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Green production of 5-hydroxymethylfurfural (HMF) in biphasic continuous microreactor using terpenoid-based solvents

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ABSTRACT

The synthesis of bio-based molecules from biomass offers a sustainable alternative to petrochemical-derived products. This study explores the continuous production of 5-hydroxymethylfurfural (HMF) from glucose using a biphasic microreactor system catalyzed by Lewis ($AlCl_3$) and Brønsted (HCl) acids. Natural solvents with high affinity for HMF were identified using the COSMO-RS method. Carvacrol and the natural deep eutectic solvent (NADES, mix of carvacrol:thymol) outperform conventional solvents like MIBK and ethyl acetate in extraction efficiency. Under optimized conditions 160 °C, an organic to aqueous (O/A) volume ratio of 2:1, equimolar catalyst concentrations ($AlCl_3$/HCl) of 40 mM, and a residence time of 12 min a maximum HMF yield of 55 mol% was achieved with carvacrol and 52 mol% with carvacrol:thymol, compared to 43 mol% obtained with MIBK, all at similar glucose conversions (~85 mol%). MALDI-TOF MS analysis demonstrated that terpenoid-based solvents inhibit the formation of humin precursors, enabling selective HMF production. The proposed first-order kinetic model further revealed that the use of carvacrol minimizes the formation of by-products such as formic acid and levulinic acid, enhancing the HMF yield to as high as 65 mol% under optimized conditions but increasing the residence time in 12 min compared to the experimental conditions. Additionally, calculated overall liquid–liquid mass transfer coefficient indicates the absence of significant mass transfer limitations within the studied parameters. These findings highlight the effectiveness of combining terpenoid-based solvents with $AlCl_3$/HCl catalysts for sustainable and efficient HMF production.

1. Introduction

Growing concern about the depletion of fossil resources as starting material for chemicals and fuels and its associated environmental impacts have driven the research for its replacement [1]. In this context, lignocellulosic biomass, an abundant, low-cost and widely available feedstock, stands out as a key renewable source for obtaining high value-added chemicals [2]. Among these, 5-hydroxymethylfurfural (HMF) has emerged as a central compound for the transition to a more sustainable economy, due to its versatility for the synthesis of products such as fuel additives, polymers and chemical compounds of industrial interest, including 2,5-diformylfuran (DFF), 5-hydroxymethyl-2-furancarboxylic acid (HMFCA), 2,5-dihydroxymethylfuran (DHMF) and 2,5-furandicarboxylic acid (FDCA) [3]. Therefore, the efficient and high-quality production of HMF is a crucial step in enhancing the value of biomass resources.

HMF is produced from hexoses such as glucose and fructose through two main reactions: (1) isomerization of glucose to fructose using Lewis acid catalysts (e.g., metal salts) and (2) dehydration of fructose to HMF, using Brønsted acid catalysts (e.g., mineral acids) [4]. However, the formation of by-products like organic acids and soluble and insoluble oligomers/polymers (known as humins) represents a significant challenge as they decrease yield and selectivity towards HMF [5]. To mitigate these problems, researchers have developed and tested biphasic batch or continuous reactor systems to minimize the formation of unwanted by-products. These systems consist of an aqueous phase for

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dehydration reactions and an organic phase, usually one or mixtures of hydrophobic solvents, for *in situ* HMF extraction [6]. Various organic solvents, such as methyl isobutyl ketone (MIBK) [7], tetrahydrofuran (THF) [8], and 2-butanol [9], have been explored using different homogeneous and heterogeneous catalysts, demonstrating the successful extraction of HMF. However, conventional solvents remain ineffective for extracting HMF efficiently. As a result, it is crucial to explore alternative solvents capable of minimizing humin formation, which leads to fouling in reactors and other process equipment [10].

In this context, terpenes and terpenoids, a class of green solvents derived from renewable sources, have aroused great interest due to their advantages over petroleum-based solvents, being non-toxic, renewable and offering a high degree of biodegradability [11]. These compounds can be extracted from a wide range of natural sources, such as fruits and aromatic plants; some of them are menthol, limonene, citral, linalool, eugenol, carvacrol, and thymol [12]. Carvacrol, for example, can be obtained from oregano and exhibits negligible toxicity in mammals, along with well-documented therapeutic properties including antioxidant, antimicrobial, and anti-inflammatory activities [13]. Moreover, due to their broad application in the pharmaceutical, food, and cosmetics industries, several terpenoids exhibit market prices that are competitive with those of conventional organic solvents. Due to their hydrophobic nature, terpenes and terpenoids have been successfully used for the extraction of various compounds from aqueous solutions, such as drugs [14], phenolic compounds [15], and furan compounds [16]. Terpenoids such as menthol and thymol have been tested for the extraction of HMF from aqueous solutions at 25 °C, obtaining high partition coefficients compared to control solvents, such as toluene [17]. Additionally, these compounds have the advantage of being able to be combined to obtain natural deep eutectic solvents (NADES), which have emerged as a sustainable alternative to ionic liquids, since they have a high capacity to adapt to the characteristics of the solute, providing high partition coefficients for HMF, low preparation cost and produce fewer toxic emissions during their production [17]. However, research on the use of terpene and terpenoid-based solvents and their application in HMF synthesis and extraction is still limited.

In recent years, continuous flow microreactors have established themselves as an innovative and efficient technology to produce HMF, offering significant advantages over conventional batch reactors. Their ability to provide high mass and heat transfer rates, and precise control over reaction conditions, positions them as a key tool for optimizing chemical processes. For example, Tuercke *et al.* [9] using a glass microreactor achieved an HMF yield of 85 % and a selectivity of 82 % with a residence time of 1 min at 185 °C, using a mixture of MIBK and 2-butanol (70:30 %) as the extraction solvent. Although conversion and selectivity were not significantly different between batch and continuous processes under similar reaction conditions, reaction time was reduced to 1 min in continuous-flow reactions, enhancing the spatial–temporal performance [9]. In 2016, Shimanouchi *et al.* [18] achieved efficient synthesis of HMF in microreactors using fructose as a substrate in a biphasic system composed of water/MIBK and HCl at 180 °C. The study reported fructose conversions of 97 % and an HMF yield of 89 %. On the other hand, the conversion of glucose, a cheaper and more abundant raw material but less reactive than fructose, has also been investigated in continuous flow microreactors. Guo *et al.* [19] reported the synthesis of HMF in a biphasic slug-flow capillary microreactor using a water/MIBK system and a combination of catalysts, HCl and $AlCl_3$, achieving an HMF yield of 66 % at 160 °C with a residence time of 16 min using glucose as substrate. Similarly, Muranaka *et al.* [20] demonstrated an HMF yield of 76 % in a residence time of 47 min using a biphasic stainless steel microreactor, with a catalytic phase of buffer saline (PBS), $AlCl_3$, and 2-*sec*-butyl phenol as extraction solvent.

Nonetheless, the efficient production of HMF in biphasic aqueous/terpenoid systems using continuous flow microreactors remains an unexplored area. So far, the use of terpene and terpenoid-based solvents in the extraction of HMF has been studied by Mai *et al.* [21], who demonstrated that NADES composed of octanoic acid and thymol can serve as an extraction medium. In their study, they obtained an optimal HMF extraction yield of 69 % with an organic to aqueous (O/A) volume ratio of 1:1. Along the same lines, Chelstowska *et al.* [22] used systems based on deep magnetic eutectic solvents made from terpenoids to extract HMF from hydrolysates of plants and agri-food residues. Using menthol, thymol and $FeCl_3$ in a 1:1:0.5 ratio, they managed to extract 78 % of HMF at 25 °C with a 2:1 O/A ratio demonstrating that terpenoid-based solvents have been successful in the recovery of HMF from an aqueous phase. Despite the good results, these investigations pointed out that the high viscosity of the solvents limited the transfer of HMF from the aqueous to the organic phase. In this context, the unique properties of microreactors, such as the improvement in mass transfer between phases, and the operational advantage of organic extraction solvents in the production of high-value chemicals such as furans, represent an opportunity to optimize these processes and move towards a continuous and efficient production of HMFs in biphasic continuous-flow systems.

Therefore, the aim of this research is to study the potential of combining the operation of a microreactor and a biphasic system for the continuous production of HMF from glucose using $AlCl_3$ and HCl. In this sense, three solvents were tested; MIBK as classic solvent, carvacrol and carvacrol:thymol mixture, which were selected by applying the COSMO-RS method based on their activity coefficients at infinite HMF dilution and physicochemical properties such as relatively low viscosity and melting point that make it more favorable for use in microreactors.

2. Materials and methods

2.1. Selection of natural solvents by molecular simulation with COSMO-RS

2.1.1. Solvent screening based on affinity with HMF

An initial selection of suitable solvents from a list of 49 compounds was conducted using molecular simulations based on the COSMO-RS method for its use in a biphasic system for HMF production. The geometry optimization of the compounds list was carried out using BIOVIA TmoleX 2023 version 23.0.0 software, employing the COSMO continuum solvation model with the computational level of theory BVP86/TZVP. The resulting COSMO-optimized files were subsequently processed in BIOVIA COSMOtherm 2023 software version 23.0.0. The activity coefficients at infinite dilution (γ^{∞}) for HMF in 23 terpenes, 24 NADES, and 2 conventional solvents were calculated at a temperature of 25 °C. These calculations utilized the computational level of theory BVP86/TZVP/DGA1 and the BP_TZVP_23 parameterization. For eutectic solvents, which are binary mixtures of compounds, the system was modeled assuming an equimolar composition (1:1 ratio) between the hydrogen bond donor and acceptor, as commonly reported in the literature [23,24].

2.1.2. Testing selected solvents

From the list of 49 compounds, two terpenoids (carvacrol and eugenol), one terpene (limonene), one NADES (carvacrol:thymol), and two commercial solvents (MIBK and ethyl acetate) were selected based on molecular simulations using COSMO-RS. The chemical characteristics, including suppliers, purities, CAS numbers, molecular structures, and physical properties of the solvents and solutes used in this study, are detailed in Table S1. To prepare the eutectic mixture, carvacrol and thymol were precisely weighed using a gravimetric method, ensuring an equimolar ratio. The components were then mixed in a round-bottom flask and heated in a thermostatic bath at 50 °C with continuous stirring until a uniform, homogenous liquid was formed [15]. The eutectic mixture was then used in subsequent extraction experiments.

2.1.3. Liquid-Liquid extraction of HMF from an aqueous solution

Aqueous solutions containing 8 mM of HMF were prepared for the extraction experiments, reflecting typical concentrations found in

reaction media [25]. The natural solvents were tested as extraction agents, using organic to aqueous (O/A) volume ratios of 1:1, 2:1, and 4:1. Each experiment involved mixing the 3 mL of aqueous HMF solution with the selected solvent at an O/A ratio in 50 mL Falcon tubes. The mixtures were stirred at 600 rpm in an orbital shaker for 4 h at a controlled temperature of 25 °C to ensure complete mass transfer between phases. After the stirring step the samples were centrifuged at 6500 rpm to promote thorough phase separation, allowing the formation of a distinctive boundary between the aqueous and organic phases. The separated phases were then allowed to equilibrate for 24 h at a fixed temperature in a thermoregulated oven to ensure full phase equilibrium [26]. All extraction experiments were performed in triplicate to ensure reproducibility and evaluate statistical significance.

