignin from the matrix, and the electromagnetic field (non-thermal effect) causes a realignment of the polar molecules, triggering the rupture of hydrogen bonds [41]. Those changes prepare the biomass for subsequent chemical or enzymatic treatment [38].

Ultrasound waves in the ranges from 20 kHz–1 MHz are sound waves used in chemistry processing [45]. They alter the structure of lignocellulosic biomass by the formation of oxidizing radicals and the development of bubbles. These effects cause the rupture of α -O-4 and β -O-4 linkages of lignin, separating it from the polysaccharides [41, 47]. The effects of ultrasound waves can be explained by the differences in pressure into a liquid for mechanoacoustic and sonochemical processes. The regions of high pressure suffer from compression, and those of low-pressure present rarefaction, stretching the liquid molecules and creating cavities or bubbles. Some bubbles can collapse during

compression of the wave reaching localized high temperatures and pressure, thus resulting in the formation of radicals [48].

Ultrasounds are usually combined with other pretreatments such as organosolv or ionic liquids. For example, Lee et al. (2020) utilized an ultrasound assisted organosolv pretreatment for oil palm fruit bunches. The biomass contained 44.4 % of cellulose, 23.0 % of hemicellulose, and 23.2 % of lignin, and the optimal conditions were 48.2 °C, 30 min and 192.5 W (sonication power) using ethanol (60 %) as the solvent. Ultrasound power over 210 W resulted in a lower reducing sugars yield, maybe due to the high amount of cavitation bubbles formed, which impede the energy transfer. The concentration of ethanol had a direct correlation with lignin removal, however, when using a concentration higher than 60 %, the reducing sugars degraded [49].

2.2.2 Chemical pretreatments

Under this classification, we can find the application of acids, bases or solvents for the dissolution of different components of lignocellulosic biomass, making easier the access to cellulose or hemicellulose for further processing.

The use of organic or inorganic acids is common to degrade and solubilize hemicellulose into monomeric sugars such as arabinose and xylose, making cellulose more accessible for reaction [50]. However, strong mineral acids are corrosive, and organic acids such as acetic acid, oxalic acid or maleic acid can be used instead [51]. Liu et al. (2021) pretreated wheat straw using maleic acid, a dicarboxylic acid, and compared the results against sulfuric acid. According to the results obtained, sulfuric acid, hydrolyzed hemicellulose into xylose obtaining a good recovery yield (more than 74 %) at a temperature of 130 °C, however, at higher temperatures, xylose decomposed into furfural. Using maleic acid, the best results were obtained at 150 °C, and furfural was obtained in a low yield (7 %). Although the use of strong acids can appear as an advantage for the production of furans, the furan derivatives can rapidly degrade into levulinic acid and various decomposition products at long reaction times [52].

In the case of an alkaline pretreatment, the process delignifies the biomass by breaking the bonds between the lignin and polysaccharides (ester, aryl ether and C-C bonds) [41, 53]. It also causes the swelling of the biomass and reduces the crystallinity and the degree of polymerization of cellulose [50]. However, it is inefficient in the case of biomass with high lignin content such as woody biomass (around 25 % lignin content), and for biomass with low syringyl-to-guaicayl ratio, particularly softwood [41, 54]. Moreover, dissolved lignin can form hydrophobic components which can precipitate back on the cell wall surface. One strategy is the use of surfactants which interact with the hydrophobic molecules, impeding the re-deposition of lignin onto the surface of biomass. As an example, Xu et al. [55] utilized a technique called surfactant-mediated alkaline pretreatment and combined a pretreatment of NaOH with Tween 40 as the surfactant. The yield of reducing sugars significantly increased from 287.8 mg/g in 0.6 % NaOH without tensioactive agent to 402.5 mg/g with Tween 40 and same NaOH concentration. Finally, it reached a value of 566 mg/g when using 1 % NaOH and 1 % of Tween 40 at 121 °C for 10 min [55].

On the other hand, organosolv pretreatment uses a wide variety of organic solvents sometimes in combination with acids or bases as catalysts, at a certain temperature (between 77-220 °C) and pressure, which can vary from atmospheric pressure to solvent-dependent pressure in closed vessels. Hemicellulose and lignin are dissolved in the organic solvent while cellulose remains in the solid fraction [56]. Organic solvents commonly used include low boiling point solvents, high boiling point solvents, organic acids, among others [57].

One of the advantages of low boiling point solvents such as methanol or ethanol, is that they are low cost, water miscible and can be easily recovered by simple distillation [58]. However, due to the volatility and flammability of these solvents, high pressure reactors are required. Unlike short chain alcohols, high boiling point solvents such as polyhydroxy alcohols can be used at atmospheric pressure. Some examples include ethylene glycol and glycerol [58], but contrary to low boiling point solvents, the energy demand for recovery is high. For that reason, organic acids are usually used instead, since their boiling point is between the aforementioned solvents. That condition allows to perform lignin extraction at mild temperature and pressure. Acetic acid and formic acid are commonly used organic acids [56].

Erdocia et al [59] observed that the chemical composition of the lignin extracted from olive tree pruning using acetic acid, formic acid or a mixture of acetic acid/formic acid was similar, however the average molecular weight (M_w) varied considerably between the treatments. In all the cases, 0.2 % HCl was used as the catalyst. However, when using acetic acid and acetic acid/formic acid, higher molecular weights and polydispersity were obtained (lignin $M_w = 16,416$ and 15,088 respectively), and in the case of formic acid, the M_w and polydispersity were lower (lignin $M_w =$ 7924). The authors attributed those differences to two effects. The first one was the formation of a carbocation in the side chains of lignin, which lead to condensation. The second effect is due to formic acid being stronger than acetic acid, therefore, the degree of cleavage of the ether bonds was higher using formic acid, obtaining lower molecular weights [59].

More novel solvents, such as ionic liquids (ILs) and deep eutectic solvents (DES), have been applied recently in the pretreatment of lignocellulosic biomass, as well as in the transformation of biomass into valuable chemicals, as will be explained later in this review.

ILs are organic salts, usually consisting of an organic cation and an inorganic anion. They are usually liquid at room temperature due to the asymmetric nature of the ions. They have good thermal stability, chemical stability, low vapor pressure, and are non-flammable. These properties make them suitable for biorefining applications during the pretreatment of biomass and the hydrolysis step [60, 61].

They are used during the pretreatment of biomass due to their ability to solubilize cellulose. This ability is mediated by the inorganic anion of the IL and its hydrogen bond basicity, which enables the formation of hydrogen bonds with the hydroxyl groups of the polysaccharide. For instance, chloride ions possess high hydrogen bonding basicity, thus, ILs containing Cl⁻ are good candidates for the pretreatment of biomass [61].

Ji et al [62] used [Bmim]Cl as the IL for the pretreatment of sugary food wastes and further conversion of carbohydrates into furanics. The pretreatment was coupled with ultrasounds and, according to the authors, the anions in ILs deprotonated the hydroxyl groups of the cellulose, allowing the interaction of the deprotonated oxygen with the organic cations of ILs, while the

ultrasounds enhanced the reaction. They also observed that the IL used as the solvent helped to obtain a higher yield during the catalytic conversion of carbohydrates into the final product [62].

Despite the advantages of ILs in the pretreatment of lignocellulosic biomass, these type of solvents are usually expensive and some of them have shown toxicity in model organisms such as *Vibrio fischeri* and *Daphnia magna* [63], hindering their use for industrial processes. DESs have surged as a good alternative due to the similarity on the physicochemical properties of the ILs but with the advantage of being cheaper and usually less toxic [64].

A DES is a fluid composed of two or more components able to self-associate usually by the formation of hydrogen bond interactions, which are combined in a specific molar ratio, which lowers the melting point of the mixture to a minimum. The most important characteristic of a DES is that at the eutectic composition, the mixture has lower melting points than its components, making possible to form fluids at low temperatures. In fact, the eutectic mixtures are composed of Lewis or Brønsted acids and bases, and are usually obtained by the complexation of a quaternary ammonium salt such as choline chloride with an anhydrous metal halide (type I), an hydrated metal halide (type II) or an hydrogen bond donor (HBD) such as carboxylic acids, alcohols or amides (type III) (Fig. 3) [65, 66]. Some eutectic mixtures of choline chloride are formed with carboxylic acids, and according to Abbott et al. (2004), two carboxylic acids are required to complex each chloride ion, therefore, molecules with one carboxylic group such as phenylacetic and phenylpropionic acids need to be combined in a proportion of 1:2 to reach the lowest melting point, while dicarboxylic acids such as malonic and oxalic acids are combined in a proportion of 1:1 with choline chloride.

The melting temperature of a DES is usually below 100 °C, and some of them are liquid at room temperature. In addition, they are non-volatile, nonflammable and some of them are biodegradable [67].

Lignin presents good solubility in DES while cellulose is basically insoluble, thus, DES can be used for lignin and hemicellulose removal from lignocellulosic biomass [68]. Different DES systems have been developed for the pretreatment of biomass, for instance, choline chloride/boric

acid/polyethylene glycol-200 for the pretreatment of wheat straw [69]; choline chloride/oxalic acid dihydrate for the extraction of polyphenols from chestnut shell [70]; choline chloride–glycerol and choline chloride–ethylene glycol for fermentable sugars production from common agri-food wastes [71].

