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Optimization Study of Glucose Synthesis to 5-Hydroxymethylfurfural (5-HMF) by Using Low Transition-Temperature Mixtures (LTTM)

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Abstract: 5-Hydroxymethylfurfural (5-HMF) is a potential value-added product gaining popularity due to its wide range of applications. Glucose is widely used for 5-HMF production because it is abundant and more cost-effective than other resources. In the current research, a combination of microwave irradiation and low transition-temperature mixture (LTTM) for 5-HMF production was sustainably created. A preliminary study was conducted to derive 5-HMF using LTTM as a green solvent in various ratios of glucose: LTTM (MA/ChCl): water (10:100:15) and (10:48:100) via microwave heating at 90 °C for 10–60 min reaction time. The product analysis revealed that the 10:100:15 combination ratio of glucose: LTTM: water produced more 5-HMF (20.5%) than the 10:48:100 (0.28%) ratio. Following the preliminary results, an optimization study was conducted, focusing on the reaction temperature, LTTM mass, and water to assess the impact on 5-HMF yield and glucose conversion, using CCD in Design-Expert software. The quadratic model fit for 5-HMF yield and the 2FI model for glucose conversion yielded R^2 values of 0.9861 and 0.8610, respectively. Both responses had a significant p value of 0.0061 for glucose conversion and <0.0001 for 5-HMF yield. An optimum point was achieved at 100 °C, 100 g of LTTM, and 20 g of water, with an expected 5-HMF yield and glucose conversion of 45.77% and 69.03%, respectively.

Keywords: 5-hydroxymethylfurfural (5-HMF); optimization; low transition-temperature mixtures (LTTM); green solvent; malic acid/ChCl

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1. Introduction

5-Hydroxymethylfurfural (5-HMF) is a promising chemical building block [1] with a range of applications including serving as starting raw material for liquid fuels [2], fuel additives, pharmaceuticals [3], thermoresistant polymers, anti-corrosion materials, and preservative agents [4]. This useful compound has been the subject of ongoing research into its production from biomass and sugars using green reagents and solvents [5]. Generally, the production of 5-HMF involves an acid-catalyzed reaction [1] (dehydration) whereby three water molecules are removed from simple sugars of monosaccharides, disaccharides [6,7], or direct conversion from polysaccharides such as starch and cellulose [8]. However, the 5-HMF synthesis route can be complex and uncontrollable in terms of selectivity, with the potential for the production of by-products, side reactions, degradation reactions, and low sugar conversion that can influence the yield of 5-HMF [9].

To ensure a higher yield of 5-HMF, literature suggests combining organic solvents and catalysts (homogeneous or heterogeneous) to facilitate the dehydration process in C_6 carbohydrate sugars to 5-HMF, furan, and its derivatives [10,11]. The highest yield of 5-HMF, at 96%, was successfully achieved from glucose under a mixed solvent of ionic liquid (ILs) 1-Butyl-3-methylimidazolium chloride [BMIM]Cl and chromium (II) or chromium (III) chloride, together with N-hetero-cyclic carbene (NHC) ligands [12]. Moderate yields of 68% 5-HMF were achieved via the conversion of glucose using ILs 1-sulfonic acid-3-methyl imidazolium ([SMIM]) tetrachloroferrate [FeCl4], while biphasic system methylisobutyl ketone (MIBK) and phosphate buffer saline (PB) achieved 85 mol% of 5-HMF [13]. Furthermore, 80% yield was obtained using ([SMIM]) chloride (Cl) [14]. By combining organic solvents such as dimethyl sulfoxide (DMSO) with aluminium chloride ($AlCl_3$) as the catalyst, glucose can be converted into 52.4% 5-HMF in just 5 min at 120 °C. In another study, HT-Amberlyst-15 was employed as a catalyst to convert glucose at 100 °C for 180 min, resulting in the production of 42.3% 5-HMF [15]. ILs are known for their thermal and chemically stability and can be used as both catalysts and solvents in the dehydration of biomass or sugar into chemical intermediates [15,16].

Although incorporating homogenous or heterogeneous catalysts and solvents in a reaction offers advantages, it is expensive, requires a high-temperature reaction (120 °C to 180 °C), and leads to poor biodegradability, high toxicity, and difficulties in isolation for further 5-HMF purification and recovery [13]. Therefore, environmentally and economically friendly approaches are necessary to investigate and establish green synthesis reaction pathways, such as using an LTTM at a low temperature (<100 °C) for 5-HMF production. LTTMs are imperative green solvents and catalysts for 5-HMF synthesis because they are low in toxicity, abundantly available, inexpensive, and require low energy usage, making them more economical and favourable for these purposes [17]. Interestingly, LTTM mixtures require only low-temperature reaction conditions to activate (due to their low melting point) and are considered mild synthesis reactions. Additionally, LTTMs can be reused and recycled while maintaining catalytic activity during the synthesis [18].

Generally, LTTMs are mixtures of hydrogen bond acceptors (HBA), such as choline chloride (ChCl) and betaine hydrochloride (BHC), and hydrogen bond donor (HBD) (e.g., organic acids or glycerol), also known as natural deep eutectic solvents (NADESs), which have shown promising results [19] for solvating and catalysing reactions under mild conditions. According to research by Gomes et al. [20], 94% 5-HMF was produced from 0.1 mmoL of fructose in the presence of 1.0 mmoL of BHC, malic acid (MA), and water with the ratio of 1:1:1 as a catalyst/solvent for the reaction at a temperature of 140 °C in 11 min. These results provide insight that the 5-HMF yield of the method utilizing LTTM is comparable to that incorporating ILs as solvents in the reaction system. The dehydration reaction using an LTTM mixture of ChCl-malonic, oxalic, or citric acid produced 78% 5-HMF yield in 60 min at a reaction condition of 80 °C [21]. Similarly, Sert et al. used ChCl as an HBA by varying HBD to determine the mixture that offered the best 5-HMF yield [22]. Approximately 0.04 g of sunflower stalk was synthesized to 5-HMF in three different ChCl-HBD mixtures (10 g each): ChCl-oxalic acid, ChCl-citric, and ChCl-tartaric acid. The results showed that among these three mixtures, the ChCl-oxalic acid mixture produced the highest yield of 5-HMF, i.e., 4.07% in 1 min at 180 °C [15]. It is evident from the results reported by Sert et al. [22] that the use and compatibility of different HBA and HBD significantly influenced the 5-HMF yield and sugar conversion.

Several techniques have been investigated for 5-HMF production, including conventional heating, ultrasonic propagation, and microwave irradiation. Compared with the conventional method, these techniques reduce the reaction time and enhance the 5-HMF production. Among the available techniques, microwave and ultrasonic irradiation are the most promising. It was reported that ultrasonic irradiation resulted in a 5-HMF yield up to 20.31% when 5 wt.% of glucose was converted in the presence of 1.8 M LTTM at 85 °C for

2 h [23]. Similarly, under microwave irradiation, a 5-HMF yield of 22.1% was produced using glucose as the starting material in the presence of titanium oxide nanoparticles as the catalyst in an aqueous medium at 120 °C for 2 min [24]. These results show that both technologies offer distinct benefits where higher temperatures must be employed under microwave systems at lower reaction time, in contrast to the ultrasonic system. However, the efficiency of the reaction process may be significantly affected by the compatibility of the technology when employing the catalyst and solvent.

5-HMF synthesis is preferable for catalytic systems comprising Lewis and Brønsted acidic sites [25]. A combination of MA and ChCl can produce LTTM and show good capability to produce 5-HMF [23,26,27]. Following the green and sustainable strategy, this study utilizes LTTM to synthesize 5-HMF, which can simultaneously act as solvent and catalyst to dehydrate glucose to 5-HMF. The reaction was carried out under microwave heating at a low temperature (<100 °C) using different ratios of glucose: LTTM: water. Microwave-assisted synthesis has been proven to be a better method for converting sugar into 5-HMF, accelerating the synthesis of 5-HMF with higher extraction/reaction rates and uniform heating. Therefore, the application of microwaves was anticipated in the production of 5-HMF.

2. Results

2.1. Heating of Low Transition Temperature Mixture

The synthesis of LTTM is crucial and is the tested parameter in this study. Initially, MA and ChCl were mixed in solid form under conventional heating. However, the mixture was sticky in nature and required manual stirring for the first 10 min until it melted. After 98 min, the solution became cloudy and sticky. After an additional 2 h of heating, the mixture turned into a colorless and less sticky solution, indicating that the heating could be stopped. Typically, it takes around 4 h to complete synthesis of 200 g of solid mixtures. Finally, the mixture must be cooled down before being transferred into the glass bottle.

