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Batch and continuous flow production of 5-hydroxymethylfurfural from high concentration of fructose using acidic ion exchange catalyst

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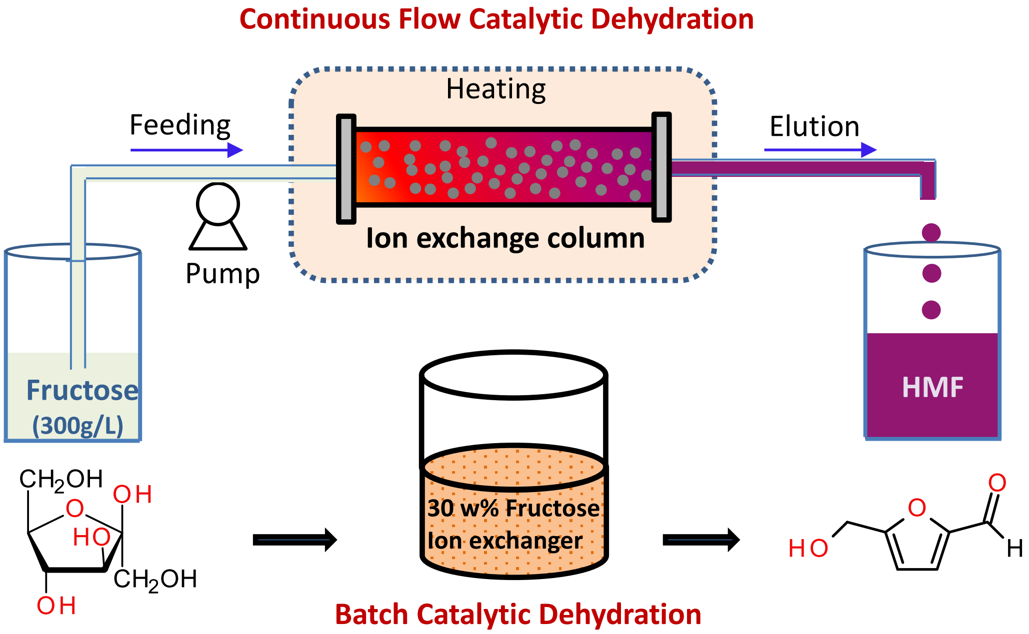
Continuous Flow Catalytic Dehydration
Heating
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Elution
Ion exchange column
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Fructose
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Batch Catalytic Dehydration

ABSTRACT

5-Hydroxymethylfurfural (HMF), a product of catalytic dehydration of C6 sugar, is a versatile and key renewable platform chemical. The possibility to use high substrate concentration with high yield in a single solvent system is one of the solutions to reduce solvent usage, energy consumption, reaction volume and operating cost. A heterogeneous catalyst and single solvent system were employed to develop a facile and green process for production of HMF from fructose at high concentration under moderate conditions in batch and continuous flow mode. In the batch process, at 0.1 and 0.2 w/w of ion exchange resin DR-2030 as catalyst, 98.8% fructose conversion with 82.2% HMF yield, and 99.7% fructose conversion with 85% HMF yield, respectively, were obtained from 300 g/L (30%, w/w) fructose in DMSO at 110 °C. The catalyst could be reused for at least five consecutive batches. Continuous dehydration of 300 g/L fructose was carried out at 110 °C in a simple flow reactor packed with the ion exchange resin. Fructose conversion of 98% and HMF yield of 82% were obtained. HMF was purified by liquid-liquid extraction, concentration and silica chromatography.

KEYWORDS.

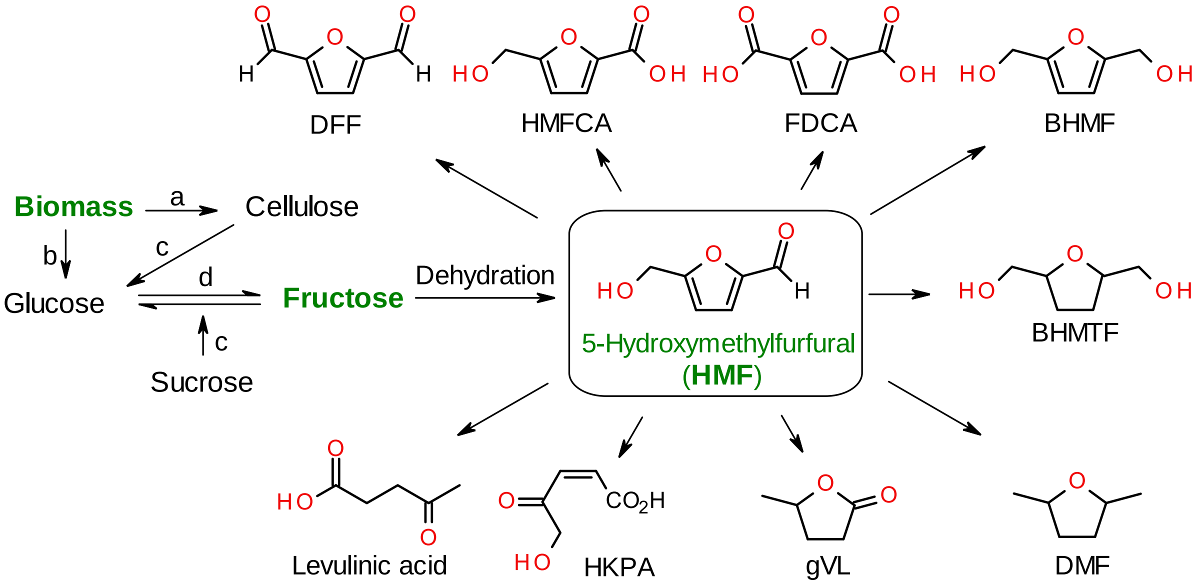
5-hydroxymethylfurfural (HMF), fructose, heterogeneous catalysis, ion exchange resin, continuous flow dehydration

