

Editorial

New Intensification Strategies for the Direct Conversion of Real Biomass into Platform and Fine Chemicals: What Are the Main Improvable Key Aspects?

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Abstract: Nowadays, the solvothermal conversion of biomass has reached a good level of development, and now it is necessary to improve the process intensification, in order to boost its further growth on the industrial scale. Otherwise, most of these processes would be limited to the pilot scale or, even worse, to exclusive academic investigations, intended as isolated applications for the development of new catalysts. For this purpose, it is necessary to improve the work-up technologies, combining, where possible, reaction/purification unit operations, and enhancing the feedstock/liquid ratio, thus improving the final concentration of the target product and reducing the work-up costs. Furthermore, it becomes decisive to reconsider more critically the choice of biomass, solvent(s), and catalysts, pursuing the biomass fractionation in its components and promoting one-pot cascade conversion routes. Screening and process optimization activities on a laboratory scale must be fast and functional to the flexibility of these processes, exploiting efficient reaction systems such as microwaves and/or ultrasounds, and using multivariate analysis for an integrated evaluation of the data. These upstream choices, which are mainly of the chemist's responsibility, are fundamental and deeply interconnected with downstream engineering, economic, and legislative aspects, which are decisive for the real development of the process. In this Editorial, all these key issues will be discussed, in particular those aimed at the intensification of solvothermal processes, taking into account some real case studies, already developed on the industrial scale.

Keywords: process intensification; alcoholysis; hydrolysis; solvothermal process; alkyl levulinate; levulinic acid; 5-hydroxymethylfurfural; furfural; humins

1. Importance of the Solvothermal Processes for the Synthesis of Platform and Fine Chemicals

The use of biomass for the production of platform and fine chemicals is strongly imposing as a valid alternative to the employment of traditional fossil sources [1]. However, despite the progress achieved in the optimization and development of many carbohydrate-based processes, it is still necessary to invest resources in research and development, to overcome the significant gap between the academic and the industrial world, and this is possible only by improving the process intensification [2]. Process intensification favors equipment size reductions, leading to enhancement in chemical reaction kinetics, energy efficiency, process safety, minimization of waste generation, and reduction in capital costs. Maximum atom-economy and minimum energy requirements are fundamental features for the development of more sustainable and greener processes. For example, in the hydrothermal processes, which fall into the broader solvothermal processes, the use of sub- and supercritical water, as the reaction medium, provides a valuable and sustainable path for reducing the

use of organic solvents. This technology can be integrated for the development of safer, more flexible, economical, and ecological biomass conversion processes, in particular carbonization, liquefaction, and gasification, which differ mainly in the adopted pressure, temperature, and residence time [3]. Moreover, hydrothermal technology offers the advantage of directly converting raw biomasses, also those with relatively high-moisture content, without any energy-intensive pretreatment [4]. In the last years, increasing research has been devoted to the optimization of hydrothermal processes, in particular under sub-critical conditions, in the absence or presence of a suitable acid catalyst, for the selective production of reducing sugars or platform chemicals. Some noteworthy examples are the furanic intermediates, such as furfural and 5-hydroxymethylfurfural, deriving from the dehydration of C5 and C6 carbohydrates, respectively [5], and organic acids (levulinic plus formic acids), resulting from the rehydration of C6 furanic intermediates [6]. Most recent advances in the production of these valuable platform chemicals will be discussed in the following paragraph.

