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Article

Optimization of 5-HMF Synthesis by Using Catalytic Dehydration in Biphasic System with a Packed-Bed Continuous Flow Reactor

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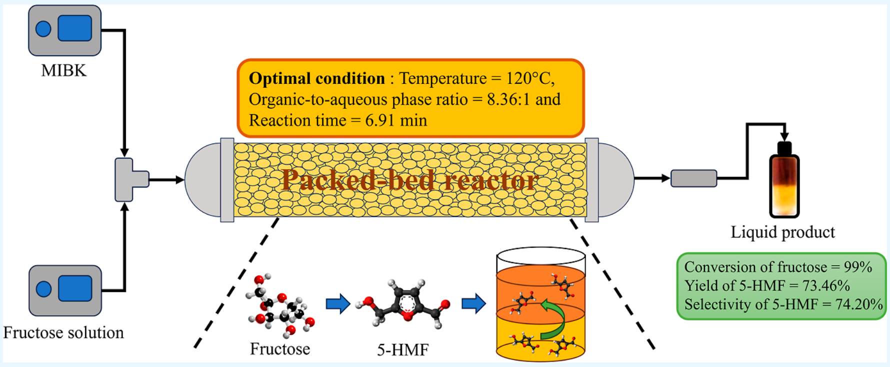

ABSTRACT: The depletion of fossil fuels and their associated environmental concerns necessitate the exploration of sustainable alternatives. 5-Hydroxymethylfurfural (5-HMF), a versatile platform chemical derived from biomass, holds significant potential for the production of biofuels, industrial intermediates, and polymers. This study employs a factorial experimental design to investigate the impact of fructose concentration, organic-to-aqueous phase ratio, and reaction time on 5-HMF yield using a biphasic system with a cation exchange resin catalyst. Optimal conditions predicted by the model, including a 100 g/L fructose solution, an organic-to-aqueous phase ratio of 8.36:1, and a reaction time of 6.91 min, were validated experimentally, resulting in a 73.45% 5-HMF yield. Subsequent purification steps, involving activated carbon adsorption for the organic phase and a two-stage extraction with butanol and NaCl for the aqueous phase, achieved 92.63% and 92.13% purity and recovery, respectively. These findings offer valuable insights for the efficient production of 5-HMF.

1. INTRODUCTION

The escalating global energy crisis, primarily driven by the depletion of fossil fuel reserves and their detrimental environmental impact, has intensified the search for sustainable alternatives. Fossil fuels, the cornerstone of energy production and consumption, have significantly contributed to greenhouse gas emissions, air pollution and climate change.[1,2] The World Health Organization's 2024 report highlighted the significant health burden associated with air pollution, attributing approximately 6.7 million annual deaths globally to this environmental hazard.[3] Research indicates that the true costs of fossil fuels, including environmental externalities, far exceed retail prices, driving excessive consumption. A study in Iran demonstrated that implementing policies to increase fossil fuel prices can effectively reduce air pollution and improve public health outcomes. To address these challenges, policymakers should prioritize transitioning to cleaner energy sources and implementing policies that reduce reliance on fossil fuels.[4] To mitigate these challenges, the conversion of biomass into value-added chemicals and fuels has emerged as a promising strategy.[5,6] Among the potential platform chemicals, 5-hydroxymethylfurfural (5-HMF) has garnered significant attention due to its versatility and potential to replace petroleum-derived products.[7−9]

5-HMF serves as a versatile precursor for a wide range of chemicals, including fuels like dimethylfuran (DMF), fine chemicals such as levulinic acid and 2,5-furandicarboxylic acid (FDCA), and polymers like polyethylene furanoate (PEF).[10−14] The shortest pathway for the synthesis of 5-HMF is the dehydration of fructose, which has been identified as a promising feedstock for 5-HMF production.[15,16] However, homogeneous catalysts, while offering high reaction rates,

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suffer from drawbacks such as catalyst separation, recovery, and corrosion.[17] Heterogeneous catalysts, including cation exchange resins, activated carbon, and zeolites, provide potential solutions to these challenges.[18−21]

Solvent selection plays a crucial role in efficient 5-HMF synthesis. While water is environmentally benign, its use can lead to lower yields due to side reactions. Organic solvents, such as DMF, DMA, and DMSO, can suppress these side reactions but often require energy-intensive separation processes. Ionic liquids, although effective, are generally expensive. Biphasic solvent systems have emerged as a promising alternative, enabling efficient 5-HMF extraction and reducing byproduct formation.[22,23] Additionally, organic solvents typically have lower boiling points, facilitating the separation of 5-HMF from the solvent. Methyl isobutyl ketone (MIBK) was selected as the organic phase for this study, based on its demonstrated effectiveness in extracting 5-HMF from aqueous solutions. The low boiling point of MIBK facilitates its facile separation from the target product. While the volatility of MIBK raises valid environmental concerns, specifically regarding potential contributions to air pollution and respiratory hazards, the implementation of a robust recycling strategy can substantially mitigate these impacts. A comprehensive life-cycle assessment (LCA) can be conducted following the completion of the experimental work to rigorously evaluate and minimize the overall environmental footprint of the process.

Batch reactors, commonly employed for 5-HMF production, present inherent limitations, including difficulties in catalyst separation, precise reaction control, effective heat transfer, and scalability. Continuous-flow systems offer distinct advantages by enabling efficient catalyst packing and streamlined product separation.[24−26] In this approach, the catalyst is immobilized within the reactor, effectively preventing its leakage and contamination of the product stream. This inherent advantage has driven significant interest in continuous-flow systems as a promising alternative to overcome the limitations associated with batch reactors. While previous studies have investigated 5-HMF synthesis within packed-bed reactors, these studies typically employed low substrate concentrations. This work differentiates itself by exploring 5-HMF production within a packed-bed reactor using a significantly broader range of fructose concentrations, spanning from 25 to 200 g/L. Furthermore, a comprehensive optimization study was conducted to maximize 5-HMF yield, conversion, selectivity, and productivity. The experimental findings were rigorously validated, and catalyst stability was assessed over an extended period of 50 h of time-on-stream. To the best of our knowledge, this study represents the first comprehensive investigation combining high fructose concentrations, rigorous optimization, and extended stability testing within a packed-bed reactor configuration for 5-HMF production. Notably, the productivity achieved under the optimized conditions in this study surpasses those reported in comparable studies, demonstrating a significant advancement in the field.

This study focuses on optimizing 5-HMF production from fructose utilizing a heterogeneous cation exchange resin within a biphasic system. The influence of key process parameters, including fructose concentration, reaction time, and solvent ratio, on 5-HMF yield and selectivity was systematically investigated. A rigorous optimization strategy was employed to identify reaction conditions that maximize 5-HMF yield, fructose conversion, and 5-HMF selectivity. Furthermore, the stability of the process was evaluated, and effective purification strategies for 5-HMF from both aqueous and organic phases were explored. This comprehensive approach culminated in the development of a robust process scheme for the efficient and sustainable production of 5-HMF.

2. MATERIALS AND METHODS

2.1. Materials. All chemicals used in this study were commercially sourced. 1-Methyl-2-pyrrolidinone (NMP), acetonitrile (HPLC grade), and 5-hydroxymethylfurfural (AR grade, for HPLC calibration) were obtained from Sigma-Aldrich. Methyl isobutyl ketone (MIBK, AR grade) was purchased from Merck. D-fructose (AR grade) was acquired from Fisher Scientific. The ion-exchange resin catalyst (DIAION RCP160M) was kindly provided by Mitsubishi Chemical Corporation.

2.2. Determination of the Catalyst Properties. Prior to characterization and each experimental run, the catalyst was dried at 60 °C until a constant mass was achieved to remove any adsorbed moisture. The dried catalyst was then stored in a desiccator until use. The RCP160M catalyst was studied for its functional groups using Fourier Transform Infrared (FT-IR) spectroscopy with a PERKIN ELMER Spectrum one instrument. Subsequently, using the BET (Brunauer−Emmett−Teller) method with a Micromeritics Instrument Corporation 3Flex analyzer to determine specific surface area. The total pore volume and average pore size were calculated using the Barrett−Joyner−Halenda (BJH) method. The stability of the catalyst was analyzed through Thermogravimetric Analysis (TGA) using a METTLER TOLEDO TGA/DSC^{3+} instrument, with analysis conducted in the temperature range of 30−600 °C.