2.2. Experimental Setup and Procedure for HMF synthesis from glucose using a biphasic microreactor system.

The conversion of glucose to HMF was conducted using HCl and $AlCl_3$ as catalysts in a continuous flow microreactor (Fig. 1). Initially, monophasic aqueous experiments were performed to evaluate the effect of temperature, ranging from 140 to 180 °C, with fixed concentrations of 40 mM $AlCl_3$ and HCl as reported in literature [27]. During this stage, the residence time (τ) was varied between 2 and 12 min. Subsequently, based on COSMO-RS simulation results (Sec. 2.1), biphasic experiments were carried out under a selection of the previously studied conditions to investigate the effect of the solvent on glucose conversion to HMF. Additionally, using the optimal reaction-extraction system, the effect of Lewis/Bronsted catalyst ratio ($AlCl_3$/HCl), ranging from 0.5 to 2, was analyzed.

In a typical experiment, the aqueous feed consisted of a mixture of 0.1 M glucose as well as HCl and (or) $AlCl_3$ catalyst, and the organic feed was the solvents selected from prior experiments. Both aqueous and organic phases were fed into the microreactor using two HPLC pumps (Young Lin SP930D, and Jasco PU-2080) and the desired τ was varied by adjusting the flow rates (details on the calculation of τ and flow rates are given in Table S2 in the Supplementary Material). The PFA capillary microreactor (d_c = 1.58 mm, and typically length of L_c = 3.0 m) was coiled around an aluminum block in an oven maintained at a reaction temperature. The outlet of the microreactor was passed through a water bath (approx. 20 °C) to quench the reaction. The pressure in the microreactor was maintained at least. 17 bar by a back-pressure regulator at the end of the microreactor to maintain the reactor content in the liquid state. Product samples were collected once the system reached a steady state (at least 3 times τ). The collected aqueous and organic phases were filtered through a polytetrafluoroethylene (PTFE, 0.22 μm) filter, and subsequently analyzed by high-performance liquid chromatography (HPLC) and gas chromatography (GC), respectively.

The above biphasic experiments under representative conditions were conducted in triplicated, with results reproducible within a 5 % standard deviation. In addition, the thermal stability of solvents were evaluated via thermogravimetric analysis (TGA), which indicates that the solvents used in the system were stable without degradation at a reaction temperature of 160 °C (see more information in Section S3 of the Supporting Material).

2.3. Analytical methods

2.3.1. Chromatographic analysis

For liquid–liquid extraction experiments, the HMF concentrations in the aqueous phase were analyzed using HPLC. The HPLC system (Jasco, Japan) using an Inertsil ODS-4, C18 reversed-phase analytical column (GL Science, Japan). The mobile phase consisted of a 90:10 v/v mixture of acetonitrile and water in isocratic elution, flowing at 1 mL/min. The column temperature was maintained at 40 °C, and the detection wavelength was set to 280 nm to quantify HMF. For continuous flow experiments, the composition of the aqueous phase was diluted 5x by methanol and the resulting aqueous solution was analyzed by HPLC, equipped with a refractive index detector (RID), a diode array detector (DAD) as well as a Bio-Rad organic acid column Aminex HPX-87H. A diluted aqueous H_2SO_4 solution (5 mM, 0.6 mL/min) was used as the eluent, and the column temperature was maintained at 55 °C. The analysis was completed within 60 min. Sugars and organic acids were determined using RID, and HMF was determined with DAD. The organic phase was diluted 10x by MIBK and the resulting organic solution was analyzed by GC (Perkin Elmer Clarus 600), equipped with a flame ionization detector (FID) and a Perkin Elmer Elite-WAX column. The concentrations of the components in the aqueous and organic phases were determined from the calibration curves obtained using the standard solutions with known concentrations.

2.3.2. Analysis of the by-products by MALDI-TOF

The mass spectrometry (MS) analysis for identifying soluble precursors of humins was performed using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF MS). To facilitate co-crystallization of the samples, 2,5-dihydroxybenzoic acid (DHB) was used as the matrix [28]. A concentrated sodium chloride (NaCl) solution at 10 mg/mL in deionized water was also added to enhance the ionization of the analytes. The samples were analyzed in positive ion mode, covering an *m/z* range from 100 to 1000. This range enables the detection of oligomers relevant to humin formation as well as other potential soluble by-products.

2.4. Definitions and calculations

The conversion of substrate *i* (X_i) and the yield of product *j* (Y_j) in the microreactor are defined by Eqs. (1), (2).

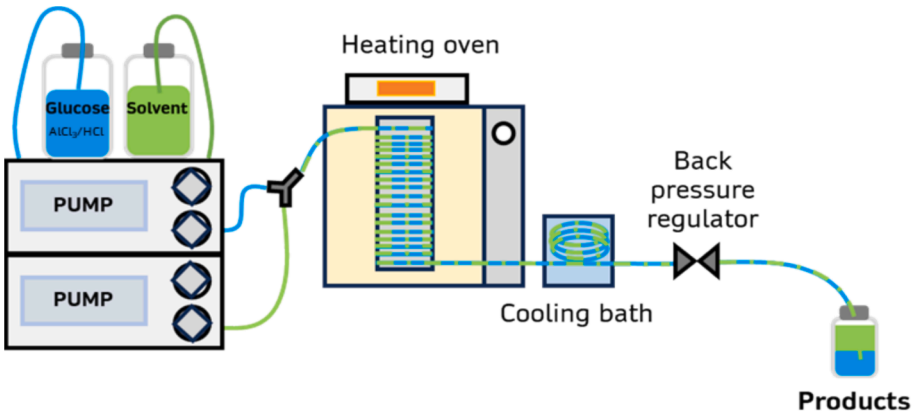


Fig. 1. Schematic diagram of the capillary microreactor system for continuous biphasic HMF synthesis from glucose.

$$X_i(\%) = \frac{Q_0^{aq} C_{i,0}^{aq} - Q_1^{aq} C_{i,1}^{aq}}{Q_0^{aq} C_{i,0}^{aq}} x100\% \quad (1)$$

$$Y_j(\%) = \frac{Q_1^{aq} C_{j,1}^{aq} + Q_1^{org} C_{j,1}^{org}}{Q_0^{aq} C_{i,0}^{aq}} x100\% \quad (2)$$

Where, Q^{aq} and Q^{org} represent the flow rates of the aqueous and organic phases, respectively. C^{aq} and C^{org} are the concentrations in the aqueous and organic phases, respectively. The subscripts 0 and 1 refer to the start of the reaction at the microreactor inlet and the end of the reaction at the microreactor outlet after being cooled, respectively. Due to the partial miscibility of organic and water phases, the volumetric flow rates of two phases at the microreactor outlet (Q_1^{aq} and Q_1^{org}) differ from the inlet flow rates, and were corrected using a correction factor which represents the ratio of flow rates at outlet and inlet for either the aqueous or organic phase, respectively. The values of φ^{aq} and φ^{org} were estimated experimentally and provided in Table S3.

The carbon balance is defined by

$$Carbon\ balance(\%) = \frac{mol\ C\ in\ the\ products}{mol\ C\ in\ the\ starting\ substrate} x100\% \quad (3)$$

Which is based on the quantifiable products by HPLC and GC (e.g., glucose, fructose, HMF, LA and FA). It does not account for the non-identified soluble/insoluble by-products [8].

3. Results and Discussion

3.1. Conversion of glucose to HMF in aqueous monophasic microreactor

The experimental findings from the microreactor study utilizing a glucose solution (0.1 M) with 40 mM of $AlCl_3$ and HCl as Lewis/Brønsted acid catalysts in a temperature range of 140 to 180 °C within a monophasic aqueous system provide valuable insights into the kinetics of the conversion process. At 140 °C, a noteworthy glucose conversion of 33 % was achieved after 12 min (Fig. 2.a), resulting in the generation of fructose, and HMF at 24 mol%, and 3 mol%, respectively (Fig. 2.b). Initially, glucose is converted to fructose, and this is gradually converted to HMF. At 160 °C, a clear maximum in the yields of fructose and HMF suggest their susceptibility to sequential transformation (Fig. 2.c). A maximum fructose and HMF yield of 35 mol% and 26 mol%, respectively, were obtained at a glucose conversion of 76 mol% at a τ of 10 min. As expected, at longer τ, the formation of by-products such as formic acid (FA) and levulinic acid (LA) was much more noticeable [5]. As τ increased, higher molecular weight compounds, such as solid humins, and products not identifiable by HPLC, were visually observed inside the microreactor. These compounds frequently caused blockages in the back-pressure regulator. Notably, enhanced conversion of glucose was achieved at 180 °C (Fig. 2.a). A maximum HMF yield of 17 mol% with 99 mol% glucose conversion was obtained in a remarkably short τ of 4 min (Fig. 2.d). The observed stoichiometric excess of FA over LA suggests multiple reaction routes contributing to FA formation, including direct thermal degradation of sugars and HMF (Fig. 2.d) [29]. The simultaneous formation of excess humins, leading to the total blockage of the back pressure regulator at a τ of 6 min, emphasizes the need for careful consideration of reaction conditions.

Our experimental results clearly illustrate the temperature-dependent effects on glucose conversion and HMF yield. Elevating the temperature from 140 to 180 °C yielded a remarkable enhancement in glucose conversion, increasing from 33 mol% to 99 mol%. This notable improvement was achieved with reduced residence times of 12 and 6 min, respectively, as depicted in Fig. 2.a. Concurrently, the maximum HMF yield exhibited a substantial rise from 3 mol% to 27 mol% as the temperature increased from 140 to 160 °C. However, further rises in