Kohli et al [72] pretreated samples of miscanthus and birchwood using a DES assisted by microwaves, achieving more than 80 % of delignification of the biomass using the combination of choline chloride/formic acid and choline chloride/oxalic acid DES at a temperature of 130 °C in a reaction time of 30-60 min [72].



Figure 3. a. Types I, II and III DES, b. Example of a DES and the corresponding melting temperatures (Tm)

2.2.3 Physicochemical pretreatment

Physicochemical pretreatments combine physical and chemical factors for the pretreatment of biomass. This classification includes hydrothermal/liquid hot water, steam explosion and the combination with physical and chemical pretreatments.

Hydrothermal pretreatment uses hot water in the range of 170-230 °C, at high pressure, up to 5 MPa [47]. These conditions cause the formation of hydronium ions which act as catalysts and induce the release of acetic acid from the acetyl groups present in the xylan units of hemicellulose, with the production of uronic acid [73]. These acidic conditions induce the separation of lignocellulosic components [41]. With the aim of comparing the different hydrothermal pretreatments, a severity factor (R_0) is usually calculated in the literature, considering the time needed to achieve the maximum temperature of each autohydrolysis treatment, the time required for the entire heating cooling cycles, and the temperature profiles in heating and cooling processes [73-75].

On the other hand, steam explosion processing combines the chemical effect due to the hydrolysis of acetic acid and the mechanical fracture of biomass due to pressure changes. The main difference between steam explosion and liquid hot water is that for the first one, the pressure is not controlled, and the water is vaporized, thus the release of high pressure occurs suddenly, while for the second one, by maintaining the water as a liquid, the system is pressurized but the release occurs slowly and is more controlled [73].

2.2.4 Biological pretreatment

The biological approach utilizes enzymes and microorganisms to selectively degrade the lignocellulosic biomass. There are cellulolytic enzymes, ligninolytic enzymes, hemicellulolytic enzymes and lytic polysaccharide monooxygenases, which degrade selectively the substrate to convert it into saccharides and other valuable products. Those enzymes are usually produced by bacteria and fungi [76].

The biological pretreatment is considered eco-friendly, low energy, and simple in operation, but it is usually costly [77]. However, the process cost of enzymatic hydrolysis can be reduced by different approaches, for example, Marzo et al [78] produced their own enzymes for reducing sugar production by a technique called fungal solid-state fermentation. In this approach, the solid carbon source, which was the feedstock (sugar beet pulp), served as a support and an inducer for fungal growth and subsequent enzyme production [78].

In general, the whole process is affected by physical, chemical and biological factors, for example, the preferred levels of temperature vary between species; there exist psychrophiles (-15 to 10 °C), mesophiles (20–45 °C) and thermophiles (41–122 °C) microorganisms. Surface area also plays a vital role in the degradation of lignocellulosic biomass, higher surface areas can be achieved by mechanical reduction of particle size. Another important factor is the pH of the culture medium. After a few days of incubation, variations of pH levels are expected, and those changes can affect the enzymatic activity since the enzyme configuration changes. Near the optimum pH, the enzymes have the maximum activity, and the activity decreases as it moves away from the optimal value. At extreme pH values, the enzymes can denaturate and lose their activity [76, 79].

2.3 Synthesis of valuable chemicals from biomass

The polysaccharides obtained from the feedstock after pretreatment can be hydrolyzed to obtain simple carbohydrates, which can be converted into a wide range of biofuels, monomers, drug substances, and platform chemicals by different chemical pathways (Fig. 4).

For instance, aldohexoses (such as glucose, mannose and galactose) obtained from the hydrolysis of the saccharides, can be isomerized to the corresponding ketohexoses (as fructose in the case of glucose and mannose, and tagatose in the case of galactose)[80, 81]. Thereafter, ketohexoses can be dehydrated to form one of the most promising platform chemicals in sugar-based biorefineries, HMF, which is an aromatic heterocyclic compound containing an aldehyde and an alcohol group [12]. The presence of functional groups allows further reactions, making this compound a platform chemical. Just to mention some examples, it can be converted into 2,5-dimethylfuran (DMF), a fuel; 2,5-furandicarboxylic acid (FDCA), a monomer; or 2,5-diformylfuran (DFF), a pharmaceutical precursor [82]. More recently, new derivatives have been explored, as illustrated (Fig. 4.) 2,5-dihydroxymethylfuran (DHMF) is obtained by the selective hydrogenation of the aldehyde group in HMF, and is used as an intermediate for the production of resins, foams and polymers. With the full hydrogenation, the derivative obtained is 2,5dihydroxymethyltetrahydrofuran (DHMTHF), and it serves as a precursor of polyols and polymers

[82]. Another remarkable derivative is maleic anhydride (MA). MA is currently obtained from nbutane, a petrol-based compound, and is used for the production of resins and coatings. However, it can be also produced by the oxidation of HMF using vanadium based catalysts [82].

Many studies have been conducted in order to elucidate the transformation of HMF into different valuable chemicals, nevertheless, its synthesis still presents some complications since HMF tends to decompose into humins and polyfuranic resins under acidic conditions in aqueous media. One possible option to overcome that problem is the production of 5-(chloromethyl)furfural (CMF) instead. CMF has a similar reactivity to HMF with the advantage of being more hydrophobic, which allows its extraction using an hydrophobic organic media, maintaining the product safe from decomposition [6]. As a furanic compound, it can be converted into the same products as HMF, for example, into FDCA or into FDMC (2,5-furandimethylcarboxylate), which are both suitable for the production of polyethylene 2,5-furandicarboxylate (PEF) plastics [6].

Moreover, both HMF and CMF can be rehydrated to produce levulinic acid, another important platform chemical which can be transformed into levulinate esters, 5-aminolevulinic acid (DALA), 2-methyltetrahydrofuran (MTHF), and gamma-valerolactone (GVL), which can be used in the production of resins, pesticides, drug products, flavors, solvents, surfactants, among others [83].

Aldopentoses, such as xylose and arabinose, can be converted into furfural (FF), as shown in Fig. 4, and subsequently transformed into furfuryl alcohol, a precursor of resins, lubricants and synthetic fibers [84].

Lignin can potentially be used as a source of aromatic building blocks by depolymerization, for the generation of particles and nanocomposites for direct use as fillers, or for the formation of glues, resins and binders by repolymerization [25].



Figure 4. Diagram of reactions from carbohydrates to some derivatives[6, 81, 82, 84, 85]

2.3.1 Synthesis of HMF

The synthesis of HMF has been more studied starting from pure carbohydrates as feedstock, and the main goal is to achieve good yields using cheap and safe reagents with mild reaction conditions and scalable processes. Under the premise that food wastes contain polysaccharides, mainly starch and cellulose, the main steps involve the hydrolysis of glycosidic bonds in order to obtain monomers, mainly glucose, followed by the isomerization of glucose or other aldohexoses to obtain fructose, or the corresponding ketohexose, and finally a dehydration step to obtain HMF. The hydrolysis and dehydration steps can be mediated by a Brønsted acid, such as HCl, H_2SO_4 , or other donating H⁺ species; while the isomerization can be catalyzed by a Lewis acid [10]. The proposed systems to carry out those reactions include different types of Lewis and Brønsted acids as catalysts both in water or organic solvents and more recently, using ILs and DESs with or without any additional catalyst (Fig. 5) [10].



Figure 5. General representation of one-pot conversion of biomass into HMF

The isomerization step is usually one of the most challenging during the production of HMF. Industrially, it is performed using enzymes as catalyst (i.e. glucose isomerase), however, the use of enzymes is costly. Alkaline isomerization has been proposed as an alternative, by using Mg–Al hydrotalcites, and MgO, obtaining yields of isomerization of more than 50 % [80]. Nonetheless, Lewis acid catalysts have been more studied for the production of HMF to be combined with other acids that help in the dehydration step. For example, $CrCl_3$ in aqueous solution forms a $[Cr(H_2O)5OH]^{2+}$ complex and in contact with glucose, some water molecules are displaced from the complex sphere, allowing the ring-opening and therefore the isomerization of glucose into fructose [86]. Other active metal salts serving during the isomerization are Al(III) [87], Zn(II) [88], and Sn(IV) [89] salts. As an alternative to metal catalysts, boric acid has been proposed as a Lewis acid for the conversion of glucose into fructose as it can form borate complexes with carbohydrates [90].

Regarding the solvents, aqueous systems are commonly employed. Just to mention some examples, AlCl₃·6H₂O can reach a HMF yield of 61 % from glucose in a biphasic H₂O–NaCl/THF

system [87], SnCl₄ can produce 26-27 % mol of HMF from bread waste in ACN/H₂O, acetone/H₂O, and DMSO/H₂O systems [89], and a combination of FeCl₃ with AlCl₃ achieves a maximum yield of 49 % HMF from cellulose using choline chloride as an additive in an aqueous medium [91]. In this last case, choline chloride, at a maximum concentration of 50 % with water, helped to improve the yield by coordinating with the metal (Table 3) [91].