2.2. Characterization of LTTM

2.2.1. TGA of Low Transition-Temperature Mixture

Thermal degradation analysis (TGA) was conducted on LTTM to evaluate its thermal stability. Figure 1 shows that there no mass loss was observed between 0 and 100 °C, indicating the lack of moisture in the mixture. From 100 to 210 °C, LTTM showed a modest weight reduction, which is attributed to the loss of water content (around 4.75%) [28]. Between 210 °C to 300 °C, LTTM started to continuously degrade with a significant weight loss of 91.17%. This degradation is possibly due to the breakdown of MA at around 210 °C. ChCl, on the other hand, began to degrade at 300 °C onwards. The Delta Y value represents the percentage of weight lost by the sample between two specified temperatures. In this case, the Delta Y from 210 to 300 °C was approximately 86.904%. These LTTM mixtures exhibited slightly higher thermal stability at 210 °C than those in a study by Xern et al. [23], who reported a thermal degradation temperature of 200 °C, and Dana et al. [29] at 206.85 °C for similar LTTM mixtures and ratios. The TGA curves' degradation temperatures imply that LTTM can be employed in various reactions occurring below 210 °C. Additionally, LTTM functionalities can contribute to a promising percentage of synthesized 5-HMF at lower temperatures without degradation. Therefore, to maintain LTTM's functionality and thermal stability for glucose-to-5-HMF conversion, the maximum synthesis temperature should be limited to 210 °C.

2.2.2. Density of LTTM

The density of LTTM was measured to observe its changes at different temperatures. Therefore, measurements relevant to the reaction conditions and material used in this study were taken at temperatures of 25 °C, 80 °C, and 90 °C. The initial density of starting materials, MA and ChCl, were 1.61 g/cm^3 and 1.10 g/cm^3 at room temperature, respectively. The density of the LTTM mixtures at room temperature was observed to decrease to

1.2731 g/cm^3, which is comparable to the density of a similar LTTM mixture prepared by Dana et al. [29] of around 1.278 g/cm^3. However, as the temperature increased, the density of the LTTM mixtures slightly reduced from 1.2731 g/cm^3 (at 25 °C) to 1.2336 g/cm^3 (at 90 °C). This may be due to the temperature-dependent density of the binary mixtures, meaning higher temperatures result in a lower LTTM density. According to Francisco et al. [30], high molecular activity can lead to a boost of volume and density at certain limits [29].

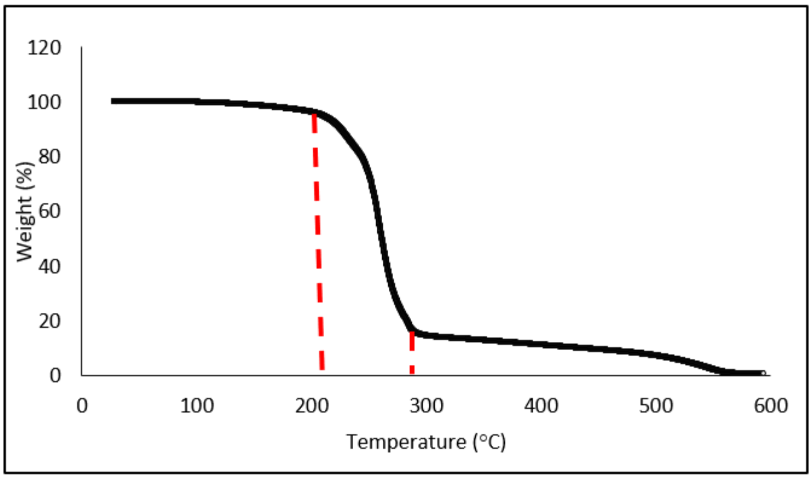
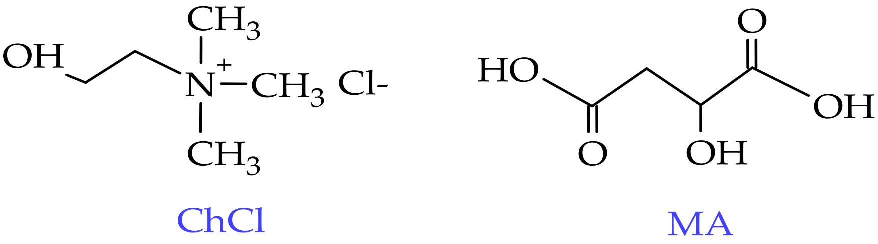


Figure 1. TGA of synthesized LTTM.

The high viscosity can limit the interaction of molecules during the conversion process. In glucose-to-5-HMF conversion, the high viscosity of LTTM hinders molecular interaction. Francisco et al. [31] reported that LTTM's high viscosity results was from its low free volume. Lower free volume increases the structure and decreases molecular mobility. High salt-to-HBD ratios simultaneously develop LTTM structures and increase their viscosity. On the other hand, water strongly binds to the mixture, reduces the reaction temperature and preparation time, improves LTTM solubility, and lowers its viscosity. Nonetheless, prolonged dilution can break the H-bond and special structure of the LTTM combination [32]. Therefore, it is possible to modify the physical and phase behaviour by selecting the ideal composition of LTTM and water content.

2.2.3. FTIR Analysis

Fourier-transform infrared (FTIR) spectroscopy analysis was performed to identify the structure and bonding in the LTTM, which was confirmed by the bond peaks as reported in [27]. The overall structure of starting material can be observed in Scheme 1, where the functional groups are compared with the analysed FTIR data. Figure 2 illustrates the representative peaks of the bonds involved in the starting materials for LTTM, including ChCl, MA, and LTTM. Additionally, shifts were observed in the peak (3000–3600 cm^{-1}) regions, demonstrating hydrogen bond interactions in the resultant LTTM [28]. The peaks at 3500 cm^{-1} and 2500 cm^{-1} indicate the presence of O-H stretching from carboxyl and hydroxyl groups in the MA structures. Peaks shifted broadly between 2500 cm^{-1} and 3400 cm^{-1}, indicating hydrogen bond interactions between HBAs and HBDs [28]. Meanwhile, the peaks between 1750 cm^{-1} and 1690 cm^{-1} represent the carboxylic groups. The C-O and C-H stretching and O-H bending can be observed at 1450 cm^{-1} to 800 cm^{-1}. For ChCl, the peaks are better separated, with reported peaks at wavenumbers 3200 cm^{-1} (-H stretching), 2850 cm^{-1} (C-H stretching from alkane groups), 1300 cm^{-1}, 1150 cm^{-1}, 957 cm^{-1}, 816 cm^{-1}, and 623 cm^{-1} [29].



Scheme 1. Structure of ChCl and MA.

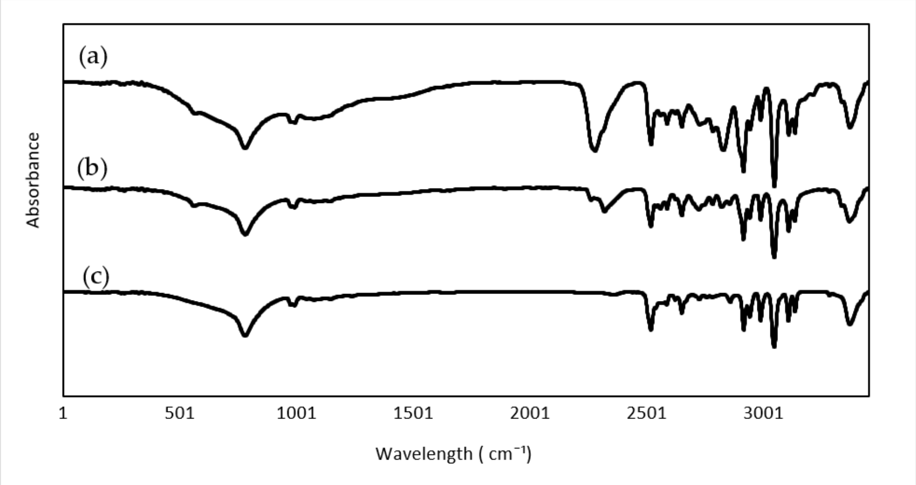


Figure 2. FTIR spectra: (**a**) LTTM; (**b**) MA, and (**c**) choline chloride.

The peaks at 1300 cm^{-1} to 1000 cm^{-1} represent the C-H bending in the alkane group, C-N stretching in the amine, and C-O stretching in primary alcohol. The broadening of the peak at 3500 cm^{-1} and 2500 cm^{-1} shows the existence of hydrogen bonding in the LTTM [27]. Additionally, peaks at 3200 cm^{-1} and 2900 cm^{-1} [29] were observed to have shifted to 3278 cm^{-1} and 2931 cm^{-1}, respectively. By comparison, in the study by Dana et al. [29] the peak of the carboxylic group shifted from 1693 cm^{-1} to 1724 cm^{-1}, while in the present study it shifted to 1722 cm^{-1}. It was confirmed that the shifting of the peaks occurred after preparing the starting materials in the LTTM mixture. Peaks at 1450, 1300, 1150, 1109, 957, 816, and 623 cm^{-1} [29] shifted to 1478, 1343, 1167, 1101, 952, 825, and 626 cm^{-1}, sequentially. Based on the FTIR spectra, most functional groups present are comparable to the functional group and bond assignment of the starting materials.