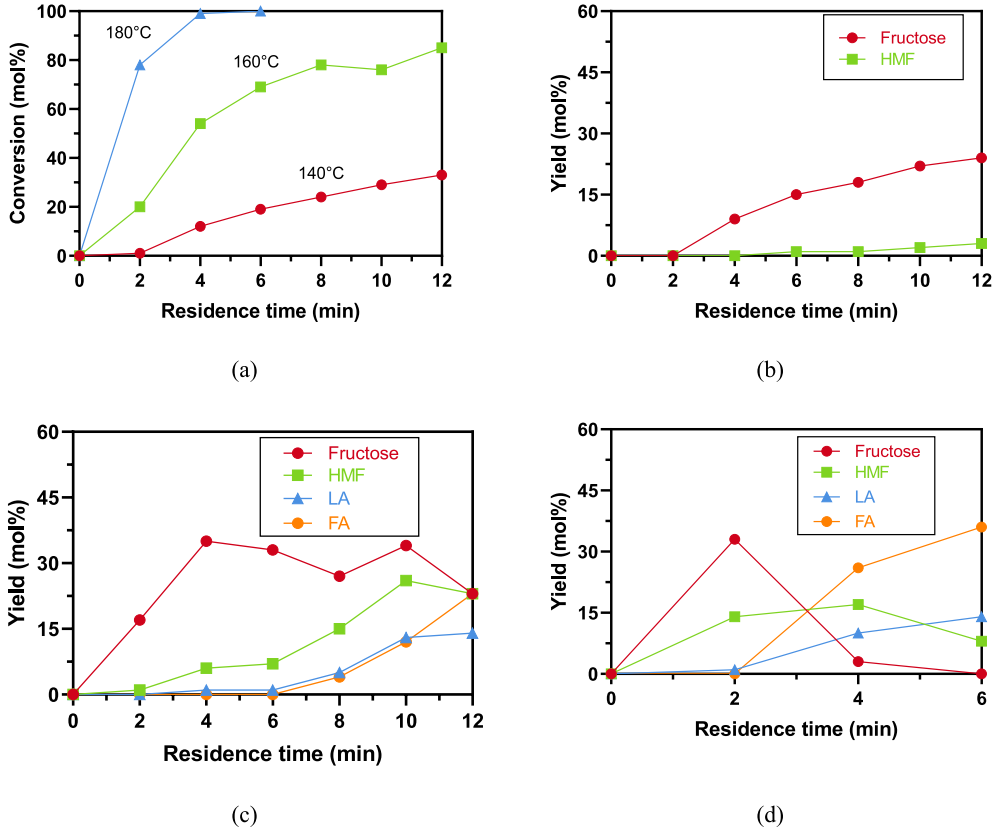


Fig. 2. Effect of temperature on the (a) glucose conversion and yield of products at different temperatures (b) 140 °C (c) 160 °C (d) 180 °C in monophasic aqueous microreactor. Reaction conditions: 0.1 M glucose, 40 mM $AlCl_3$, 40 mM HCl.

temperature resulted in the rapid formation of undesirable by-products, such as FA, LA and humins, ultimately yielding 17 mol%. Similar results were obtained by Guo *et al.* [30], where they worked with a solid catalyst composed doped with Brønsted and Lewis sites. The authors found for a temperature range between 145 and 175 °C, the glucose conversion increased from 37 % to 97 %. Additionally, they found a maximum HMF yield of 45 % at 160 °C which diminished to 25 % at 175 °C. Therefore, it is evident that higher treatment temperatures accelerate the degradation of HMF leading to the formation of by-products such humins, FA, and LA [30,31]. Thus, 160 °C is the optimum temperature for HMF production in this monophasic microreactor system.

3.2. Solvent Screening by molecular simulation with COSMO-RS

To avoid excessive formation of humin and other unwanted by-products during HMF synthesis, the COSMO-RS method was used in this work to select the most suitable natural solvent from a wide range to extract HMF and establish a biphasic production system. This approach has been widely recognized for solvent selection, including terpenes and eutectic solvents, as it enables the prediction of key properties such as extraction yields and activity coefficients [11]. The COSMO-RS method allowed for the estimation of activity coefficients at infinite HMF dilution for both natural and conventional solvents at 25 °C, using COSMO*therm* software. The capacity factor at infinite dilution, C^{∞}, which represents the inverse of activity coefficients at infinite HMF dilution, for terpenes and terpenoids, NADES, and conventional solvents is shown in Fig. 3.a and 3.b, respectively.

The C^{∞} for HMF indicates strong interactions between the solute and the solvent. Therefore, solvents with a high value of C^{∞} were expected to achieve good HMF extraction yields. The results suggested that terpenoids and eutectic solvents, particularly oxygenated and aromatic alkenes, exhibited the best performance for HMF extraction. Specifically, carvacrol, and eutectic solvents based on carvacrol demonstrated the highest affinity for HMF. These findings also indicated that carvacrol, and the eutectic mixture carvacrol:thymol are likely to outperform conventional solvents, such as MIBK and ethyl acetate, the latter of which was initially considered promising in preliminary reports [25,26].

Conversely, non-oxygenated alkanes or non-aromatic solvents, such as limonene, eucalyptol, or menthol, exhibit the lowest C^{∞}. This is primarily due to the absence of hydrogen bond acceptor groups or π-electrons, which are critical for solubilizing HMF through interactions such as hydrogen bonding and π-π stacking [16]. Additionally, eutectic solvents formed from eucalyptol and menthol display similar behavior, reinforcing the need for functional groups capable of strong solute–solvent interactions to enhance HMF extraction efficiency. The findings underscore the importance of molecular structure in determining solvent performance, where the presence of oxygenated functional groups and aromatic rings significantly improves the solubilization of HMF, particularly in biphasic extraction systems.

To validate the COSMO-RS predictions, solvents with higher C^{∞} than conventional solvents were selected, along with those exhibiting intermediate capacity factors, to encompass a wide range of solvent efficiencies. The solvents chosen for evaluation included two terpenoids (carvacrol and eugenol), a terpene (limonene), a NADES (carvacrol:thymol), and two conventional solvents (MIBK and ethyl acetate), which served as benchmarks for comparison. It is worth noting that thymol alone presents challenges for use in continuous flow processes within microreactor systems due to its relatively high melting point (52 °C). However, the formation of NADES has been shown to significantly lower the melting point, as exemplified by the carvacrol:thymol mixture, which exhibits a melting point below −18 °C. This characteristic enhances its compatibility with microreactors, ensuring it remains in a liquid state under experimental conditions.

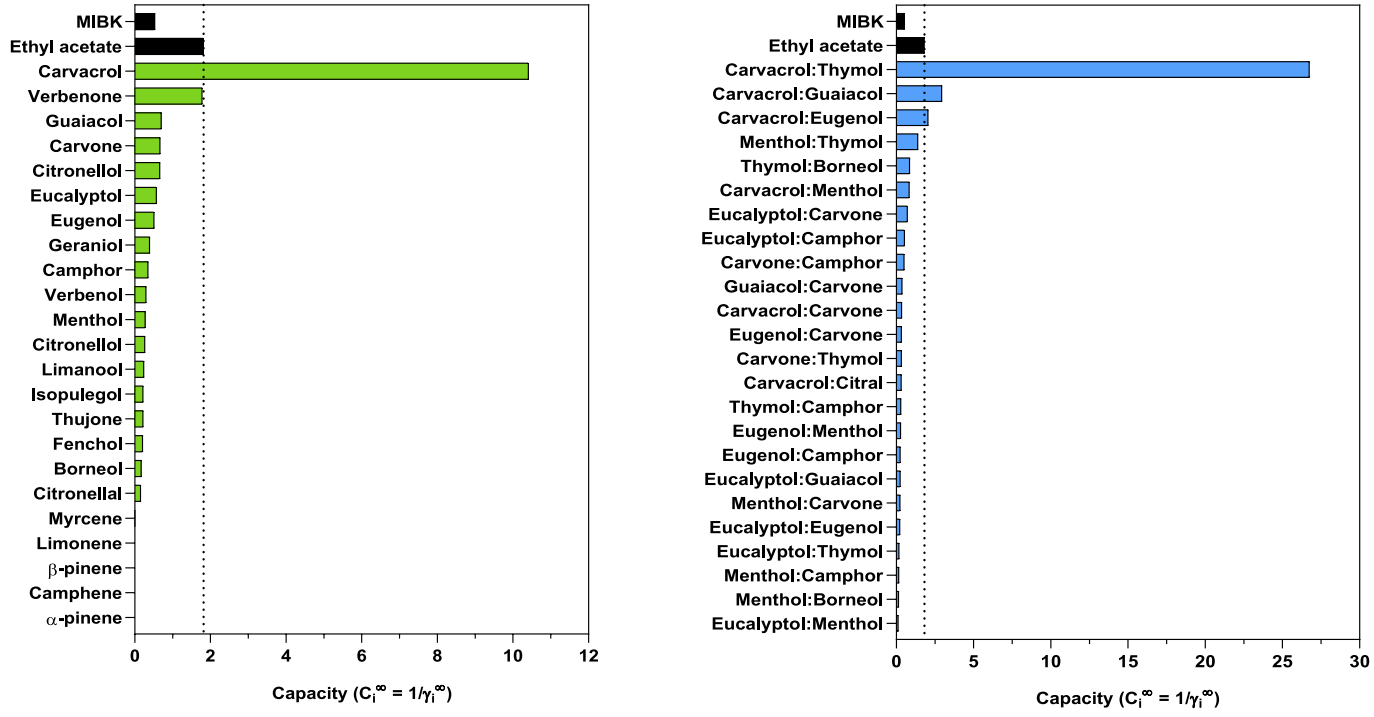


Fig. 3. Capacity factor at infinite dilution (C^{∞}) of different solutes in (a) terpenes and terpenoids, and (b) NADES at 25 °C using the COSMO-RS method.

3.3. Extraction of HMF using Terpenes, Terpenoids, conventional Solvents, and NADES

Based on molecular simulation results, six solvents were selected for testing in the extraction of HMF. The extraction yields were calculated using the following equation:

$$E_{Yield}(\%) = \frac{C^{aq}_{HMF,0} - C^{aq}_{HMF}}{C^{aq}_{HMF,0}} x100\% \quad (4)$$

Where $C^{aq}_{HMF,0}$ represents the initial HMF concentration in the aqueous solution, and C^{aq}_{HMF} corresponds to the aqueous HMF concentration after the extraction process. The extraction yield results are presented in Fig. 4.a as a function of the O/A.

The carvacrol:thymol solvent demonstrated the highest efficiency for HMF extraction, followed by pure carvacrol and eugenol solvents. The extraction yields obtained with the eutectic mixture and terpenoids were significantly superior to those achieved with conventional solvents such as MIBK and ethyl acetate. This difference was especially pronounced at a high O/A ratio of 4:1, where both carvacrol:thymol and carvacrol achieved extraction yields of approx. 96 %, in contrast to 80 % for MIBK. Limonene, which lacks a high density of oxygenated functional groups and aromatic rings, showed consistently poor extraction yields, around 1 %, for all O/A ratios tested.

Overall, COSMO-RS predictions aligned well with experimental results, with carvacrol:thymol and carvacrol showing the greatest potential for HMF extraction, significantly outperforming MIBK, a commonly used solvent in HMF synthesis. Furthermore, extraction yields increased as the O/A ratio rose from 1:1 to 4:1 for all solvents tested. For example, carvacrol extraction efficiency at O/A of 1:1 was 85 %, compared to 96 % at O/A of 4:1. However, extraction yields showed minimal differences between O/A ratios of 2:1 and 4:1. Additional experiments demonstrated that varying the initial HMF concentration in the aqueous phase (from 1.6 to 32 mM) had negligible impact on extraction efficiency (≈ 93.6 %) when using carvacrol at an O/A ratio of 2:1. This behavior is primarily attributed to the high affinity and solubility of HMF in the organic solvent (see Fig. S3 in the supplementary material). Given the high extraction efficiencies achieved with these solvents at an O/A ratio of 2:1, this ratio was selected as the optimal condition to balance solvent and equipment costs while ensuring maximum HMF extraction.