These acid aqueous systems sometimes lead to high formation of levulinic and formic acids due to the rehydration of HMF. As an alternative, ILs have surged as novel solvents due to their particular characteristics such as their ability to dissolve biomass, and the possibility of customizing them by adding functional groups that can facilitate the reaction, thus improving the yields. Some of the most common ILs used are 1-butyl-3-methylimidazolium chloride [Bmim]Cl; 1-butyl-3-methylimidazolium bromide [Bmim]Br; 1-ethyl-3-methylimidazolium chloride [Emim]Cl and 1-ethyl-3-methylimidazolium bromide [Emim]Br [92]. Just to mention some examples, a yield of 65.6 % HMF was achieved from glucose [93] and 64% HMF from starch [94] using [Bmim]Cl as the solvent and chromium chloride (CrCl₃) and aluminum chloride (AlCl₃) respectively as the catalysts.

In the other hand, DESs can be used as both solvents and catalysts for the conversion of different substrates into HMF. For example, the eutectic mixtures of ammonium salts containing carboxylic acids can provide an acidic media able to catalyze the hydrolysis and dehydration steps. Hu and coworkers [95] reported an impressive yield of more than 90 % HMF from fructose using a DES of choline chloride/citric acid. Moreover, the yield was as high as 64 % from inulin, a fructan polysaccharide using a choline chloride/oxalic acid system with a temperature as low as 80 °C, for two hours of reaction [96]. However, the yields obtained from glucose are less promising, around 21 % in choline chloride/citric acid using H₂SO₄ as co-catalyst (Table 3) [97]. This shows that the system does not catalyze the isomerization from glucose into fructose. To overcome this drawback, metal chlorides such as SnCl₄ have been added as co-catalysts to help with the isomerization step, achieving yields up to 64.3 % from glucose and choline chloride in the presence of water [98].

The direct use of lignocellulosic biomass for HMF production is more challenging due to the extra pre-treatment required, but there are some examples in the literature such as Kougioumtzis, M.A.

and coworkers (2018) [99], who modeled the production of HMF starting from hemicellulose free biomass. According to their study, the first step was the hydrolysis of cellulose using H₂SO₄, followed by the glucose dehydration with Sn20/ γ -Al₂O₃ catalyst in a DMSO/H₂O mixture. The unreacted solid fraction, consisting in lignin and humins, was separated and used for combustion. Other co-products produced were levulinic acid, formic acid, and lactic acid. Lactic acid is not frequently reported, and probably produced by the retro-aldol fragmentation of the hexoses [100]. The produced HMF (20.6 wt% yield) was extracted in dichloromethane to separate it from other products [99].

When using other lignocellulosic residues containing hemicellulose (such as wood, corn stove, and bagasse), the co-production of FF is expected (Table 3), as the reaction mechanism for the dehydration of pentoses to produce FF is very similar to the dehydration of hexoses to HMF. Usually the production of FF is faster due to the accessibility of xylan in the amorphous hemicellulose region as compared to the rigid crystalline structure of cellulose. One interesting example was reported using metal halides in combination with THF in water. The combination with FeCl₃ and THF/water demonstrated to be good for the co-production of HMF and FF in a one-pot reaction by presoaking the biomass in the THF/catalyst solution overnight (to let the acid catalyst penetrate into the pores of the biomass previous to the reaction). Up to 51% and 95% of HMF and FF respectively were obtained from maple wood [101]. Similarly, by using AlCl₃·6H₂O in a biphasic H₂O–NaCl/THF system, up to 35 % of HMF and 66% of FF from lignocellulosic biomass were obtained by microwave heating, without need of presoaking the biomass [87].

Fruit wastes are also a great feedstock option (Table 3). As previously discussed, these are a good source of simple sugars and starch, in addition to lignocellulose. One approach is the use of ILs that help to solubilize the biomass while serving as the reaction medium. For example, the pre-treatment of apple and orange wastes with the help of ultrasounds maximized the penetration of [Bmim]Cl, causing the breakage of hydrogen bonds and further hydrolysis of cellulose. That in combination with an acidic resin activated with -SO₃H groups as catalyst, the produced yields ranged between 42 and 44% of HMF from fruit wastes [62].

A very interesting study was recently published, using a mechanoenzymatic approach. This approach combined the mechanic ball milling of biomass with enzymes, in a way that the mechanical forces helped to deconstruct the biomass, allowing the enzymes to get introduced into the matrix for hydrolysis. By this method, the conversion of banana peels into HMF improved from 22.7 mol% without pretreatment to 71.9 mol% with the mechanoenzymatical pretreatment, using AlCl₃·H₂O/HCl as catalyst in a DMSO/water system [44].

As discussed, the development of methods that combine the pre-treatment of lignocellulosic feedstock and its conversion into platform molecules is of utmost importance for the future development of biorefineries from food wastes.

Feedstock	System	Conditions	HMF yield (%)	Ref.
Fructose	Imidazole and benzenesulfonic acid	100 °C / 3min	90.1 %	[102]
Fructose	Choline chloride / Maleic acid	90 °C / 1h	80 %	[103]
Inulin	Choline Chloride/Citric acid	50 °C/ 2h; 80 °C/ 2h	57 %	[96]
Inulin	Choline Chloride/ Oxalic acid	80 °C / 2h	64 %	[96]
Glucose	Water /MIBK Choline chloride AlCl ₃	150 °C / 15min Microwave	70 %	[91]
Glucose	Choline dihydrogen citrate / glycolic acid Boric acid	140 °C / 4h	60 %	[90]
Starch	Water /MIBK choline chloride, boric acid	195 °C / 60min	35.9 %	[104]

Table 3. Synthesis of HMF from different substrates

Rice waste	ChCl / water / MIBK, SnCl ₄	130 °C / 2h	61.3%	[105]
Cellulose	Water /MIBK Choline chloride AlCl ₃ / FeCl ₃	150 °C / 15min in microwave. Pretreated by ball- milling or [Bmim]Cl	49 %	[91]
Cotton	Choline Chloride/ pTSA	100 °C/ 90min	10.2 %	[106]
Herbal residues ¹	Choline chloride/ formic acid SnCl ₄	140 °C / 30 min One-pot	77.5 %	[107]
Maple Wood	THF/ water FeCl ₃	170 °C / 60 min One-pot	HMF: 51 % FF: 95%	[101]
Corn stover	THF/ water FeCl ₃	170 °C / 60 min One-pot	HMF: 45 % FF: 95%	[101]
Sugarcane bagasse	Choline chloride /lactic acid/water	100 °C / 4h in the DES as pre-treatment 140 °C / 1h	HMF: 54.75 % FF: 3.81%	[108]
Collected food waste	Water only	230°C / 15 min Microwave hydrothermal pre- treatment	4.61 %	[109]
Mango pulp and skin	H ₂ SO ₄ / water	150 °C, 20 min Thermal microwave treatment	21.2 %	[110]
Apple wastes	[Bmim]Cl / macroporous acidic resin	140 °C, 60 min, Ultrasound-[Bmim]Cl pre-treatment	44.66 %	[62]
Orange wastes	[Bmim]Cl / macroporous acidic resin	140 °C, 60 min, Ultrasound-[Bmim]Cl pre-treatment	42.15 %	[62]
Banana peel	Activated carbon in [Bmim]Cl	110 °C, 90 min Presoaked in H ₃ PO ₄	42.12 %	[105]

Pineapple peel	Activated carbon in [Bmim]Cl	110 °C, 90 min Presoaked in H ₃ PO ₄	47.82 %	[111]
Banana peel	DMSO/ Water, AlCl ₃ , HCl	140 °C / 1h, Mechano-enzymatic hydrolysis as pre- treatment	71.9%	[44]

¹ Anemarrhena asphodeloides Bunge

2.3.2 Synthesis of FDCA from HMF

2,5-furandicarboxylic acid (FDCA) is the monomer of polyethylene 2,5-furandicarboxylate (PEF), a potential substitute of polyethylene terephthalate (PET), that can be obtained by the catalytic oxidation of HMF by the aldehyde group oxidation or by the hydroxyl group oxidation (Fig. 6) The preferred route depends on the system conditions [112].



Figure 6. Possible routes of oxidation from HMF to FDCA

The synthesis reaction requires an oxidant, such as O_2 , air, H_2O_2 or other oxidizing agents; and usually an alkaline medium that helps to deprotonate the alcohol, and to solubilize the FDCA avoiding its deposition onto the catalyst surface [113]. The most common catalysts for this reaction are metals such as Pt, Pd, and Au, and are usually used in heterogeneous systems, which means that the catalyst is in a different physical state (Table 4). This can facilitate the later separation of the catalyst for reutilization. The use of a catalyst is imperative for the reaction to take place, otherwise the HMF is converted into levulinic acid, formic acid, furan and humins under basic oxidizing conditions [113]. Some researchers have also observed that the metal ions, such as Pd²⁺, are unable to catalyze the reaction, therefore the metallic particles with neutral charge are used
during the reaction, usually supported onto other materials. The supporting materials will also have an effect on the final yield, for example, a yield of 52 % FDCA was obtained from Pd supported onto TiO₂, in contrast to a 91 % yield obtained from Pd supported onto KF/Al₂O₃ [113].