2.3. Preliminary Study

2.3.1. Product Examination

5-HMF is a light yellowish liquid that is soluble in water [33]. Thus, detection of 5-HMF was conducted visually by observing the samples for any colour changes. The liquid by-products of the synthesis are depicted in Figure 3 and were calculated using the reaction parameters listed in Table 1. It was observed that the colour of samples A1 to A6 changed from colourless to light yellow with the increase in reaction time from 10 min to 60 min. The presence of 5-HMF was confirmed by the light to deep yellowish colour in sample B6 at 10 to 60 min reaction time, which correlates well with the HPLC analytical result. Sample A had a low pH of 0.74, while sample B had a pH of 0 [33]. This acidity could be attributed to the organic acid (present in LTTM mixtures) or 5-HMF.

Figure 3. Samples from preliminary study.

Table 1. Experimental runs for two different glucose: LTTM: water ratios.

Sample	Time (min)	Glucose: LTTM: Water Ratio (g)
A1	10	10:48:100
A2	20	
A3	30	
A4	40	
A5	50	
A6	60	
B1	10	10:100:15
B2	20	
B3	30	
B4	40	
B5	50	
B6	60	

2.3.2. Effect of Reaction Time and Glucose: LTTM: Water Ratio

The effect of reaction time (10 to 60 min) on glucose conversion was studied for all A and B samples in a microwave reactor at a temperature of 90 °C. As shown in Figure 4, glucose conversion in both samples was significantly influenced by the reaction time from 10 to 60 min. The results revealed an increase in glucose conversion up to 20 min for sample A and 30 min for sample B, followed by a decline in glucose conversion at 60 min. The maximum glucose conversion of 65.95% was observed at 30 min of reaction time for sample B, whereas sample A reached a maximum of 50.75% glucose conversion at 20 min. Based on these results, longer reaction time led to up to 10% decrease in glucose conversion. This could be attributed to the reduction of the LTTM to glucose ratio, resulting in a gradual decrease in conversion after 20 min (for sample A) and 30 min (for sample B). Additionally, the solution's high viscosity could have restricted the interaction between reacting molecules [10,34], indicating that solution viscosity could be a factor affecting glucose conversion and 5-HMF yield, representing a crucial parameter in 5-HMF production. Moreover, a reversible reaction between glucose and fructose occurred during the synthesis, resulting in low glucose detection, possibly due to the conversion of fructose into undesirable products [35].

The analysis of the product revealed that the reaction time had no significant effect on the yield of 5-HMF for samples A and B (Figure 4). However, a short reaction time (10–20 min) resulted in a decreased 5-HMF yield. This may be due to glucose undergoing only single dehydration, rather than proceeding to its second dehydration into 5-HMF [23]. Therefore, by extending the reaction time from 30 min to 60 min, the conversion of glucose increased from 46.26% to 65.95%, and the yield of 5-HMF increased to 20.50% for sample B. This study suggests that a longer reaction time facilitates glucose isomerization to fructose, while simultaneously dehydrating to 5-HMF [36]. A similar trend in 5-HMF yield was observed in a study by Mankar et al. (2021), where the yield increased by 27.8% as the reaction time increased from 5 min to 30 min [37]. In the current study, a higher 5-HMF yield of 20.50% for sample B was achieved, compared with only 0.28% for sample A after 60 min reaction time in the microwave (90 °C), indicating the influence of LTTM, water, and glucose ratio on 5-HMF production. In contrast, Eminov et al. [38] reported a 5-HMF yield of 28 mol% and glucose conversion of 33 mol% in IL, 1-butyl-3-methylimidazolium chloride ([C_4C_1 im] Cl) at 90 °C in 30 min [38]. Conventionally, 5-HMF requires a longer reaction time of at least 3 h at a temperature $\leq$ 100 °C to achieve up to 80% 5-HMF yield, depending on system conditions [23,39,40]. However, a prolonged reaction time may lead to the production of unwanted side reactions and products [23]. For instance, degradation of 5-HMF leads to the formation of humins, while rehydration of 5-HMF results in the production of organic acids, including fumaric acid, levulinic acid, formic acid, and acetic acid [36].

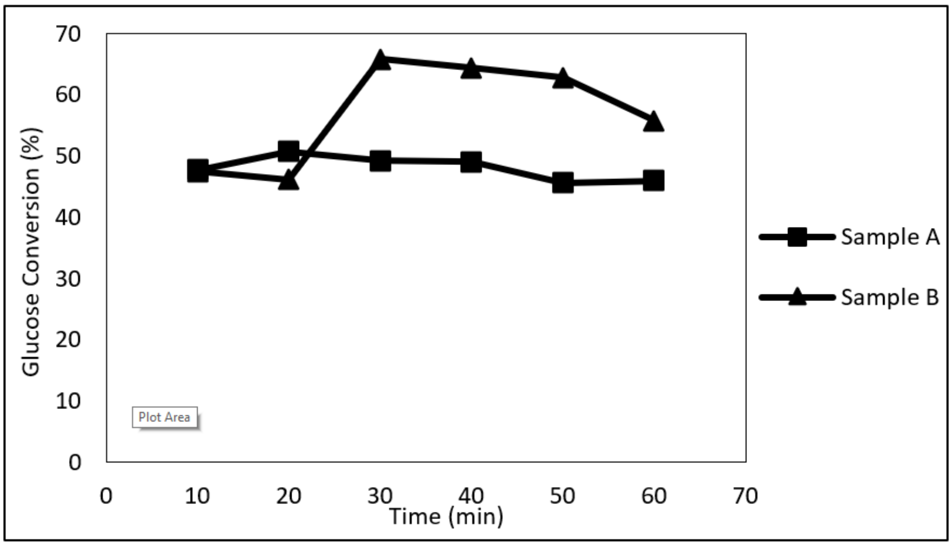


Figure 4. Glucose conversion at different reaction times.

The ratio of LTTM and water is crucial in the study of the potential solvent for converting glucose to 5-HMF. Both samples consist of different mixture ratio: where in sample A is water-rich system with 63.29 wt.% water content, while sample B is LTTM-rich system having only 12 wt.% water content. The results from sample A indicated a maximum glucose conversion of 50.75% and a 0.28% 5-HMF yield. As the reaction time increased to 60 min, no significant changes in glucose conversion or 5-HMF yield were observed, indicating that a higher water content did not promote glucose dehydration to 5-HMF, as illustrated in Figure 5. The presence of a high proportion of water lowered the catalytic efficiency of the acids, promoting the degradation of 5-HMF into humins or acids [41]. In this study, a low amount of LTTM in the solvent system may have contributed to lower interaction within the reaction mixture for the isomerization of glucose to fructose and further dehydration to 5-HMF [23]. Xiang et al. reported that the production of 5-HMF using only water as the solvent did not significantly improve the conversion of glucose to 5-HMF. Dehydrating agents such as Lewis acid or Brønsted acid sites are required to promote sugar dehydration to 5-HMF [42].

Figure 4 depicts the maximum glucose conversion of 65.95% and the highest 5-HMF yield of 20.31% for sample B. As illustrated in Figure 5, LTTM as the solvent resulted in a significant increase in 5-HMF yield from 0.28% (water solvent system) to 20.31%. ChCl acted as HBA, donating its electron ion to the acceptor compound. Therefore, ChCl's presence increased the amount of free chloride ions in the reaction system, improving the ability of electron pairs to donate for the dehydration reaction [23]. This resulted in higher rates of conversion towards 5-HMF as Lewis acid sites increased and facilitated higher isomerization of glucose into fructose [23]. Meanwhile, MA in the reaction mixture was responsible for the HBD reaction with oxygen during dehydration. This suggests that the increase in LTTM mass in the ratio promoted the dehydration of fructose to 5-HMF, which raised the 5-HMF yield.

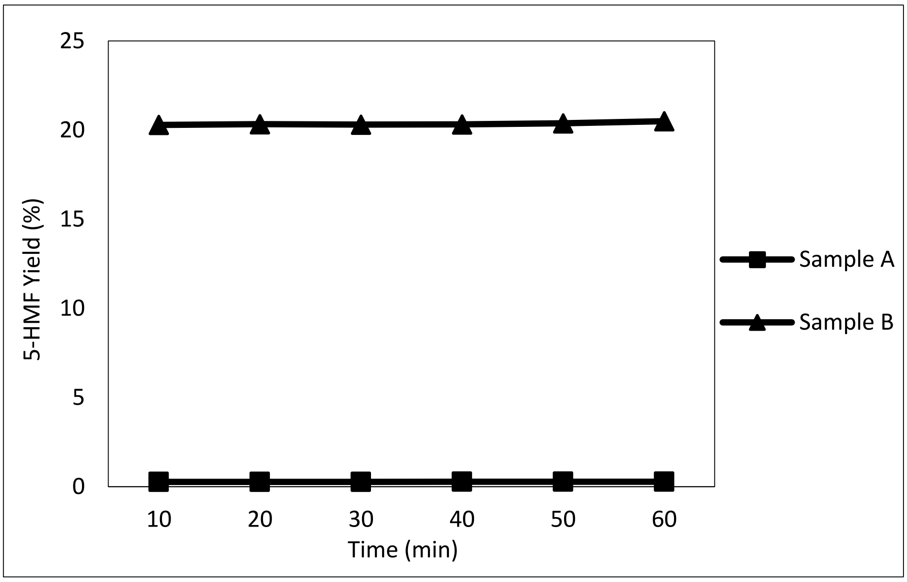


Figure 5. 5-HMF yields at different reaction times.