2.3. Determine the Total Acid Number of the Catalyst. The total acid number (TAN) of the catalyst was determined by back-titration. Briefly, 30 mg of catalyst was mixed with 20 mL of 0.1 M sodium hydroxide solution and stirred for 4 h. The mixture was then sonicated for 1 h at room temperature. Subsequently, the solution was titrated with 0.1 M hydrochloric acid using phenolphthalein as an indicator to reach a neutral end point.

2.4. Dehydration Reaction. Prior to use, the cation-exchange resin catalyst was dried at 60 °C to remove residual moisture. Subsequently, 0.7 g of the catalyst was loaded into a 1/4 in. diameter, 10 cm long stainless steel (SS316) reactor tube. Glass wool was positioned at both ends of the catalyst bed to prevent particle migration. A fresh catalyst bed was used for each experiment.

MIBK and fructose solutions were separately fed into the packed-bed reactor using ISCO series D pump controllers equipped with 260D syringe pumps. The organic-to-aqueous phase ratio was adjusted by controlling the respective volumetric flow rates prior to the T-mixer. Both solutions were preheated before mixing in the T-mixer, which was subsequently connected to the reactor. The entire system, including the T-mixer and reactor, was placed within a convection oven to maintain a constant reaction temperature. The desired dehydration reaction occurred exclusively within the reactor. The reaction mixture flowed through the T-mixer, reactor, and a back pressure regulator (as illustrated in Figure 1) to maintain a system pressure of 75 psi and prevent solvent vaporization. All experiments were conducted in duplicate.

2.5. Product Analysis. Following the reaction, the product mixture was separated into aqueous and organic phases and

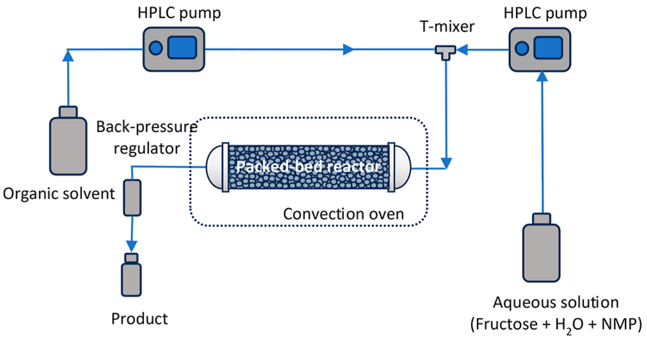

Figure 1. Schematic diagram of the experimental setup.

stored at −5 °C prior to HPLC analysis. HPLC analysis was performed using a Shimadzu LC-10AT VT high-pressure pump, a Varian model 2550 variable wavelength UV detector, a YL Instrument model YL9170 refractive index detector (RI), and a Waters model TCM-004076 column oven.

Fructose concentration in the aqueous phase was determined using the RI detector with an APS-2 Hypersil column (4.6 mm × 250 mm, 5 μm particle size, Thermo Scientific) at 40 °C. The mobile phase consisted of a 75:25 (v/v) acetonitrile−water mixture delivered at a flow rate of 1.0 mL/min.

5-HMF quantification in both aqueous and organic phases was achieved using the UV−vis detector at 320 nm with an ACE Excel 5 super C18 reverse-phase column (4.6 mm × 250 mm, 5 μm particle size, Advanced Chromatography Technologies) at 30 °C. The mobile phase consisted of a 1:9 (v/v) acetonitrile−water mixture delivered at a flow rate of 0.7 mL/min.

Reaction performance was evaluated based on fructose conversion, 5-HMF selectivity, 5-HMF yield, % extraction, and % distribution of 5-HMF, as calculated according to eqs 1−6.

$$\%\ \text{Conversion off ructose} = \left(1 - \frac{\dot{n}_{\text{fructose,f}}}{\dot{n}_{\text{fructose,ini}}}\right) \times 100 \qquad (1)$$

$$\%\ \text{yield} = \frac{\dot{n}_{\text{product}}}{\dot{n}_{\text{fructose,ini}}} \times 100 \qquad (2)$$

$$\%\ \text{selectivity} = \frac{\%\ \text{yield}}{\%\ \text{conversion}} \times 100 \qquad (3)$$

$$\text{productivity} = \frac{\%\ \text{yield} \times \dot{n}_{\text{fructose,ini}}}{m_{\text{cat}}} \qquad (4)$$

$$\%\ \text{extraction} = \frac{\text{g. 5-HMF in organic phase}}{\text{g. 5-HMF in aqueous and organic phase}} \times 100 \qquad (5)$$

$$\%\ \text{distribution ratio} = \frac{\dot{n}_{5\text{-HMFinorganicphase}}}{\dot{n}_{5\text{-HMFinaqueousphase}}}\text{x100} \qquad (6)$$

where $\dot{n}_{\text{fructose,f}}$ and $\dot{n}_{\text{fructose,ini}}$ represent the molar flow rate of fructose in the feed and output stream, respectively. $\dot{n}_{5\text{-HMF}}$ is the molar flow rate of 5-HMF, m_{cat} is the amount of catalyst and g.5-HMF is the amount of 5-HMF.

2.6. Recovery and Purification of 5-HMF.

To purify 5-HMF from the organic phase, activated carbon (0.25−1 g) was added to 10 mL of the organic phase and mixed for 5 min at room temperature using a vortex mixer. The mixture was then centrifuged at 4000 rpm for 15 min to remove the activated carbon. The recovered organic phase was further purified by rotary evaporation at 66 °C and −13.8 psi to remove the solvent (MIBK).

To recover 5-HMF from the aqueous phase, a solvent extraction process was employed. A series of solvents, including MIBK, butanol, and toluene, were evaluated to determine their effectiveness in extracting 5-HMF. The impact of the organic-to-aqueous phase ratio and the number of extraction stages on 5-HMF recovery was investigated. In each extraction, a specific volume of solvent was added to 5 mL of the aqueous phase. The mixture was vortexed for 5 min at room temperature, followed by HPLC analysis of the extract.

The purification performance was assessed by evaluating the purity and recovery of 5-HMF, as calculated using eqs 7−9.

$$\%\ \text{Purity of 5-HMF} = \frac{\text{area of sample}}{\text{area of pure 5-HMF}} \times \frac{\text{weight of pure 5-HMF}}{\text{weight of sample}} \times 100 \qquad (7)$$

$$\%\ \text{recovery (aqueous)} = \frac{\text{moles of 5-HMF in the extract solution}}{\text{moles of 5-HMF in aqueous phase before extraction}} \times 100 \qquad (8)$$

$$\%\ \text{recovery (organic)} = \frac{\text{moles of 5-HMF after purification}}{\text{moles of 5-HMF before purification}} \times 100 \qquad (9)$$

3. RESULTS AND DISCUSSION

3.1. Characterization of Catalyst.

FT-IR analysis of the cation-exchange resin (Figure 2) revealed characteristic peaks at 3500, 1700, 1200, and 1000 cm^{-1}. The broad band at 3500 cm^{-1} corresponds to O−H stretching vibrations, while the peak at 1700 cm^{-1} indicates the presence of a carbonyl group (C═O). Additionally, the peaks at 1200 and 1000 cm^{-1} are

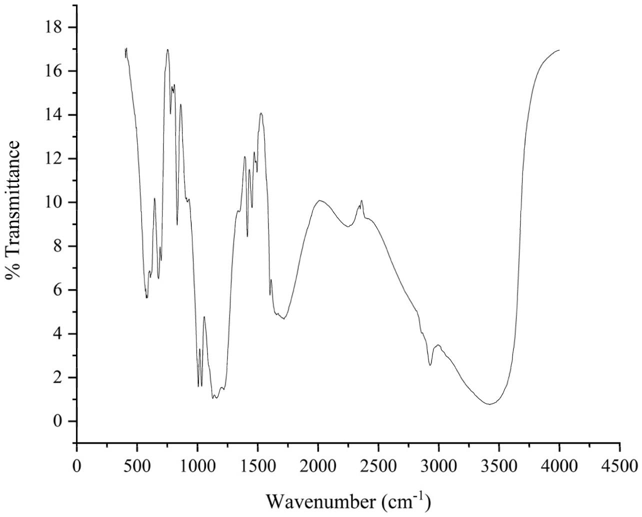

Figure 2. FTIR spectrum of RCP160M.

attributed to the S=O stretching vibrations of sulfonic acid groups ($-SO_3H$). These findings, in conjunction with the known structure of the resin, confirm the presence of sulfonic acid functional groups, which are essential for the catalytic conversion of fructose to 5-hydroxymethylfurfural (5-HMF).