INTRODUCTION

The main source of functional carbon building blocks for fuel, chemical and polymer industry is still based on fossil resources. Sustainable production of these materials from bio-based renewable resources using environmentally friendly routes for reducing the carbon footprint is drawing increasing attention.[1-5] 5-Hydroxymethylfurfural (HMF), ranked as one of the valuable bio-platform chemicals, has become a hot research topic and its production by catalytic dehydration of carbohydrates is a subject of a large number of publications during the past decade. [3, 4, 6, 7] Although fructose is the preferred substrate for HMF production with respect to yield and selectivity, several reports on its production from glucose via isomerisation to fructose, as well as directly from cellulose are also available, however with low yields. [8, 9]

HMF constitutes a platform not only for the biofuel dimethylfuran (DMF),[8] but also for various valuable chemicals such as levulinic acid,[10] 5-hydroxymethylfuran-2-carboxylic acid (HMFCA), [11-13] 2,5-furandicarboxylic acid (FDCA),[14-16] 2,5-diformylfuran (DFF), [17-19] dihydroxymethylfuran,[20, 21] 5-hydroxy-4-keto-2-pentenoic acid (HKPA),[22] and γ-valerolactone (gVL),[23, 24] which are important building blocks in the polymer industry (Scheme 1). FDCA is currently being developed as an alternative monomer to terephthalic acid (TPA) for production of a new polymer polyethylene furanoate (PEF) with superior barrier properties than polyethylene terephthalate (PET).[15, 25] Furthermore, a new route to TPA from bio-based HMF was also proposed via several reaction steps.[26, 27] Hence, a facile and scalable process for production of HMF would satisfy the demands of several important biobased products.

Production of HMF in different solvent systems using a variety of homogeneous and heterogeneous acid catalysts is well-reviewed.[3, 6, 28] Mostly moderate conversion of fructose and HMF yield of 40–90% from carbohydrates were observed in reactions performed under pressure in a temperature range of 140-200 °C in various homogeneous solvent systems using HCl or H_2SO_4 as catalysts.[2, 5, 29, 30]



Scheme 1. 5-Hydroxymethylfurfural (HMF) production pathway from biomass and its conversion to building blocks. a. Pretreatment; b. Pretreatment and hydrolysis; c. hydrolysis; d. isomerization. Diformylfuran (DFF), 5-hydroxymethylfuran-2-carboxylic acid (HMFCA), 2,5-furan dicarboxylic acid (FDCA), 2,5-bis(hydroxymethyl)furan (BHMF), 4-hydroxy-2-keto-pentanoic acid (HKPA), γ-valerolactone (gVL), 2,5-Bishydroxymethyl Tetrahydrofuran (BHMTF), and 2,5-Dimethylfuran (DMF) .

The drawbacks associated with the use of mineral acids, such as the corrosion of equipment and human tissue, difficult recovery and recyclability have prompted the development and use of heterogeneous acid catalysts that are not only easily recovered but also provide relatively high conversions of carbohydrates and selectivity of HMF.[3, 6, 31, 32] The solvent systems used for fructose dehydration can be basically divided into monophasic systems including polar solvents,[31, 33] and ionic liquids,[34-38] and biphasic systems. Among the monophasic systems, dimethyl sulfoxide (DMSO) has so far provided high fructose conversions with high HMF yields with relatively lower content of by-products including humins.[39, 40] This is due to stronger binding of DMSO to both the hydroxyl and carbonyl groups of HMF, which reduces its susceptibility to nucleophilic attack and undesirable side reactions including humin formation.[41] DMSO has also been used in mixtures with other low boiling solvents such as tetrahydrofuran (THF), acetone and isopropyl alcohol.[42, 43] Mixing DMSO with THF, a low boiling point solvent, for the dehydration of fructose (5% w/w) catalyzed by a sulfonated carbonaceous catalyst at 160 °C under pressure, resulted in increased selectivity and yield of HMF to 98.0%.[43] Majority of the studies have however used fructose at a relatively low concentration, thus resulting in a dilute product solution and consequently high recovery costs. Additionally, mixed solvents need additional steps and more complex equipment for their separation, recovery and recycling inspite of the low energy consumption in the recovery of the low boiling solvent.[3, 6, 28]

As an example of green and recyclable heterogeneous catalysts, ion exchange resins, which are commercially available, and can be directly used in the reaction, have been used for fructose dehydration.[31] Examples include the use of a strong acidic cation-exchange resin catalyst (DOWEX 50WX8-100) for fructose dehydration in acetone/DMSO mixture by microwave heating [44], and D001-cc resin as catalyst in ionic liquids (ILs).[34] The latter system used a very low fructose concentration (6.7 wt%) and high ratio of the catalyst (1 equivalent) and [Bmim]Cl (15 equivalents) at 75 °C for 20 min, to yield 93% HMF. [34] Using the heterogeneous catalysts including ion exchange resins in packed-bed reactors in a recirculating batch or continuous mode has been shown to be more efficient, e.g. for the production of biodiesel, fructose–oleic acid esters, and cyclic carbonates.[45-47] Recently, even the continuous flow production of HMF from fructose has been successfully demonstrated using the ion exchange catalyst Amberlyst-15.[48, 49]

However, these dehydrations were performed using relatively low fructose concentration (5 wt%) in mixed solvent systems comprising 1,4-dioxane/DMSO (9:1 v/v) and isopropyl alcohol/DMSO, respectively.

In the present study, fructose dehydration to HMF was investigated using an acidic ion exchange resin as catalyst for dehydration of fructose used at high concentration under moderate reaction conditions in batch and continuous flow modes. The reusability of the catalyst was evaluated in repeated batch reactions, and based on the results a flow reaction was set up using a column packed with ion exchange resin for continuous production of HMF at high concentration. Furthermore, recovery of HMF in a pure form from the product mixture was also demonstrated.