The combination of MA and ChCl in a low water content (12 wt.%) improved the functionality for glucose conversion to 5-HMF. It has also been reported that adding 15% water to the reaction mixture with fructose as the initial reactant resulted in a high 5-HMF yield of 53.2%, whereas adding 40% water resulted in a low yield of 30.2% [41]. Therefore, water in the reaction mixture is critical for sugar dehydration, but excessive water may promote the degradation or rehydration of 5-HMF, resulting in reduced yield. This study indicates that different solvent systems (LTTM: water) influence the 5-HMF yield, and the combination of MA and ChCl in the reaction mixture enhances their functionality for conversion to 5-HMF. However, no study has yet reported a similar 5-HMF yield trend at 90 °C, showing almost constant values for samples A and B. A longer reaction time might help to identify the gap between the values for the samples.

2.4. Optimization Study

2.4.1. Sample Observation

The first step in the analysis was to perform a physical observation by monitoring changes in sample colour. Figure 6 displays samples obtained from the optimization method, showing a range of colours, from colourless to dark yellow. Samples 1, 7, 17, 19, and 20 may have higher 5-HMF yields than the others, indicated by their dark yellow colour properties. However, it is worth noting that 5-HMF may still be present in other samples at lower yields. The results of the 20 optimization runs are presented in Table 1, according to the generated CCD table. The data show that the yield of 5-HMF ranged from 0.37% (lowest in Run 2) to 49.02% (highest in Run 1). Runs 1, 6, 7, and 20 had high reaction temperatures (≥100 °C), which promoted the 5-HMF yield. Notably, 5-HMF yields exceeding 30% were obtained on Runs 1, 7, 17, and 20, where the content of LTTM in the system was at least 50 wt.% of water mass. Furthermore, the glucose conversion rate for all runs fell within the range of 99.19% to 99.93%. However, as the difference in glucose conversion values was too low, the glucose conversion was recalculated.

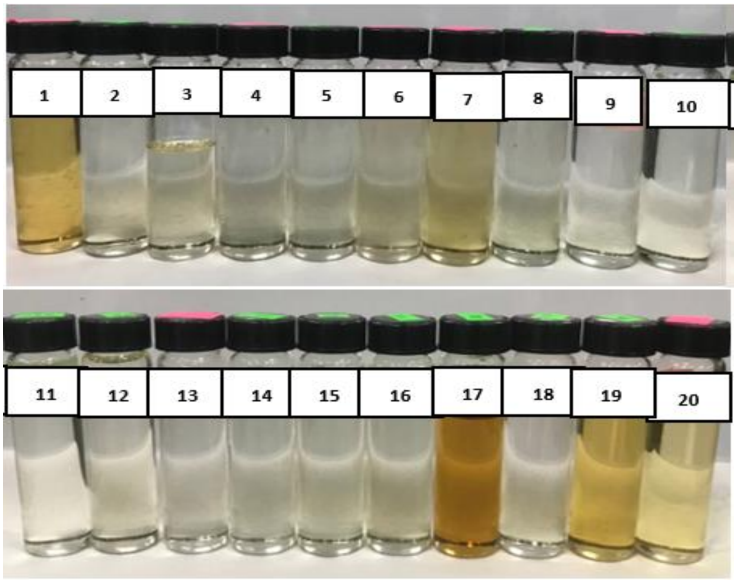


Figure 6. Samples from optimization run.

2.4.2. Model Fitting

The experiments were conducted in a randomized arrangement, and the runs of experiment are presented in Table 2. The experimental data were analyzed using ANOVA to perform regression analysis and interpretation. The 5-HMF yield (%) and glucose conversion (%) were chosen as the responses for the experimental design.

Table 2. Run of the experiment for optimization.

Std	Run	Temperature (°C)	LTTM Mass (g)	Water Mass (g)
4	1	100	100	20
5	2	80	60	60
1	3	80	60	20
17	4	90	80	40
3	5	80	100	20
8	6	100	100	60
10	7	107	80	40
12	8	90	113.64	40
6	9	100	60	60
18	10	90	80	40
14	11	90	80	73.63
15	12	90	80	40
9	13	73	80	40
11	14	90	46.36	40
20	15	90	80	40
16	16	90	80	40
13	17	90	80	6.36
7	18	80	100	60
19	19	90	80	40
2	20	100	60	20

2.4.3. Development of Model

After inputting data for both responses, the software generated the summary statistics of potential models that could explain the experimental results. The optimal model for the responses was selected from a series of sequential models that incorporated linear, two-factor interactions (2FI), quadratic, and cubic relationships. To evaluate the model fit to the experiment, a lack of fit test was conducted to examine the significance of the regression model and individual model coefficients. The significant factors were ordered using the *F* value and *p* value with a 95% confidence level [43]. The summary in Tables 3 and 4 displays the *p* value, *F* value, and coefficient of determination (R^2), which confirm the significance of the selected model. The proposed model for 5-HMF yield is the quadratic model, which was not aliased, and additional terms are significant.

Table 3. The sequential model sum of squares for 5-HMF yield.

Source	Sum of Squares	df	Mean Square	*F*-Value	*p*-Value	Remarks
Mean vs. Total	159.06	1	159.06			
Linear vs. Mean	60.37	3	20.12	24.85	<0.0001	
2FI vs. Linear	2.28	3	0.7590	0.9237	0.4568	
Quadratic vs. 2FI	9.66	3	3.22	31.68	<0.0001	Suggested
Cubic vs. Quadratic	0.6151	4	0.1538	2.30	0.1736	Aliased
Residual	0.4017	6	0.0670			
Total	232.39	20	11.62			

Table 4. The sequential model sum of squares for glucose conversion.

Source	Sum of Squares	df	Mean Square	*F*-Value	*p*-Value	Remarks
Mean vs. Total	856.61	1	856.61			
Linear vs. Mean	17.82	3	5.94	3.52	0.0412	
2FI vs. Linear	18.19	3	6.06	10.23	0.0013	Suggested
Quadratic vs. 2FI	1.12	3	0.3730	0.5601	0.6546	
Cubic vs. Quadratic	3.08	4	0.7696	1.32	0.3770	Aliased
Residual	2.92	5	0.5833			
Total	899.74	19	47.35			

According to Table 3, the quadratic model is significant because it fits the conditions where the *p* value must be less than 0.05. Meanwhile, the 2FI and cubic models had *p* values greater than 0.05, which is considered insignificant. Equation (1) depicts the final equation in terms of coded factors for 5-HMF yield (%):

$$\begin{aligned} 5-\text{HMF Yield }\% = \ & 2.07+1.64\text{A}+0.2606\text{B}-1.29\text{C}+0.3854\text{A}-0.3281\text{AC}+0.1686\text{BC}+ \\ & 0.5718\text{A}^2-0.0864\text{B}^2+0.6070\text{C}^2 \end{aligned} \tag{1}$$

where:

A = Reaction temperature (°C)
B = LTTM mass (g)
C = Water mass (g)

Furthermore, the 2FI model outperformed the other models regarding glucose conversion, as seen in Table 4. With a *p* value of 0.0013, substantially lower than 0.05, it offers the highest order polynomial where the additional terms are significant and not aliased. Equation (2) represents the final equation in terms of the coded factor for glucose conversion (%):

$$\text{Glucose conversion }\% = 6.98 + 0.7360\text{A} + 0.8671\text{B} + 0.1754\text{C} - 0.5565\text{AB} + 0.9652\text{AC} - 1.02\text{BC} - 0.2809\text{A}^2 - 0.0918\text{B}^2 + 0.0334\text{C}^2 \quad (2)$$

where:

A = Reaction temperature (°C)
B = LTTM mass (g)
C = Water mass (g)

Subsequently, the experiment was modelled based on the ANOVA results, as shown in Table 5. The significant *F* value of 79.01 indicates that the model is significant, with only a 0.01% possibility that such a high *F* value might be due to noise. The *p* values of 0.05 suggest that the model terms are statistically significant, with terms A, B, C, AB, AC, A^2, and C^2 being significant. *p* values greater than 0.1000 indicate that the model terms BC and B^2 are insignificant. The lack of fit *F* value of 3.48 implies a 9.88% chance that a significant lack of fit *F* value could occur due to noise. The value of R^2 shows the closeness of the selected model to the experimental data points, which can be observed in Figure 7. Meanwhile, the adjusted R^2 measures the amount of variation in the mean explained by the model. The predicted R^2 of 0.9089 is in reasonable agreement with the adjusted R^2 of 0.9737, with the difference being less than 0.2, which is considered acceptable since the value is very close to unity. Adeq precision measures the signal-to-noise ratio, and a ratio greater than 4 is desirable. The ratio of 28.292 indicates an adequate signal, which means this model can be used to navigate the design space.