The RCP160M catalyst exhibited a specific surface area of 48.468 m^2/g, a total pore volume of 0.433 cm^3/g, and an average pore size of 357.24 Å. Thermal analysis (Figure 3) revealed a weight loss between 60 and 160 °C, attributed to water desorption. Further weight loss at higher temperatures suggested catalyst decomposition. To prevent catalyst degradation, an operating temperature of 120 °C, as recommended by the supplier, was selected.

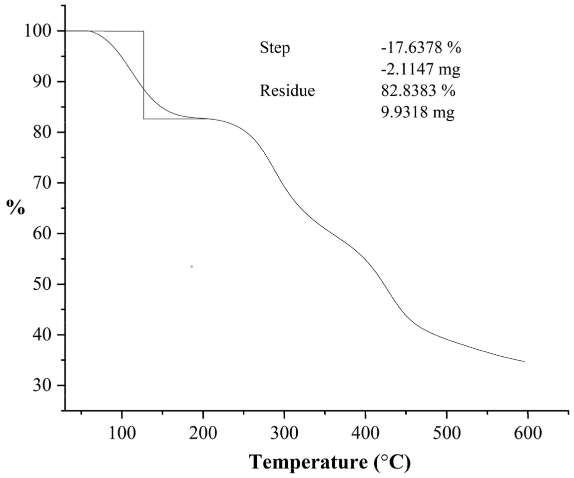

Figure 3. TGA plot of RCP160M.

Acidic catalysis plays a pivotal role in 5-HMF production. The total acid number of RCP160M was determined via titration. A comparison with literature values (Table 1) revealed that catalysts with higher acid densities generally exhibit higher 5-HMF yields. Notably, RCP160M, with an acid content of 5.14 mmol/g, exhibits a comparable acid density to Amberlyst-15 (4.65 mmol/g), a well-established catalyst in this field. This suggests that RCP160M is likely to demonstrate favorable catalytic performance in the hydrolysis of fructose to 5-HMF.

Table 1. Total Acid Number of Catalyst

catalyst	total acid number (mmol/g)
$SiO_2-Al_2O_3$	0.85[27]
HZSM-5	0.58[27]
TiO_2-SO_3H	0.30[28]
Amberlyst-15	4.65[29]
RCP160M (this work)	5.14

3.2. Effect of NMP-to-H_2O Ratio.

To investigate the influence of water on 5-HMF synthesis, *N*-methyl-2-pyrrolidone (NMP) was introduced as a water replacement. The NMP-to-water ratio was systematically varied from 0% to 75%, while reaction time, temperature, and organic-to-aqueous phase ratio were maintained at 5 min, 120 °C, and 5:1, respectively. As illustrated in Figure 4, increasing the NMP-to-water ratio correlated with enhanced fructose conversion and 5-HMF yield. This improvement is attributed to NMP's ability to accelerate the transformation of fructose into furanose intermediates, facilitating efficient high-yield reactions.[30] Additionally, NMP effectively suppresses side reactions, such as the formation of levulinic and formic acids, and acts as a protective agent against humin formation. Horvat et al. (1985) reported that excess water can induce 5-HMF degradation. Under these conditions, 5-HMF carbonyl groups at positions 2 and 3 undergo polymerization to form humins, while decarboxylation at positions 4 and 5 leads to the formation of levulinic and formic acids.[31] NMP mitigates these detrimental effects. Based on the observed trends, a 50% NMP-to-water ratio was selected for subsequent investigations due to its promising conversion and yield values, comparable to those achieved with a 75% NMP-to-water ratio.

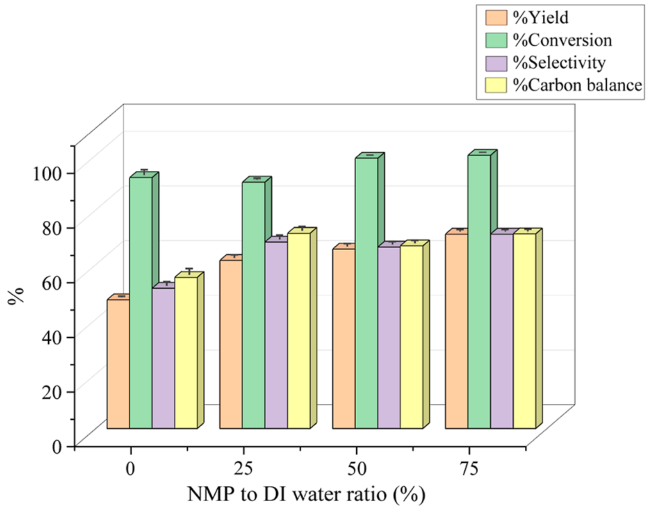

Figure 4. Effect of the NMP-to-water ratio on the synthesis reaction of 5-HMF (reaction time of 5 min, temperature of 120 °C, concentration of fructose solution at 100 g/L, and organic-to-water ratio of 5:1).

3.3. Effect of Reaction Time.

To investigate the impact of reaction time on 5-HMF synthesis, residence time within the reactor was varied from 1 to 15 min while maintaining a constant temperature of 120 °C, an organic-to-water ratio of 5:1, a 50% NMP-to-water ratio, and a fructose concentration of 100 g/L. As depicted in Figure 5, fructose conversion and 5-HMF yield exhibited an initial increase, rising from 75.79% to 94.63% and from 52.27% to 65.70%, respectively, as the reaction time was extended from 1 to 5 min. However, a further increase in reaction time to 15 min resulted in complete fructose conversion (100%) while concomitantly decreasing 5-HMF yield to 31.84%. This decline suggests the prevalence of side reactions, likely involving 5-HMF consumption or the degradation of its intermediates.

Furthermore, the pH of the aqueous phase decreased from 5.69 in the feedstock solution to 4.83 in the 5-HMF product solution after the 15 min reaction. This pH drop indicates the potential occurrence of a rehydration reaction, where 5-HMF interacts with water to form levulinic acid and formic acid. Consequently, 5-HMF selectivity diminished at longer reaction times beyond the optimal 5 min period.