2. Some Relevant Examples of C5 and C6 Derivatives of Industrial Interest

Nowadays, furfural is exclusively produced from the acid-catalyzed hydrolysis of the pentosan fraction of lignocellulosic biomasses to xylose and its subsequent dehydration. Its industrial process provides one or two separate steps, carried out in batch or continuous reactors, and in the presence of a mineral acid as the reaction catalyst [7]. Due to the quick degradation of furfural occurring in the liquid phase, it must be readily removed once synthesized and, for this purpose, traditional separation techniques can be adopted, such as steam or nitrogen stripping, supercritical carbon dioxide extraction, mono/biphasic solvent extraction, and adsorption on resins. Moreover, on an industrial scale, significant technological improvements have been achieved, always aimed at minimizing its residence time in the liquid phase, enhancing its concentration in vapor products, and effectively reusing the acid catalyst [7]. Going towards a more intensified process development, also reactive distillation has been proposed, adopting zeolite H-mordenite as the solid catalyst and xylose as the starting feedstock [8]. In this way, the immediate separation of furfural from the reaction system can be advantageously achieved, minimizing the formation of undesired condensation products and leading to significant heat integration benefits. The furfural market size is projected to grow from EUR 500 million in 2019 to EUR 630 million by 2024, with Austria, Belgium, China, Dominican Republic, India, Italy, Slovenia, South Africa, and US being the key market players, and with furfuryl alcohol, tetrahydrofuran, maleic anhydride, 2-methyl tetrahydrofuran, and 1,5-pentanediol as the main derivatives, already manufactured on a commercial scale [5]. Further, in the case of 5-hydroxymethylfurfural (5-HMF) production, the formation of by-products, separation, and purification issues, as well as catalyst regeneration, have been identified as major challenges [9]. To solve these drawbacks, many efficient solutions have been continuously proposed, such as that of Yan et al. [10], who have performed the continuous production of 5-HMF in a flow-reactor, achieving high yields, starting from fructose or glucose, using HCl and AlCl₃ as the catalysts and water as the reaction medium. Moreover, in this case, high yields can be reached thanks to a very efficient extraction step, which allows the continuous removal of this reactive furan from the reaction environment: the produced 5-HMF is extracted into the organic phase in real time, thus avoiding its further degradation, while the unreacted carbohydrates re-enter spontaneously into the reaction phase for another reaction cycle. Moreover, the authors have performed a techno-economic analysis, demonstrating that 5-HMF could be produced at a minimum selling price of USD 1716/ton and USD 1215/ton from fructose and glucose, respectively, which brings motivation and a real chance for its further commercial production in greater volumes. The industrial production of 5-HMF is already available and carried out by AVA Biochem [11], with a monophasic water-based hydrothermal process, which has been optimized and acknowledged as sustainable, efficient, and robust and certainly economically advantageous. In recent studies of environmental sustainability assessment, the concrete feasibility of the 5-HMF oxidation to 2,5-furandicarboxylic acid has been also demonstrated [12,13]. The latter is one of the 12 uppermost chemical building blocks, which can be used for the production of polymers and resins, such as polyethylene furanoate, which is

a promising substitute for polyethylene-terephthalate [14]. Acid-catalyzed hydrolysis of 5-HMF leads to levulinic acid, another valuable platform chemical of great interest, and also an assessment of this hydrothermal process has been recently evaluated and discussed, demonstrating its environmentally friendly and neutral safety performances [15]. The interest in the scale-up of these hydrothermal processes on an industrial scale is further strengthened by the continuous development of new conversion strategies of the above platform chemicals into more added-value fine chemicals, which are industrially more attractive, due to their ready-to-use applications [16,17]. However, considerable improvement opportunities are possible, in particular finding more environmentally friendly solvents for performing the reactions and the recovery of the desired product(s) and developing new catalysts, aimed at improving the process efficiency and reducing the energy consumption. Besides the water medium, involved in the hydrothermal approach, solvothermal processes can be also performed with other green and sustainable solvents, such as alcohols, in some cases attaining remarkable advantages. Taking into account the hydrothermal process for levulinic acid production as the reference example, the main advantages of the alcoholysis route consist of (i) the development of more value-added products, the alkyl levulinates, now exploitable as oxygenated additives for gasoline and diesel fuels; (ii) an easier work-up procedures, generally by distillation, thanks to the lower boiling points of the esters; and (iii) a reduced number of process units and enhanced performances of new technological solutions, such as reactive distillation, conducive to the process intensification [18]. In this way, it is possible to combine reaction and separation unit operations, allowing simpler, more efficient, economical, and cleaner production processes. Further, in this case, worldwide techno-economic and environmental assessment of alkyl levulinates production has been recently proposed, highlighting a promising economic outlook of these bio-products [19].