Table 5. ANOVA quadratic model for 5-HMF yield.

Source	Sum of Squares	df	Mean Square	*F*-Value	*p*-Value	Remarks
Model	72.31	9	8.03	79.01	<0.0001	significant
A—Reaction temperature	36.78	1	36.78	361.75	<0.0001	
B—LTTM mass	0.9272	1	0.9272	9.12	0.0129	
C—Water mass	22.66	1	22.66	222.80	<0.0001	
AB	1.19	1	1.19	11.69	0.0066	
AC	0.8610	1	0.8610	8.47	0.0156	
BC	0.2274	1	0.2274	2.24	0.1657	
A^2	4.71	1	4.71	46.33	<0.0001	
B^2	0.1077	1	0.1077	1.06	0.3277	
C^2	5.31	1	5.31	52.22	<0.0001	
Residual	1.02	10	0.1017			
Lack of fit	0.7898	5	0.1580	3.48	0.0988	not significant
Pure error	0.2271	5	0.0454			
Cor total	73.33	19				
Std. dev	0.3189		Adjusted R^2	0.9737		
Mean	2.82		Predicted R^2	0.9089		
R^2	0.9861		Adeq precision	28.2925		

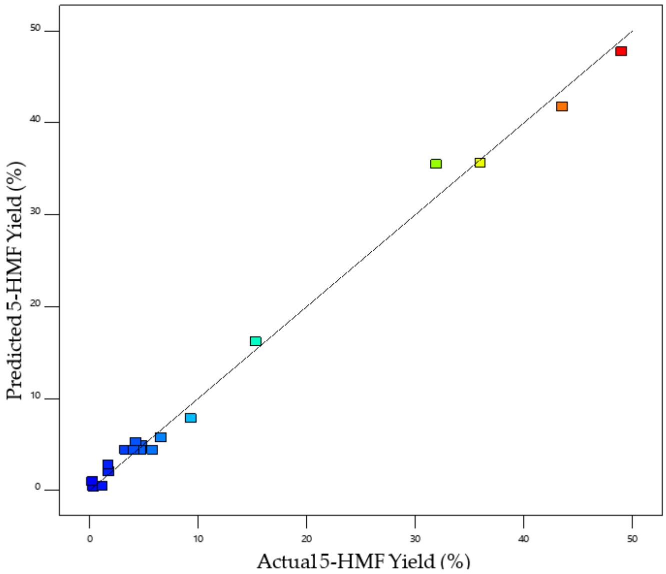


Figure 7. Predicted vs. actual values plot for 5-HMF yield (%).

For the glucose conversion data, the ANOVA of the 2FI model is tabulated in Table 6. Based on the table, the model *F* value of 6.20 implies that the model is significant, with only a 0.61% chance that an *F* value this large could occur due to noise. Furthermore, A, B, AC, and BC are significant model terms since the *p* values are lower than 0.050. However, the reduction model needs to be applied to improve the model because of many insignificant terms, i.e., C, A^2, $B^{2,}$ and C^2. The lack of fit *F* value of 1.32 implies that the lack of fit is insignificant relative to the pure error. There is a 37.70% chance that a lack of fit *F* value this large could occur due to noise. Figure 8 shows the actual and predicted percentage for glucose conversion. It was found that the predicted R^2 of 0.1936 is not as close to the adjusted R^2 of 0.7220; i.e., the difference is more than 0.2. This indicates a significant block effect or a possible problem with the model and/or data. Thus, model reduction, response transformation, and outliers need to be considered for model improvement. All empirical models should be tested by doing confirmation runs. Adeq precision for this model is 8.3917 showing adequate signal and proving this model can be used to navigate the design space.

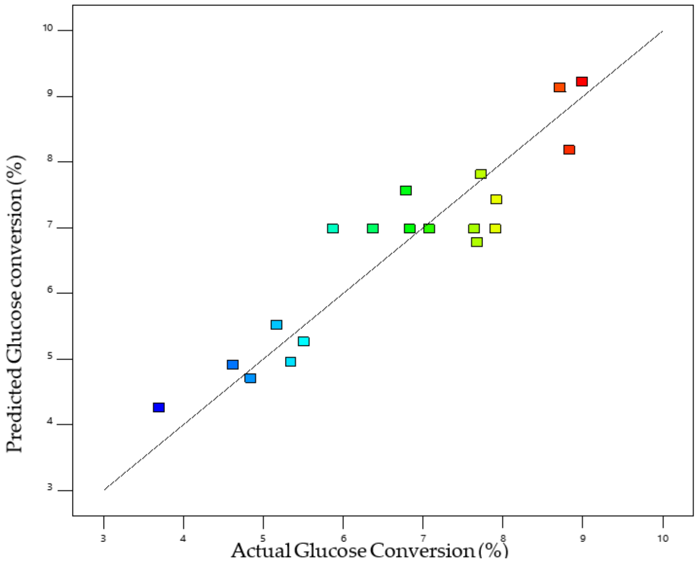


Figure 8. Predicted vs. actual values plot for glucose conversion (%).

Table 6. ANOVA 2FI model for glucose conversion.

Source	Sum of Squares	df	Mean Square	*F*-Value	*p*-Value	Remarks
Model	37.14	9	4.13	6.20	0.0061	significant
A—Reaction temperature	7.40	1	7.40	11.11	0.0088	
B—LTTM mass	10.27	1	10.27	15.42	0.0035	
C—Water mass	0.2752	1	0.2752	0.4131	0.5364	
AB	2.48	1	2.48	3.72	0.0859	
AC	7.45	1	7.45	11.19	0.0086	
BC	8.26	1	8.26	12.41	0.0065	
A^2	1.08	1	1.08	1.62	0.2345	
B^2	0.1156	1	0.1156	0.1736	0.6867	
C^2	0.0094	1	0.0094	0.0141	0.9080	
Residual	5.99	9	0.6661			
Lack of fit	3.08	4	0.7696	1.32	0.3770	not significant
Pure error	2.92	5	0.5833			
Cor total	43.13	18				
Std. dev	0.8161		Adjusted R^2	0.7220		
Mean	6.71		Predicted R^2	0.1936		
R^2	0.8610		Adeq precision	8.3917		

2.4.4. Effect of Independent Variables on 5-HMF Yield

Figures 9–11 display 3D surface plots that depict the interactions between the variables and their effects on the 5-HMF yield. Figure 9 specifically shows the relationship between the reaction temperature (A) and LTTM mass (B) and the effect on the 5-HMF yield. The plot reveals that an increase in both reaction temperature and LTTM mass resulted in a higher 5-HMF yield. This observation is supported by a study conducted by Feng Guo that found a high 5-HMF yield produced at temperatures below 120 °C [6]. Additionally, high LTTM in the process can result in a lower percentage of conversion and reduced 5-HMF yield due to the high viscosity of the solution, which limits the interaction of molecules [23]. However, in this case, the water content in the system was sufficient to prevent viscosity and resulted in an excellent 5-HMF yield.

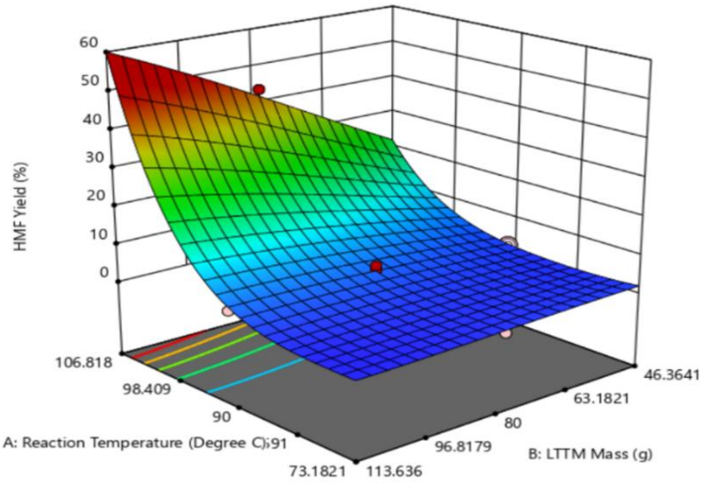


Figure 9. The 3D surface plot of interactions between A and B for 5-HMF yield %.