Sometimes, a promoter can be added in order to enhance the activity, selectivity and durability of the catalysts. Some examples of promoters are copper in the case of gold catalysts and bismuth or lead in the case of platinum catalysts. This promoting effect was observed when Bi was applied onto Pt at a molar ratio of 0.2, enhancing the FDCA yield from 51 % to 83 % [114]. The addition of Bi protected the platinum from oxidation, therefore, increasing the durability of the catalyst [115].

Although the catalysts are usually removed by centrifugation or filtration, these steps result in some loss of the catalyst. Therefore, the separation and recycling properties need to be improved. One interesting approach to ease the separation is the use of magnetic catalysts. These can be recovered from the reaction medium by using a simple external magnet. Some examples of this approach are the use of palladium nanocatalyst prepared onto a support of magnetic hydroxyapatite containing Fe₂O₃, which can reach a yield of 92.9 % FDCA [116], and the use of platinum catalyst supported onto graphene oxide containing Fe₃O₄, which can yield 98 % of FDCA [117]. Recently, the development of electro catalytic systems has been explored for the selective transformation of HMF to FDCA. In this type of systems, the oxidation and reduction reactions require the use of electrodes, and some of the systems produce H₂ from the water split as shown in Eq. 1 [118]:

$$HMF + 2H_2O \rightarrow FDCA + 3H_2 \tag{1}$$

Depending on the configuration of the system, two electrodes, an anode and a cathode, are used for galvanostatic electrolysis, where the current is maintained constant. A three electrode system requires a working electrode, a reference electrode, and a counter or auxiliary electrode for potensiostatic reactions, where the potential applied to the working electrode is controlled [119]. In this last case, the auxiliary electrode needs to be introduced into a separate cell, which can be achieved using H-cell type cells. Some examples of reference electrodes are Ag/AgCl and saturated calomel electrodes (SCE). For counter electrodes, a Pt gauze or platinized Ti electrodes can be used. The yield of FDCA can reach 90 % by using Ni/NiOOH foam as working electrode [118].

Catalyst	Conditions	Oxidant	Base	FDCA yield	Ref.
Pd- ZrO ₂ /La ₂ O ₃	$T = 90 \text{ °C, } pO_2 = 1 \text{ bar,}$ 8 h, water	O ₂	NaOH 0.5 mol/L	> 90 %	[113]
Pt-Bi/TiO ₂	T = 100 °C, p air = 40 bar, 6 h, water	Air	Na ₂ C ₃	> 99 %	[115]
Au/TiO ₂ , microwave heating method	T~97 °C, p = 1 atm, 30 min, water	H ₂ O ₂	NaOH	> 99 %	[120]
Magnetic catalyst. Graphene oxide: rGO (Pt/Fe ₃ O ₄ /rGO)	T = 368 K, P= 0.5 MPa of O ₂ , 8 h, water	O ₂	base free	98 %	[117]
Magnetic catalyst. MnFe ₂ O ₄	T = 100 °C, 5 h, acetonitrile	tert-butyl hydroperox ide	base free	85 %	[121]
	Electrochemical	oxidation syste	ems		
Catalyst (working electrode)	Electrodes configu	iration	Media	FDCA yield	Ref.
Ni/NiOOH foam electrodes	Potentiostatic electrolysis in perforated platinized electr and Ag/AgCl as referen	flow cell using ode as cathode ce electrode	Alkaline media	~90 %	[118]
Ni2P nanoparticle arrays on nickel foam	Two-electrode electrolyzer, Ni ₂ P NPA/NF catalyst couple on both cathode and anode. Cell voltages of 1.65 and 1.80 V		Alkaline media	> 90 %	[122]
MnOx anode	Potentiostatic electrolysis, 6 Reference Ag/AgCl, coun	0 °C and 2.0 V. ter: Pt cathode	Acidic media	53.8 %	[123]

Table 4. Catalytic oxidation of HMF for the production of FDCA

2.4 Separation and purification methods

The separation of the final products in a biorefinery is a topic that has not yet been well addressed, despite its great importance for scalability. While the separation of ethanol in more traditional biorefineries can be achieved by simple distillation, this method is not preferable for furanic compounds, due to their poor thermal stability. For that reason, other separation techniques need to be assessed, such as liquid to liquid extraction, precipitation, adsorption, membrane separation, among others.

2.4.1 Liquid to liquid extraction

This technique is based on the affinity of solutes between two immiscible liquid phases, depending on their polar or non-polar character. When the system is at equilibrium, the solutes will be distributed mostly in the phase with which they have the highest affinity, in a proportion that is given by the partition coefficient, which is the ratio of the solute concentration between the extraction solvent and the reaction solvent.

Different methods are used in order to select the most suitable extraction solvent, and those methods take into consideration the molecular affinity and the capacity of dissolution of the solvent [124]. The Hansen solubility parameters (HSP) for example, calculates the affinity of a solvent with a solute using the cohesive force given by the sum of non-polar dispersion parameter, polar parameter, and hydrogen bonding parameter [125]. COSMO-RS is another method which help to estimate solvation and partition coefficients between a solute and certain solvents or mixtures, as well as other thermodynamic parameters [126, 127]. Apart from the partition coefficient, the solvent safety is another parameter to consider. For that reason, some guidelines, such as the CHEM21 selection guide [128], have been created to rank the solvents into safety categories, like problematic, hazardous and highly hazardous solvents [125].

Liquid to liquid extraction can be applied in several situations in biorefineries, for example, for the in-situ extraction of a product, the selective separation of a solute in a mixture, the recycling of the reaction solvent, or just as a preliminary step for the purification of a substance. HMF can be extracted in situ, which is beneficial when the synthesis is carried out in aqueous media, due to its decomposition. In the presence of water, there is a risk that HMF rehydrates and form levulinic and formic acids, and in the presence of a catalyst, it can polymerize to humins, decreasing the overall yield. Solvent extraction can help to avoid those side reactions, by using a biphasic system. In that way, HMF can be extracted from the aqueous medium as soon as it is generated. Some of the solvents frequently used are methyl isobutyl ketone (MIBK) and ethyl acetate [124, 129].

Sometimes, liquid extraction can be used to separate two compounds with similar characteristics from the same reaction mixture. For example, Wang and coworkers [130] tested the selective extraction of FF from a mixture of HMF and FF in aqueous media, which can be produced from biomass containing both cellulose and hemicellulose. In this study, different possible extraction solvents were tried, firstly by computational screening using COSMO-RS, and then tested experimentally. They found that FF can be selectively recovered from the mixture without carrying HMF, but HMF cannot be recovered selectively from the mixture. Suitable solvents for the selective extraction of FF were those which possessed a high partition coefficient for FF (P_{FF}), and a high separation factor (P_{FF} / P_{HMF}). In this case, toluene was the most suitable solvent to extract FF [130].

The liquid-to-liquid extraction can also be applied for the separation of HMF from ILs. HMF can be synthesized using ILs as the reaction media with good yields, however, the separation of HMF and recyclability of the IL is challenging [131, 132]. The main reason for the poor separation of HMF is the strong hydrogen bonding between ILs and HMF. For example, those IL containing an inorganic anion, such as Cl⁻ anion, which acts as a hydrogen bond acceptor, interacts with the hydroxyl group present in HMF [131]. Also other types of interactions such as van der Waals and π - π -interactions are present [133]. To overcome those problems, a good pair of solvent and IL anion needs to be found. To achieve this, the solvent should form strong hydrogen bonds with HMF, should have low boiling point for further separation, the IL and the solvent must present low mutual solubility, and the anion and the cation of the IL should have strong interactions [134]. In other words, the solvent with the highest hydrogen bond acceptor strength will be a better extraction solvent, and the IL with the anion with the lowest hydrogen bond acceptor strength will be the best IL due to the weak interaction with HMF. For instance, HMF can be extracted at 99 % after 3 successive extractions from [Hemim]BF₄ (low hydrogen bond acceptor strength) using THF (high hydrogen bond acceptor strength) as the extraction solvent [134].

Another approach to enhance the extraction of HMF from ILs is the addition of a promoter into the system. Promoters are molecules that interact with the IL (i.e. by hydrogen bonding formation) and compete with the solute. As an example, low chain alcohols like methanol and ethanol in a [Bmim]Cl/MIBK biphasic system can act as promoters to extract HMF, and due to their low boiling point, they can be recovered by distillation [131]. Water is also effective as a promoter in the [Bmim]Cl/MIBK system, but it was found that its presence can negatively affect the ability of [Bmim]Cl to dissolve cellulose if recycled [132].

Similar to promoters, the salting-out effect is widely used to stimulate the solute extraction from the reaction solvent, and this approach is known as "salt assisted liquid-liquid extraction" (SALLE). This consists in adding a salt, such as NaCl, Na₂SO₄ or MgSO₄, to favor the solvation of the salt in the solvent (for example water or an IL) and therefore decrease the interaction between the reaction solvent and the solute of interest, and promote its extraction [135, 136]. For instance, by adding NaCl into a MIBK/water system, the partitioning and separation factor of HMF can improve up to two times [137]. In the case of miscible systems, such as THF/water, by adding a salt, the system can become a biphasic system, able to extract the HMF from the aqueous medium [138].