RESULTS AND DISCUSSION

Dehydration of fructose to HMF is generally accompanied by many side reactions, which lead to the generation of humins and organic acids, and can be divided into pathways involving cyclic or acyclic intermediates.[50] In this study, production of HMF with high selectivity and yield from fructose used at high concentration using an acidic ion exchanger as catalyst in a single solvent system in batch and continuous flow reaction was evaluated. We selected DR-2030, a strong cation exchanger resin based on a polymer matrix, as the catalyst based on the knowledge about its stability at temperatures up to 130 °C. In the batch process, the effects of the parameters including initial fructose concentration, reaction temperature and the ratio of catalyst to substrate, and also reusability of the catalyst on the substrate conversion and product yield were evaluated. Based on the results obtained from the batch process, continuous flow dehydration of fructose was performed using a column packed with the catalyst. The choice of a solvent system is an important factor for the dehydration of fructose to HMF. Although water is preferable as a solvent for attaining minimal environmental impact, it is inefficient for the dehydration reaction of fructose because HMF is easily rehydrated into levulinic acid and formic acid and other by-products in acidic aqueous solution, leading to low yield of HMF.[44] DMSO was selected as the solvent as it shows good solubility of fructose, highest HMF yields reported so far, and even good stability without high vapor pressure during reaction at high temperature (95-125 °C in this study). A drawback however is the high boiling point of both DMSO and HMF that makes product recovery from the system by distillation quite challenging due to the formation of humins and other by-products.[33, 44, 51] Hence, considering overall process economics, a process resulting in high volumetric productivity product yield and concentration, including downstream processing for the recovery of pure HMF is of interest.

Effect of initial fructose concentration on dehydration in a batch reaction

Production of HMF was monitored at different initial fructose concentrations (10-40% w/w) in DMSO by using 0.1 equivalent of the catalyst to fructose at 110 °C (Figure 1). The substrate conversion (over 98%) and HMF yields (76-84%) were not significantly different at 3h reaction time for the different substrate concentrations (Table S1, Supporting Information) although the rate of conversion was slightly lower at fructose concentration of 10% w/w (Figure 1A). The final molar yield of HMF was lower (76%) with 40% w/w fructose solution than that at other concentrations (Figure 1B). The profile of increase in HMF concentration was in agreement with that of its yield followed the profile of fructose conversion at all concentrations (Figure C).

The results were redrawn to depict fructose conversion, and HMF yields and selectivity with change in fructose concentration at 180 min of the reaction (Figure 1D), showing similar profiles with high yield (over 82%) and selectivity (over 83%) at 10-30% w/w fructose, while 76% product yield with 77.3% selectivity were obtained using 40% w/w fructose solution.

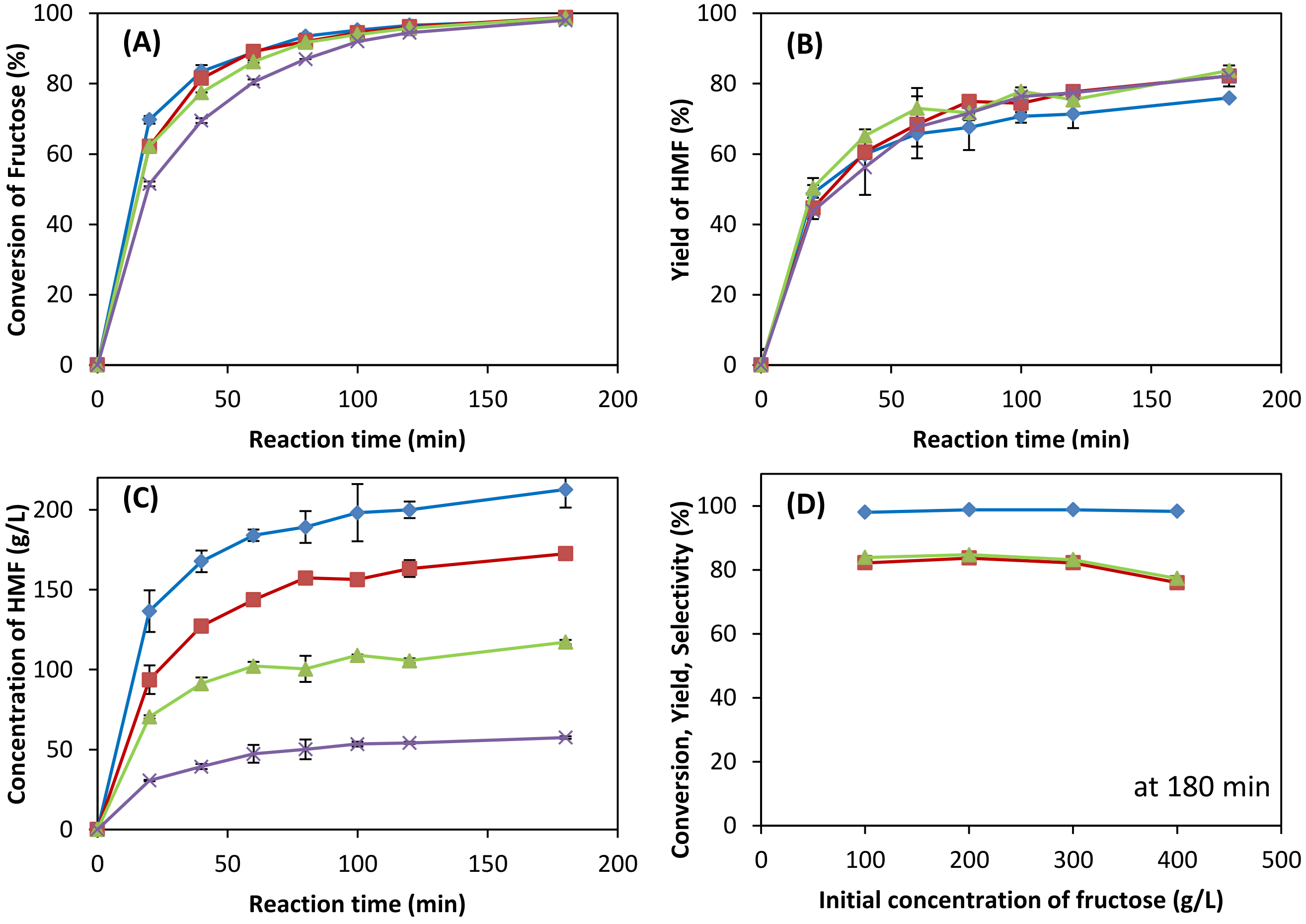


Figure 1. Effect of initial fructose concentration on its dehydration to HMF catalyzed by DOWEX DR-2030 (0.1 equivalent ratio (w/w) to fructose) at 110 °C. The different graphs show: (A) fructose conversion (%), (B) molar yield of HMF (%), and (C) concentration of HMF (g/L). The initial fructose concentrations used were 10% (x), 20% (▲), 30% (■) and 40% w/w (□), respectively. (D) Fructose conversion (□), and HMF molar yield (■) and selectivity (▲) at 180 min reaction time.