Although solvothermal biomass processing has been recognized as a really promising technology for converting lignocellulosic and waste biomasses into valuable bio-chemicals and bio-fuels, some key aspects should be still considered, for improving the development of their industrial applications, in particular in the perspective of the intensification process development. Some common drawbacks of these processes are already well known, in particular the corrosion of the equipment, due to the use of concentrated mineral acids for the catalysis, the precipitation of inorganic salts of biomass source in the presence of sulfuric acid as acid catalyst, char/coke formation, associated with the presence of unconverted biomass, and thermal decomposition of the bio-oil [20]. However, most of these problems can be solved after an appropriate optimization study, preferring the use of heterogeneous catalysts in the presence of a soluble substrate (for instance, when beverage or sugar industry waste is converted) and, if this is not possible, adopting very dilute mineral acids, which must be properly recovered. In the next paragraphs, we discuss more in detail about some additional choices, which should be carefully done upstream of the process development, to significantly improve the next intensification phase for the production of C5 and C6 derivatives on a larger scale.

3. Choose Strategic Reaction Components

3.1. About the Starting Biomass

First of all, the efficiency of the hydrothermal-solvothermal processes can be improved upstream, choosing a starting biomass feedstock with a suitable chemical composition, depending on the chemical process to develop. Given the importance of the catalytic upgrading of C5 and C6 sugars, a promising biomass feedstock for the production of biofuels and bioproducts should have a good content of carbohydrates and low recalcitrance to their conversion, which is favored by a low lignin content [21–23]. Besides, biomasses of low cost, low input cultivation, and wide availability in the territory should be preferred, even in laboratory investigations [24]. Lignocellulosic biomass comprising of agricultural and forest residues (such as wheat straw, rice straw, rice husk, corn stover, sugarcane bagasse) and energy crops are extremely attractive for these purposes. Even more so, at an advanced stage of process intensification, an economic analysis of biomass supply chains, including collection,

processing, and transport, is necessary for identifying the best plant locations that balance economic, environmental, and social criteria, making all actors (farmers, investors, industrial entrepreneurs, government) aware that success relies on agreement advances [25,26]. Flexible hydrothermal processes are advisable, allowing the use of different kinds of biomass, an aspect of paramount importance taking into account their certain seasonality. Even waste biomasses, such as food and cooked food waste, can be effectively exploited to platform chemicals, compensating for seasonality issues of the lignocellulosic biomasses [27]. Cellulosic waste materials from papermaking processes, which cannot be re-used for the production of new paper, are valuable feedstocks for the synthesis of bio-products, such as levulinic acid, thus saving the costs deriving from their traditional disposal in landfills or from their use in waste-to-energy plants [28]. Hydrothermal treatment of sewage sludge is a promising strategy for sustainable management, allowing its conversion into useful products, and simultaneously mitigating the environmental risks [29]. In this case, besides the catalyst recovery issue, the recirculation of the liquid effluent within the process could overcome the legal thresholds, such as chemical oxygen demand (COD) and heavy metals [30,31]. These possible drawbacks suggest that European and/or national legislation improvements are still necessary for allowing the development of this process intensification [30,31].