It is important to wisely select the extracting solvent so it can be recovered by vacuum evaporation or used as the solvent for the following conversion steps of the product of interest.

2.4.2 Precipitation

Precipitation is a simple way to obtain a solute from a solution for further purification, and in this case, the solubility properties of the desired compound play a vital role. The compound of interest can be recovered from the solvent as an insoluble solid by changing the pH or adding an anti-solvent.

For example, Al Ghatta [139] separated FDCA from ILs by adding water to the system. The IL used, [Bmim]Cl, is highly hydrophilic, due to the hydrogen-bond interactions between the Cl⁻ anion and water, while FDCA presents low solubility in water. FDCA was dissolved in mixtures of [Bmim]Cl and water and it was found that FDCA can be dissolved in a system with 20 % water content, but its solubility decreases with further addition of water, and precipitates from the system [139]. This anti-solvent effect can be applied for the separation of FDCA and DFF dissolved in DMSO, a common reaction solvent for FDCA production, and in other ionic liquids such as [Bmim]Br and [Bmim]OTf. FDCA is not only insoluble in water, but also insoluble in other organic solvents such as GVL and THF, therefore, by adding water or one organic solvent, the FDCA can be precipitated from DMSO, thanks to the strong interaction of water with DMSO which makes DMSO unavailable to interact with DFF or FDCA [140].

Although the oxidation of HMF into FDCA has been widely studied in aqueous systems, FDCA remains soluble because the vast majority of systems are alkaline, therefore, the precipitation of FDCA requires to lower the pH of the medium. However, this approach needs high quantities of acid and can generate a large amount of salts [123]. To overcome that problem, Kubota and Choi [123] developed an electrochemical oxidation process for HMF by using a manganese oxide (MnO_x) anode at low pH, which allowed the formation of FDCA and its spontaneous precipitation from the aqueous medium [123].

Another interesting approach for isolating the compound of interest can be the precipitation of the reaction media. For example, HMF can be synthesized in tetraethylammonium bromide (TEAB) using Amberlyst-15 as the catalyst. For its isolation, the reaction medium was dissolved in hot ethanol, and then ethyl acetate was added to crystallize the TEAB. After filtration, HMF was recovered from the organic layer by evaporation of the ethanol/ethyl acetate mixture. By this method, up to 91% HMF with purity up to 99% was obtained from fructose [141]

2.4.3 Adsorption-based processes and nanofiltration

The adsorption-based methods utilize an adsorbent with affinity to the desired product, allowing the flush of the solvent and other solutes, followed by a recovery of the product using a solvent with good affinity. This needs to be combined with another separation process for separating the solute from the new solvent. Hsiao et al [142] developed a process of adsorption-desorption using a fixed-bed adsorption column made of polymer-based spherical activated carbon (PBSAC), to separate HMF from the aqueous reaction media, containing levulinic acid, formic acid, and fructose. They found that the hydrophobicity of the adsorbent was crucial for the selective adsorption of HMF. In this study, isopropyl alcohol was found to be an excellent desorption solvent, and was also used for the hydrodeoxygenation process to convert HMF into DMF [142].

The fixed bed adsorption method can be applied for the separation between HMF and FF. The difference in molecular size between HMF and FF allows the separation of the two compounds using modified zeolites. Zhao, Y. and co-workers [143] prepared imidazolate zeolites frameworks (ZIF) with the same chemical composition but different pore structure. In the case of MAF-6, it had spherical-shaped pores that allowed interaction with both HMF and FF, while in the case of MAF-5, the structure contained ellipsoidal pores with narrower windows. Thanks to the ellipsoidal shape, MAF-5 was more selective for the separation of the compounds, presenting higher affinity for FF due to its smaller size while HMF was scarcely adsorbed. After its adsorption, FF was recovered with ethanol, at a recovery rate of 93.5 % [143].

Simulated moving bed is another interesting chromatographic technique already used industrially for purification of pharmaceuticals and petrochemicals. This type of chromatography is more efficient than the traditional one, and can be used as a continuous process. The idea behind this technique is that in a mixture of two compounds, one of them will interact more strongly with the stationary phase (compound A) while the other will elute more rapidly with the mobile phase (compound B) (Fig. 7). If the stationary phase was able to move in the opposite direction to the mobile phase, compound A could be extracted at one end of the column and compound B at the other end. Of course, this is not physically possible, however, this movement can be simulated (simulated moving bed) by using a system with several interconnected columns with input and

output ports (Fig. 7). While the mixture is being separated, the compound that elutes first (compound B, raffinate) can be obtained from one output port and the other compound (compound A, extract) from another output port. If the input ports (desorbent and feed) and output ports (raffinate and extract) are interchanged in a series of steps, the raffinate and extract can be eluted continuously while the feed and the solvent are injected into the system, resulting in a more continuous and efficient process [144].



Figure 7. Representation of simulated moving bed chromatography

Simulated moving bed chromatography was applied for the separation of DMF from butanol, by using a zeolitic imidazolate framework-8 (ZIF-8) as the stationary phase and ethyl acetate as the desorbent. The difficulty in the separation of DMF and butanol lies in the high affinity between the two compounds, and their tendency to form azeotropes. However, DMF strongly interacted with ZIF-8 framework, allowing its separation from butanol. Moreover, the selected desorbent, ethyl acetate, does not form azeotropes with DMF, making feasible their separation [145].

Nanofiltration is a membrane-liquid separation method that requires the application of pressure through a semi-permeable membrane. This method can be cheaper than adsorption-based methods, thus being a promising alternative for the separation of products and solvent recovery. It was applied for the separation of HMF from [Bmim]Cl, after the reaction of glucose with chromium chloride as the catalyst. The reaction mixture was first filtrated to remove the insoluble humins,

and after the nanofiltration process, up to 95 % of HMF was recovered, while the recovered IL was reutilized for new reactions [93]

2.4.4 Sublimation, Distillation and Evaporation

In some cases, the sublimation and distillation are feasible techniques for the recovery of products. For example, DFF can be sublimated from ILs and collected onto a cooled surface (such as cold finger) due to the low volatility of ILs. Around 97 % of DFF can be recovered in high purity at 100 °C under vacuum from [Bmim]Cl and [Bmim]NTf₂. Even after 3h at 60 °C, more than 90% of the DFF can be recovered [139].

In the case of distillation, it can be used for the recovery of 5-methylfurfuryl alcohol (MFA) and 2-methylfuran (MF). MFA is the major intermediate for the synthesis of the biofuel DMF, and MF can be used as a fuel and fuel additive. They are synthesized from HMF and FF respectively. MFA can be obtained at a purity of >99 % when extracted with diethyl ether, by fractional distillation of the solvent, while MF can be directly recovered from the reaction mixture as vapor and collected into a condenser. After a re-distillation step, a purity of >95 % can be obtained [146].

FF has a boiling point of 161.7 °C and form an azeotropic mixture with water. Industrially, it is purified by distillation after its production. However, the distillation itself is an energy intensive process which results in high costs of production. Reactive distillation has been proposed as an alternative for FF purification. This approach consists in a different equipment design, which combines the reactor tank and the distillation column in a single unit [147].

Regarding evaporation, HMF and CMF have been recovered after the evaporation under vacuum from low boiling point solvents such as THF [148], ethyl acetate [149] and dichloromethane [149].

2.5 Concluding remarks

The use of biomass as a replacement for fossil fuels for the production of a wide variety of products, such as pharmaceuticals, additives, polymers, and fuels is a promising alternative that is aligned with the principles of circular bioeconomy. Much of the current research on the production of platform molecules such as HMF and FDCA focused on the search for more sustainable processes, the use of less dangerous solvents, and catalysts that are less harmful to the environment. Many improvements have been made over older processes, such as the replacement of corrosive acids with less dangerous ones; the development of catalysts with cheaper and less toxic metals; synthetic processes with lower reaction times and temperatures; the introduction of novel systems such as the deep eutectic solvents which can help to improve the yields without sacrificing the sustainability of the reaction, while keeping the cost reasonable. However, despite the great advances that have been made in the synthesis of these molecules, research continues facing two major challenges: the difficulty to directly use real biomass instead of purified carbohydrates, and the lack of definition regarding the separation of products for later use. Regarding the first point, some researchers have chosen to combine pre-treatment with hydrolysis and dehydration in the same reactor in two steps, and even in a single step, by the combination of physical and chemical techniques, which is an ideal approach for the creation of biorefineries. With regard to the second point, the separation of products of interest remains poorly addressed in the current literature, and it is a critical step for the feasibility to scale up these processes in the industry. Since complex mixtures of various high value-added products are obtained when working with biomass, it is of the utmost importance that the technology allows to extract each of these products, as it occurs in traditional refineries otherwise, biorefineries may not outperform their counterpart.