This indicates that the initial fructose concentration can be increased up to 300 g/L (30%) in DMSO, and accordingly the usage of solvent is reduced.

In the previous reports dealing with fructose dehydration in DMSO, significantly lower concentrations of fructose ranging between 3 and 10 wt% have been used. For example, dehydration of 3 wt % fructose using Amberlyst 15 as catalyst in DMSO at 120 °C gave 92%yield of HMF after 2 hours reaction time,[52] 5 wt % of fructose was efficiently dehydrated in the mixed solvent system of DMSO/THF using a sulfonated carbonaceous catalyst,[43] while only 2% (w/w) fructose was used to produce HMF (77-86% yield) using high equivalent ion exchange resin (0.5-2 times) in acetone/DMSO (70:30 w/w) at 150 °C by microwave heating.[44] The presence of DMSO in the co-solvent systems was essential for the reactions, necessitating additional step to separate and recycle the solvents. DMSO (boiling point, 189 °C at 760 mmHg) can be distilled at 50 °C under 5-10 mmHg, while HMF (boiling point, 291.5 °C at 760 mmHg) needs higher temperature and/or higher vacuum (114 - 116 °C at 1 mm Hg) for distillation. The possibility to use high substrate concentration with high product yield in a single solvent system is thus one of the solutions to reduce solvent usage, energy consumption, reactor/reaction volume and operating cost.

Effect of temperature on fructose dehydration in batch reaction

The choice of temperature is influenced by many reaction factors including kind of reaction, properties of substrates and solvents used, and also the catalyst. In case of HMF production higher temperatures increase further the side reactions resulting in the formation of humins.

The reaction efficiency and product profile were investigated for the reaction of 30% w/w fructose in DMSO using 0.1 (w/w) equivalent of catalyst to fructose at 95, 110, and 125 °C, respectively.

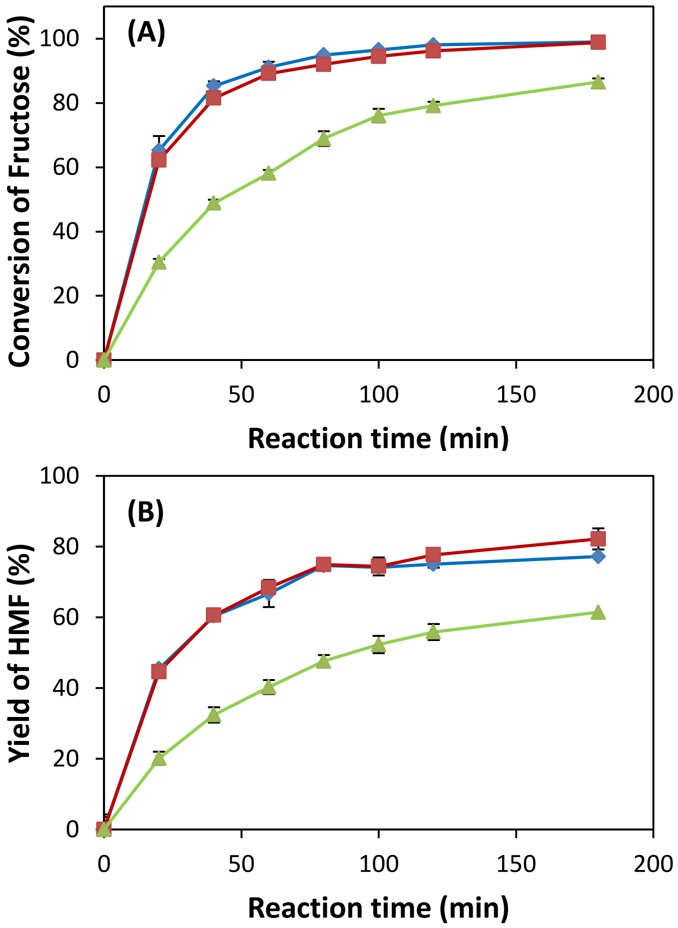


Figure 2. Effect of catalytic dehydration of 30% w/w fructose solution using DOWEX DR-2030 (0.1 equivalent ratio (w/w) to fructose) at 95 °C (▲), 110 °C (■), and 125 °C (□), on (A) conversion of fructose, and (B) molar yield of HMF.

There was only a marginal increase in the rate of fructose conversion on increasing the temperature above 110 °C (Figure 2A), however selectivity of HMF formation was the highest at

110 °C (Figure 2B), resulting in over 98 % fructose conversion with 82.2% HMF yield after 3 hours of reaction (Table S1). The lowest conversion rate and yield were obtained at 95 °C (Figure 2). It may be possible to utilize the ion exchange resin, DR-2030, which is recommended to be used below 130 °C for long term reactions although lower temperatures, e.g. 80 °C are recommended due to the risk of thermal inactivation and decomposition of polymer matrix, which limit its reusability.

Effect of catalyst amount on fructose dehydration in batch reaction

The resin, DR-2030 was used at ratios of 0.05, 0.1 and 0.2 equivalents (w/w of fructose), respectively, for dehydration of fructose in DMSO at 110 °C. As shown in Figure 3A, increase in fructose conversion rates were observed with increasing catalyst ratio in the order of 0.05 > 0.1 > 0.2 equivalents with respect to the substrate. Near linear increase in the fructose conversion and HMF yield was obtained within 40 min (Figure 3A, 3B (insert)), and the reaction continued thereafter at a slower rate leading to 90% conversion for 0.05 ratio (w/w) catalyst, and over 95% for 0.1 and 0.2 ratio of catalyst within 120 min. Conversions of 98.9% and 83.3% within 60 min were achieved with the catalyst ratios of 0.2 and 0.1, respectively (Table S1). The highest yield of HMF of over 85% at near 100% fructose conversion was obtained using 0.2 ratio of the catalyst to fructose at 3 h (Table S1). Based on these results, higher conversion rate of fructose accompanied with high product yield could be obtained in a shorter time with less side reactions with increase in catalyst concentration. Meanwhile, the turnover frequency (TOF) calculated based on fructose conversion during the initial 20 min was 32.6, 22.0, 14.7 mol/h/eq for 0.05, 0.1 and 0.2 ratio of catalyst, respectively, suggesting the highest efficiency to be at the lower catalyst ratio (0.05).

