

Article

Production of 5-Hydroxymethylfurfural from Direct Conversion of Cellulose Using Heteropolyacid/ Nb_2O_5 as Catalyst

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Abstract: This study aimed to select the best reaction conditions to produce 5-hydroxymethylfurfural (HMF) from cellulose using heterogeneous catalyst based on a heteropolyacid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$ —HPW) and Nb_2O_5 . Initially, the influence of the temperature (160 or 200 °C), acetone:water ratio (50:50 or 75:25 *v/v*), cellulose load (5% or 10% *w/v*) and catalyst concentration (1% or 5% *w/v*) on HMF production from cellulose was evaluated through a Taguchi's L_{16} screening experimental design. Afterwards, the main variables affecting this process, namely the temperature (160–240 °C) and acetone:water ratio (60:40–90:10 *v/v*), were optimized using a central composite rotatable design. Next, a kinetic study on HMF production from cellulose was carried out. Finally, HMF production from cellulose obtained from different biomass sources was evaluated. It was found that the reaction conditions able to result in maximum HMF yield, i.e., around 20%, were 200 °C, acetone:water ratio of 75:25 (*v/v*), 10% *w/v* of cellulose, and 5% *w/v* of catalyst concentration. The kinetic study revealed that the Langmuir–Hinshelwood–Hougen–Watson approach fit to the experimental data. Under the optimized conditions, the catalyst HPW/ Nb_2O_5 was also effective in converting different sources of cellulose into HMF.

Keywords: 5-hydroxymethylfurfural; cellulose; heteropolyacid catalyst; optimization; kinetic

1. Introduction

5-hydroxymethylfurfural (HMF) is a very important building block chemical in the context of biorefineries, since it can be converted into high quality fuels, as well as used as precursor of polymers, solvents, ethers and esters. Thus, from this platform molecule, a variety of compounds can be produced for use in different fields, such as medicine, chemistry and energy [1–4]. HMF can be obtained through acid catalysis of monosaccharides (fructose or glucose) or even directly from cellulose [5,6]. Since cellulose is more abundant and is considered a non-edible and less expensive carbohydrate, this polysaccharide can be considered a more interesting option than hexoses as feedstock for HMF production, although cellulose presents a more rigid and chemically stable structure than hexoses [3,7–9].

HMF production from cellulose basically occurs in three stages: cellulose hydrolysis into glucose, promoted by Brønsted acid; glucose isomerization into fructose, catalyzed by Lewis acid; and fructose

dehydration into HMF, which also occurs in the presence of Brønsted acid (Figure 1) [6,10,11]. Therefore, the acid catalyst significantly affects the direct conversion of cellulose into HMF, given that the reaction requires the use of catalysts that combine both, Lewis and Brønsted acidity.

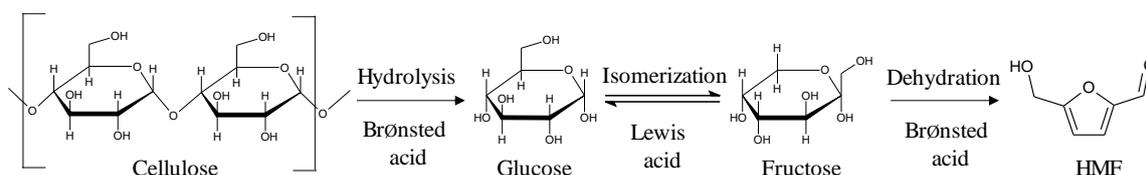


Figure 1. 5-hydroxymethylfurfural (HMF) production from cellulose.

Multiple catalysts have been studied for HMF production from cellulose. In the literature, it was found that homogeneous catalysts (HCl, H₂SO₄, among others) have usually yielded substantial amounts of HMF [2,3,12,13]. However, these catalysts are associated with corrosion of equipment, environmental pollution, and difficulty of separation from the reaction medium. An alternative to homogeneous catalysts would be the use of heterogeneous catalysts, which have some advantages, such as easy recovery from the reaction medium and the possibility of reuse [3,10,14,15]. Despite being potentially advantageous, heterogeneous catalysts have not been much explored for HMF production from cellulose (bibliometric analysis, Table S1 in the Supplementary Materials). In recent years, heterogeneous catalysts based on oxides, such as ZrO₂, WO₃, Nb₂O₅, among others, have been the most commonly used for cellulose conversion into HMF [10,14,16–19]. Jing et al. [14] obtained HMF yields of around 16% from α -cellulose powder (90 μ m particle size) by using TiO₂/ZrO₂ as heterogeneous catalyst at 200 °C for 50 min, and the reaction medium was also composed of an aqueous solution of NaCl/THF (1:4 *v/v*). HMF yields of around 20% from microcrystalline cellulose were achieved by Li et al. [10] in a biphasic system composed of an aqueous solution of NaCl/THF (1:3 *v/v*), by using niobium/carbon composite (Nb/C-50) at 170 °C within 4 h of reaction in a 1:1 cellulose:catalyst ratio. When the authors doubled the reaction time to 8 h, they could reach HMF yield of 53.3%. Tang and Su [16] obtained HMF yield of 58.4% using γ -AlOOH as catalyst, temperature of 160 °C, 2 h of reaction and a reaction medium composed of BMIMCl:DMSO:H₂O (4:2:1 *m/m*), which is a medium more expensive and aggressive to the environment than water, acetone and methyl isobutyl ketone (MIBK). Nandiwale et al. [17] studied HMF production from microcrystalline cellulose using water as reaction medium and bimodal-HZ-5 zeolite as catalyst at 190 °C within 4 h of reaction. In these conditions, the authors achieved 13 g/L and 46% yield of HMF, with 67% cellulose conversion. Kawamura et al. [18] and Yang et al. [19] exclusively used an aqueous reaction medium for HMF production from microcrystalline cellulose and cotton cellulose, respectively, and both obtained HMF yields below 12%. Kawamura et al. [18] utilized WO₃ as heterogeneous catalyst at 200 °C and 3 h of reaction and obtained 5.71% of HMF yield; Yang et al. [19] employed SO₄²⁻/SnO₂ as catalyst at 190 °C within 3.5 min of reaction and obtained 11% of HMF yield. From these results, it is possible to conclude that HMF production from cellulose depends on various factors, such as the catalyst type, reaction medium composition, and temperature, among others, which therefore must be properly adjusted in order for maximize the HMF yield.