Connecting statement

The literature review (Chapter 2) presented an introduction to carbohydrate-based biorefineries for the production of furan derivatives with emphasis on 5-hydroxymethyl furfural (5-HMF) and 2,5-furandicarboxylic acid (FDCA) in different catalytic systems, such as deep eutectic solvents, and their separation strategies. 5-chloromethylfurfural (5-CMF), a molecule analogue to 5-HMF was introduced as an emerging platform and it is presented in more depth in the chapter 3. In this experimental section, the production of 5-HMF and 5-CMF using a deep eutectic solvent system is studied. As the separation strategy, a liquid to liquid extraction is used and the 5-CMF is recovered after evaporation of the solvent. The reaction conditions of the proposed system are optimized by means of the response surface methodology.

Chapter 3

One-pot conversion of starch into 5chloromethylfurfural and 5-hydroxymethylfurfural in a low transition temperature mixture

3.1 Introduction

The synthesis of platform molecules from biomass which serve as substitutes for petroleum products has been a topic of interest in recent years due to the environmental concerns caused by fossil fuel use. 5-hydroxymethylfurfural (5-HMF) is a very versatile platform molecule, as it can be converted into fine chemicals, monomers, and biofuels by its reduction, oxidation, and or esterification [150]. Amongst the methods used for the synthesis of 5-HMF from carbohydrates, it is common to find the direct addition of acids such as H₂SO₄ or HCl as Lewis acids, and the use of metal chlorides such as CrCl₂, CrCl₃, FeCl₃, and SnCl₄ as Brønsted acid catalysts. Regarding the solvents, water, DMSO, ionic liquids (IL) and deep eutectic solvents (DES) are often used [5].

The Low Transition Temperature Mixtures (LTTMs) have become popular due to their physicochemical properties such as low vapour pressure, low flammability and high tunability. LTTMs include DES and ILs, which are terms often confused, due to the shared characteristics between them. According to some authors, the term LTTMs refers to a mixture of molecules that present a low transition temperature from liquid to solid. More specifically, the ILs are organic salts and the DES are mixtures of hydrogen bond donors and hydrogen bond acceptors [151, 152].

The synthesis of 5-HMF using a DES of choline chloride/citric acid (ChCl/CA) in a molar ratio of 2:1 was reported with good yields from fructose (91.4% [95]) and inulin (57% [96]), However, 5-HMF production has not been as effective from glucose or starch in this same system [97], indicating that although the system is effective for hydrolysis and dehydration of fructose, it is not effective for isomerization of glucose to fructose. Therefore, a system that includes a Lewis acid could maximize the yields from substrates such as glucose or starch. Istasse et al. (2020) tried the formation of tetrahydroxyborate esters to enhance the isomerization step, reaching a yield of 19 mol% 5-HMF from glucose in choline chloride/o-hydroxybenzoic acid/boric acid [153]

5-HMF has the disadvantages of being unstable in acidic aqueous mediums, and to be difficult to isolate, which might limit its use for industrial purposes. 5-chloromethylfurfural (5-CMF) has been proposed as a functional alternative due to its hydrophobicity that favors its extraction from aqueous systems [6]. 5-CMF can be converted into fuel precursors such as 2,5-diformylfuran (DFF), furan-2,5-dicarbonyl chloride (FDCC), 2,5-dimethylfuran (DMF). Also, it can be converted into p-xylene, an important chemical for the polyethylene terephthalate (PET) industry. It can also be converted into levulinic acid (LA), another important platform chemical, by its hydrolysis with hot water [6, 154, 155] (Fig. 8)



Figure 8. Schematic representation for the conversion of 5-CMF into DFF in DMSO under heat, further conversion of DFF into FDCC with tert-butyl hypochlorite (t-BuOCl). Conversion of 5-CMF into DMF in Pd/C catalyst and an H-donor such as H₂ or polymethylhydrosilo

However only a few studies focusing on the synthesis of 5-CMF have been published, most of them limited to the use of concentrated HCl for its preparation, as proposed by Mascal and coworkers [156, 157]. Some variations of the process have been reported, by the addition of CrCl₃/ZnCl₂ as metal catalyst [158], the use of microwave heating [159], and the addition of benzyltributylammonium as phase transfer catalyst [160]. Other studies have reported blends of metal chlorides as part of eutectic solvents for the synthesis of 5-CMF from glucose and starch [161], showing that these are effective for the isomerization of glucose and for the halogenation of 5-HMF together with choline chloride. Likewise, boric acid has been shown to be a good catalyst

for isomerization of glucose [104]. On the other hand, methyl isobutyl ketone (MIBK), dichloromethane (DCM), and dichloroethane (DCE) have shown to be good extracting solvents for 5-CMF [149, 156, 162]. To date, no system for the synthesis of 5-CMF in eutectic solvents which does not use direct addition of HCl nor metal chlorides has been reported. The present study shows a recyclable alternative for the production of 5-CMF and 5-HMF from starch in LTTMs of choline chloride (ChCl), boric acid (BA) and citric acid (CA). The obtained product can be easily separated by liquid extraction and subsequent evaporation of the solvent.

3.2 Materials and methods

3.2.1 Materials

Choline chloride (>98%, Sigma), citric acid (>99.5%, Sigma-Aldrich), and boric acid (Fisher-Scientific) were used for the preparation of low melting mixtures. Starch (Sigma Aldrich), glucose (Sigma-Aldrich), and D-fructose (99%, Alfa Aesar) were used as substrates. Dichloromethane (anhydrous, >99.8%, Sigma-Aldrich), d-chloroform (99.8% atom% D, 0.03% v/v TMS, Aldrich), methanol (HPLC, >99.9%, Sigma-Aldrich), acetic acid (>99.7%, Sigma Aldrich) were used as purchased. Deionized water was added to the low melting mixtures as specified. 5-HMF (\geq 99%, Sigma-Aldrich) and 5-CMF (TRC, Toronto Research Chemicals) were used to build the calibration curves.

3.2.2 Low transition temperature mixtures preparation

ChCl was dried overnight in a vacuum oven prior to its use. The specified quantities of ChCl, CA and BA were weighted and mixed into a vessel (Table 5). The chemicals were heated at 90 °C using an oil bath with a magnetic stirrer until a uniform clear liquid was formed. The LTTMs were stored into a desiccator until use to avoid humidity absorption. The pH of the diluted LTTMs at 10% w/w in deionized water was determined using a digital pH meter from Fisher Scientific (Accumet, AB150). For the viscosity measurements, an Anton Paar modular compact rheometer (MCR-302) fitted with a parallel plate geometry was used. The complex viscosity was determined after equilibrating the samples at defined temperatures (30 °C, 40 °C and 100 °C) applying a shear rate of 1 Hz for 5 min at a constant strain of 0.4%.

Abbreviation	LTTM 1	LTTM 2	LTTM 3	LTTM 4	LTTM 5
ChCl (mol)	2	17	3	13	1
BA (mol)	-	3	1	7	1
CA (mol)	1	7	1	3	-

Table 5. ChCl, CA and BA molar ratio for the preparation of LTTMs

3.2.3 Conversion of substrate into 5-HMF and 5-CMF

For the conversion of carbohydrates into 5-HMF and 5-CMF, the LTTMs were weighted and mixed with water (5% w/w water content). The substrate loading was at 3% w/w, for a total of 5 g of reaction phase. For the monophasic reactions, the reagents were added into Pyrex tubes fitted with a high temperature seal. For the biphasic systems, due to the high boiling point of MIBK and difficulty during recovery, DCM was selected as the extracting solvent. The choice of DCM was also justified as it can be recycled after evaporation. The reaction phase along with 15 mL of DCM were added into a hydrothermal stainless-steel reactor. The samples were heated at the corresponding temperature during the reaction time, using an oil bath with magnetic stirring. At the end of the reactions, the samples were immediately cooled in a water bath to quench the reaction. For the biphasic reactions, the samples were mixed using a vortex to ensure complete extraction of the products before the separation of the phases and further analysis.

For the recyclability tests, after the separation of the phases, a new sample of substrate and 15 mL of DCM were added to the used LTTM phase, and the cycle was repeated 5 times.