3.2. About the Reaction Medium

Hydrothermal technology involves the use of water as the preferred green reaction solvent, promoting the process sustainability, and shifting the attention towards the development of more efficient and economical work-up strategies, such as solvent extraction, distillation, and/or membrane separation. Process intensification provides the combination of multiple process tasks or equipment into a single unit and the development of material/energy integration, as occurs for the production of furans, such as furfural [32] and 5-HMF [9], and organic acids [33], such as the previously mentioned levulinic acid [34,35]. Subcritical water represents a promising reaction medium for successful biomass exploitation, due to its interesting physicochemical properties, at the typical reaction conditions [36]. However, the replacement of water with an alcoholic solvent should lead to bio-products of higher added-value, such as alkyl-glucosides/xylosides [37,38], alkoxymethyl furfural [39], or the previously mentioned alkyl levulinates [40]. To improve the poor solubility of biomass in water and organic solvents, ionic liquids and deep eutectic solvents can be effectively used, exploiting their high solvation capacity towards the dissolution of carbohydrates and lignin, even in the case of the raw biomass [41,42]. However, ionic liquids still suffer from several disadvantages, having environmentally unfriendly aspects and requiring cost-intensive preparation procedures, whilst deep eutectic solvents solve many of these disadvantages, in many cases being green, environmental-friendly, and highly tunable. In particular, deep eutectic solvents have been recently proposed not only for the pretreatment of biomass, mainly aimed at the delignification and solubilization of cellulose and a decrease in its crystallinity degree, but also for their further conversion to added-value bio-chemicals [43]. Some noteworthy examples are cellulose modification by acetylation [44], cationic [45], and anionic functionalization [46], the dehydration of C5 and C6 carbohydrates to furfural and 5-HMF, respectively [47], and cellulose oxidation to gluconic acid [48]. However, despite the exciting performances, further research in this field is necessary, in particular for improving the separation and the purification of these deep eutectic solvents, further lowering their cost, and justifying their use on a larger scale.

3.3. About the Catalyst

Regarding the appropriate choice of catalyst, it should be made after that of the biomass, and properly tuned, based on the reaction of interest. For example, the acidity of high-pressure CO₂ can be advantageously exploited for biomass pre-treatment purposes, for improving the biomass digestibility before enzymatic hydrolysis, or performing the hemicellulose fractionation by mild autohydrolysis [49]. In both cases, cellulose and lignin components remain almost unaltered in

the solid phase, which could be further fractionated and upgraded [49]. The use of CO₂ as an acid catalyst for biomass pre-treatments is certainly attractive, thanks to its non-toxicity, low cost, and ready availability, but its acidity is generally insufficient to perform harsher acid conversion routes, which require the use of stronger acid catalysts. From a practical and environmental perspective, it is imperative to develop heterogeneous catalysts that are hydrothermally stable at the process conditions. In this context, much work has been done, testing synthesized metal-based catalysts on many transformations of C5 and C6 carbohydrates involving the breakage of the C-O bonds for the synthesis of biofuels and bio-products, such as isomerization, dehydration, aldol condensation, ketonization, and hydrogenation [50,51]. Based on our experience, Nb-based catalysts are particularly promising for many of these purposes, showing excellent water tolerance, low cost, easy synthesis, tunable compositions, good acid properties (acid types, amount, and strength), and promising surface properties (specific surface areas, pore size, and volume) [52]. However, despite the numerous advances in the development of efficient heterogeneous catalysts, these often suffer from uninspiring performances due to mass transfer issues, deactivation due to coking and water corrosion at the reaction conditions, clogging of the active pores, poisoning, and recycling issues. Consequently, even if new efficient catalysts are hourly synthesized and deeply characterized, their use for the synthesis of base chemicals has been mostly limited to academic investigations. On the other hand, the use of commercial catalysts, which are widely available and cheap, should be preferred for faster development of the bio-product applications, focusing rather on the improvement of other parameters related to the intensification process. The use of homogenous catalysts generally greatly improves biomass accessibility, giving back a better product yield/selectivity. For acid-catalyzed biomass conversion processes, the reactivity of a mineral catalyst is related to several prominent factors, such as its strength and concentration, type/loading of the biomass, and reaction conditions, in particular temperature and reaction time [36], and all these parameters should be properly considered and tuned, preferably by multivariate optimization. In the case of the levulinic acid production, the safety assessment due to the use of mineral acids does not present significant risks [15], whilst the catalyst recovery, together with the isolation/purification of the product(s), both with minimum energy input, still represent a challenging topic [6,20]. For example, the recovery of the acid catalyst within the levulinic acid process can be carried out by flash separation, if volatile hydrochloric acid is the chosen catalyst, whilst organic solvent extraction is still preferred to separate the product from the high-boiling sulfuric acid, which remains in the water solution, ready to be reprocessed [53]. Instead, regarding product isolation/purification, atmospheric/vacuum distillation and steam stripping are adopted for the separation of LA, which can be obtained with a final purity of about 95–97% [17]. However, the high boiling point of levulinic acid is not energetically favorable for distillation, and solvent extraction could be a viable alternative, but the high amounts of solvent which need to be evaporated make also this operation energy-intensive and costly [54]. Significant improvements are still possible in the work-up procedures, which are decisive for further lowering the production costs of these bio-products.