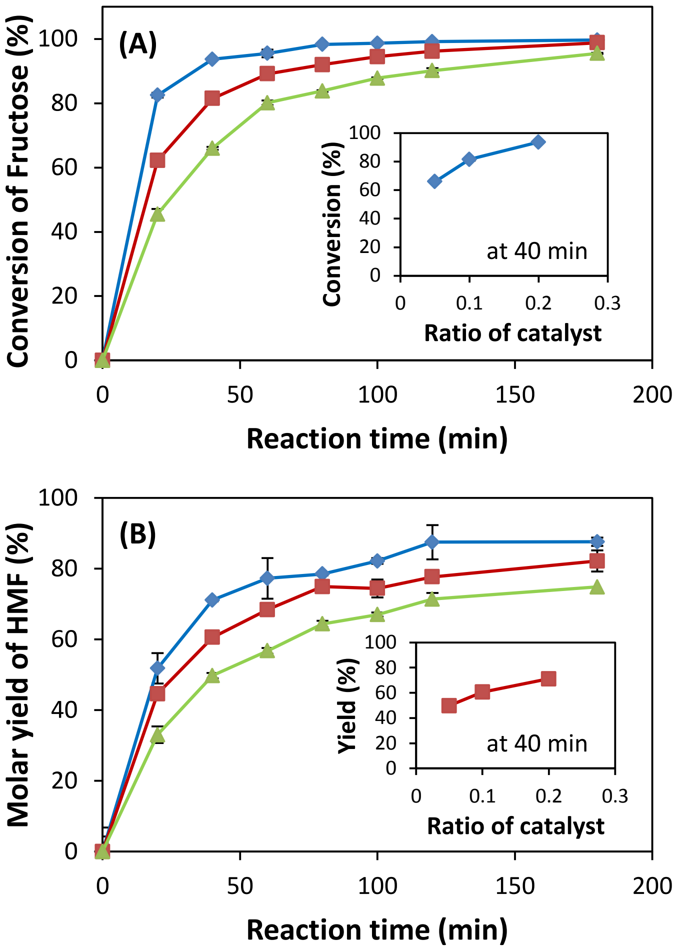


Figure 3. Effect of catalytic dehydration of 30% w/w fructose solution to HMF at 110 °C using DOWEX DR-2030 at 0.05 (▲), 0.1 (■) and 0.2 (◆) equivalent ratio (w/w) to fructose, on (A) conversion of fructose (insert shows conversion at 40 min of reaction time with different ratios of catalyst to fructose), and (B) molar yield of HMF (insert shows yield at 40 min of reaction time with different ratios of catalyst).

Stability and reusability of the ion exchange catalyst

Stability and reusability of catalyst, especially ion exchange resin, are important concerns due to the risk of thermal inactivation and decomposition of the polymer matrix at elevated temperatures. In process stability of DR-2030 was investigated by recycling the catalyst for 5 consecutive batch reactions for dehydration of fructose at initial concentration of 30% w/w using 0.1 (w/w) ratio of catalyst to fructose at 110 °C.

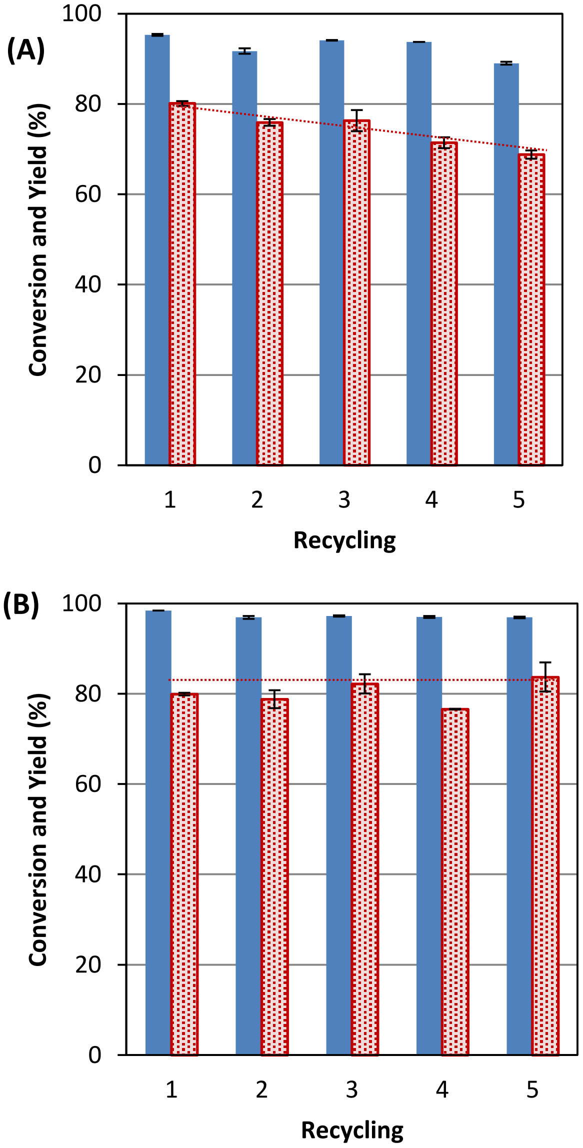


Figure 4. Reusability of DR-2030 catalyst (0.1 equivalent ratio (w/w) to fructose) for dehydration of fructose (300 g/L) using ion exchange resin in consequent 5 batches at 110 °C. Fructose conversion (█), and HMF yield (▒) at 2 h (A), and 3 h (B).