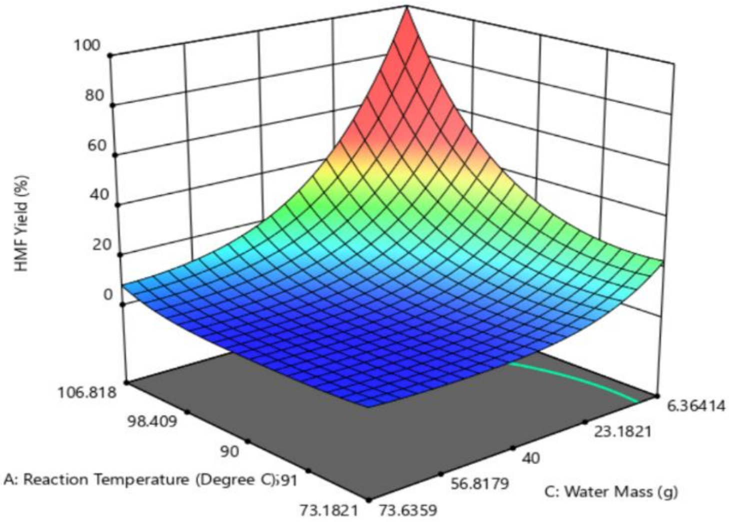


Figure 10. The 3D surface plot of interactions between A and C for 5-HMF yield %.

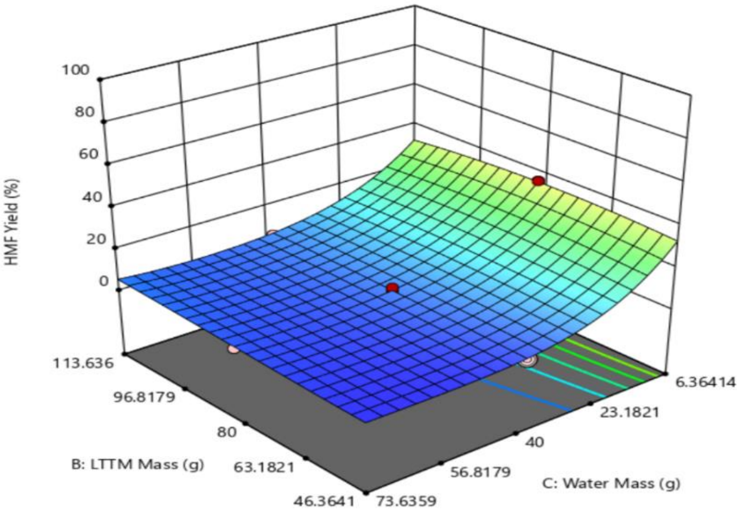


Figure 11. The 3D surface plot of interactions between B and C for 5-HMF yield %.

Figure 10 illustrates that a high 5-HMF yield is expected with low water mass (C) at a high reaction temperature (A). The literature suggests that water present in the reaction mixture can decrease the catalytic efficiency of acids and promote the degradation of 5-HMF to humins or acids [41]. Although water is crucial for the initial dehydration of fructose, excess water can inhibit 5-HMF production. The interaction between B and C is illustrated in Figure 11, where a high 5-HMF yield is obtained with low water mass and high LTTM mass. Reports also suggest that the use of water alone as a solvent does not significantly convert glucose into 5-HMF, and requires coupling with dehydrating agents such as Lewis acid or Brønsted acid to promote sugar dehydration to 5-HMF [42]. A 15% water addition to the reaction mixture resulted in a high 5-HMF yield of 53.2%, whereas 40% water addition resulted in a low yield of 30.2% when fructose was the initial reactant, as reported in the literature [41]. In the present study, it is predicted that a maximum of 30% 5-HMF yield can be achieved when the system has around 90 wt.% of LTTM.

2.4.5. Effect of Independent Variables on Glucose Conversion

Figure 12 depicts the relationship between the reaction temperature (A) and LTTM mass (B) in terms of its influence on glucose conversion. The results indicate that as the reaction temperature increased at a constant LTTM mass, low glucose conversion occurred. However, when the mass of LTTM increased, glucose conversion also increased. This is due to the increased free chloride ions from ChCl in the reaction system, which improved electron pair donation. In other words, Lewis's acid sites were increased, enhancing the isomerization of glucose into fructose, consequently resulting in higher conversion rates towards 5-HMF. Moreover, an abundance of hydrogen bonding is available in the reaction mixture when a significant amount of MA is present and acts as the hydrogen bond donor. However, A and B did not affect glucose conversion in this case, as their *F* values were only 3.72.

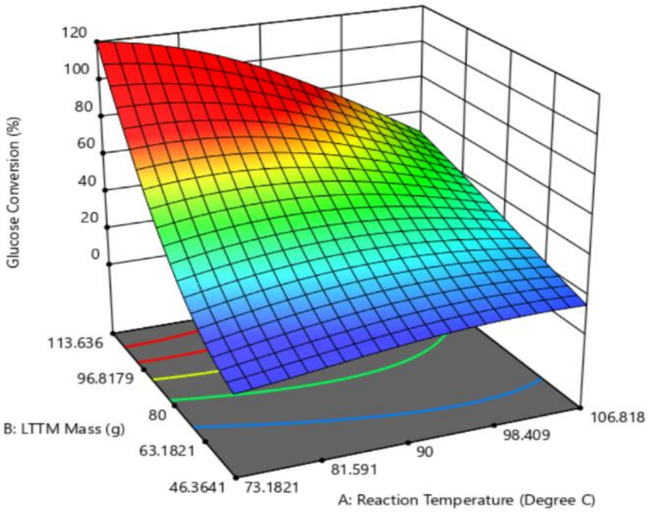


Figure 12. The 3D surface plot of interactions between A and B for glucose conversion %.

Figure 13 illustrates the interaction between reaction temperature (A) and water mass (C) to glucose conversion. The experiment showed that an increase in temperature led to higher glucose conversion, whereas increased water mass reduced glucose conversion. As discussed, the reaction temperature played a significant role in both 5-HMF yield and glucose conversion. Because the reaction must include the isomerization and dehydration process, a higher reaction temperature can assist in promoting glucose conversion. The interaction between LTTM and water mass is illustrated in Figure 14, with a maximum of 11 wt.% water mass resulting in glucose conversion as high as 84%. However, the water mass did not have a significant effect on glucose conversion as shown by the *p* value higher than 0.1.

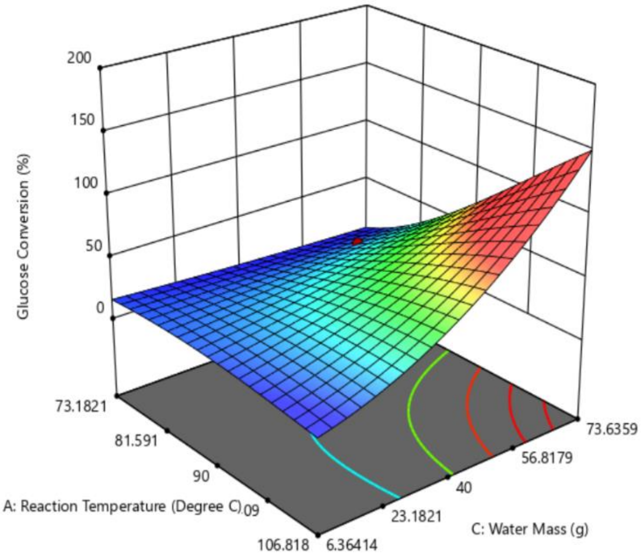


Figure 13. The 3D surface plot of interactions between A and C for glucose conversion %.

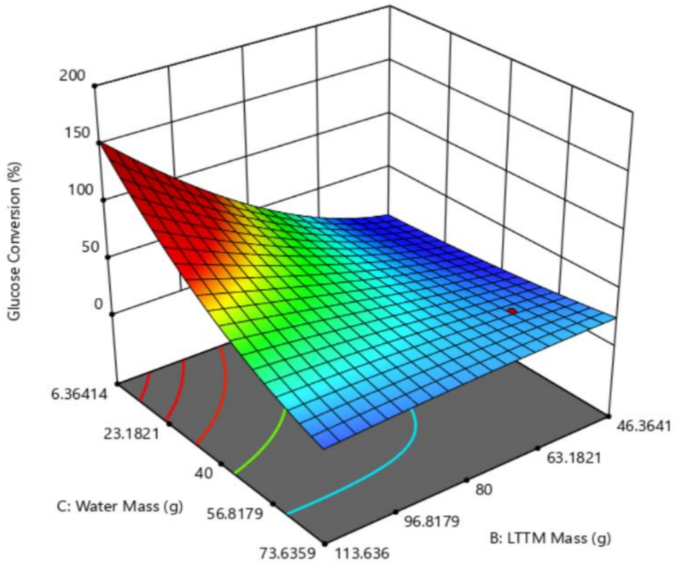


Figure 14. The 3D surface plot of interactions between B and C for glucose conversion %.

2.4.6. Selection of Optimal Level and Estimation of the Optimum Response Characteristics

The primary objective of this experimental study was to determine the optimal conditions for the reaction to achieve the highest possible yield of 5-HMF and glucose conversion. Utilizing a numerical optimization technique, the researchers optimized the parameters and ran the software three times to confirm the results. The optimum operating conditions were observed at a reaction temperature of 100 °C, 100 g of LTTM, and 20 g of water for 60 min of reaction time. Under ideal conditions, the predicted and measured values for 5-HMF yield were 47.72% and 45.77%, respectively (with a standard deviation of 4.403%). Meanwhile, the predicted and experimental glucose conversion values were 57.85% and 69.03% (with a standard deviation of 12.379%), respectively.