3.4. Effect of Organic to Aqueous Phase Ratio.

To investigate the impact of the organic-to-aqueous phase ratio on 5-HMF synthesis, experiments were conducted at a reaction temperature of 120 °C, reaction time of 5 min, a 50% NMP-to-water ratio in the aqueous phase, and a fructose concentration of 100 g/L. The organic-to-aqueous phase ratio was varied

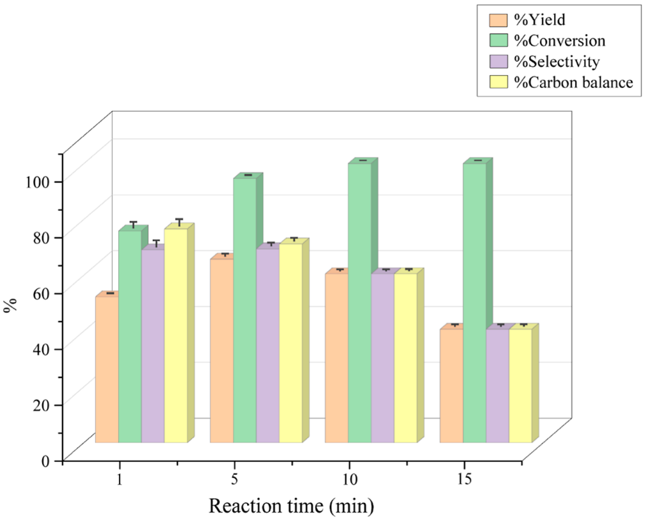

Figure 5. Impact of reaction time on the synthesis of 5-HMF (at a temperature of 120 °C, with a concentration of fructose solution at 100 g/L, an NMP-to-water ratio of 50%, and an organic-to-water ratio of 5:1).

from 0:1 (without organic solvent) to 10:1. Note that experiments with a pure organic phase were not conducted due to two key factors. First, the sulfonic acid functional groups on the RCP160M catalyst require water for effective catalytic activity. Second, fructose exhibits limited solubility in the organic phase. Therefore, a pure organic phase would be detrimental to both catalyst performance and fructose availability for the reaction. As depicted in Figure 6, increasing the organic-to-aqueous phase ratio resulted in a corresponding increase in fructose conversion, 5-HMF yield, and selectivity. This enhancement is attributed to the reduced water content in the system, which facilitates the efficient extraction of 5-HMF into the organic phase and suppresses side reactions. Excess water is known to promote the formation of levulinic and formic acids.[32]

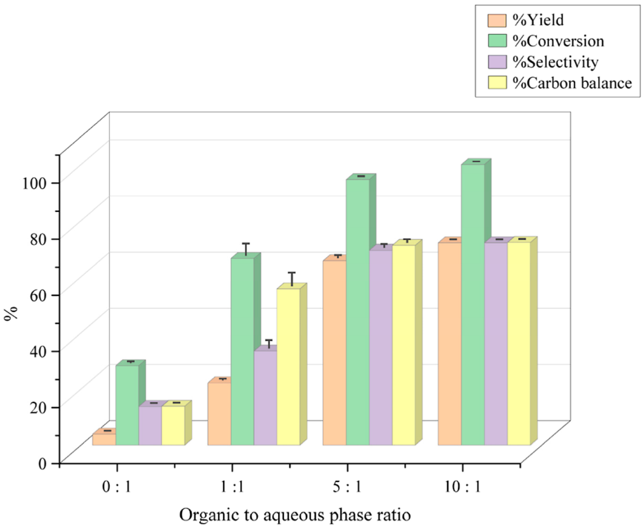

Figure 6. Effect of the ratio of organic to aqueous in the synthesis reaction of 5-HMF (at a temperature of 120 °C, with a concentration of fructose solution at 100 g/L, an NMP-to-water ratio of 50%, and a reaction time of 5 min).

3.5. Effect of Concentration of Fructose.

To assess the influence of fructose concentration on 5-HMF synthesis, a series of experiments were performed using varying fructose concentrations (25−200 g/L) while maintaining consistent reaction conditions: 120 °C, 5 min reaction time, 50% NMP-to-water ratio, and an organic-to-aqueous phase ratio of 10:1. As depicted in Figure 7, a gradual increase in fructose concentration from 25 to 100 g/L resulted in a concomitant increase in 5-HMF yield. This observation suggests that under these conditions, the catalyst was present in sufficient excess, enabling the dehydration reaction to proceed more effectively with increasing reactant concentration. Consequently, both fructose conversion and 5-HMF selectivity improved, with near-complete conversion achieved across the entire experimental range. However, a further increase in fructose concentration to 200 g/L led to a decline in 5-HMF yield, despite complete fructose conversion. This unexpected decrease can be attributed to the prevalence of side reactions, resulting in a diminished 5-HMF selectivity.

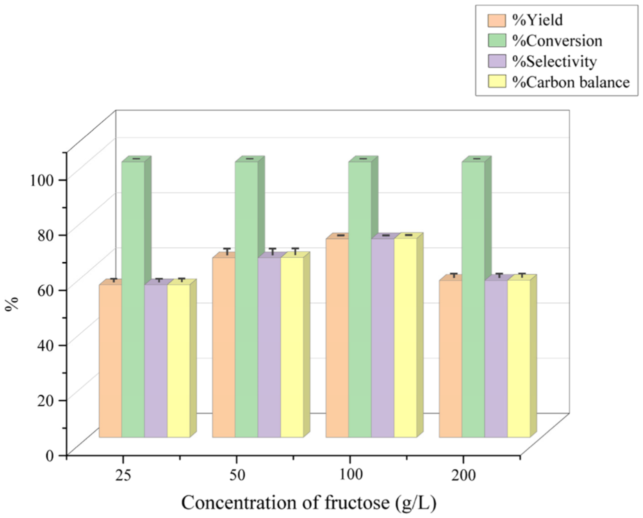

Figure 7. Effect of the concentration of fructose solution in the synthesis reaction of 5-HMF (at a temperature of 120 °C, an NMP-to-water ratio of 50%, an organic-to-water ratio of 10:1, and a reaction time of 5 min).

3.6. Regression Analysis and Optimization.

A full factorial design of experiment (DoE) was employed to systematically investigate the impact of key parameters on the catalytic conversion of fructose to 5-hydroxymethylfurfural (5-HMF) in a continuous flow reactor. The biphasic system utilized RCP160M as the catalyst, with fructose concentration, organic-to-aqueous phase ratio, and contact time as the variables of interest.

To validate the reliability of the experimental data, a comprehensive residual analysis was conducted. Figure 8A illustrates the normal distribution of residuals, which are randomly scattered around a horizontal line. Furthermore, Figure 8B demonstrates the independence of residuals, as no discernible patterns or trends are observed in their relationship with observation order. Finally, Figure 8C confirms the stability of variance across different factor levels, as the residuals are evenly dispersed above and below zero. Based on these findings, the experimental data exhibit adequate reliability and suitability for subsequent statistical analysis, including regression modeling.