To elucidate the observed trends, σ-profiles of HMF and the selected solvents were obtained using the COSMOtherm software, as presented in Fig. 4.b. Polarized charge density values (σ) ranging from −0.0082 to 0.0082 e/Å^2 correspond to non-polar segments, while values below −0.0082 and above 0.0082 e/Å^2 correspond to electrophilic (hydrogen bond donors) and nucleophilic (hydrogen bond acceptors) groups, respectively [32]. The candidate's carvacrol and the eutectic mixture composed by carvacrol and thymol exhibit prominent peaks in the non-polar region and smaller peaks around σ ~ 0.013 e/Å^2, corresponding to the hydrogen bond accepting capability of the hydroxyl group. On the other hand, HMF shows broad non-polar regions with intensities similar to carvacrol and thymol Furthermore, HMF displays peaks at σ > 0.0082 e/Å^2 and σ < -0.0082 e/Å^2, attributable to the aldehyde and alcohol groups, respectively, present in the molecule. Esteban *et al.* [25] explored the behavior of HMF by analyzing its σ-profile and comparing it with the σ profiles of a reactive phase, commonly water, and the solvents used in extraction. The research concluded that the greater similarity between the σ-profile of HMF and organic solvents compared to the water profile may explain HMF's propensity to migrate from water to organic extracting agents.

3.4. HMF synthesis of glucose using conventional and natural solvents in a biphasic microreactor.

3.4.1. Solvent effect on glucose conversion and HMF yield

Kinetic experiments were performed to evaluate the effect of selected terpenoid-based solvents on HMF yield. Experimental results using glucose (0.1 M) in the microreactor with a combination of $AlCl_3$ and HCl (both at 40 mM) as catalysts, operating at 160 °C in biphasic systems are shown in Fig. 5. A comparison between the organic solvents used revealed similar glucose conversions (approx. 85 mol% at 12 min), indicating that the presence of an organic phase does not significantly affect glucose conversion (Fig. 5.a). This behavior of sugar reactions in aqueous media aligns with previously reported literature, where glucose conversion is independent of the type of solvent employed [16]. In the water/MIBK system, an HMF yield of 43 mol% was achieved with a residence time of 12 min (Fig. 5.b). As expected, fructose was the primary product of glucose conversion, with a maximum yield of 25 mol%. At longer residence times, by-products such as LA and FA were observed. Although, their yields were lower compared to those obtained under monophasic conditions, with values of 4.88 mol% and 1.75 mol% for FA and LA, respectively. In the water/carvacrol system, the yield of HMF was comparatively higher than in the MIBK system, reaching 54.8 mol% (Fig. 5.c). The fructose yield reached a maximum of 22 mol% at a residence time of 6 min, lower than that obtained using MIBK due to the rapid formation of HMF. In addition, through HPLC and GC analyses, traces of LA (bellow to 0.05 mol%) were detected. The behavior of the water/carvacrol system was similar to that of the water/carvacrol: thymol system but slightly lower, in terms of yields of fructose, HMF, and LA which were around 22 %, and 51 mol%, and 3 mol%, respectively, at a residence time of 12 min (Fig. 5.d). It is important to note that

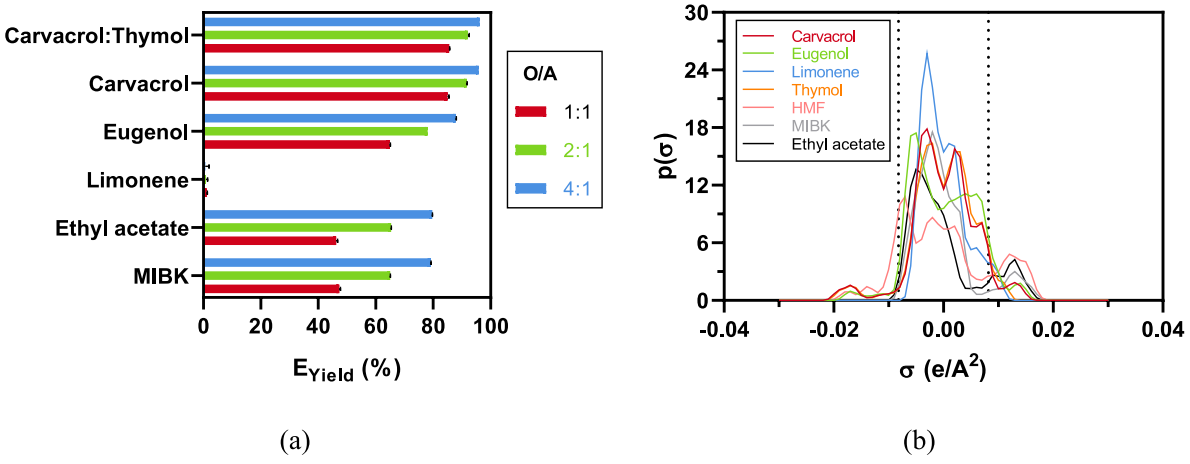


Fig. 4. (a) HMF extraction yields using conventional solvents (MIBK and ethyl acetate), NADES (carvacrol:thymol), terpene (limonene), and terpenoids (carvacrol and eugenol) as a function of the O/A solvent ratio at 25 °C; (b) Sigma profiles of HMF, conventional solvents, terpene, terpenoids, and NADES.

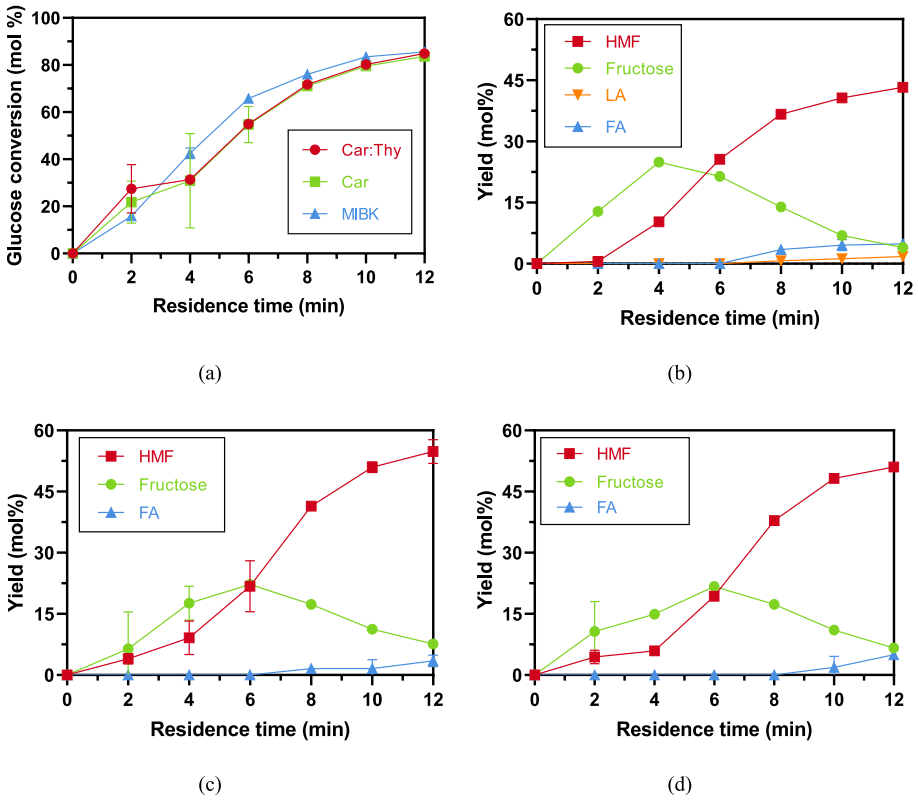


Fig. 5. Effect of solvents in (a) glucose conversion, and yield of HMF in the presence of (b) MIBK, (c) carvacrol, and (d) carvacrol:thymol solvents. Reaction conditions: 160 °C, 0.1 M glucose, 40 mM $AlCl_3$, 40 mM HCl, O/A = 2:1.

the reaction was carried out at an optimized temperature and O/A ratio of 2:1. However, the $AlCl_3$/HCl catalyst ratio could be further optimized to achieve even higher HMF yields.

3.4.2. Carbon balance

The formation of humins represents a significant loss of carbon that could otherwise be utilized for HMF production, negatively impacting the overall process efficiency. Fig. 6 presents a carbon balance for the three solvents used in the synthesis of HMF from glucose. In general, as reaction time increases, the carbon balance worsens due to the greater formation of high-molecular-weight compounds such as oligomers and humins. At a residence time of 12 min, the carbon balances were 64 mol %, 79 mol%, and 84 mol% for the MIBK, carvacrol:thymol, and carvacrol solvents, respectively. To date, knowledge about the formation mechanisms and composition of humins is very limited. However, infrared spectra of humins formed during catalytic dehydration of glucose to HMF indicate the presence of the furan ring and the hydroxyl group of HMF in humins [33]. Based on this, several studies suggest that humins are formed mainly through dimerization of HMF and its reaction with 2,5-dioxo-6-hydroxy-hexanal (DHH), a by-product of HMF rehydration [34,35]. Consequently, the selective and rapid separation of HMF using carvacrol as solvent not only prevents its decomposition, but also reduces the formation of oligomers and humins, thus improving the overall carbon balance of the process.

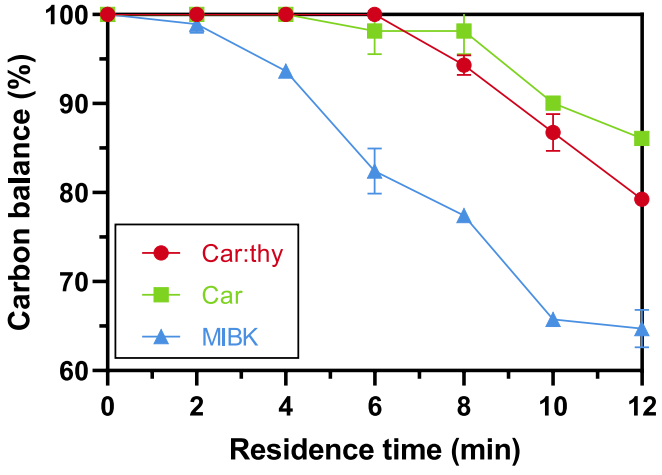


Fig. 6. Solvent effect on carbon balance of reaction. Reaction conditions: 160 °C, 0.1 M glucose, 40 mM $AlCl_3$, 40 mM HCl, O/A = 2:1.

3.5. Characterization of the By-Products by MALDI-TOF

3.5.1. Identification of soluble humin precursors

The study of the mechanism behind humin formation is crucial for developing effective methods to suppress their generation, a critical challenge in HMF production [36]. For this reason, significant efforts have been made to understand in detail the chemical pathways responsible for their formation. HMF is generally identified as one of the main precursors of humins. According to published studies, two primary routes are associated with the formation of humins from HMF: one involves electrophilic substitution without opening the furanic ring, while the other is based on aldol condensation of aldehyde-rich compounds generated through the hydrolytic opening of the HMF ring [37]. However, these are not the only relevant pathways in this process. Recent research, such as that conducted by Shi *et al.* [38] has shown that humins can also form from carbohydrates like glucose. Under aqueous hydrothermal conditions, these carbohydrates generate α,β-unsaturated aldehydes, such as 3-deoxyglucosone, which contribute to humin formation. Furthermore, this research group identified that α-carbonyl aldehydes, such as DHH play a key role in humin formation through pathways involving the opening of the HMF furanic ring [39].