2.4.7. Identification of Compounds by GC-MS Analysis

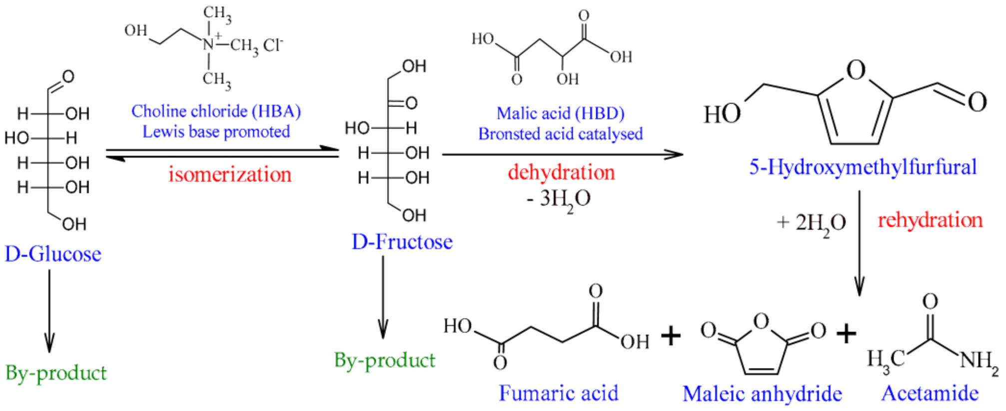
Table 7 displays the main and side products of the optimized sample reaction synthesis. The results indicate that 17.20% 5-HMF yield was produced. Moreover, organic acids with an area% ranging from 13–21% were detected, including dimethylaminoethanol (a precursor of acetylcholine from LTTM), acetamide (acetic acid amide), and maleic anhydride (MA from LTTM). Additionally, propenoic acid, chloroacetic acid, fumaric acid, and carbonic acids were also detected in concentrations ranging from 2–10%. Some minor side products were identified; other aliphatic and heterocyclic organic compounds were present in trace amounts ranging from 0–1%, such as propanenitrile and methylhomopiperazine. The identified reaction pathways indicate that there was still unconverted MA in the products, and some of the 5-HMF had undergone rehydration, as some organic acids were identified [2,36]. In addition, a small amount of fructose (0.498%) was detected using HPLC, indicating that glucose isomerization to fructose occurred, and not all fructose was converted to 5-HMF during dehydration. Thus, Scheme 2 proposes the pathway for glucose conversion to 5-HMF in the presence of LTTM.

2.4.8. Proposed Mechanism

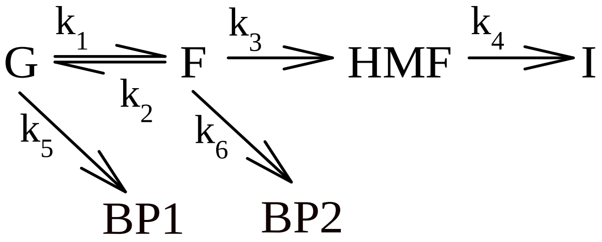
The formation of 5-HMF from sugar dehydration is a complex process that is subject to constraints due to the possibility of side reactions that form other compounds. When fructose is decomposed in the presence of water at high temperatures, various by-products may form including products of isomerization dehydration, decomposition, and condensation [44]. A study by Marhaini [36] identified two pathways for producing 5-HMF from glucose. The first involves the reversible isomerization of glucose to fructose. However, the unstable state of glucose may cause it to react with other compounds in the system, resulting in a low glucose concentration without conversion to 5-HMF. Based on the GC-MS and HPLC analyses conducted on the optimized product, a proposed reaction mechanism is presented, as shown in Scheme 3. This mechanism is almost identical to that proposed in [45,46], wherein the reaction of 5-HMF from glucose involves a first reversible step of isomerization of glucose (G) to fructose (F), followed by the dehydration of fructose to 5-HMF and the rehydration of 5-HMF to intermediates (I) such as fumaric acid, maleic anhydride, and acetamide. Villanueva et al. [46] reported that glucose is subject to other reactions as well as isomerization to fructose, which may lead to the creation of additional by-products (BP1). In addition, acidic conditions during the reaction may cause the breakdown of fructose, leading to an undesirable product (BP2).

Table 7. The compound identification from the optimized product via gas chromatography analysis.

No	Compound	Area (%)	Retention Time (min) (RT)
1	N,N-Dimethylaminoethanol	21.015	6.841
2	5-Hydroxymethylfurfural	17.208	5.826
3	Acetamide, 2,2,2-trifluoro-N-methyl	13.130	2.317
4	Maleic anhydride	10.609	3.439
5	2-Propenoic acid	10.374	6.431
6	1,3-Dioxolan-4-on-5-acetic acid, -trichloromethyl-	8.516	6.593
7	Dimethyl fumarate	7.576	4.536
8	2-Propenoic acid, 2-(dimethylamino)ethyl ester	6.811	8.272
9	6-Pentadecanone	4.275	5.217
10	3-Acetoxy-3-hydroxypropionic acid, methyl ester	4.292	7.208
11	Chloroacetic acid, 4-methoxy-2-methylbutyl ester	4.074	7.457
12	Fumaric acid	2.380	6.932
13	Propanenitrile, 3-(dimethylamino)	2.110	4.139
14	Carbonic acid	2.692	7.839
15	Propanenitrile, 3-(ethylamino)-	1.001	5.994
16	N-Methylhomopiperazine	0.810	3.545
17	2-(Ethylamino)ethanol, N,O-diacety	0.529	8.488
18	Ethanamine, 2-chloro-N,N-dimethyl-	0.334	2.923



Scheme 2. Postulated reaction pathway for glucose conversion to 5-HMF and its side products via LTTM–water–solvent system.



Scheme 3. Proposed mechanism.

Assuming all reactions are a first-order reactions [46,47], based on Scheme 3, the rate of reaction and differential equations that describe concentrations of glucose, fructose, 5-HMF, intermediates, and by-product are represented by Equations (3)–(12):

$$r_1 = k_1 C_G \tag{3}$$

$$r_2 = k_2 C_F \tag{4}$$

$$r_3 = k_3 C_F \tag{5}$$

$$r_4 = k_4 C_{HMF} \tag{6}$$

$$r_5 = k_5 C_G \tag{7}$$

$$r_6 = k_6 C_F \tag{8}$$

$$\frac{dG}{dt} = -k_1 C_G + k_2 C_F - k_5 C_G = -r_1 + r_2 - r_5 \tag{9}$$

$$\frac{dF}{dt} = k_1 C_G - k_2 C_F - k_6 C_F = r_1 - r_2 - r_6 \tag{10}$$

$$\frac{dHMF}{dt} = k_3 C_F - k_4 C_{HMF} = r_3 - r_4 \tag{11}$$

$$\frac{dI}{dt} = k_4 C_{HMF} = r_4 \tag{12}$$

2.5. Insight in 5-HMF Purification

The production of 5-HMF by utilizing reaction media such as ionic liquids or deep eutectic solvents makes the purification procedure more difficult because the product frequently has a high solubility in the reaction mixture. To obtain 5-HMF of high purity from these reaction media, efficient and effective purification processes are vital. The LTTM and 5-HMF molecules must be understood to enable their purification from the reaction media. Numerous purification approaches have been studied, such as solvent extraction, distillation, adsorption, membrane separation, and crystallization [48]. The most popular approach is liquid–liquid extraction employing an organic solvent, specifically ethyl acetate, methyl propionate [49], and dichloromethane [50], which can be used for purifying 5-HMF. After removing the LTTM from the reaction mixture, the 5-HMF is extracted using the organic solvent. The organic phase is then concentrated, and further purification may be performed if required.

3. Materials and Methods

3.1. Preparation of Starting Materials

D-(+)-glucose monohydrate with (99.3%) purity was purchased from Bendosen, America, and used as a starting material. L-(-)-malic acid (≥95%) and choline chloride (≥98%) were purchased from Sigma Aldrich, Malaysia, for LTTM preparation. Analytical standards of glucose and 5-HMF were purchased from Sigma Aldrich, Malaysia, as external calibration in HPLC for product analysis.

3.2. Preparation of LTTM

MA and ChCl in solid form were used as starting materials, mixed to produce LTTM via conventional heating. Both chemicals were solid and mixed in a 500 mL beaker with a mass ratio of MA: ChCl of 1:1. (75 g:75 g). The beaker containing the solid mixture was then immersed in a preheated silicone oil bath at 90 °C with a stirring rate of 350 rpm for 4 h until the solution became homogeneous and transparent. The resulting LTTM solution was then transferred into a 500 mL scotch bottle and sealed with parafilm to prevent moisture adsorption.