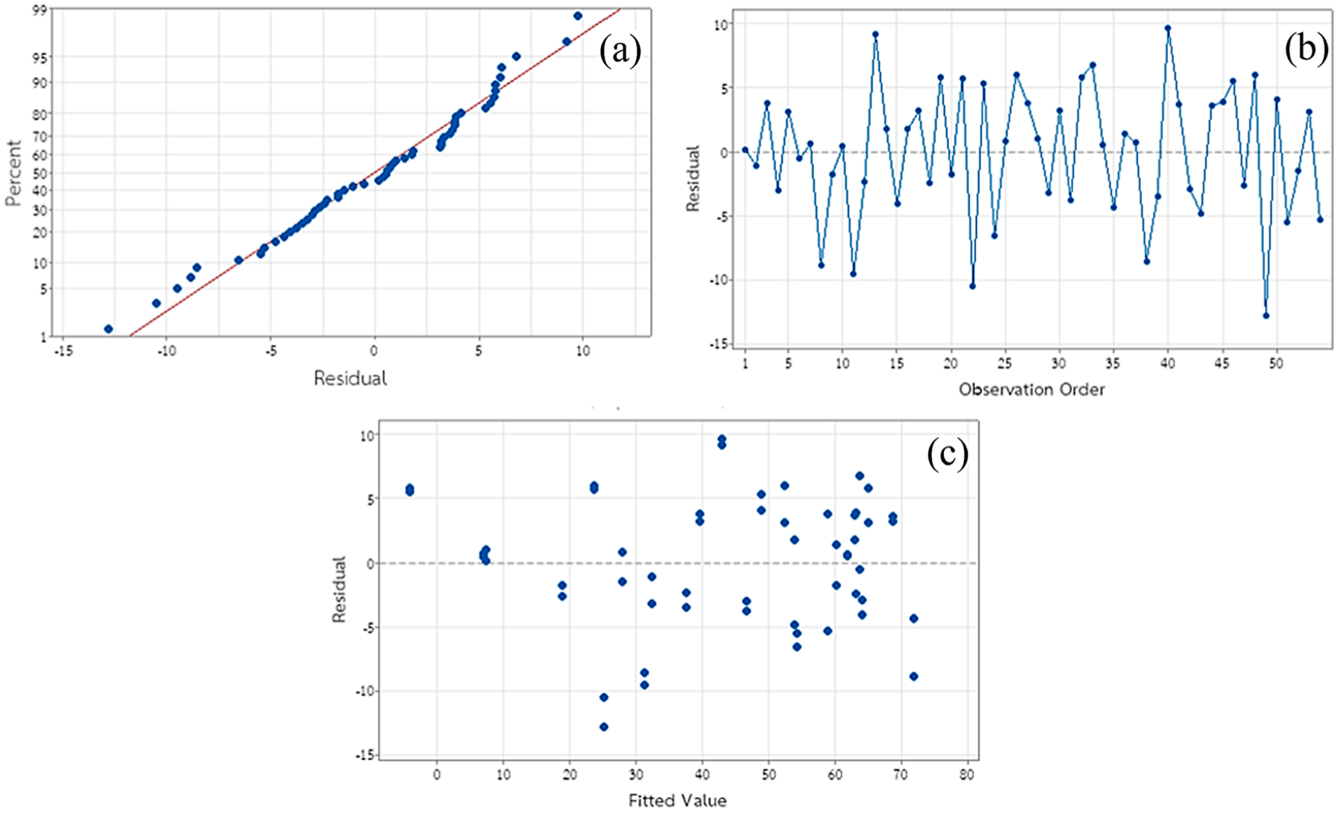

Figure 8. Residual plots (a) normal probability of the residuals, (b) residuals versus the order of the data and (c) residuals versus the fitted values.

Table 2. Variance Analysis of % Conversion of Fructose, % Yield, % Selectivity and Productivity of 5-HMF

source	% yield		% conversion		%Selectivity		% productivity	
	F-value	*P*-value	*F*-value	*P*-value	*F*-value	*P*-Value	*F*-value	*P*-value
[fructose] (X_1)	246.89	0	0.01	0.989	273.29	0	913.62	0
organic ratio (X_2)	1264.27	0	2349.57	0	353.52	0	700.2	0
reaction time (X_3)	491.71	0	1003.85	0	133.83	0	1983.73	0
X_1X_2	18.06	0	13.38	0	13.78	0	78.51	0
X_1X_3	21.05	0	20.42	0	22.73	0	216.66	0
X_2X_3	35.67	0	234.14	0	17.3	0	140.81	0
$X_1X_2X_3$	16.11	0	13.72	0	21.38	0	22.13	0
	R-sq (adj) = 98.81%		*R*-sq (adj) = 99.33%		*R*-sq (adj) = 97.26%		*R*-sq (adj) = 99.42%	

To assess the statistical significance of main and interaction effects on yield, conversion, selectivity, and productivity of 5-HMF synthesis in the packed-bed reactor, a linear regression model was constructed and analyzed using ANOVA at a 95% confidence level. Table 2 presents the statistically significant terms identified based on *p*-values. The resulting linear regression models are shown in equs 10−13.

Importantly, all terms in the models were found to be statistically significant ($p < 0.05$), except for the fructose concentration term in the conversion model. Due to its insignificance, this term was omitted from eq 11. However, eqs 10, 12, and 13 retain all main and interaction effect terms.

The high *R*-squared values of 98.81%, 99.33%, 97.26%, and 99.42% for the correlations of yield, conversion, selectivity, and productivity, respectively, indicate that the developed models can accurately predict these parameters within the specified operating conditions.

The linear regression model was used to correlate the yield, conversion, selectivity, and productivity of 5-HMF synthesis in a packed-bed reactor with specified operating conditions. The parameters for each model are presented in eqs 10−13. Figure 9 illustrates the correlation between the predicted and experimental values for 5-HMF yield, fructose conversion, selectivity, and productivity. The linear relationship, with a maximum deviation of ±2%, underscores the model's ability to reliably predict these key performance indicators.

$$\begin{aligned}\%\ \text{Yield} =& -21.21 + 0.1779X_1 + 14.51X_2 + 9.81X_3 \\ & - 0.000924X_1X_1 - 0.6707X_2X_2 - 0.5396X_3X_3 \\ & - 0.01692X_1X_2 - 0.00378X_1X_3 - 0.393X_2X_3 \\ & + 0.001629X_1X_2X_3\end{aligned} \tag{10}$$

$$\begin{aligned}\%\ \text{conversion} =& -0.89 + 20.27X_2 + 10.08X_3 \\ & - 0.000669X_1X_1 - 1.1962X_2X_2 \\ & - 0.4802X_3X_3 + 0.00428X_1X_2 \\ & - 0.493X_2X_3 + 0.000238X_1X_2X_3\end{aligned} \tag{11}$$

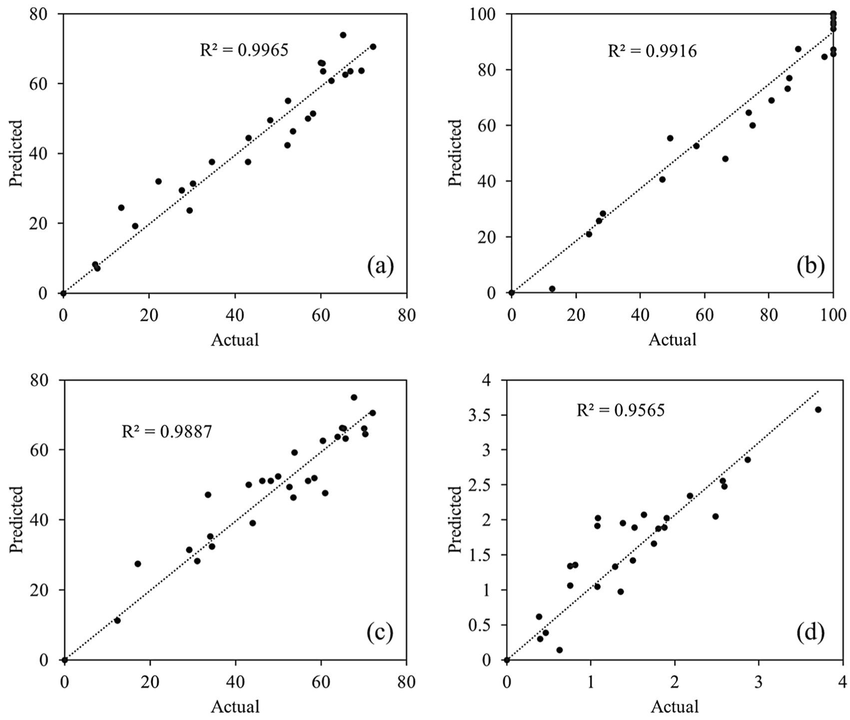

Figure 9. Parity plots of (a) % yield of 5-HMF (b) % conversion of fructose (c) % selectivity of 5-HMF (d) productivity.

$$\begin{aligned}\%\ \text{selectivity} = {} & 17.54 + 0.042X_1 + 7.59X_2 + 7.16X_3 \\ & - 0.000697X_1X_1 - 0.2786X_2X_2 \\ & - 0.4435X_3X_3 - 0.00851X_1X_2 \\ & + 0.00483X_1X_3 - 0.288X_2X_3 \\ & + 0.0007X_1X_2X_3 \qquad (12)\end{aligned}$$

$$\begin{aligned}\text{productivity} = {} & 1.264 + 0.02272X_1 - 0.215X_2 - 0.132X_3 \\ & - 0.0001X_1X_1 + 0.00664X_2X_2 \\ & - 0.0071X_3X_3 + 0.000921X_1X_2 \\ & + 0.002124X_1X_3 + 0.0088X_2X_3 \\ & - 0.000256X_1X_2X_3 \qquad (13)\end{aligned}$$

3.7. Selection and Estimation of Optimal Levels and Responses. This study employed a numerical optimization technique to identify the reaction conditions that maximize the yield, conversion, selectivity, and productivity of 5-hydroxymethylfurfural (5-HMF) from fructose dehydration. The optimization constrained maximum conversion to 100% for complete fructose utilization and targeted maximum 5-HMF yield for optimal product output. The predicted optimal conditions were: a reaction temperature of 120 °C, a fructose concentration of 100 g/L, an organic-to-aqueous phase ratio of 8.36:1, and a reaction time of 6.91 min. Under these conditions, the model predicted a yield of 73.74%, conversion of 99%, selectivity of 74.48%, and a productivity of 1.22 mol 5-HMF/gcat h. Experimental validation with the predicted optimal conditions yielded results that closely mirrored the model's predictions. The observed yield was 73.46%, conversion was 99%, selectivity was 74.20%, and the productivity was 1.25 mol 5-HMF/gcat h. The observed yield deviated from the predicted value by only 0.38%, demonstrating a high degree of consistency between the model and the experimental data. These results represent the best conditions identified for 5-HMF production from fructose dehydration in this study.