To evaluate the effect of different solvents used in HMF synthesis, it is essential to identify the primary precursors responsible for humin formation. It has been demonstrated that aldol condensation reactions of α-carbonyl compounds, such as aldehydes formed during the hydrothermal degradation of glucose, lead to the formation of carbocyclic compounds. These compounds are considered the main monomers in the early stages of humin formation [38]. Therefore, their identification not only helps monitor the impact of solvents on the synthesis but also allows an assessment of the degree of soluble humin formation. In the present study, the type and relative amounts of carbocyclic compounds after the reaction were investigated by analyzing the aqueous products collected from a typical microreactor experiment (0.1 M glucose, 40 mM $AlCl_3$, and 40 mM HCl at 160 °C with a 12-minute residence time) using MALDI-TOF (Fig. 7). Fragment peaks of glucose such as $[(Glu) + H_2O]^+$, $[(Glu) + Na]^+$, and $[2(Glu) + Na]^+$ were observed in the mass spectra of all samples, with higher intensity in the initial glucose sample (before the reaction, Fig. 7.a). No carbocyclic compounds were detected prior to the reaction. When the reaction was conducted with a 12-minute residence time using MIBK as the extraction solvent, distinctive peaks were identified at m/z = 193.02, 195.13, and 215.25, primarily assigned to $[C_{11}H_{12}O_3 + H]^+$, $[C_{11}H_{12}O_3 + Na]^+$, and $[C_{11}H_{14}O_4 + H]^+$. Here, $C_{11}H_{12}O_3$ and $C_{11}H_{14}O_4$ are potential carbocyclic precursors of humin formation [37] (Fig. 7.b). In addition, peaks corresponding to $[C_6H_{10}O_5 + H]^+$ and $[C_6H_{10}O_5 + Na]^+$ were detected at m/z of 180.72 and 185.09 corresponding to 3-deoxyglucosone. In comparison, when carvacrol or the eutectic mixture of carvacrol:thymol was employed as extraction solvents, no characteristic peaks of $C_{11}H_{14}O_4$ were detected, and the relative intensity of $[C_{11}H_{12}O_3 + H]^+$ was significantly lower compared to the experiments with MIBK (Fig. 7.c, 7.d). This suggests that the use of terpenoid-based solvents reduces or inhibits completely the formation of carbocyclic molecules responsible for humins generation. It is hypothesized that the high affinity of HMF for terpenoid-based solvents facilitates its extraction from the reactive phase, preventing the formation of DHH and subsequently humins, thus increasing the reaction yield. This hypothesis is supported by the carbon balance of the reaction (Fig. 6), where a significant carbon loss was observed with MIBK compared to terpenoid-based solvents. Therefore, to effectively reduce humin production, it is crucial to employ biphasic solvent systems with a high affinity for HMF. Such systems enable the selective extraction of HMF, reducing its concentration in the reactive phase and preventing the formation of reactive intermediates in the aqueous phase.

3.5.2. *Conversion route of glucose*

Based on the detected by-products, potential pathways for the conversion of glucose to HMF in biphasic systems were proposed (Fig. 8). First, glucose can be converted into HMF through a route involving isomerization to fructose, followed by the loss of three moles of water to form HMF. Once produced, HMF can rehydrate to yield LA and FA or undergo hydrolytic ring-opening, resulting in compounds such as DHH. Alternatively, glucose can undergo β-elimination to generate 3-deoxyglucosone to produce HMF subsequently. Both 3-deoxyglucosone and DHH can participate in aldol condensation reactions, forming carbonyl compounds such as $C_{11}H_{12}O_3$ and $C_{11}H_{14}O_3$, considered the main compounds for humin formation. These dimers can undergo further condensation or polymerization, leading to more complex humin-like structures. It is noteworthy that when terpenoid-based solvents were used, no formation of carbonyl compounds was detected. This confirms that these solvents avoid the degradation pathways responsible for

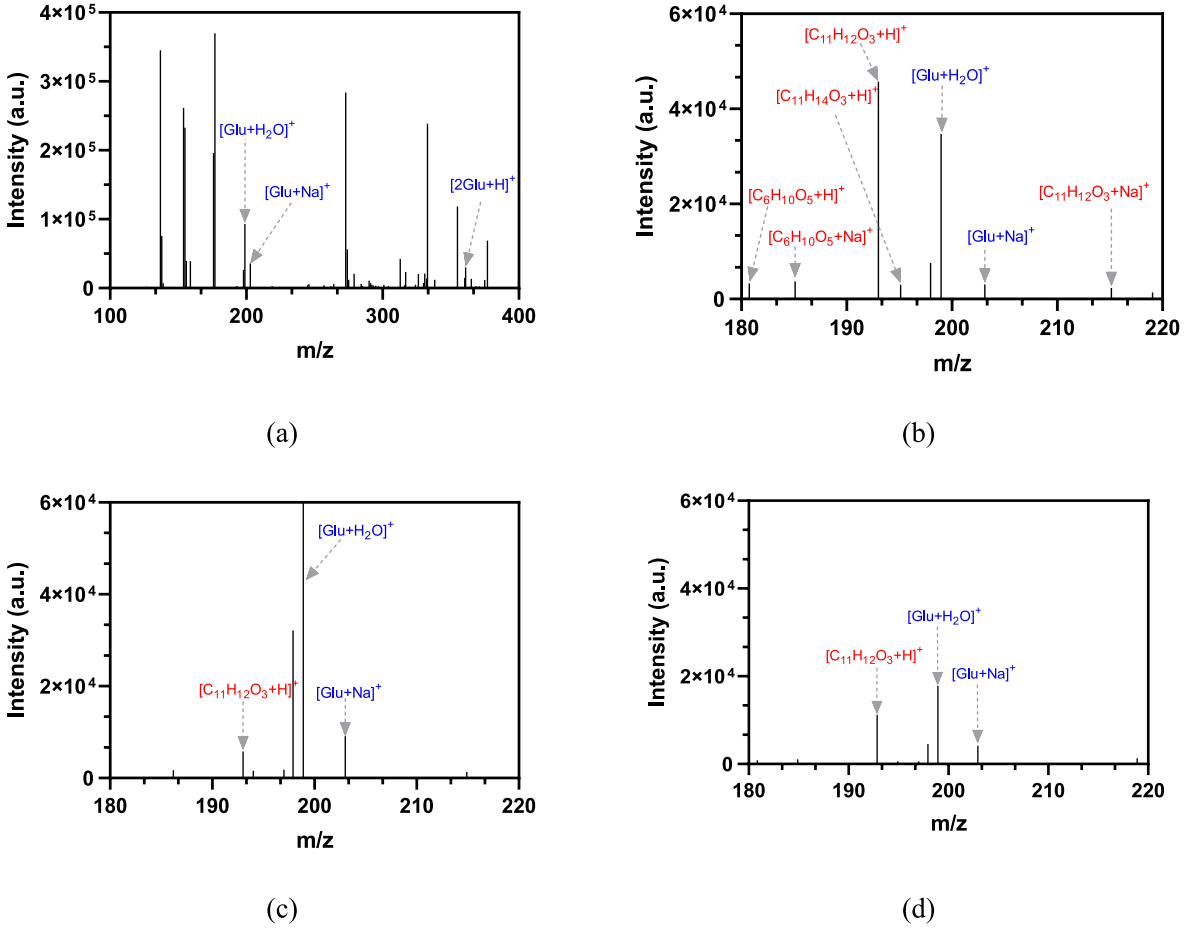


Fig. 7. MALDI-TOF spectra of (a) initial 0.1 M glucose solution containing 40 mM $AlCl_3$ and 40 mM HCl and the aqueous product sample after using (b) MIBK, (c) carvacrol, (d) carvacrol:thymol as extraction solvents in the biphasic microreactor for a residence time of 12 min.

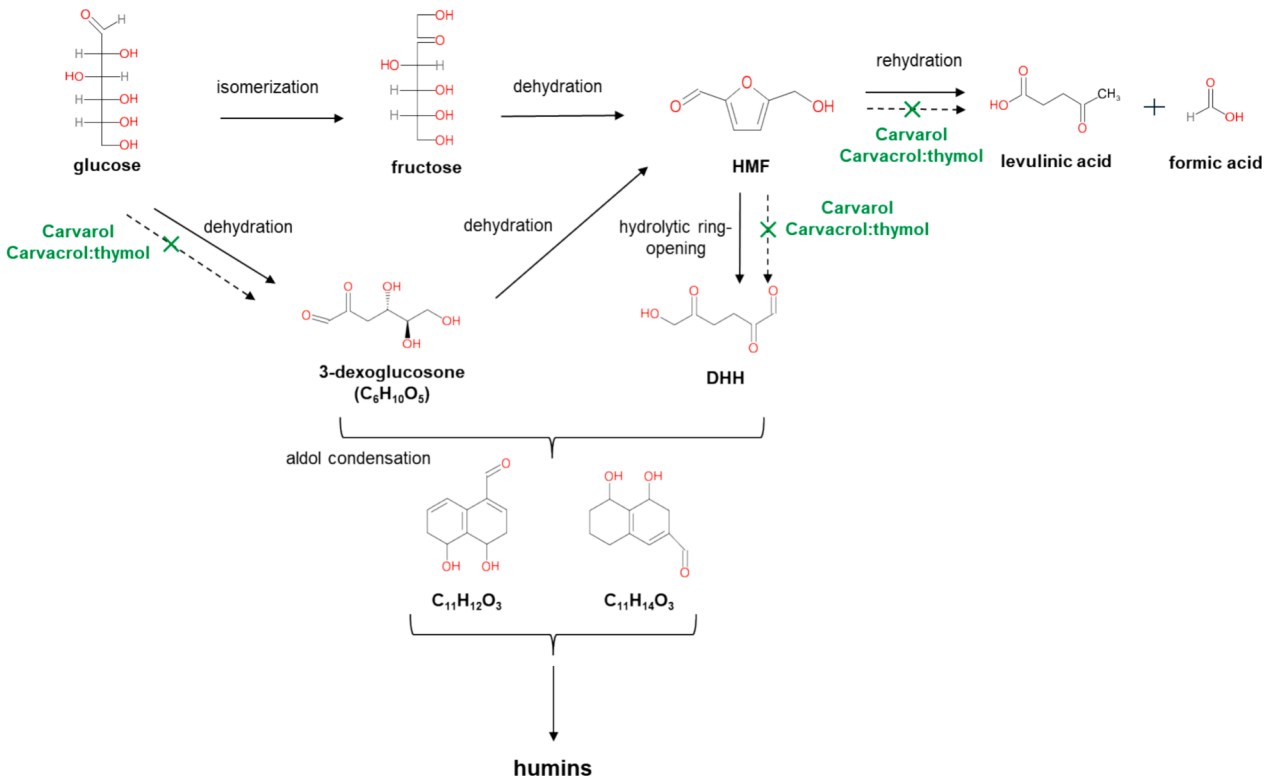


Fig. 8. Proposed route of conversion of glucose to HMF using biphasic solvents.

humin formation, contributing to a more efficient and selective process.