3.3. LTTM Physical and Chemical Analysis

The thermal stability of LTTM was analysed using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). TGA was performed using Perkin Elmer STA6000, United Kingdom, from 40 °C to 600 °C with a heating rate of 20 °C/min in the presence of nitrogen as the carrier gas with a 50 mL/min flow rate. The DSC curve was recorded for the temperature range from −75 °C to 10 °C using a TA instrument Q2000, US, at a 2 °C/min rate. The heating and cooling process was conducted in the presence of nitrogen with a flow rate of 50 mL/min. The pH of the LTTM was analysed using OHAUS starter 3100 pH bench, China. The density of LTTM was measured using a density-specific gravity meter KEM DA-645, Japan, at temperatures of 25 °C, 80 °C, and 90 °C. Lastly, FTIR analysis was carried out by FTIR Perkin Elmer Frontier 01, US, equipped with attenuated total reflectance (ATR).

3.4. Synthesis of 5-HMF

The synthesis of 5-HMF was inspired by [23,41] with some innovations. The effect of glucose: LTTM: water ratio (g) and reaction time on 5-HMF yield and glucose conversion were studied at different reaction times (10–60 min) and gram ratios (10:48:100 (A) and 10:100:15 (B)). The synthesis was performed in a modified Dixson 103L microwave synthesis reactor in Malaysia, using a two-neck round bottom flask at a fixed temperature of 90 °C, stirring rate of 200 rpm, and 3000 watts. The experiment setup was as in Figure 15a–c following the experimental run tabulated in Table 1.

3.5. Design of Experiment

The optimization process was carried out through Design Expert software (Stat-Ease Inc., Minneapolis, MN, USA) for regression and graphical analysis of the data obtained. The CCD reliably predicts the center point and is independent of the absence of data points. As a result, the glucose dehydration reaction in this study was assessed using the CCD approach [51], the best design that applies response surface methodology (RSM). The independent variables of significant effect on the system and the dependent variables were selected through screening studies followed by the restriction of the experimental region. Based on the preliminary evaluation, the reaction time does not impact the 5-HMF yield significantly, but it does influence glucose conversion. This study investigated the impact of varying the temperature, LTTM, and water mass in synthesizing 5-HMF for 60 min per run using 10 g glucose as the substrate. Table 8 lists the values for each parameter in this step.

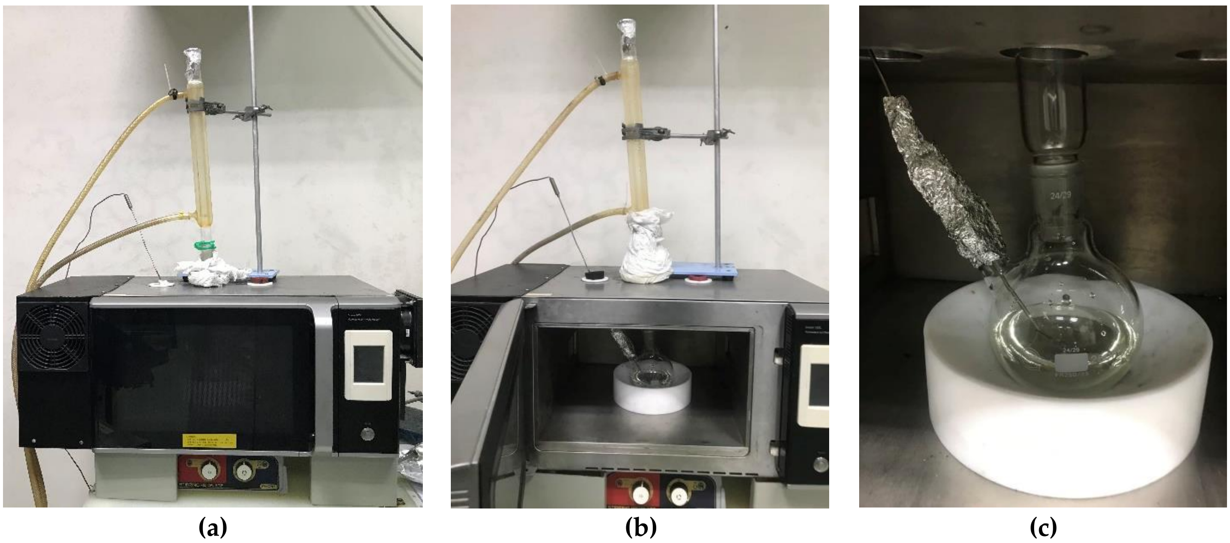

(a) **(b)** **(c)**

Figure 15. Microwave: (**a**) equipment; (**b**) overall setup, and (**c**) inside overview.

Table 8. Reaction parameters and their values.

Reaction Parameters	Type	Low	High
Reaction temperature (°C)	Factor A	80	100
Mass of LTTM (g)	Factor B	60	100
Mass of water (g)	Factor C	20	60
5-HMF yield (%)	Response A		
Glucose conversion (%)	Response B		

Next, the type of experimental design to carry out the experimental run was selected according to the designated value of the set of factors. Then, the obtained experimental data were tabulated, as shown in Table 1, and analyzed statistically according to the model fitting. The model fitting was investigated before obtaining the optimum values for each studied variable. The analysis of data and model suitability in representing the real relationship was conducted using analysis of variance (ANOVA). The relation between the independent variables and responses can be evaluated using ANOVA, and surface and contour plots can be generated for the manipulated reaction parameter.

3.6. Quantification of Extraction

Glucose, fructose, and 5-HMF were analysed using HPLC UV-Vis, Shimadzhu; Japan adopted from reference method DIN 10751-3, equipped with an Agilent Hi-Plex H column (7.7 × 300 mm, 8 μm) with 0.0085 M H_2SO_4 at 0.6 mL/min flow rate, oven temperature of 60 °C, 284 nm wavelength detection. Here, 20 μL of the sample was injected for 5-HMF detection. Fructose was detected using 0.005 M H_2SO_4 at 0.4 mL/min flow rate, oven temperature of 65 °C, and a RID detector, with a 20 μL sample using the same column. Fructose detection was conducted only for identification purposes. Meanwhile, glucose detection was performed using the Agilent Infinity Lab Poroshell EC-C18 column (4.6 × 250 mm, 4 μm) with a RID detector. For the mobile phase, 80% acetonitrile and 20% water were used at a flow rate of 1.2 mL/min, oven temperature of 30 °C, with a 5 μL sample injection volume. The 5-HMF yield, and glucose conversion were calculated based on the peak area of the external standard calibration curve plotted and calculated using Equations (13) and (14):

$$\text{5-HMF yield \%} = (\text{Moles of 5-HMF in product}/\text{Initial moles of glucose}) \times 100\% \quad (13)$$

$$\text{Glucose Conversion \%} = ((\text{Initial moles of glucose-unconverted glucose})/\text{Initial moles of glucose}) \times 100\% \quad (14)$$

3.7. GC-MS Analysis

Compound identification by GC-MS was carried out using Agilent 7890A coupled with a DB-5MS column to analyse sugars and the by-products of synthesis. For sugar analysis, 1 mL/min of helium gas was used as carrier gas. The oven temperature was maintained at 70 °C for 4 min and raised to 310 °C at a rate of 5 °C/min, with a holding time of 10 min. The injection volume was 1 µL with a split ratio of 10:1. Meanwhile, the injector inlet and transfer line temperature were maintained at 290 °C and 280 °C, respectively. The samples were analysed at a mass range of 40–510 amu [52]. For 5-HMF and LA detection, 1 µL of the reconstituted sample was injected with helium of 99.999% purity at a flow rate of 1 mL/min. The oven temperature was programmed as follows: 50 °C (hold for 1 min), 25 °C/min to 150 °C, 20 °C/min to 170 °C, and 80 °C/min to 250 °C for 3 min. The total run time was 10 min. Products were detected using the triple axis detector (m/z 50–250) [53].

4. Conclusions

5-HMF is a promising platform for building-block chemicals, making it an attractive area of study. Due to its diverse applications in industries such as packaging, textiles, cosmetics, food, and health, there is high demand for the production of 5-HMF. A new approach that utilizes LTTM as a potential green solvent for sugar conversion into 5-HMF has been the subject of investigation. This optimization study focused on the effect of reaction temperature, LTTM mass, and water mass on 5-HMF yield and glucose conversion. Based on the 3D results, reaction temperature and water mass more significantly affect 5-HMF yield, and glucose conversion compared with LTTM mass. A high reaction temperature (100 °C) with adequate water promotes the system's conversion to 5-HMF. Therefore, the optimum conditions according to this study were a reaction temperature of 100 °C, 100g of LTTM, and 20 g of water to produce a maximum 5-HMF yield of 45.77% and glucose conversion of 69.03%. Compared to other reported methods, this shows that efficient conversion to 5-HMF can potentially be achieved at a low temperature (100 °C) in the presence of LTTM.

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