3.8. Sensitivity Analysis. To assess the robustness of the optimal conditions, a sensitivity analysis was conducted by independently varying key process parameters: fructose concentration, organic-to-aqueous phase ratio, and reaction time. Each parameter was perturbed by ±20% from its optimal value, and the resulting impact on 5-HMF production metrics (% conversion, % yield, % selectivity, and % productivity) was evaluated. As shown in Figure 10a, fructose concentration exhibited the most pronounced influence on productivity. A 20% increase in concentration led to an 4.04% increase in productivity, while a 20% decrease resulted in a 4.98% decrease. In contrast, variations in fructose concentration had a negligible impact (<3%) on % conversion, % yield, and % selectivity of 5-HMF. Figure 10b illustrates that increasing the organic-to-aqueous phase ratio negatively affected productivity. A 20% increase in the ratio led to a 5.12% decrease in productivity, accompanied by reductions in both % yield and % conversion. As depicted in Figure 10c, adjustments to reaction time also impacted productivity. A 20% increase in reaction time resulted in a 6.15% decrease in productivity, while a 20% decrease led to a 5.76% increase.

To maintain consistent 5-HMF production, it is recommended to control fructose concentration within ±10% of the optimal value. The organic-to-aqueous phase ratio and reaction time can be allowed to deviate by ± 15% from their optimal values.

While the single-parameter sensitivity analysis provided valuable insights into the individual influence of each variable on conversion yield, selectivity, and productivity, real-world operation rarely involves the fluctuation of a single parameter in isolation. Therefore, a two-parameter sensitivity analysis was conducted to evaluate the combined effects of parameter

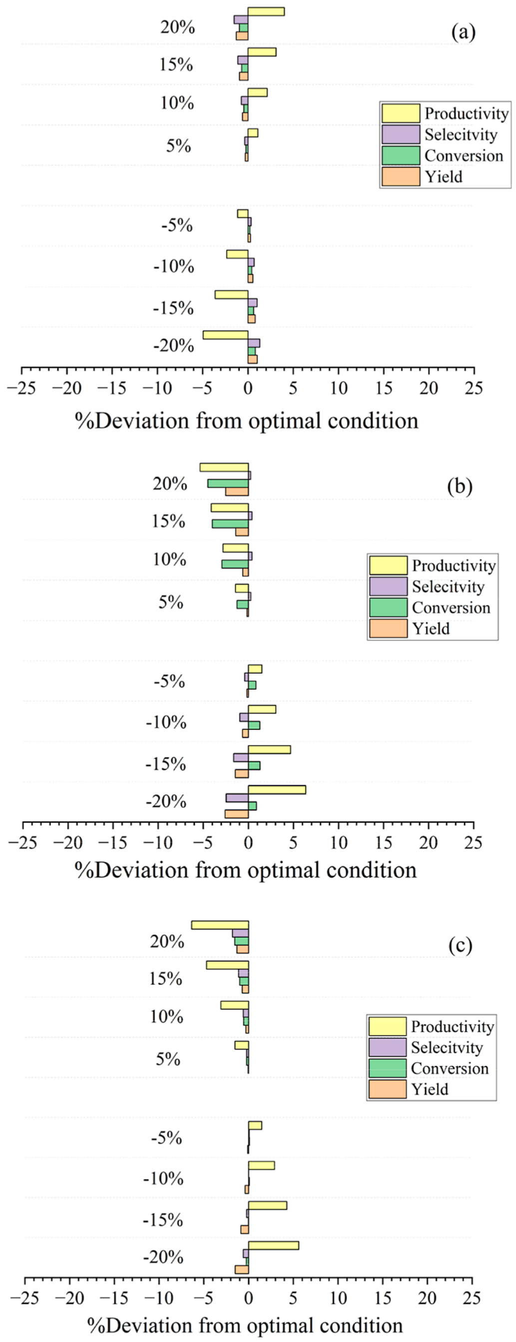

Figure 10. Sensitivity analysis of (a) concentration of fructose (b) organic to aqueous ratio (c) reaction time.

variations on these key performance indicators. Specifically, the coupled influence of fructose concentration and organic-to-aqueous ratio, fructose concentration and reaction time, and reaction time and organic-to-aqueous ratio were investigated. The results of these analyses are visualized as surface plots in Figure 11. Simultaneous variations in these parameter pairs generally resulted in relatively minor impacts on conversion, yield, selectivity, and productivity. While most deviations had a negligible effect, it was observed that larger, concurrent variations in both reaction time and organic-to-aqueous ratio (e.g., −20% for both) could lead to a change in productivity of approximately 7%. Despite this specific scenario, the overall analysis confirms the robustness of the identified optimal operating conditions, suggesting their reliability even with anticipated process variations.

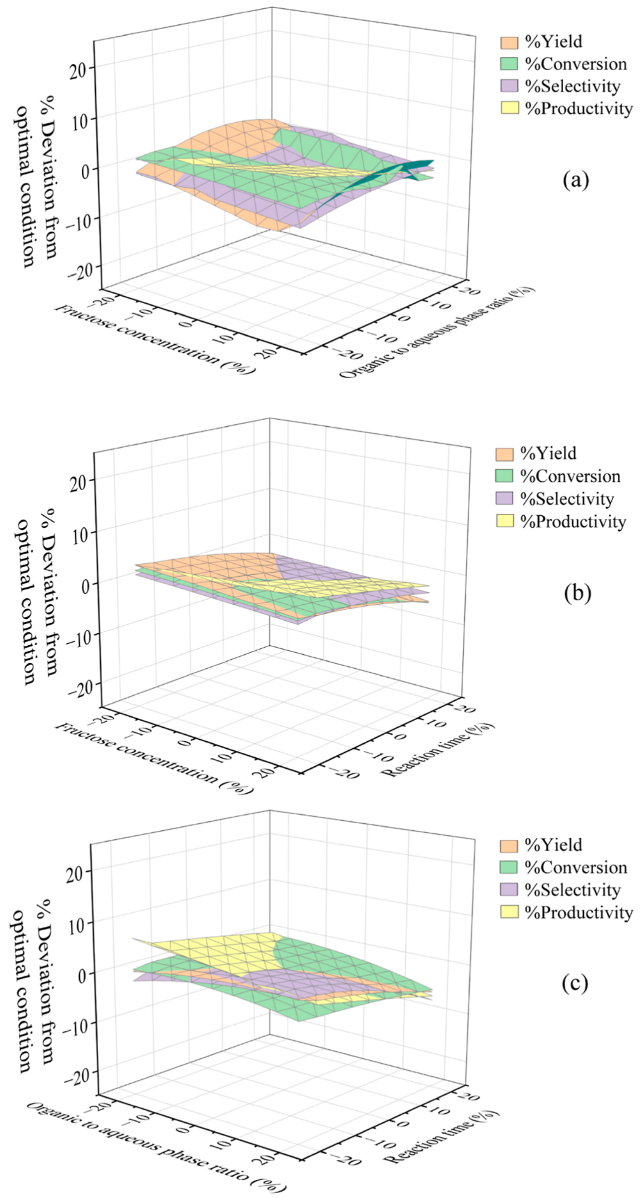

Figure 11. Multivariate sensitivity analysis of (a) Fructose concentration and organic to aqueous ratio (b) fructose concentration and reaction time (c) reaction time and organic to aqueous ratio.