3.6. Role of $AlCl_3$/HCl catalyst concentration on glucose conversion and HMF yield in a Water/Carvacrol system

To investigate the interaction between Lewis ($AlCl_3$) and Brønsted (HCl) acids in the conversion of glucose to HMF, different ratios of acid catalysts were evaluated. Initially, the glucose conversion was considerably low by employing only HCl as Brønsted catalyst in the water/carvacrol system, reaching only 26 mol% (Fig. 9.a). Neither HMF nor by-product formation (e.g., FA or LA) was observed, suggesting that isomerization of glucose to fructose did not occur under the catalytic action of Brønsted acid (Fig. 9.b). Instead, in the presence of only $AlCl_3$ as a Lewis catalyst, fructose was initially formed, which was rapidly converted to HMF (Fig. 9.b), accompanied by traces of by-products such as FA. The HMF yield increased progressively as the glucose conversion progressed, reaching a maximum of 26 mol% at 12 min and achieving a glucose conversion close to 99 mol% (Fig. 9.a). The higher yield of HMF obtained with $AlCl_3$ can be attributed to the rapid hydrolysis of $AlCl_3$ in water (see Equations (5) to (8), which generates several aluminum species, mainly $Al(OH)_2^+$, responsible for the isomerization of glucose and the release of H^+ which, accompanied by $Al(OH)_2^+$ species, are responsible for the dehydration of fructose to HMF [29,40].

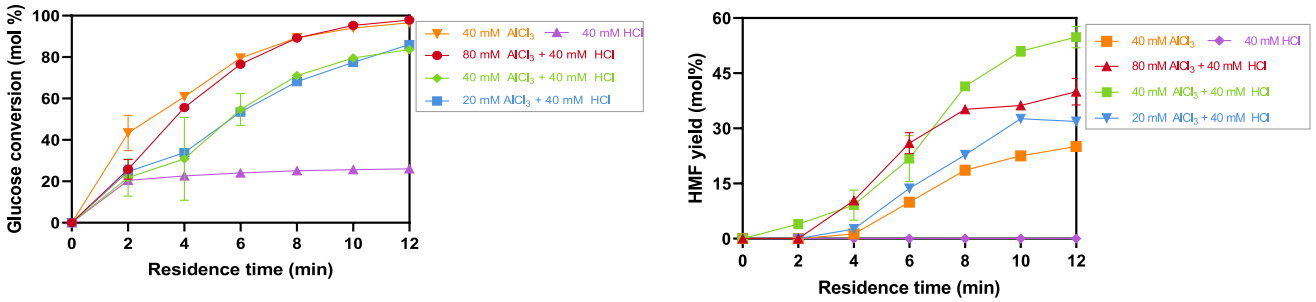
$$Al^{3+} + H_2O \leftrightarrow Al(OH)^{2+} + H^+ \quad (5)$$

$$Al^{3+} + 2H_2O \leftrightarrow Al(OH)_2^+ + 2H^+ \quad (6)$$

$$Al^{3+} + 3H_2O \leftrightarrow Al(OH)_3^0 + 3H^+ \quad (7)$$

$$Al^{3+} + 4H_2O \leftrightarrow Al(OH)_4^- + 4H^+ \quad (8)$$

Comparatively, the combined $AlCl_3$/HCl catalyst system gave a higher HMF yield than the use of $AlCl_3$ and HCl catalyst themselves. Increasing the concentration of $AlCl_3$ while maintaining a fixed HCl concentration demonstrated that the HMF yield could be enhanced up to a specific



(a) (b)

Fig. 9. Effect of the $AlCl_3$/HCl molar ratio on (a) glucose conversion and (b) HMF yield in the water/carvacrol biphasic system using a microreactor. Reaction conditions: 160 °C, 0.1 M glucose, O/A ratio of 2:1.

limit (Fig. 9.b). The results revealed that at a Lewis/Brønsted acid ($AlCl_3$/HCl) ratio of 1, a maximum HMF yield of 55 mol% was achieved, accompanied by a glucose conversion of 84 mol%. In contrast, an $AlCl_3$/HCl ratio of 2 resulted in a nearly complete glucose conversion (99 mol %) after 12 min, but the maximum HMF yield decreased to 39 mol% (Fig. 9.b). In this sense Guo *et al.* [41] demonstrated that at a constant HCl concentration, the addition of $AlCl_3$ promotes alternative reaction pathways leading to by-products, reducing the product yield. This aligns with the observed catalytic behavior in our system; at $AlCl_3$/HCl ratios below 1, the formation of the reactive $Al(OH)_3^+$ species is insufficient, limiting the glucose-to-fructose isomerization and subsequently lowering the maximum HMF yield. At $AlCl_3$/HCl ratios above 1, the increased $Al(OH)_2^+$ concentration accelerates by-product formation, further diminishing HMF yields. Notably, at an L/B ratio of 1, the concentration of $Al(OH)_2^+$ becomes stabilized, thus maximizing HMF production.

Previous studies have demonstrated the catalytic effects of Lewis and Brønsted acids in various systems. For instance, Wang *et al.* [42] explored the use of $AlCl_3$ and HCl as catalysts in a biphasic water/cyclopentyl methyl ether system. Their results indicated that the combined application of Lewis and Brønsted acids led to a synergistic enhancement in the conversion of glucose to HMF, surpassing the individual catalytic effects of each acid. This synergy can be attributed to the dual catalytic role, where $AlCl_3$ facilitates the isomerization of glucose to fructose, and HCl promotes the dehydration of fructose to HMF. Notably, they found that introducing a specific amount of HCl (pH = 2.5) reduced the concentration of reactive $Al(OH)_2^+$ species, slightly decreasing glucose conversion from 90 % to 89.5 %, but significantly boosting the HMF yield from 46 % to 54.5 % which these results align with our findings.

3.7. Development of the kinetic model from continuous experiments in a biphasic microreactor system

To elucidate the consistency of the experimental data with the proposed reaction scheme, simple kinetic modeling was performed. In general, the reaction network for glucose conversion in water remains a debated topic in the literature, and various possibilities have been proposed [29,43,44]. Based on our findings, the proposed mechanism is summarized in Fig. 10. In this reaction scheme, the reversible isomerization of glucose to fructose is primarily catalyzed by $Al(OH)_2^+$ species in aqueous solution. The subsequent dehydration of fructose to HMF, the rehydration of HMF to FA and LA, as well as the direct transformation of glucose to HMF, are jointly catalyzed by $Al(OH)_2^+$ and H^+, originating from the $AlCl_3$ and HCl catalysts, respectively [19,29]. Additionally, these catalytic species promote secondary pathways, including the degradation of glucose and HMF to FA and their polymerization into humins, which account for the increased formation of undesired by-products [45]. The kinetic model thus incorporates a detailed reaction network, encompassing the parallel and sequential processes of isomerization, dehydration, decomposition, and polymerization of glucose.

3.7.1. Kinetic modelling of continuous experiments in the biphasic microreactor system

In microreactors, the flow pattern and the extent of axial and radial diffusion are critical factors influencing the residence time distribution (RTD). For the biphasic flow systems, microreactors exhibit a RTD closely approximating the ideal plug-flow [46]. Therefore, a plug-flow behavior was assumed for kinetic modeling. Based on the reaction network illustrated in Fig. 10, the molar balance for the various species in water can be expressed as follows:

$$\frac{dC_{Glu}^{aq}}{d\tau} = -R_{1G} - R_{2G} - R_{3G} - R_{4G} + R_{1F} \tag{9}$$

$$\frac{dC_{Fru}^{aq}}{d\tau} = -R_{1F} - R_{2F} + R_{1G} \tag{10}$$

$$\frac{dC_{HMF}^{aq}}{d\tau} = -R_{1H} - R_{2H} - R_{3H} + R_{2F} + R_{4G} \tag{11}$$

$$\frac{dC_{FA}^{aq}}{d\tau} = R_{1H} + R_{3H} + R_{3G} \tag{12}$$

$$\frac{dC_{LA}^{aq}}{d\tau} = R_{1H} \tag{13}$$

Here C_{Glu}^{aq}, C_{Fru}^{aq}, C_{HMF}^{aq}, C_{FA}^{aq}, C_{LA}^{aq} represents the molar concentration of glucose, fructose, HMF, FA, and LA in the aqueous phase, respectively. During the reaction, HMF is extracted into the organic phase. Assuming no further reaction of HMF in the organic phase, the concentrations of HMF in the water and organic phase (i.e., C_{HMF}^{aq}, C_{HMF}^{org}) may be calculated by the molar balances given in Eqs. (14)-(15):

$$\frac{dC_{HMF}^{aq}}{d\tau} = -R_{1H} - R_{2H} + R_{2F} + R_{2G} - J_{1H} \tag{14}$$

$$\frac{dC_{HMF}^{org}}{d\tau} = J_{1H} \tag{15}$$

where J_{1H} is the extraction rate of HMF from the aqueous phase to the organic phase assuming a valid film model theory, and is calculated as:

$$J_{1H} = K_L a\left(C_{HMF}^{aq} - \frac{C_{HMF}^{org}}{m}\right) \tag{16}$$

here $K_L a$ is the overall liquid–liquid mass transfer coefficient, and m is the partition coefficient of HMF between water and the organic solvent.

In the literature, kinetic studies on the conversion of glucose to HMF over combined Lewis and Brønsted catalysts demonstrate that the chemical reactions follow a first-order kinetic model [29,47]. Thus, the reaction rates R_{ij} (where i = 1,2, 3 or 4 and j = G, F, or H) are expressed as:

$$R_{iG} = k_{iG}^{obs} C_{Glu}^{aq} \tag{17}$$

$$R_{iF} = k_{iF}^{obs} C_{Fru}^{aq} \tag{18}$$

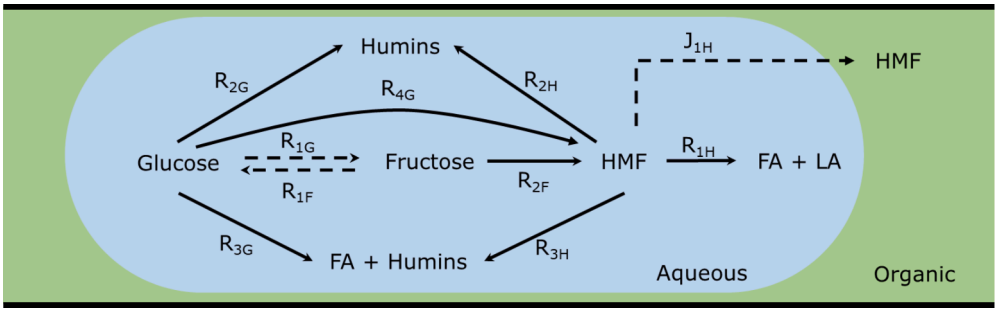


Fig. 10. The reaction network of the glucose conversion to HMF.

$$R_{iH} = k_{iH}^{obs} C_{HMF}^{aq} \quad (19)$$

In summary, the kinetic model for the conversion of glucose in biphasic microreactors involves a set of nonlinear ordinary differential equations (Eqs. (9)-(16)), alongside reaction rate equations (Eqs. (17)-(19)). Apparent rate constants (k_{ij}^{obs}) were estimated by fitting experimental data in MATLAB R2022b (MathWorks) using the *lsqcurvefit* nonlinear least-squares fitting function, based on a trust-region-reflective algorithm to minimize errors between experimental and predicted concentrations. A comparison of the experimental data with the predictions of the kinetic model shows a good fit for the biphasic reaction systems employed, as corroborated by the parity plot (Fig. 11). The goodness of fit was assessed by the coefficient of determination (R^2) which was calculated using Eq. (20).