4. Fractionate and Exploit Each Biomass Component

4.1. Selective Biomass Fractionation

Another aspect to be improved for achieving the best process intensification is the selective fractionation of the biomass in its components, by optimizing each step, in agreement with the biorefinery concept [55]. For example, reactive furanic compounds, such as furfural, must be produced and recovered upstream of integrated processes, through very mild pre-treatments, and possibly applying the key concepts of the process intensification. In this context, Zang et al. [56] have proposed the biorefinery of switchgrass biomass for the integrated production of furfural, lignin, and ethanol. The chosen reaction system is composed of a biphasic solvent [choline chloride/methyl isobutyl ketone], with a deep eutectic solvent which enables the fast hemicellulose solubilization/conversion to furfural, which is simultaneously extracted by methyl isobutyl ketone. Regarding the fate of the remaining

fractions, cellulose is subsequently converted into ethanol by enzymatic hydrolysis, whilst lignin is properly precipitated and recovered, for further added-value applications. Despite the use of a biphasic system and the improvable extraction/purification of the lignin fraction, the developed techno-economic analysis clarifies that the proposed biorefinery is still cost-competitive and has a low-economic risk, with the reaction temperature and the solid loading having the largest impacts on the minimum furfural selling price (estimated at 625 USD/t, in the best case of study). Another interesting approach has been proposed by Rivas et al. [57], who studied the hydrothermal conversion of eucalyptus (*Eucalyptus globulus*) to levulinic acid, the latter being further upgraded to γ -valerolactone. In the perspective of developing an integrated approach, a mild hydrothermal pretreatment was optimized upstream, which allowed the almost quantitative solubilization of thermolabile extractives and hemicelluloses, recovering a cellulose-rich solid, which was subjected to harsher hydrolysis to the desired levulinic acid.

4.2. Recovery/Exploitation of By-Products: New Trends

About the lignin component, many biomass-integrated biorefineries underestimate its importance, considering it as a not particularly valuable by-product, more similar to waste, rather than a resource. In the hydrothermal process for levulinic acid production, lignin is recovered as the main waste stream at the end of the process, being a carbonaceous solid residue, or hydrochar, whilst simple phenols are solubilized in the liquid phase. Regarding the solid hydrochar, it can be immediately used for energy recovery, which is generally impactful for these processes. Alternatively, this hydrochar, which is rich in hydroxylic and carboxylic functionalities [58,59], can be advantageously used to replace traditional fossil-based polyols, for example, for the formulation of flexible polyurethane foams [60], but also for applications as adsorbents, precursors of catalysts, soil amendment, anaerobic digestion and composting, and energy storage materials [61]. On the other hand, the solubilized phenols can be advantageously used as efficient antioxidants, as already demonstrated in the case of the hydrothermal treatment of the *Arundo donax* L. [62], and their separation from the other compounds can be well integrated with the available process technologies. The new lignin exploitation strategies are generally carried out on the lignin solid residue recovered from the hydrothermal process of levulinic acid, significantly improving the overall process economy, which is already rewarded by the levulinic acid production, at the same time minimizing the waste disposal.