3.2.4 Optimization using Box-Behnken design

For the optimization, the response surface methodology (RSM) with a Box-Behnken design was selected. This model is ideal to find the optimal conditions of the reaction and the variables interactions [163, 164]. The central point was replicated 5 times to estimate the variance. The chosen independent factors were temperature, time and proportion of BA over CA, which were selected according to preliminary experiments. The quantity of water, load of substrate, volume of DCM, stirring speed (rpm), and amount of LTTM, were kept constant for all experiments. The proportion of ChCl over CA was 2:1 and over BA was 1:1. The response variables were 5-HMF

yield (mol%), 5-CMF yield (mol%) and combined yield (mol%) (5-HMF yield (mol%) + 5-CMF yield (mol%)). The coded and uncoded values for the 3 required levels are shown in Table 6. The results were analyzed using SAS software (version 9.4). The adequacy of the model was studied by testing R^2 and lack of fit (p < 0.05)

Experiments	Time	Temperature	Boric Acid over	
	(min)	(°C)	citric acid (%)	
1	45 (-1)	80 (-1)	50 (0)	
2	135 (1)	80 (-1)	50 (0)	
3	45 (-1)	120 (1)	50 (0)	
4	135 (1)	120 (1)	50 (0)	
5	45 (-1)	100 (0)	30 (-1)	
6	135 (1)	100 (0)	30 (-1)	
7	45 (-1)	100 (0)	70 (1)	
8	135 (1)	100 (0)	70 (1)	
9	90 (0)	80 (-1)	30 (-1)	
10	90 (0)	120 (1)	30 (-1)	
11	90 (0)	80 (-1)	70 (1)	
12	90 (0)	120 (1)	70 (1)	
13	90 (0)	100 (0)	50 (0)	
14	90 (0)	100 (0)	50 (0)	
15	90 (0)	100 (0)	50 (0)	
16	90 (0)	100 (0)	50 (0)	
17	90 (0)	100 (0)	50 (0)	

Table 6. Box Behnken design with coded and uncoded values. The coded value is shown in parenthesis

3.2.5 Determination of 5-HMF and 5-CMF

The quantification of 5-HMF and 5-CMF was done using the method suggested by Antonyraj and coworkers [165] in a HPLC (Agilent 1100) using a reversed phase column Gemini C18 (150 x 4.5 mm, 5 μ m) at 30 °C, with a mixture of methanol and acetic acid 0.5% (70:30 v/v) as the mobile phase, using a flow rate of 0.5 mL/min and an injection volume of 5 μ L. The calibration curves were built at concentrations below 0.5 mg/mL for both 5-HMF and 5-CMF. The organic layer of the samples was diluted 6 times in DCM and the LTTMs phases were brought to a volume of 15 mL and then diluted by a factor of 5 in deionized water. All the samples were filtered through PTFE acrodisc filters (0.2 μ m) before injection.

The 5-CMF yield (mol%) and 5-HMF yield (mol%) were calculated as follows:

Eq. 1)

$$\frac{moles \ of \ product}{moles \ of \ substrate} \times 100$$

That is,

$$\frac{C_p\left(\frac{mg}{mL}\right) \times DL \times V(mL) \times MW_s\left(\frac{g}{mol}\right)}{W_s(mg) \times MW_p\left(\frac{g}{mol}\right)} \times 100$$

Where:

 C_p is the concentration of the product (5-CMF or 5-HMF) in the sample, calculated from the calibration curves, *DL* is the dilution factor, *V* is the final volume of the sample, W_s is the weight of substrate added, *MW_s* is the molar weight of the substrate, for starch it is considered the molar weight of anhydroglucose = 162 g / mol, *MW_p* is the molar weight of the product, for 5-HMF it is 126 g/mol, for 5-CMF it is 144 g/mol

The organic layer was used to identify the platform chemicals in a 6890N Agilent GC-MS equipped with a mass detector 5973 Network, using a HP-5 Agilent (30 m x 0.25 mm x 0.25 μ m) column. The temperature program used was 70 °C (3 min) – 20 °C/min – 250 °C (5 min) – 260 °C (10 min). The carrier gas was helium.

The collected organic layers from the samples were evaporated using a Rotavap. The brownish oily liquid obtained was diluted in d-chloroform. ¹H and ¹³C NMR spectra were recorded on Bruker 500 MHz spectrometer. Chemical shifts are reported relative to the resonances of CHCl₃ at δ (H) 7.27 ppm. The results were analyzed in MestReNova software (version 14.2.3).

3.3 Results and discussion

3.3.1 Low transition temperature mixtures preparation

Although the present work used a system that can correspond to a DES, without a complete physico-chemical characterization, the solvents in this work were referred as LTTMs, as suggested in the literature [151]. All LTTMs formed a single translucent phase that were liquid at room temperature, except for the LTTM 5 (BA: ChCl 1:1), which solidified at room temperature. LTTM 2 had the lowest pH (Table 7), which can be related to the lower pka of CA ($pka_1 = 3.09$, $pka_2 = 4.75$, $pka_3 = 5.41$) with respect to BA (pka 8.92-9.24 [166]). On the other hand, BA can react with alcohols and carboxyls, leading to the formation of esters with lower pKa values, which may explain why LTTMs containing all three components (ChCl, BA, CA) have lower pH values than LTTM 1 and LTTM 5 [166, 167].

With regards to viscosity, it can be observed that all LTTMs presented high viscosities (> 1000Pa.s) at 30 °C. The LTTMs 2, 3 and 4 had a decrease in their viscosity as the temperature increased however, LTTM 2 had the most substantial reduction (from 3728 Pa.s at 30 °C to 624 Pa.s at 40 °C, and 25.5 Pa.s at 100 °C) which is beneficial for the mass transfer of any reaction. LTTM 5 (containing only ChCl and BA) had the highest viscosity (1209 Pa.s at 100 °C).

A high viscosity value may be related to a strong molecular interaction and this may be due to the formation of hydrogen bonds, which reduce the mobility of molecules in LTTMs. A possible explanation of this is given by the hole theory. This theory states that an ionic material under melting conditions contains empty spaces due to the local fluctuation in density. Those empty spaces or holes are of random size and location and the distribution of hole sizes will determine the probability of movement [168]. This can be applied to DES, where the flow of molecules or ions within the matrix will depend on the free volume and probability of finding an empty space. With larger number of hydrogen bonds, smaller hole diameter, which lead to less mobility and higher viscosity [169, 170].

Temperature also has an effect on viscosity due to the structural changes that eutectic solvents undergo as the temperature increases [169]. This same temperature-dependent behavior has been observed in other studies where the viscosity of different LTTM and DES decreased with increasing temperature [171-173].

Abbreviation	LTTM 1	LTTM 2	LTTM 3	LTTM 4	LTTM 5
pH (10 % w/w)	1.86 ± 0.00	1.46 ± 0.03	1.49 ± 0.03	1.56 ± 0.01	5.26 ± 0.03
Viscosity at	n.d.	3727.5 ± 16.6	3392.0± 9.2	1999.5± 2.4	n.d.
30°C (Pa.s)					
Viscosity at	n.d.	624.2 ± 1.5	2318.1 ± 5.4	1238.0 ± 1.6	n.d.
40°C (Pa.s)					
Viscosity at	1.7 ± 0.1	25.5 ± 0.0	913.9 ± 6.3	376.9 ± 1.8	1208.9± 6.2
100°C (Pa.s)					

Table 7. Low transition temperature mixtures, pH and viscosities

n.d. not determined

3.3.2 Conversion of substrate into 5-HMF and 5-CMF, and their optimization

In a preliminary experiment, the monophasic reaction of starch for the production of 5-HMF was measured in LTTM 1 (ChCl: CA 2:1), LTTM 5 (ChCl: BA 1:1), and a mixture 1:1 of both solvents, corresponding to LTTM 3 (ChCl: CA: BA 3:1:1). The selected conditions for the experiment were 100 °C for 60 min, considering other published papers using DES and LTTMs, and the low thermal stability of 5-HMF [174, 175]. It was observed that the mixture containing both CA and BA had an enhanced performance (HMF yield < 1 mol% in ChCl:CA 2:1 and 7.4 mol% in ChCl:BA 1:1 vs 14.8 mol% in ChCl:CA:BA 3:1:1), meaning that both components synergized each other during the reaction.

As pointed out before, BA can react with carboxylic acids and alcohols leading to the formation of esters. When mixing with a carboxylic acid, such as CA, the pH of the system drops, increasing the reactivity of the medium for the hydrolysis of starch and dehydration of fructose into 5-HMF. On the other hand, BA also acts as a catalyzer for the isomerization of glucose into fructose via

ene-diol mechanism by stabilizing the intermediate species. First, a complex between boron and glucose is formed, which promotes the ring opening of glucose. After the protonation of the specie, the ene-diol intermediate is formed. Subsequent proton transfers give rise to the protonated open form of fructose-boron complex which, after deprotonation can form the closed-ring form of fructose-boron complex [104, 176].

It was also interesting to observe that when the reaction mixture was extracted with MIBK or DCM at the end of the reaction, 5-CMF was being identified, along with 5-HMF. The chlorine ion from the ChCl was available in the medium for the substitution of the hydroxyl group in 5-HMF to form 5-CMF. This anion is donated due to the acidity of the medium, probably from the in-situ formation of HCl as pointed out in other studies [161, 162]. The 5-HMF and 5-CMF are in equilibrium in the aqueous medium and therefore, the substitution is reversible. Additionally, 5-HMF can degrade into humins or can be hydrolyzed into levulinic and formic acids in the LTTM phase. When an extracting solvent is added (biphasic system), the extracted 5-CMF cannot be re-converted into 5-HMF [165] therefore, by using a biphasic system, the yield of 5-CMF can be maximized. Also, it is important to point out that 5-CMF was only present in the organic layer (complete extraction), while 5-HMF was being partially extracted, remaining approximately 45% of the total amount in the aqueous phase. That is advantageous for 5-CMF, as almost all the product can be recovered from the organic layer without additional extraction steps.

The presence of 5-CMF was demonstrated by means of GC-MS (Fig. 9) and NMR ¹H, ¹³C. As can be seen, the mass spectrum shows the molecular ion peak m/z at 144, and the major fragment ion peaks m/z at 109.1, 81.1 and 53.1 correspond to the 5-CMF [158, 162]. The NMR spectra also confirmed the identity of 5-CMF [149, 158]:

¹³C NMR (126 MHz, CDCl₃) δ 37.71, 111.60, 121.49, 177.77

¹H NMR (500 MHz, CDCl₃) δ 4.62, 6.60, 7.22, 9.66.