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(x_i - \hat{x}_i)^2}{\sum_{i=1}^{n}(x_i - \bar{x}_i)^2} \quad (20)$$

Where x_i is the experimental data (conversion or yield of the components), $\hat{x}_i$ is the value predicted by the kinetic model, $\bar{x}_i$ denotes the mean of the experimental data, and n denotes the number of experimental data.

The kinetic parameters for the sub-reactions evaluated in the different solvent systems are summarized in Table 1. The estimated rate constants exhibit high sensitivity to the type of solvent used. Specifically, the biphasic systems employing carvacrol and the carvacrol:thymol demonstrated greater selectivity in the conversion of glucose to HMF. This is evidenced by the reduction in rate constants associated with secondary pathways leading to humins from glucose (k_{2G}^{obs}, k_{3G}^{obs}), HMF rehydration to LA and FA (k_{1H}^{obs}) and HMF degradation to humins (k_{2H}^{obs}) compared to MIBK solvent system. This suggests that terpene-based solvents effectively mitigate degradation pathways. Regarding the isomerization of glucose to fructose (k_{1G}^{obs}) and subsequent dehydration of fructose to HMF (k_{2F}^{obs}), the kinetic constants remained consistent across the three systems, indicating that this process is less dependent on solvent properties. This behavior supports the idea that the conversion of glucose into HMF is primarily governed by the catalyst and operational conditions rather than by the medium's characteristics.

The partition coefficient for HMF, m, in the water/MIBK system was modeled as 0.77, aligning with the value reported by Guo *et al.* [51] (0.78) for similar conditions and slightly lower than those obtained by Shimanouchi *et al.* [52] (0.85) and Martina *et al.* [27] (0.95). In contrast, for the water/carvacrol and water/carvacrol:thymol systems, although data availability is limited, the m values obtained (1.11–1.25) were higher than those observed in the water/MIBK system. These values also fall within the range reported by Mai *et al.* [21] (2.32) for thymol-based solvent systems, highlighting the efficiency of terpenoid-based solvents in HMF extraction. In this study, the estimated K_La ranged from 3.34 to 3.57 min^{-1}, with higher values observed for the water/MIBK system compared to the water/carvacrol and water/carvacrol:thymol systems. Although the K_La values for carvacrol (3.39 min^{-1}) and carvacrol:thymol (3.34 min^{-1}) systems were slightly lower, these solvents demonstrated significant advantages, such as a higher m, which optimizes the trade-off between mass transfer efficiency and solute affinity. This balance is essential for maximizing glucose conversion to HMF while minimizing the formation of undesirable by-products.

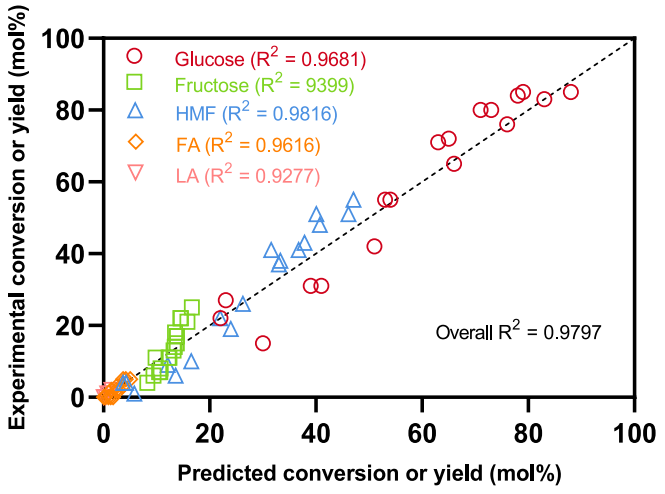


Fig. 11. Parity plots for the model predictions and experimental results for the conversion and yield of all components.

Table 1
Kinetic parameters for the glucose conversion to HMF using AlC_3/HCl catalysts in different solvent systems.

Parameters	Solvents		
	water/MIBK	water/carvacrol	water/carvacrol: thymol
$k_{1G}^{obs}(min^{-1})$	0.104 ± 0.08	0.081 ± 0.08	0.085 ± 0.09
$k_{2G}^{obs}(min^{-1})$	0.071 ± 0.06	0.042 ± 0.06	0.044 ± 0.07
$k_{3G}^{obs}(min^{-1})$	2.63 x 10^{-4} ± 0.03	2.91 x 10^{-14} ± 0.03	2.86 x 10^{-9} ± 0.03
$k_{4G}^{obs}(min^{-1})$	2.78 x 10^{-14} ± 0.08	7.74 x 10^{-10} ± 0.08	2.26 x 10^{-14} ± 0.08
$k_{1F}^{obs}(min^{-1})$	2.22 x 10^{-14} ± 0.21	3.54 x 10^{-14} ± 0.24	5.39 x 10^{-7} ± 0.25
$k_{2F}^{obs}(min^{-1})$	0.286 ± 0.29	0.215 ± 0.35	0.221 ± 0.36
$k_{1H}^{obs}(min^{-1})$	0.013 ± 0.05	8.51 x 10^{-9} ± 0.10	6.30 x 10^{-4} ± 0.11
$k_{2H}^{obs}(min^{-1})$	0.144 ± 0.31	0.002 ± 0.54	0.064 ± 0.62
$k_{3H}^{obs}(min^{-1})$	0.031 ± 0.15	0.039 ± 0.27	0.049 ± 0.31
m	0.77 ± 0.41	1.11 ± 0.75	1.25 ± 1.45
$K_La(min^{-1})$	3.57 ± 17.9	3.39 ± 14.8	3.34 ± 39.2

3.7.2. Glucose conversion and HMF yield prediction

The developed kinetic model, along with the obtained parameters, enables the simulation of reaction behavior regarding glucose conversion and product yields. Furthermore, the proposed model proves particularly useful for optimizing reaction performance in continuous flow reactors operating with plug-flow characteristics. To evaluate the influence of different solvents and higher residence times, simulations were conducted under reference conditions, considering a reaction temperature of 160 °C, 40 mM $AlCl_3$, 40 mM HCl, 0.1 M glucose, and an O/A of 2:1. The results for HMF yield as a function of glucose conversion, as well as the time-dependent behavior of reaction products, are presented in Fig. 12.

The use of carvacrol as an extraction solvent achieves a maximum HMF yield of approximately 65 % at an 85 % glucose conversion (Fig. 12.a). In contrast, employing the carvacrol:thymol eutectic mixture or MIBK as extraction solvents results in progressively lower maximum HMF yields of around 59 mol% and 47 mol%, respectively, at similar glucose conversion levels. These results align with experimental data, demonstrating that carvacrol exhibits superior capability in reducing the degradation rate of HMF into undesired by-products. Consequently, carvacrol is identified as the most efficient extraction solvent for maximizing HMF yields. Fig. 12.b illustrates the temporal evolution of glucose conversion and product yields when carvacrol is used as the extraction solvent. Over time, the modeled HMF yield steadily increases, reaching an optimal value of 63 mol% after 24 min of reaction, with glucose conversion exceeding 95 mol%. Meanwhile, the humin yield predicted remains below 25 mol%, a result that agrees with the observation inside the reactor. Then, the use of carvacrol is advantageous as it minimizes the formation and accumulation of this by-product on the reactor walls, reducing the risk of blockages or operational failures, promoting continuous and efficient reactor operation.

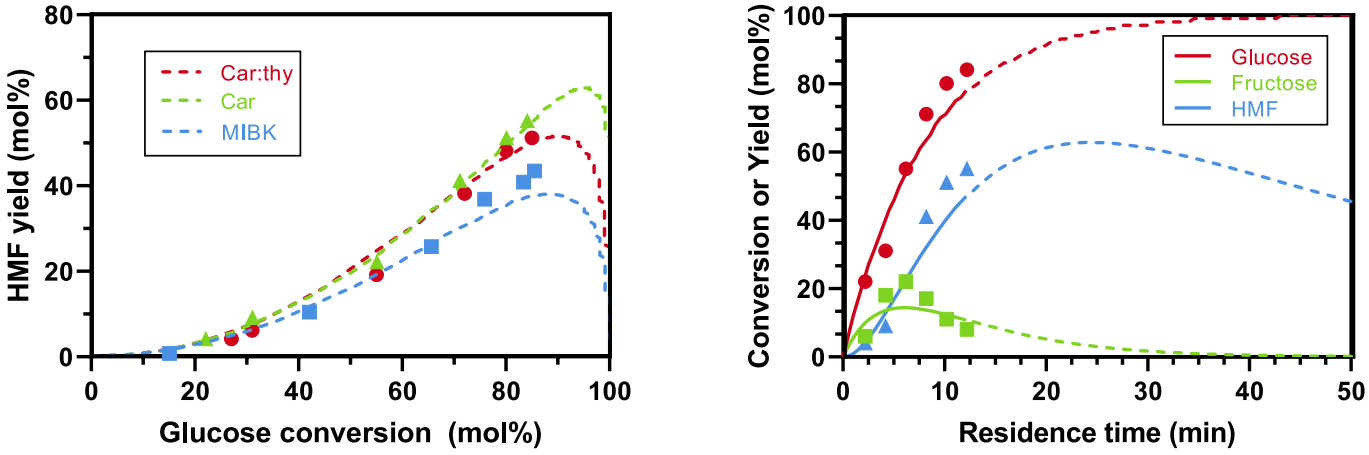


Fig. 12. Kinetic results for (a) HMF yield as a function of glucose conversion in different biphasic solvent systems using a microreactor and (b) extended reaction times in the water/carvacrol biphasic system within a microreactor. Simulated conditions: 160 °C, 0.1 M glucose, O/A ratio of 2:1, 40 mM $AlCl_3$, and 40 mM HCl.

3.8. Analysis of mass transfer phenomena in microreactors

To investigate possible mass transfer limitations, the values of the K_La were roughly estimated under typical reaction conditions in microreactors using water/carvacrol system. Under biphasic operation, the produced HMF was extracted *in situ* from the reactive aqueous phase (as droplets) to the continuous phase via (i) the caps of droplet and (ii) the carvacrol film between the droplet and the microreactor wall. Based on the model of Hommes *et al.* [53], a simplified mass transfer analysis for liquid–liquid slug-flow was conducted, in which the pathway (i) was estimated to be dominant in mass transfer and the pathway (see the calculations details in section S7 of the Supporting information).