In between the consecutive reactions, the catalyst was easily collected from the reaction medium, washed with 0.5 mL DMSO and 1N HCl, and then reused in the next reaction using fresh fructose solution. All reactions were monitored every hour for 3 hours, and fructose conversion and HMF yield were evaluated to compare the reactions rates and the catalyst stability. In the first batch the conversion reached up to 98% within 2 h with the highest HMF yield of 80% (Figure 4). The reactions slowed down with consecutive batches compared to the previous run at 2 h reaction time (Figure 4A), while identical conversion rates and yields were obtained in 3 hours (Figure 4B) in all the batches. The initial catalyst could thus be reused for at least five consecutive batches to obtain HMF at an average yield of about 80%, although the catalyst activity decreased slightly during the batches. This indicates that the catalyst is quite stable without significant mechanical damage in the reaction medium at the operating temperature. The inactivation could be caused by the deposition of humins leading to blocking and replacement of the catalyst surface or active sites. [44]

Continuous flow single-pass catalytic dehydration of fructose to HMF

Our interest was to design and verify the continuous dehydration of fructose to HMF in order to obtain high productivity and applicability in a flow reaction under mild conditions without the use of high pressure and temperature. The use of a continuous flow process has increasingly gained importance for organic synthesis using heterogeneous catalysts as it prevents the mechanical damage of the catalyst and consequent loss of recyclability encountered in stirred batch reactors.[45, 53-55] However, the employment of flow process has been limited for the heterogeneous catalytic dehydration since the reactions require high temperature and pressure, and/or biphasic solvent system. Since resins are considered to be useful below 100 °C, higher temperature needed for HMF production could limit the application of the ion exchange resin. [44]

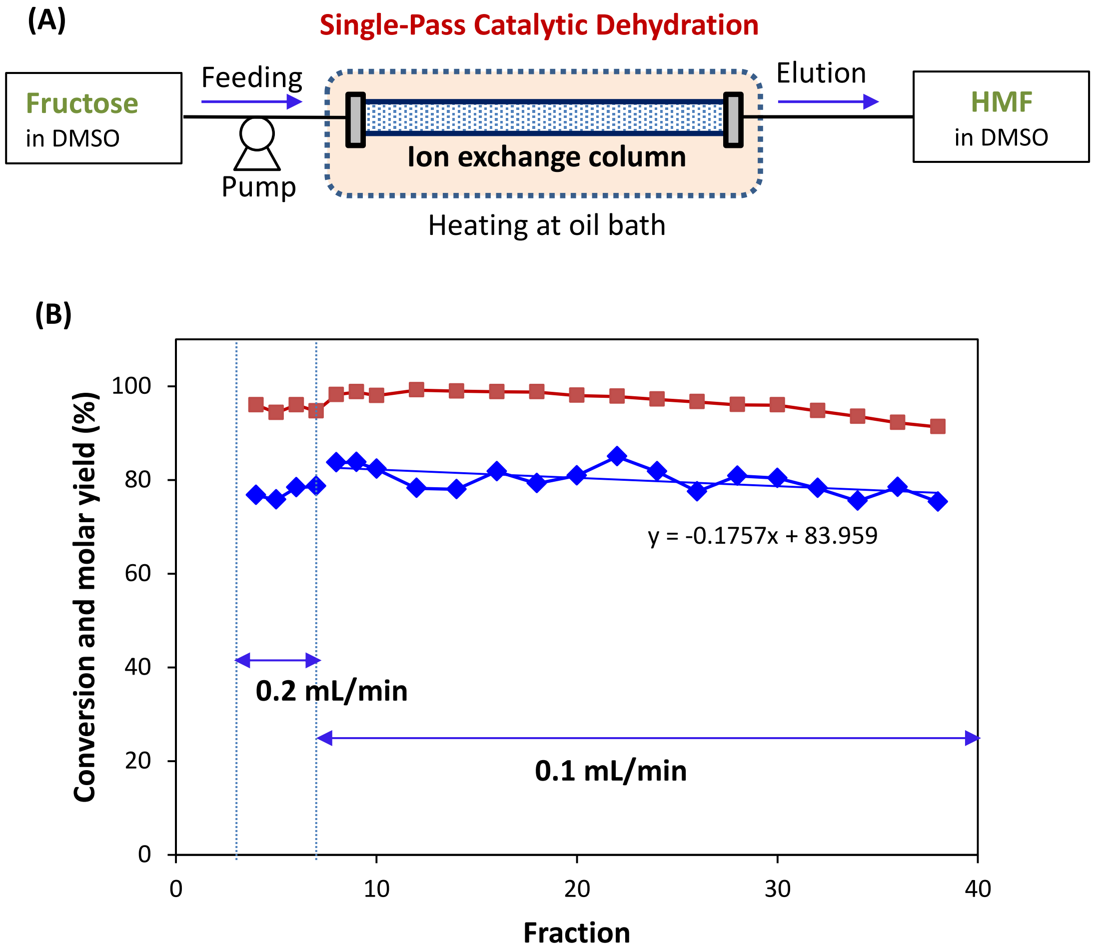


Figure 5. Continuous flow dehydration of fructose (300 g/L) using a fixed bed column packed with DR-2030 catalyst maintained at 110 °C: (A) Schematic diagram of continuous flow reactor consisting of stainless steel column (4.6 mm x 15 cm) and quantitative pump, (B) fructose conversion (■), and HMF molar yield (◆) in the 3 mL fractions collected over time.

Efficient dehydration of D-(−)-fructose (4.5% (w/v) concentration) to HMF (60 – 95% yield) in isopropyl alcohol/DMSO as the solvent system in continuous flow conditions at 80 - 110 °C using the cation exchange resin, Amberlyst-15 (0.9 weight ratio to substrate) was recently demonstrated.[49] In another study, dehydration of cello-oligomer to HMF (53% yield) by phosphate TiO_2 catalyst in the biphasic (water/methyl isobutyl ketone/N-methyl-2-pyrrolidone) continuous flow reactor was reported,[54] however, the reaction required harsh conditions of 210-230 °C with 60 bar back pressure to dehydrate the 5% oligomer solution.