For the optimization, LTTMs of ChCl, BA and CA were prepared in different proportions and the effect of time and temperature as well as the percentages of BA over CA were tested according to the experimental design (Table 7). The significance of the model was evaluated by means of ANOVA (Table 8) and the response surfaces were plotted (Fig. 10-12).

Model	HMF yield	CMF yield	Combined yield
Response mean	9.33	11.05	20.38
Standard deviation	2.72	2.82	1.89
R square	0.93	0.96	0.99
Lack of fit (p value)	0.36 (non-significant)	0.52 (non-significant)	0.02 (significant)
Total model (p value)	0.0031 (significant)	0.0004 (significant)	<0.0001 (significant)

Table 8. Model fitting parameters from ANOVA



Figure 10. A. Response surface by plotting temperature (°C) versus time (min) and B. Contour plot for HMF yield (mol%)



Figure 11. A. Response surface by plotting temperature (°C) versus time (min) and B. Contour plot for 5-CMF yield (mol%)



Figure 12. A. Response surface by plotting temperature (°C) versus time (min) and B. Contour plot for combined yield (mol%).

According to the RSM, there are significant linear, quadratic and interaction effects for all the variables (Table 9) however, it is interesting to note that the interaction between time and temperature has a negative effect on the 5-HMF yield and combined yield, but a positive effect on the 5-CMF yield. That can be explained since higher temperatures and reaction times lead to the decrease of 5-HMF due to the formation of 5-CMF. This can also be observed from the surface plots. At the beginning of the reaction, the amount of 5-HMF and 5-CMF formed increased with time until the midpoint, where the 5-HMF yield reached a maximum. After this point, the 5-HMF yield decreased with time and temperature while the 5-CMF yield increased. As for the ratio of BA to CA, it is observed that the predominance of CA over BA is favorable for the reaction, which can be due to the excess in the number of active sites and reversible isomerization in the presence of BA. Additionally, the solvent with predominance of CA presented lower viscosity and pH, which can contribute to the better performance.

	Li	inear effe	cts	Quadratic effects		Interaction effects			
Parameter	Т	М	В	T*T	M*M	B*B	T*M	T*B	M*B
5-HMF	+	+		-		-	-		
5-CMF			+		-		+		-
Combined	+	+	+	-	-	-	-		-

Table 9. Parameter effects on the models

Temperature (T), Time (M), BA proportion (B) green: p < 0.05, yellow: p < 0.1, white: p > 0.1

The combined yield model shows a significant lack of fit, meaning that the error term contains not only a random component, but also a non-random error. This might be attributed to higher order terms (i.e. third order terms), and an extended model should be required to better describe the behavior [164]. However, despite the lack of fit, the model still can give useful information, as it shows that the optimal value of combined 5-HMF and 5-CMF yield is inside the tested levels. According to the 5-CMF yield surface, the 5-CMF production can be maximized by using the maximum time and temperature conditions (120 °C per 135 min), with lower BA proportion over CA (LTTM 2 solvent). To verify this, the experiment was replicated using those conditions and a maximum 5-CMF yield of 33 mol% was obtained from starch, 36 mol% from glucose and 47 mol% from fructose (Table 10). The yield obtained from fructose is lower than the one obtained without BA reported in other studies (91.4% of HMF in ChCl/CA with continuous extraction in ethyl acetate [95]). This can be explained since the BA has a strong binding with fructose and enables the reversible isomerization of fructose into glucose, as shown in other studies where the presence of BA decreased the selectivity of fructose conversion [153, 176].

Substrate	Conditions	5-HMF yield	5-CMF yield	Reference
		(mol%)	(mol%)	
Glucose	HCl conc, DCE. 100°C, 3h	-	81.2	[157, 162]
Corn stover	HCl conc, DCE. 80°C, 3h	-	80.2	[157]
Fructose	HCl /CrCl ₃ /ZnCl ₂ , 45° C,	-	80	[158]
	10h			
Bagasse pulp	HCl /CrCl ₃ /ZnCl ₂ , 45°C,	-	50.1	[158]
	10h			
Glucose*	20.2% HCl, 10 wt% benzyl	-	17	[160]
	tributylammonium chloride			
	(BTBAC), 100 °C, 3 h			
Glucose	ChCl-AlCl ₃ at 120 °C, 5 h	~ 5	16.93	[162]
Fructose	ChCl-AlCl ₃ at 120 °C, 5 h	8.1	50.3	[161, 162]
Glucose	ChCl-Oxalic acid-AlCl ₃	<1	70	[161]
	·6H ₂ O, 120°C, 30min			
Fructose	ChCl-Oxalic acid-AlCl ₃ ,	<1	86	[158, 161]
	·6H ₂ O, 120°C, 30min			
Starch	ChCl-CA-BA 120°C 2.25h	<1	33	This work
Glucose	ChCl-CA-BA 120°C 2.25h	<1	36	This work
Fructose	ChCl-CA-BA 120°C 2.25h	<1	47	This work

Table 10. Yield of 5-CMF and 5-HMF from sugars in different systems

* Concomitant with xylose to produce furfural in 53 mol% yield.

3.3.3 Recyclability

A recyclability study was conducted to determine if the system could be reused more than once. It can be seen from Fig 13 that after five consecutive reactions, the combined yield of 5-HMF and 5-CMF remains basically unchanged. It was observed that after the second recycling cycle, the yield is higher, possibly due to remaining substrate in the reaction phase. As for the proportion of 5-HMF and 5-CMF obtained, it can be seen that as chlorine is being consumed from the reaction medium, more 5-HMF is obtained.



Figure 13. 5-CMF and 5-HMF yield from catalyst recycle

3.4 Conclusion

In this study, the production of 5-CMF from starch was possible using an inexpensive and easy to prepare LTTM of ChCl, BA and CA at mild reaction conditions. The yield obtained from starch, at 100 °C and 90 min, was 17 mol% of HMF and 13 mol% of CMF, totalizing a combined yield of 30 mol% for both platform chemicals, and at the optimized conditions (120 °C, 135min) up to 33 mol% of 5-CMF with less than 1 mol% HMF was produced. The produced 5-CMF was easily extracted in DCM and separated as a brown oily liquid after evaporation of the solvent. The system proved to be recyclable up to 5 times, producing concomitantly 5-HMF and 5-CMF. This study opens a new eco-friendly alternative for the production of 5-CMF from complex carbohydrates without the direct addition of strong acids such as HCl or metal chlorides.

Chapter 4

General conclusion and recommendations

4.1 General conclusion

The overall objective of this thesis was to review the state of the art of the conversion of carbohydrates into furanic platform chemicals and to design a green catalytic system based on deep eutectic solvents for the production of 5-CMF and 5-HMF starting from starch, optimizing the reaction conditions. Some of the techniques cited in the literature review were applied.

The DES was successfully synthesized using a mixture of choline chloride, citric acid and boric acid. The citric acid imparted the Brønsted acidity required for the hydrolysis and dehydration steps in the conversion of carbohydrates into 5-HMF, while the boric acid facilitated the isomerization of glucose by ring-opening stabilization. The role of choline chloride is complex as it helps to stabilize the deep eutectic system forming a liquid phase allowing the faster reaction, it helps to stabilize the 5-HMF being formed and it provides the Cl⁻ anions for the substitution of 5-HMF to form 5-CMF. This reaction medium presented high viscosities which can be related to the great formation of hydrogen bonds between the components, however, the viscosity decreased at operating temperatures, allowing the mass transfer of the reaction. The reaction medium resulted efficient for the conversion of starch into 5-HMF and 5-CMF and the reaction was improved by in-situ liquid extraction of the products in dichloromethane.

The maximum yields of 5-CMF obtained were 33 mol%, 36 mol% and 47 mol% from starch, glucose and fructose respectively at 120 °C in 135 min, and the product was successfully recovered in the organic layer after evaporation of the solvent. These results can compare with others cited in the literature, but most importantly, this system opens new alternatives for the synthesis of 5-CMF, as emerging platform molecule. Moreover, according to the recyclability test, the system can be re-utilized up to 5 times which might make it suitable for future applications.

4.2 Recommendations and future work

Although this system showed good results, it can be improved. The main weakness of the system is the use of organic solvents (dichloromethane) for the extraction of products in every batch, as this solvent is flammable and volatile, which make its use less attractive in higher scales. One option would be to extract the products in a less flammable solvent, with higher boiling point. This other solvent would be ideal if it is used for the next conversion step, just to mention an example, the products can be extracted in MIBK for its further conversion into 2,5-diformylfuran. Additionally, the yield might be improved by trying other organic acids, such as oxalic acid and malic acid, which according to our review, have also demonstrated good performance in sugars dehydration. Therefore, the study of 5-CMF production in other similar deep eutectic solvent systems might be of interest for future works, as well as the design of other separation strategies or the use of less harmful solvents.

Moreover, 5-CMF can be further converted into biofuels such as 2,5-dimethylfuran or into monomers, such as FDCA, for the production of biopolymers, which can be the aim of future related projects.

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