On the other hand, the lignin recovery could be even more advantageous if carried out upstream of the integrated biorefinery, as provided by the available organosolv pretreatments, where an organic solvent is used to extract lignin in its native form [63]. High-purity cellulose selectively remains in the solid phase, but it is more prone to the following step of enzymatic/chemical hydrolysis, due to the increased contribution of its amorphous phase. Instead, the extracted lignin can be precipitated from the liquid phase by water dilution and recovered as a solid, while the hemicellulose fraction remains in the liquid stream, thus achieving an efficient fractionation of the biomass in its components. Focusing on the lignin fate, this component is less degraded, if compared with its downstream recovery, and therefore the “upstream” lignin is more useful for the development of higher-value applications, such as the production of carbon materials, vanillin and other oxidized compounds, phenolic antioxidants, bio-oil, BTX hydrocarbons, urethanes, epoxy resins, fire retardants, sequestering agents, nanomaterials, energy storage device, and many more [64]. The choice of “upstream” or “downstream” recovery of the different fractions depends on the value of the primary target product, which should pay off the whole process, and the possibility of obtaining economic surplus from secondary streams must be down-to-earth and supported by feasibility studies.

Although hydrothermal/solvothermal reactions can be improved and optimized by choosing appropriate reaction conditions and catalysts, some reaction by-products are inevitably formed. An example of great interest is given by the furanic humins, which are condensation products of C5 and C6 sources [65]. Their formation is particularly favored in the aqueous acid environment and under harsh reaction conditions, like those which typically occur for levulinic acid production,

but also for that of reactive furanic compounds from simple C5 and C6 sugars, e.g., furfural and 5-HMF, respectively [66]. Instead, alcoholic solvents generally stabilize these soluble furans in the liquid phase, minimizing the next humin formation, growth, and precipitation [67], and therefore alcoholysis results more advantageous for improving the selectivity to the target product and the final carbon balance. As a further complication, if real lignocellulosic biomass is chosen as the starting feedstock for developing the conversion of interest, the resulting final solid hydrochar should include both the degraded lignin (as “pseudo-lignin”) of the biomass source and humins, the latter being less important in the milder HTC processes [68]. All these by-products must be considered as a resource rather than waste of the process, and new exploitation strategies must be developed, to lower further the minimum selling price of the main bio-product(s) of interest, smartly completing the biomass biorefinery [69]. Up to now, the best-known applications of carbonaceous hydrochar/humins include energy production [70] and environmental remediation [71]. Besides, new possibilities have been recently proposed for the exploitation of humins, such as the synthesis of new biomaterials [72–74], syngas [75], and carboxylic acids [76,77]. Most of these applications have been developed by the Avantium Company [78], which produces 5-HMF on a pilot scale and a new class of furanic building blocks, called YXY, to use as bioplastics and biofuels, starting from first- and second-generation feedstocks [79]. Therefore, it is clear that the efficient and diversified exploitation of humins should improve the overall economy of their process. In our opinion, particular attention should be given to the catalytic conversion of humins by hydrotreatment, aimed at their liquefaction, depolymerization, and conversion into more valuable liquid chemicals, such as furanics, aromatics, and phenolics. For this purpose, Wang et al. [80] worked at 400 °C, using Ru/C as the hydrotreatment catalyst, and formic acid in isopropanol as the hydrogen donor, aimed at the selective production of substituted alkyl phenolics and higher oligomers, together with naphthalenes, and cyclic alkanes. Now, Sun et al. [81] have synthesized a Ru/W-P-Si-O bifunctional catalyst, testing it for the hydrotreatment of humins to give cyclic and aromatic hydrocarbons. The authors declare a high yield to cyclic hydrocarbons (up to 88.3%), working at 340–380 °C, and exploiting the cooperative catalysis between the nano-Ru particles and the strong Lewis acidity of the solid W-P-Si-O, the latter catalyzing the Diels–Alder reaction on the furan rings.

In the context of the developable applications of hydrochar/humins, the synthesis of furanic and carboxylic acid derivatives with catalysts directly developed from waste and by-products of the same hydrothermal/solvothermal processes represents a very hot topic, which should allow the improvement of the process intensification, also applying the biorefinery concept and zero waste policies. Besides, the heterogenization of the catalyst should be certainly advantageous for these processes, if the synthesized catalysts result as performing, their precursors have a low cost or, even better, a negative value, and the related synthetic procedures are simple. Sulfonation of bio- and hydro-chars deriving from thermal (e.g., pyrolysis) and hydrothermal processes fully meet these requirements [82]. Their use for some intensified biomass conversion processes has been recently proposed, including the synthesis of 5-HMF [83], furfural [84], levulinic acid [85], alkyl levulinates [86], and other esters [87]. The available data for most of these mild reactions are promising and certainly deserve further research and development.