In this study, based on the results obtained from batch experiments at high fructose concentration in DMSO, the dehydration reaction was also carried out in a simple single-pass flow reactor as shown in Figure 5A in order to study the impact of in-process residence (contact) time with the catalyst on the degree of fructose conversion and HMF yield. A 30% w/w fructose solution was passed through the ion exchange column packed with 1.4g DR-2030 at 110 °C, at flow rates of 0.2 and 0.1 mL/min. Figure 5B and Table S1 show the fructose conversion and HMF formation in the eluate up to the passage of 120 mL of the solution (36 g fructose) at different flow rates. At the flow rate of 0.2 mL/min, the fructose conversion and HMF yield were around 94% and 76%, respectively. With decreasing flow rate to 0.1 mL/min at longer residence time in the column, these parameters were increased up to 98% and 82%, respectively, and then were maintained with slight decrease during the entire experiment. During this run, 1.4 g DR-2030 could catalyze the dehydration of 36 g fructose (i.e. 1 : 0.04 ratio (w/w) of catalyst to substrate) with an overall HMF yield of about 80%, and the activity was still maintained to catalyze 91.3% conversion of fructose at the end point of the run with no significant pressure and back pressure. Overall, in comparison with the batch experiment, higher catalyst efficacy and productivity were obtained in the flow reaction. Furthermore, the product was separated from the catalyst without the need for extra processing by filtration, and the catalyst did not sustain mechanical damage and was recycled in the process (not shown) in contrast to the reaction in a batch reactor in which the catalyst is exposed to mechanical damage by stirring, and by-products that may restrict the catalytic activity and regeneration. Further increase in fructose conversion and HMF yield are possible by increasing the catalyst amount or lowering further the feed rate in accordance with the results obtained from the experiment using different catalyst amounts in Figure 3.

Recovery of pure HMF

Although high concentration of HMF was obtained in DMSO, the recovery of pure HMF still remains a challenging task due to high boiling points of DMSO and HMF, and thermal and chemical instability of HMF, which renders large scale isolation difficult by simple solvent extraction, distillation, or crystallization.[56] The isolation process and yield of HMF, especially in large scale, have not been so widely reported.[56]

The vacuum evaporation simulations predicted that evaporating DMSO with HMF levels of 10 wt % at 1.3 mbar and 343 K resulted in a 30% loss of HMF.[56] Consequently, HMF separation from DMSO with minimal losses requires the more expensive vacuum distillation process (e.g., 0.66 mbar and a bottom temperature of 386 K). Hence, distillation of HMF requires significant energy input, and the highly concentrated HMF product obtained is unstable and forms undesired byproducts, such as humins and other soluble polymers at the elevated process temperatures.[43] The entrainer-intensified vacuum reactive distillation was employed to separate HMF from the dehydration solutions of carbohydrates catalyzed by a metal chloride such as $IrCl_3$ and $CrCl_3$ in ionic liquid. Although HMF was stabilized by the metal salts at 120 °C, it started to degrade again with increasing temperature. [56]

In this study, 100 mL scale reaction was performed at 30% w/w fructose concentration with 0.2 ratio of catalyst at 110 °C, and 87% yield of HMF was obtained after 2 h. To obtain high purity HMF, a simplified purification process was employed, and involved dilution of the crude product mixture in DMSO with salt solution and quantitative extraction into ethyl acetate (boiling point, 83.6 °C). The partition coefficient of HMF in the DMSO/aqueous salt solution is about 1.1, resulting in over 95% of HMF recovery by 4 cycles of extraction. Most of the DMSO remained in aqueous phase, which can be recovered and recycled separately. After evaporation of ethyl acetate, HMF was further purified by silica chromatography. Pure HMF was obtained with an overall recovery yield of 72%, with 95% purity determined by ^{1}H-HMR. The structure was confirmed by ^{1}H and ^{13}C-NMR ($CDCl_3$) (Fig. S1, Supporting Information). Although column chromatography is not recommended for large-scale production, the process was relatively simple and effective to obtain high purity product.

Meanwhile, recently, we have demonstrated that the crude HMF obtained by liquid-liquid extraction can be used directly, without further purification, for transformation, and the resulting product can be purified in a more facile and efficient operation.[13] The crude HMF was quantitatively oxidized using resting cells of *Gluconobacter oxydans* DSM 50049 to 5-hydroxymethyl-2-furan carboxylic acid (HMFCA) by selective oxidation, which was easily recovered with 83.6% yield and 98% purity by adsorption using anion exchange resin, Amberlite IRA-400 (Cl^- form). The suggested process is a promising alternative to produce biobased HMF at intermediate purity for further utilization and transformation to HMFCA, FDCA and BHMTF.[13]

CONCLUSION

HMF has attracted much attention with respect to its production, conversion and utilization. Nevertheless, most of the reports in literature are based on dehydration of relatively low fructose concentrations. In this study, production of HMF from fructose solution at high concentration under moderate reaction conditions using an ion exchange catalyst was successfully demonstrated in batch and continuous flow reaction. The combination of high fructose concentration and heterogeneous catalysis could provide a sustainable and high yielding process for HMF production. For scaling up, further evaluation of reaction and process factors such as reactor type and size, mass transfer effect of heterogeneous catalyst, process configuration, and costs are required. Also different acidic catalysts can be evaluated with respect to activity, swelling, morphological properties and stability for the dehydration of fructose. [57] Continuous-flow processes form the basis of the petrochemical and bulk chemicals industry, where strong competition, stringent environmental and safety regulations, and low profit margins drive the need for high-performing, cost effective, safe, and atom-efficient chemical operations.[53]

EXPERIMENTAL SECTION

Materials

Hydroxymethylfurfural (HMF, 99% purity), (D)-fructose (99% purity), dimethylsulfoxide, and Dowex, DR-2030 hydrogen form, a strong cation ion exchange resin were procured from Sigma-Aldrich. DOWEX® DR-2030 is a macroporous styrene-divinylbenzene resin functionalized with sulfonic acid groups, >4.7 meq/g dry weight capacity, 16-40 mesh, 30 m^2/g surface area, and <3% moisture content, with upper limit for safe operation at 130 °C. All chemicals were used without further treatment.