Among the heterogeneous catalysts that can be potentially employed to obtain HMF from cellulose, those based on heteropolyacids, such as H₃PW₁₂O₄₀ (HPW), stand out as active phase as they offer several advantages in HMF production from cellulose. These acids have high Brønsted acidity, which is required to catalyze cellulose into glucose through hydrolysis and dehydrate fructose into HMF. In addition, they have low volatility and thermal stability [5,6,20,21]. Heteropolyacids can be supported on metallic oxides, among which niobium pentoxide (Nb₂O₅) stands out as it presents high Lewis acidity, which is essential to catalyze the glucose isomerization into fructose and, thus, generate bifunctional catalysts. Niobium pentoxide still has good chemical and thermal stability, as well as high catalytic activity, specific area, selectivity and metal–support interaction, which are necessary features

to obtain a highly stable and active catalyst [22,23]. Notwithstanding these advantages and their great potential for application, studies on bifunctional catalysts by combining Nb_2O_5 as support and HPW as active phase aimed at the production of HMF from cellulose remain scarce in the literature.

Reaction medium composition also affects HMF production, especially when cellulose is used as feedstock. An exclusively aqueous medium is usually associated with lower HMF yields since high water availability tends to increase the HMF hydration rates, producing levulinic acid and formic acid, and facilitating the production of humin by condensation reactions [7,16,24]. Nevertheless, when cellulose is used for HMF production, an aqueous medium is necessary for hydrolysis to occur [3]. An alternative to this would be to select reaction media composed of water and organic solvent in an optimized proportion in order to ensure maximum HMF yield. Among the potential solvents to be used, such as methyl isobutyl ketone (MIBK), dimethylsulfoxide (DMSO), and tetrahydrofuran (THF), among others, acetone stands out since it is a not toxic and readily biodegradable solvent, classified as “recommended” by the CHEM21 guide with regard to safety, health and environmental criteria [25]. It is important to highlight that acetone is also one of the studied solvents that presents lower cost and more easily separation from the HMF final product [26]. In addition, the presence of acetone contributes to the formation of furanoid form in the reaction medium. According to Bicker et al. [27], the dehydration of fructose to form HMF is the most selective when the carbohydrate molecule is in its furanoid form, which contributes to the increase in HMF production from sugars. The use of optimized temperature can also be a decisive factor to obtain high HMF yields from cellulose. Normally, at temperatures below $150\text{ }^\circ\text{C}$, cellulose hydrolysis into glucose in an acidic medium may not occur since it implies high energy demand. However, temperatures above $200\text{ }^\circ\text{C}$ can increase the kinetic constants involved in HMF degradation, resulting in higher concentrations of by-products, such as levulinic acid or humin [2,18,28].

Based on the above, the present study aimed to determine the optimal reaction conditions for maximum production of HMF from cellulose using HPW/ Nb_2O_5 as heterogeneous catalyst. For such a purpose, the influence of the temperature, acetone:water ratio, cellulose load and catalyst concentration on the conversion of cellulose into HMF was evaluated, and the reaction conditions able to result in maximum HMF yield were selected.