5. Prefer Efficient Heating Systems

In order to study and optimize these hydrothermal reactions, microwave heating is certainly one of the best choices, being more rapid, energy-saving, and cleaner than the traditional ones, thus suggesting that such new heating systems could lead to more compact factories in the future [21]. In comparison with conventional heating, microwave irradiation has remarkable advantages, such as fast heat transfer and short reaction time, selective and uniform volumetric heating performance, easy operation, high energy efficiency, and reduced formation of by-products, especially in the presence of highly reactive intermediates [88]. In addition to microwaves, also ultrasounds have been proposed for the development of more sustainable and intensified biomass conversion strategies,

advantageously exploiting their cavitation effects on many reaction systems. Up to now, this heating technology has been mainly applied for performing mild biomass pretreatments, aimed at the intensified recovery of reducing sugars [89,90], lipids [91], and lignin [92], also in combination with deep eutectic solvents [93], or ionic liquids [94], thus achieving a more effective fractionation of the starting biomass in its components. The efficient utilization of both microwave and ultrasound energy is expected to improve significantly the product yield, efficiency, and environmental friendliness of biomass fractionation processes.

6. Enhance the Concentration of the Target Product

Generally, hydrothermal processes benefit from the dilution of reagents, intermediates, and products, achieving better control of the cross-reactions of the involved species, e.g., a higher selectivity towards the target product. However, a low concentration of the target product would cause too high separation costs in the work-up procedures and, for this reason, it is highly desirable to enhance its final concentration in the reaction mixture, developing the *high-gravity* concept [95]. This goal can be partially achieved by increasing the loading of the starting feedstock, as the solid/liquid ratio, which positively impacts on the environmental performances of the process [31]. However, this choice is not unconditionally beneficial beyond a certain biomass loading, favoring the excessive occurrence of unwanted cross-reactions. For example, in the hydrothermal process for the production of levulinic acid, the biomass loading is limited to 10–20 wt.% [96], whilst a higher one should give practical problems of liquid recovery and promote the excessive formation of undesired solid humins [69]. On the other hand, lower biomass loadings should make the hydrothermal processing economically unviable, due to the high capital investment, power consumption, and heat loss. Therefore, achieving operational status with a high solids loading is still a cumbersome task [97], despite that some practical solutions have been proposed, such as using the pre-hydrolyzed feedstock and starch gels with cement pumps [98].

On this basis, it is crucial to tune properly both the catalytic performances (yield and selectivity) and the final concentration of the target product, preferring the improvement of the latter. A smart improvement of the product concentration could be achieved by performing sequential treatments of recovered reaction mixtures with a new batch of feedstock. In the case of levulinic acid production, this choice should allow achieving higher concentrations of this bio-product (~100 g/L) than those obtained with only one batch experiment (<30 g/L) [96]. Further, in this case, it is necessary to balance the product concentration and yield, the latter worsening excessively at very high concentrations of levulinic acid. As previously stated for the reactive furans, another smart solution provides the use of a [water-organic solvent] biphasic system, which stabilizes the reactive intermediates in the liquid phase, improving the next LA production [99] and, if the organic solvent results as immiscible with water, also allowing LA simultaneous extraction [100]. Alternatively, also the use of an uncommon biphasic system [water-paraffin oil] has been recently proposed, where the latter is used as a non-solvent for the compound of interest. This approach allows an increase in the levulinic acid concentration in the water phase, also in this case with concentrations higher than 100 g/L, leaving enough liquid phase to sustain the processability of a high loading slurry but reducing the water volume to be processed downstream. Therefore, the target product can be easily recovered from the aqueous phase, whilst the organic non-solvent can be advantageously recycled and reused, given its good thermochemical stability [101].