Dehydration of fructose to HMF in batch mode

Typically, 1 mL of fructose solution was placed in 4 mL glass vials, followed by addition of the ion exchange resin, DR-2030. The solution was heated and shaken using a ThermoMixer (HTMR 131, HLC BioTech, Germany). The effect of initial fructose concentration 100-400 g/L (10-40% w/w) in DMSO using 0.1 equivalent of the resin (w/w fructose, 10-40 mg/mL) was evaluated at 110 °C and 500 rpm, which provided suitable mixing conditions without sedimentation of the catalyst. The effect of reaction temperature (95, 110 and 125 °C, respectively) was evaluated with 30% w/w fructose solution, 0.1 equivalent of the resin and 500 rpm. The ratio of catalyst to fructose was varied between 0.05-0.2 at fructose concentration of 30% w/w.

To verify the reaction conditions in a larger volume, 100 mL of 30% w/w fructose solution in DMSO was placed in a 250 mL flask, followed by addition of 6 g ion exchange resin (0.2 (w/w) equivalent to fructose), and shaking in an oil bath at 110 °C. Samples (20 µL each) were collected at different time intervals and analyzed for concentrations of fructose and products.

Regeneration and recycling of the ion exchange resin in the batch reaction

One milliliter of 30% w/w fructose solution with 30 mg of the resin was placed in a 4 mL glass vial, heated and shaken at 110 °C and 500 rpm in a ThermoMixer. After 3 hours of reaction, the resin was separated, washed with 0.3 mL DMSO, and then regenerated by keeping in 0.3 mL 1N HCl for 12 hours and washing with deionized water until reaching neutral pH, and then with DMSO. The resin was recycled for 4 consecutive runs under similar conditions. Samples (20 µL each) were collected at 1, 2 and 3 hours of reaction, and analyzed for concentrations of fructose and products.

Continuous flow dehydration of fructose to HMF using the ion exchange resin

The catalytic dehydration of fructose was carried out as a continuous process in a flow reactor system comprising a stainless steel column (4.6 mm internal diameter x 15 cm length) packed with 1.4 g ion exchange resin DR-2030. The tubing used was of stainless steel material. The packed column was kept sealed properly and submerged in an oil bath set at 110 °C for the reaction. Fructose solution (30% w/w) was pumped through the column using a quantitative pump (Pump 2248, Pharmacia LKB, Sweden), in a single pass but at varying flow rates: 0.3 mL/min for first 3 fractions, 0.2 mL/min for next 3 fractions, and 0.1 mL/min for next 27 fractions, providing different residence times. The eluate was collected in 3 mL fractions, which were analyzed for the concentrations of fructose and products.

Purification of HMF prepared in continuous flow reaction

Twenty millilitres of the final product obtained from the continuous reaction, containing HMF, DMSO, water and by-product(s) (oligomers) was used for small scale purification. To the solution was added 20 mL of saturated NaCl aqueous solution and 20 mL ethyl acetate for phase separation in a 250 mL separation funnel, and the upper organic phase was collected. This procedure was repeated three more times, after which all the collected organic phases were pooled and concentrated by simple evaporation. The concentrated sample dissolved in 10 mL dichloromethane (DCM) was subjected to flash chromatography using a column (2 x 14 cm) packed with 20 g silica (Merck) equilibrated with DCM. The column was washed with 150 mL

DCM and elution was performed using 150 mL mixture of DCM/ethyl acetate (1/2) as the mobile phase. All the fractions were analysed by GC. The column was cleaned with 150 mL methanol prior to reuse.

Analytical procedures

The concentrations of fructose and products were determined using HPLC (JASCO, Tokyo, Japan) equipped with Aminex HPX-87H chromatographic column connected to a guard column (Biorad, Richmond, CA, USA), RI detector (ERC, Kawaguchi, Japan), a JASCO UV detector operating at 215 nm, and a JASCO intelligent autosampler. The column temperature was maintained at 65 °C in a chromatographic oven (Shimadzu, Tokyo, Japan). Samples were diluted with Milli-Q quality water and mixed with 20% $v.v^{-1}$ sulfuric acid (20 $\mu L.mL^{-1}$ sample) and then filtered. A 40 µL aliquot was injected in 0.5 mM H_2SO_4 mobile phase flowing at a rate of 0.4 $mL.min^{-1}$. The peaks for the different compounds were confirmed and quantified using external standards. Quantitative analysis of HMF was also performed using gas chromatography (GC, Varian 430-GC, Varian) equipped with FactorFour Capillary column, VF-1ms (Varian, 15 m 3 0.25mm) and a flame ionization detector. The initial column oven temperature was increased from 50 to 250 °C at a rate of 20 °C/min. The samples, diluted with acetonitrile, to a concentration of 0.1– 5 mg/mL, were injected in split injection mode of 10 % at 275 °C. The conversion and concentration of the substrates and ratio of products formed were calculated from the calibration curves of standard materials on the chromatograms. The chemical structures of HMF and by-products were confirmed using external standard materials in chromatograms of HPLC and GC, or elucidated by ^{1}H-NMR and ^{13}C-NMR ($CDCl_3$) using 400 MHz NMR (Bruker, UltraShield Plus 400, Germany).

All the data were obtained from two independent experiments and are provided as the average of the replicates ± standard deviation. The reaction parameters calculated were percent fructose conversion, percent HMF yield (with respect to the substrate) and selectivity using the following equations:

Conversion% = (consumed Fructose (g)/ inatial Fructose. (g))*100

Yield % = (HMF (mole) / consumed Frucose. (mole)) *100

Selectivity % = (HMF yield / fructose conversion)*100

ASSOCIATED CONTENT

Supporting Information

The Supporting Information (PDF) is available free of charge on the ACS Publications website at DOI:

Table S1. Dehydration of fructose to HMF under different operational conditions.
Figure S1. (A) ^{1}H and (B) ^{13}C-NMR ($CDCl_3$) spectrum of the purified HMF.

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