3.9. Stability of Catalyst.

Catalyst stability was assessed under optimized conditions: 120 °C, 100 g/L fructose, 8.36:1 organic-to-aqueous phase ratio, and 6.91 min contact time. As shown in Figure 12, a modest decline in 5-HMF yield was observed within the initial 20 h of operation. However, a substantial decrease in both 5-HMF yield and fructose conversion became evident after 50 h of continuous operation. These findings suggest that while catalyst RCP160M demonstrated acceptable stability during the initial 20 h, its catalytic performance gradually deteriorated over extended reaction periods. This deactivation may be attributed to the strong adsorption of byproduct species onto the active sites of the catalyst, thereby hindering substrate accessibility. To ensure sustained catalytic activity, the implementation of effective catalyst regeneration strategies will be crucial. Future research efforts will focus on developing robust methods for

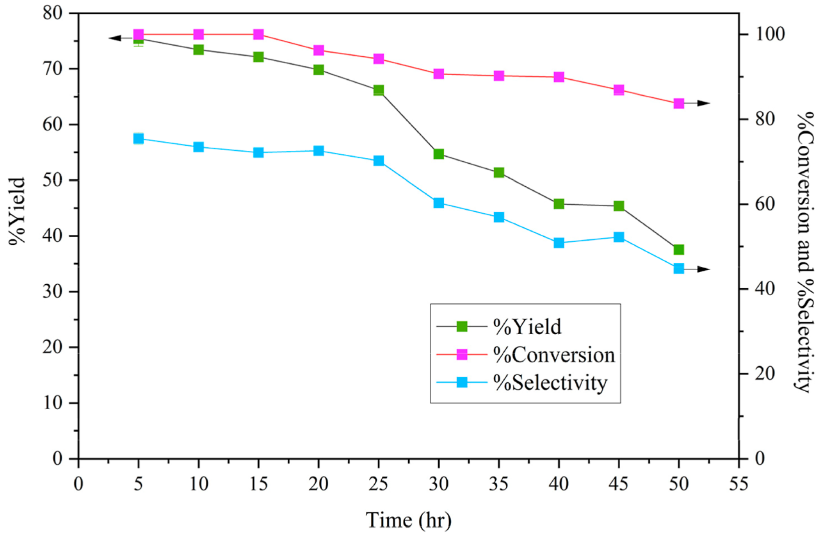

Figure 12. Reaction performance of 5-HMF synthesis over RCP160M catalyst for extended period.

recovering catalyst activity following prolonged continuous use.

3.10. 5-HMF Recovery and Purification. The reactor effluent was separated into organic and aqueous phases. Each phase was subjected to purification processes to isolate high-purity 5-hydroxymethylfurfural (5-HMF). The organic phase was treated with varying amounts of activated carbon (Table 3). This adsorbent possessed a BET surface area of 758.82 m^2/g, a pore volume of 0.73 cm^3/g, and a pore size of 38.49 Å. A trade-off between 5-HMF recovery and purity was observed. Increasing the activated carbon dosage enhanced purity but significantly reduced recovery, reaching a maximum of 93.57% purity at a cost of 72.17% recovery. This trend is attributed to the competitive adsorption of 5-HMF alongside impurities such as humins. To optimize recovery, a flow-through adsorption system with twin beds will be investigated in future work.

Table 3. 5-HMF Purity and Recovery from Organic Phase Using Activated Carbon

sample	purity (%)	recovery (%)
standard 5-HMF	99.00	
0.00 g AC	81.65	100.00
0.25 g AC	83.13	93.35
0.50 g AC	88.74	88.84
0.75 g AC	89.90	81.81
1.00 g AC	92.63	72.17

Liquid−liquid extraction was employed to recover 5-HMF from the aqueous phase using various solvents (Table 4). Toluene, being a nonpolar solvent, exhibited poor extraction efficiency. Butanol demonstrated superior extraction performance compared to methyl isobutyl ketone (MIBK), achieving recovery rates of 57.84% and 46.68%, respectively.

Subsequently, butanol and MIBK were selected for further optimization. Increasing the organic-to-aqueous phase ratio to 2:1 significantly enhanced 5-HMF recovery for both solvents, with butanol reaching a recovery rate of 75.68%. To further improve extraction efficiency, a two-stage extraction process was implemented, leveraging the concentration gradient as the driving force for mass transfer. This approach led to a substantial increase in recovery, with MIBK and butanol achieving 66.39% and 83.44% recovery, respectively, at a 1:1 organic-to-aqueous phase ratio.

Table 4. 5-HMF Extraction from Aqueous Phase Using Solvent Extraction

extractant	volume of aqueous phase (ml)	organic to aqueous phase ratio	weight of 5-HMF extracted (g)	no. of extraction cycle	% recovery
toluene	5	1:1	0.0009	1	9.67
MIBK	5	1:1	0.0047	1	46.68
butanol	5	1:1	0.0052	1	57.84
MIBK	5	2:1	0.0061	1	57.15
MIBK	5	1:1	0.0066	2	66.39
MIBK with NaCl	5	1:1	0.0075	2	79.51
butanol	5	2:1	0.0073	1	75.68
butanol	5	1:1	0.0077	2	83.44
butanol with NaCl	5	1:1	0.0081	2	92.13

The addition of 0.2 g NaCl to 5 mL of the aqueous phase significantly enhanced 5-HMF recovery, likely due to a salting-out effect. This observation aligns with the findings of Dumesic et al., who introduced the extraction ratio (*R*) as the ratio of HMF concentration in the organic to aqueous phase. Their work demonstrated that the presence of salts increases *R*, leading to improved HMF yields and a reduction in side reactions. Notably, in our study, a remarkable 92.18% HMF recovery using butanol with NaCl. Butanol is an attractive solvent due to its biodegradability, low toxicity, and relatively low volatility.

To further optimize the process and minimize solvent consumption, we propose solvent recirculation. MIBK can be recovered from the purified 5-HMF stream via vacuum evaporation and subsequently reused. Similarly, butanol can be recovered from the aqueous phase extraction effluent for subsequent extraction cycles. A conceptual representation of the proposed 5-HMF recovery process, incorporating solvent recirculation, is depicted in Figure 13.

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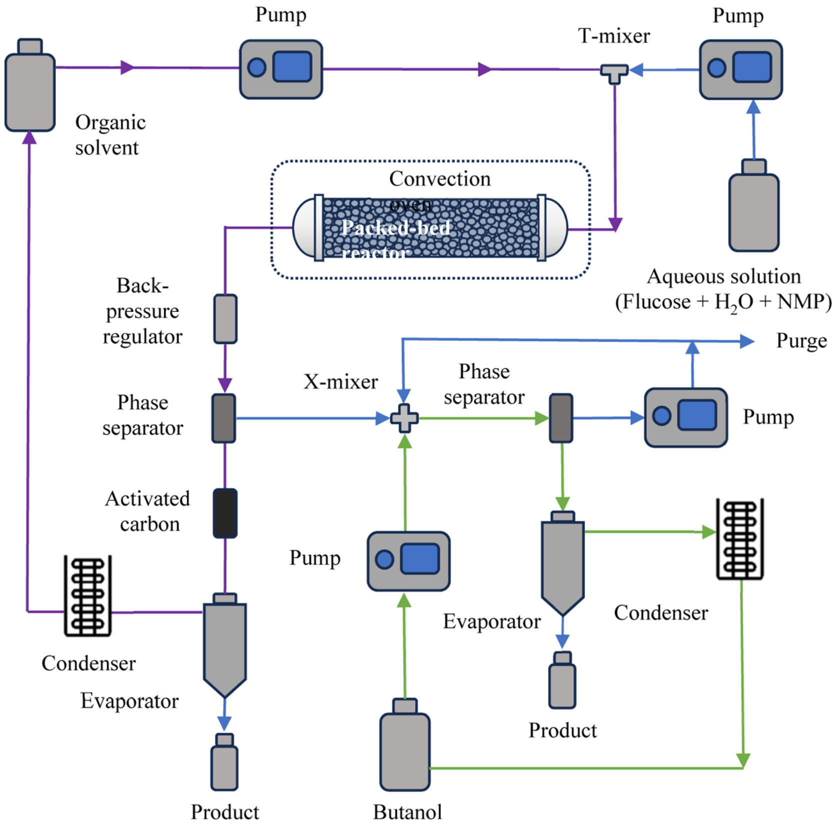

Figure 13. Schematic diagram illustrating the conceptual downstream processing for the production of 5-HMF.