7. Prefer Cascade over Stepwise Reactions

The synthesis of bio-products often involves multistep reactions, which can be carried out (i) in a stepwise manner, e.g., separating and purifying the product from the reaction mixture before performing the subsequent reaction or, more advantageously, (ii) in cascade, thus directly using the intermediates deriving from the previous step to give subsequent reactions, without their further isolation. The stepwise approach is widely used due to incompatible reaction conditions between steps and the poor catalytic specificity and selectivity of the catalysts. Instead, cascade

reactions occur directly, avoiding the isolation and purification of synthetic intermediates, and greatly simplifying the operational procedure. The one-pot cascade approach is advantageously related to atom economy, process time, labor and resource management, and waste generation [102], but requires careful tuning of the catalyst properties. Such an approach is particularly attractive when a high selectivity to the target product is desired and, for this purpose, the development of multifunctional catalytic systems, with well-tuned chemical properties, is essential. Moreover, a worsening of the final target product yield may occur, depending on the number and complexity of the involved steps, making this choice extremely attractive, especially when easy conversion steps are required. In this context, a wide and very hot topic is the improvement of mild biomass conversion processes, by developing new catalysts with bifunctional Brønsted/Lewis acid–base properties, which should be tunable in character and strength [103]. Many noteworthy examples are available from the literature, including 5-HMF production through glucose to fructose isomerization, occurring over a solid base/Lewis acid, and the subsequent fructose dehydration over Brønsted acid sites [104]; the following levulinic acid production by harsher Brønsted acid-catalyzed hydrolysis of 5-HMF, but preferably carried out in the cascade approach, starting from carbohydrate precursors [105]; the production of polyols or alkanes via hydrogenation of glucose to sorbitol over metal catalysts and the subsequent hydrogenolysis over metal-acid bifunctional catalysts [106]; the production of isosorbide from C6 carbohydrates via hydrogenation and dehydration, catalyzed by metal-promoted solid acids [107]; the γ -valerolactone production from xylose via Brønsted acid catalysis coupled with Lewis acid- or base-catalyzed Meerwein–Ponndorf–Verley hydrogen transfer, in the presence of isopropanol as the hydrogen donor [108]; the synthesis of 2-methyltetrahydrofuran by bimetallic-catalyzed hydrogenation of γ -valerolactone or, even better, levulinic acid [109]; and the condensation/oligomerization of C5/C6-derived bio-products to longer carbon-chain chemicals and their oxygen removal to give liquid alkanes, by hydrogenation [110]. Considering the multiple processes involved, issues of catalyst stability and economic feasibility remain essential priorities for the next development of the process intensification.

8. Conclusions

Process intensification is a tool that can be very helpful for the development of low-cost processes, with better use of physical spaces and low energy requirements. Chemical, technological, economic, environmental, and regulatory questions have to be considered for improving the solvothermal process intensification. Complete process integration is necessary to get significant cost advantages, preferring the use of cheap and waste biomasses, direct conversion strategies, preferably in cascade, improving the final concentration of the target product, rather than its yield (however maintaining an appreciable yield), in the case of waste starting materials, and exploiting more efficient heating systems, such as microwaves and/or sonication. The development of efficient and cheap heterogeneous catalysts starting from low-cost or negative value precursors, preferably waste produced within the same biomass biorefinery, still requires further research and development, whilst significant progress has been done on the design of multifunctional catalysts for performing cascade reactions. Technological limitations due to the purification of the product/recovery of the acid catalyst have been partially overcome and do not seem to limit the development of the intensification of these processes. On the other hand, environmental problems due to wastewater treatments and legal restrictions of certain types of waste biomasses may slow down their development. Besides, simultaneously with the optimization of the catalysis issue, other strategic business drivers should be taken into account for evaluating the real feasibility of the biomass conversion process, such as biomass transportation cost, agronomic parameters (productivity on a dry basis, input degree), and plant production capacity, thus highlighting that an interdisciplinary life cycle sustainability assessment should be carefully performed at an advanced stage of process development. An accurate evaluation of project feasibility, capital and operating costs, revenues, and profitability measures is imperative, thus helping to bridge the uncertainty associated with a lack of data on investments on larger-scale plants.



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