As such, the overall mass transfer coefficient (K_L) was assumed to be that in the cap region and can be approximated as

$$K_L = \frac{1}{\frac{1}{\frac{2\sqrt{2}}{\pi}\sqrt{\frac{D_{HMF,water}u_{slug}}{d_c}}} + \frac{1}{m\frac{2\sqrt{2}}{\pi}\sqrt{\frac{D_{HMF,carvacrol}u_{slug}}{d_c}}}} \quad (21)$$

where $D_{HMF,water}$ and $D_{HMF,carvacrol}$ are the diffusion coefficients of HMF in the aqueous and organic phases, respectively. u_{slug} is the slug velocity (i.e., equal to the two-phase mixture velocity), and m is the partition coefficient of HMF between water and carvacrol. The specific interfacial area, ratio of surface area of the slug per unit volume, can be written by neglecting the film thickness as:

$$a_{cap} = \frac{2d_c^2}{d_c^2 L_D} = \frac{2}{L_D} \quad (22)$$

were L_D is the length of the droplet.

Due to the small density difference between water and carvacrol ($\Delta\rho$ = 0.024 g/mL at 160 °C), droplets of non-uniform size were observed throughout the biphasic microreactor. To account for this variability, the average, L_D, was used to calculate the K_La. Measurements were conducted using MATLAB 2022b, employing image processing tools, and a normality test (Shapiro-Wilk) was applied to the data, confirming that the dataset followed a normal distribution. The calculated K_La values for the water/carvacrol biphasic system, based on Eqs. (21) and (22), are shown in Fig. 13 as a function of the total inlet mixture velocity under reaction conditions of 160 °C, 40 mM $AlCl_3$, 40 mM HCl, and an initial O/A ratio of 2:1. Results indicate that higher flow rates, corresponding to higher droplet and slug velocities, lead to increased mass transfer coefficients due to enhanced internal circulation within the droplets and slugs [54]. Under experimental conditions, the estimated K_La values ranged from 1.6 to 4.8 min^{-1} for a microreactor length (L_c,) of 3.0 m, with inlet mixture velocities varying between 0.69 and 4.17 cm/s. The calculated K_La values are three orders of magnitude greater than apparent rate constant of HMF degradation ($k_{1H}^{obs} \sim 0$ min^{-1}, k_{2H}^{obs} = 0.002 min^{-1}, and k_{1H}^{obs} = 0.039 min^{-1} at 160 °C with 40 mM $AlCl_3$ and 40 mM HCl). Consequently, these results indicate that the interfacial mass transfer resistance is negligible at high mixing rates, where HMF produced in the aqueous phase can efficiently transfer to the carvacrol phase before undergoing further degradation, allowing the reaction to proceed under optimal kinetic control [55].

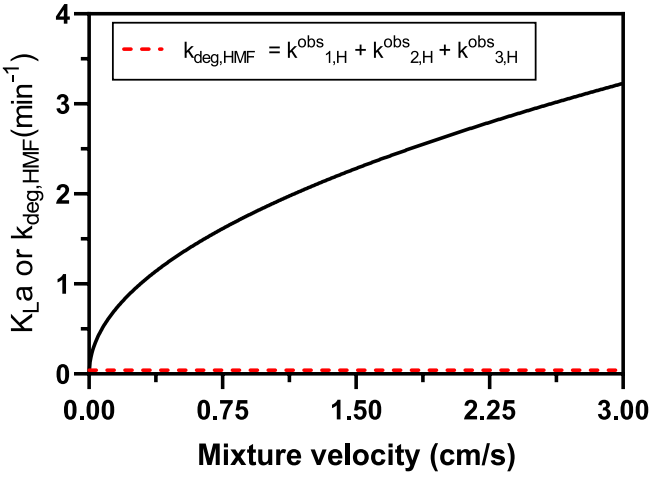


Fig. 13. The estimated overall liquid–liquid mass transfer coefficient (K_La) as a function of two-phase mixture velocity in the water-carvacrol microreactor system. Reaction conditions: 160 °C, 0.1 M glucose, 40 mM $AlCl_3$, 40 mM HCl, O/A = 2:1, L_c = 3.0 m.

3.9. Comparison of the HMF yield with literature data

The performance of our current microreactor system was benchmarked against relevant literature reporting the synthesis of HMF from glucose using microreactors with homogeneous Lewis and/or Brønsted acid catalysts. In our study, we achieved a maximum HMF yield of 55

mol% from 0.1 M glucose in a biphasic water/carvacrol microreactor system, operated at 160 °C with a residence time of 12 min. This yield is comparable to values reported in the literature, highlighting the efficiency of our approach (Table 2). For instance, Cheng *et al.* [48] achieved an HMF yield of 36 % in a monophasic microreactor (PFA capillary, 1.0 m x 500 μm I.D.) using 0.05 M aqueous glucose as the substrate and $CrCl_3$/HCl as the catalyst at 200 °C and a short residence time of 7 min. Muranaka *et al.* [20] reported an HMF yield of 75.7 % in a biphasic microreactor (SUS 316 tube, 9 m x 1 mm I.D.), using phosphate buffer and 2-*sec*-butyl phenol as the biphasic system. Their results underscored the advantage of internal circulation, which facilitated the instantaneous transfer of HMF from the aqueous to the organic phase. Similarly, Tongtummachat *et al.* [7] reported an impressive HMF yield of 81.7 % in a dispersed flow microreactor (0.81 mm I.D.) using HCl as the catalyst in a water/MIBK system at 180 °C and a residence time of just 3 min. Guo *et al.* [19] employed a slug-flow capillary microreactor (PFA capillary, 4.5 m x 1.65 mm I.D.) for HMF synthesis using $AlCl_3$/HCl as the homogeneous catalyst and MIBK as the organic extraction phase. Their process yielded 53 % HMF at 160 °C with a residence time of 16 min, and the addition of 20 wt% NaCl in the aqueous phase further improved the HMF yield to 66.2 %. In this regard, many studies have incorporated salts, mainly NaCl, to induce a salting-out effect in the aqueous phase. The use of salts can induce a salting-out effect that reduces HMF solubility in the aqueous phase, enhancing its separation and selectivity. Furthermore, incorporating co-solvents (e.g., n-butanol or THF) into the organic phase can improve interfacial properties and stabilize intermediates, thereby minimizing side reactions and improving overall process efficiency.

Early investigations regarding to the use of novel solvent systems for HMF synthesis were explored by Zhang *et al.* [49] who demonstrated the potential of DES based on quaternary ammonium salts and ethylene glycol as reaction media. An optimal HMF yield of 42 % was achieved at 150 °C within just 3.64 min using $CrCl_3$ as the catalyst. However, DES formulations involving ethylene glycol were found to impose mass transfer limitations due to their high viscosity. This hindered the efficient transfer of reaction products from the DES phase to the extraction phase, resulting in reduced HMF yields even at high flow rates in extended reactors. Using a similar reaction system, Rakhatkyzy *et al.* [50] carried out the continuous synthesis of HMF from glucose employing Tetraethyl ammonium bromide/isopropanol:water, achieving 41 % yield of HMF in 20 min of reaction. In this context, our approach, which uses water as reaction medium, terpenoid-based green organic solvents and $AlCl_3$/HCl as catalytic system, offers a promising alternative for efficient HMF synthesis. The combination of high HMF yield, low organic solvent usage and superior two-phase extraction underlines the potential of this system as a sustainable solution for HMF production.

4. Conclusions

Various terpenes, terpenoids, and natural eutectic solvents were evaluated for the extraction of HMF from aqueous solutions. The COSMO-RS computational method identified carvacrol and the eutectic mixture carvacrol:thymol as promising solvents, which was experimentally validated. These solvents demonstrated superior extraction efficiency compared to conventional solvents such as MIBK and ethyl acetate. Additionally, they enhanced HMF yields and improved the carbon balance by significantly reducing humin formation. The combination of terpenoid-based solvents with $AlCl_3$/HCl catalysts proved to be an effective strategy to maximize HMF yields from glucose in biphasic systems using continuous-flow microreactors. Maximum experimental HMF yields of 55 mol% and 52 mol% were achieved using carvacrol and carvacrol:thymol, respectively, surpassing the conventional water/MIBK system, which achieved only 43 mol%. MALDI-TOF MS analysis revealed that carvacrol and carvacrol:thymol effectively inhibit the formation of carbocyclic precursors (e.g., $C_{11}H_{12}O_3$) responsible for humins formation. This is attributed to their high affinity for HMF, facilitating rapid and selective extraction while minimizing undesired degradation pathways. Furthermore, the use of these solvents aligns with principles of green chemistry, offering a more sustainable alternative to non-renewable and potentially hazardous organic solvents. A detailed kinetic model for glucose-to-HMF conversion in biphasic microreactor systems was also developed, providing valuable insights into the reaction mechanism and process optimization. Simulations showed that carvacrol as a solvent reduces the formation of by-products (FA, LA, and humins), enabling a maximum HMF yield of up to 65 mol% with 85 mol% glucose conversion under optimized conditions. This highlights the potential for significant process improvements compared to traditional solvent systems. Mass transfer analysis indicated that the system was not significantly limited under the studied conditions, except at prolonged residence times, where larger microreactor length enhanced internal circulation contributed to further increases in HMF yield. The efficient integration of kinetic and mass transfer models in this study provides a robust framework for scaling up the process.

This work represents a significant step toward the implementation of green solvents and sustainable catalytic methods for HMF production. The results underscore the potential of terpenoid-based solvents not only to enhance HMF yields but also to reduce the environmental impact associated with non-renewable solvents, opening new opportunities for the obtaining of high-value-added products.

Table 2
Comparison of HMF yields from glucose in a biphasic terpenoid-based solvent microreactor system with reported results from the literature.

Catalyst	Solvent System	Substrate concentration (M)	O/A[a] ratio	T[b] (°C)	τ[c] (min)	Y_{HMF}[d] (mol%)	Work
$CrCl_3$/HCl	Water	0.05	–[f]	200	7	36	[48]
H_3PO_4	water/2-*sec*-butyl phenol (2BP)	0.05	3:1	180	47	76	[20]
HCl	water/MIBK	0.05	0.5:1	180	3	82	[7]
$AlCl_3$/HCl	water/MIBK	0.1	4:1	160	16	53	[19]
$AlCl_3$/HCl	water/MIBK[e]	1.0	4:1	160	16	66	[19]
$CrCl_3$	Tetraethyl ammonium chloride/ethylene glycol ($[N_{2222}]Cl$/EG)	0.3	–[f]	150	3.64	42	[49]
$CrCl_3$	Tetraethyl ammonium bromide/isopropanol:water (TBAB/IPA:water)	0.2	–[f]	170	20	41	[50]
$AlCl_3$/HCl	water/carvacrol	0.1	2:1	160	12	55	This work
$AlCl_3$/HCl	water/carvacrol:thymol	0.1	2:1	160	12	52	This work

[a] Organic-to-aqueous ratio (O/A).
[b] Reaction temperature.
[c] Residence time.
[d] HMF yield.
[e] With the addition of 20 wt% NaCl in the aqueous phase.
[f] Monophasic system.

CRediT authorship contribution statement

Matías Kopp: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pedro Anabalón:** Investigation, Formal analysis. **Marcos Larriba:** Writing – review & editing, Software, Data curation. **Sebastián Rocha:** Writing – review & editing, Methodology. **María-Eugenia González:** Writing – review & editing. **Mara Cea:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2025.164077.

Data availability

Data will be made available on request.

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