Table 5. Catalytic Performance Comparison for 5-HMF Synthesis

catalyst	solvent	temperature (°C)	reaction time	conversion (%)	selectivity of 5-HMF (%)	productivity (mol. 5-HMF/gcat.hr)	reactor
H_3PO_4	H_2O	240	2 min	98	66.6		Batch[32]
acetic acid	$NaCl_{aq}$/toluene	195.8	3.2 min	100	72.5		Batch[34]
DPhSO	DPhSO	140	11 h	100	68.4	0.062	Batch[35]
VNU-11–SO_4	[Emim]Cl	80	24 h	100	90.5	0.00125	Batch[36]
phosphoric acid	H_2O/2-*s*-butyl phenol	180	12 min	100	80.9		Flow[37]
ASB	H_2O/THF	90	5 min	95	73	1.069	Flow[25]
RCP160M	MIBK/NMP/H_2O	1f0	6.91 min	100	73.46	1.25	flow (this work)

Furthermore, we introduce a novel approach for reutilizing the spent aqueous phase from butanol extraction, specifically for the salting-out enhanced extraction using NaCl. Our hypothesis is that the residual NaCl in the spent aqueous phase can facilitate 5-HMF extraction into the organic phase during the biphasic 5-HMF synthesis, while the residual NMP can contribute to promoting the dehydration reaction. Experimental results, obtained under optimized conditions with the addition of 0.2 g NaCl to 5 mL of aqueous fructose solution, support this hypothesis. The 5-HMF yield increased from 73.46% to 78.94%, demonstrating the significant role of NaCl in enhancing 5-HMF production efficiency. This suggests that integrating the spent aqueous phase back into the process offers a promising strategy for improving overall process efficiency and reducing waste.

Regarding the cost of NMP, while currently around \$160 USD/kg (based on sources like molbase.com),[33] represents a significant fraction (approximately 20%) of the current market price of HMF (\$80.00 USD/100 g). This cost differential could indeed pose a challenge to the economic viability of the process if NMP were not efficiently recycled. Therefore, we have incorporated a robust NMP recycling strategy into our proposed process, as illustrated in Figure 13. Specifically, the NMP present in the aqueous phase after butanol recovery is recycled. This recycled NMP stream can then be mixed with the fresh feed, significantly reducing the overall demand for fresh NMP. While a detailed techno-economic analysis (TEA) and life cycle assessment (LCA) are beyond the scope of the current work, this integrated recycling approach is crucial for mitigating the cost burden associated with NMP and improving the overall economic and environmental performance of the HMF production process. Future work will focus on a comprehensive TEA and LCA to fully quantify the impact of NMP recycling on the process economics and environmental footprint.

3.11. Comparison of Reaction Performance. The performance evaluation of the RCP160M catalyst for 5-HMF synthesis from fructose was conducted. A comparative analysis with previously reported methods, operating under their respective optimal conditions, was performed. Key performance metrics, including 5-HMF yield, selectivity, and productivity, are summarized in Table 5.

While previous studies employing homogeneous catalysts, such as those reported by Asghari and Yoshida (2006) and Songtawee et al. (2021), have demonstrated high 5-HMF yields,[32,34] these methods often require harsh reaction conditions, including elevated temperatures and extended reaction times. Furthermore, the separation of the catalyst from the reaction mixture presents a significant challenge, potentially increasing production costs. Similarly, approaches utilizing ionic liquid solvents, as explored by Zhang et al. (2021),[35] and biphasic systems, as investigated by Nguyen et al. (2020),[36] have also achieved high 5-HMF yields. However, the inherent difficulties in separating 5-HMF from ionic liquid solvents contribute to increased production costs. In addition, the productivity of both these systems is often limited by the use of batch reactors, which necessitate extended reaction times.

In this work, the RCP160M, a heterogeneous catalyst, was employed. Under optimized conditions, the yield and selectivity of 5-HMF production were comparable to the findings of Morales-Leal et al. (2019), who utilized a similar flow reactor system.[25] Notably, our optimized system achieved a significantly higher productivity of 1.25 mol·5-HMF/gcat·hr. Furthermore, a two-phase extraction-reaction system was implemented, facilitating efficient separation of 5-HMF. Details regarding the separation process, including extraction from the organic and aqueous phases, and solvent recycling are presented in Section 3.10.

It is important to acknowledge that the applicability of catalyst RCP160M is currently limited to feedstocks that do not require prior hydrolysis or isomerization. While lower-cost feedstocks like lignocellulose necessitate catalysts with distinct functionalities capable of catalyzing these specific reactions, functionalities absent in RCP160M, the system proposed herein can be effectively integrated within a broader lignocellulosic biorefinery framework. Specifically, an initial hydrolysis stage would convert lignocellulose to a glucose-rich stream. Subsequently, an isomerization reactor could be employed to convert a portion of the glucose to fructose, addressing equilibrium limitations. The resulting aqueous mixture of glucose and fructose could then be separated using simulated moving bed chromatography, a commercially established process for producing purified fructose and glucose streams. The purified fructose stream could serve as the feedstock for the present process, while the glucose stream could be recycled back to the isomerization reactor. Finally, considering the environmental implications of employing solvents such as NMP and MIBK, a comprehensive environmental assessment is essential. A life cycle assessment (LCA) provides a robust framework for evaluating the environmental footprint of bioproduct production and promoting sustainable practices within this context.

4. CONCLUSIONS

A factorial experimental design was employed to investigate the influence of fructose solution concentration, organic-to-aqueous phase ratio, and reaction time on the synthesis of 5-HMF in a continuous reactor. All three factors were found to significantly impact the 5-HMF yield. Optimal conditions, predicted through statistical analysis, were determined to be 100 g/L fructose, 8.36:1 organic-to-aqueous phase ratio, and 6.91 min reaction time, leading to a predicted yield of 73.74%. Experimental validation under these conditions yielded a 73.46% yield, confirming the accuracy of the model. For purification and recovery, activated carbon adsorption was utilized to remove impurities from the organic phase. A 1.00 g carbon dosage resulted in a 92.63% pure 5-HMF product. In the aqueous phase, a two-stage extraction process using butanol, with NaCl addition and a 1:1 solvent-to-aqueous phase ratio, achieved a high 5-HMF recovery of 92.13%. The proposed process provides a solid foundation for scaling up the production of 5-HMF from fructose due to packed-bed continuous reactor configuration offers significant advantages in terms of scalability. Furthermore, the integration of solvent recycling systems can contribute to both economic and environmental sustainability. It should be noted that the applicability of this catalyst is limited to feedstocks that do not require hydrolysis and isomerization steps. The use of lower-cost feedstocks such as lignocellulose necessitates catalysts with distinct functional groups capable of catalyzing these reactions, which are not present in RCP160M. Given the environmental concerns associated with the solvents NMP and MIBK, it is imperative to conduct a thorough environmental assessment. Life cycle assessment (LCA) can provide a systematic framework for evaluating the environmental footprint of bioproduct production and supporting sustainable practices.

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Notes

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