2. Results and Discussion

2.1. Catalyst Characterization

Fourier-transform infrared (FTIR) spectroscopy was employed to verify the stability of the Keggin structure of the HPW/ Nb_2O_5 — $300\text{ }^\circ\text{C}$ catalyst. Figure 2 shows the FTIR spectra of the 30% HPW/ Nb_2O_5 — $300\text{ }^\circ\text{C}$ catalyst, the Nb_2O_5 calcined at $300\text{ }^\circ\text{C}$ (support), and the HPW (active phase). The catalyst and active phase spectra presented four IR bands at similar wavelengths: 1080 , 982 , 893 and 791 cm^{-1} . These IR bands are typically found for HPW Keggin anions ($\text{PW}_{12}\text{O}_{40}^{-3}$) and are related to oxygen bonds present in the anion, where 1071 – 1080 cm^{-1} refers to the P–O_{internal} bond, 972 – 995 cm^{-1} corresponds to the W = O_{terminal} bond, 890 – 902 cm^{-1} relates to the W–O_{corner}–W bond, and absorption bands between 756 – 810 cm^{-1} refer to the W–O_{edge-shared}–W bond [29–31]. Therefore, the HPW Keggin structure remained on the support surface even after the calcination process at $300\text{ }^\circ\text{C}$, since the 30% HPW/ Nb_2O_5 — $300\text{ }^\circ\text{C}$ catalyst FTIR spectrum showed four absorption bands related to the presence of the HPW Keggin structure, specifically located at 1080 cm^{-1} (P–O_{internal}), 982 cm^{-1} (W = O_{terminal}), 893 cm^{-1} (W–O_{corner}–W) and 791 cm^{-1} (W–O_{edge-shared}–W).

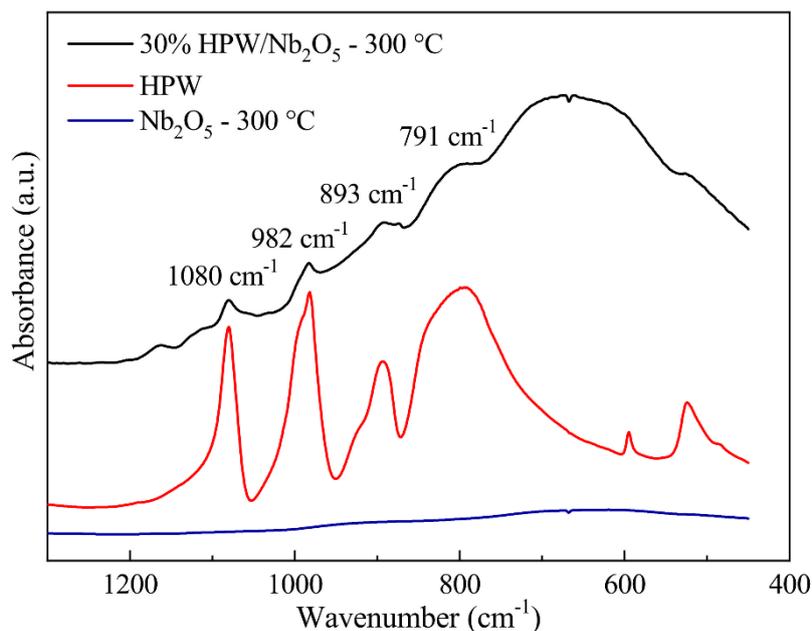


Figure 2. FTIR spectra of the heteropolyacid (HPW) active phase, Nb_2O_5 support, and HPW/ Nb_2O_5 catalyst.

Furthermore, the thermal stability of the catalyst (30% HPW/ Nb_2O_5 —300 °C), the active phase (HPW) and support (Nb_2O_5) were evaluated by thermogravimetric analysis (TGA) and derivative thermogravimetry (DTG). The TGA profiles shown in Figure 3a revealed that the main weight loss of HPW (approx. 7%) and Nb_2O_5 (approx. 12%) occurred until 250 °C. In regard to the catalyst, the TGA profile showed that its weight loss (approx. 13%) was gradual until 1000 °C, i.e., the highest temperature evaluated in this analysis. The DTG curve (Figure 3b) of HPW revealed four main stages of weight loss that represent active phase degradation steps. The peaks of 75 and 120 °C correspond to the loss of water physically adsorbed in the material; at 208 °C, the loss due to crystallization water occurs; at 305 °C the loss of acidic proton; and at 545 °C, the decomposition of the Keggin structure starts [32]. The Nb_2O_5 DTG curve showed only one large peak below 200 °C, probably related to the loss of physically adsorbed and crystallized water, which is in agreement with the TGA profile of the support. The DTG curve of the catalyst (HPW/ Nb_2O_5 —300 °C) presented two peaks, a large one below 250 °C, possibly related to the water loss from physical adsorption by the material, and a second peak at around 590 °C, probably associated with the final stage of HPW degradation, i.e., when the Keggin structure of the active phase starts decomposing, thus producing P_2O_5 and WO_3 at temperatures higher than 500 °C [32]. Therefore, the results obtained from the thermal stability analysis reveal that the catalyst 30% HPW/ Nb_2O_5 —300 °C can be considered thermally stable in the applied reaction condition (below 300 °C), since its weight loss was of approximately 6% until 300 °C, which was assigned to water loss, and the HPW starts decomposing at temperature of over 300 °C, thus confirming the HPW Keggin structure presence on the catalyst surface according to the FTIR analysis.

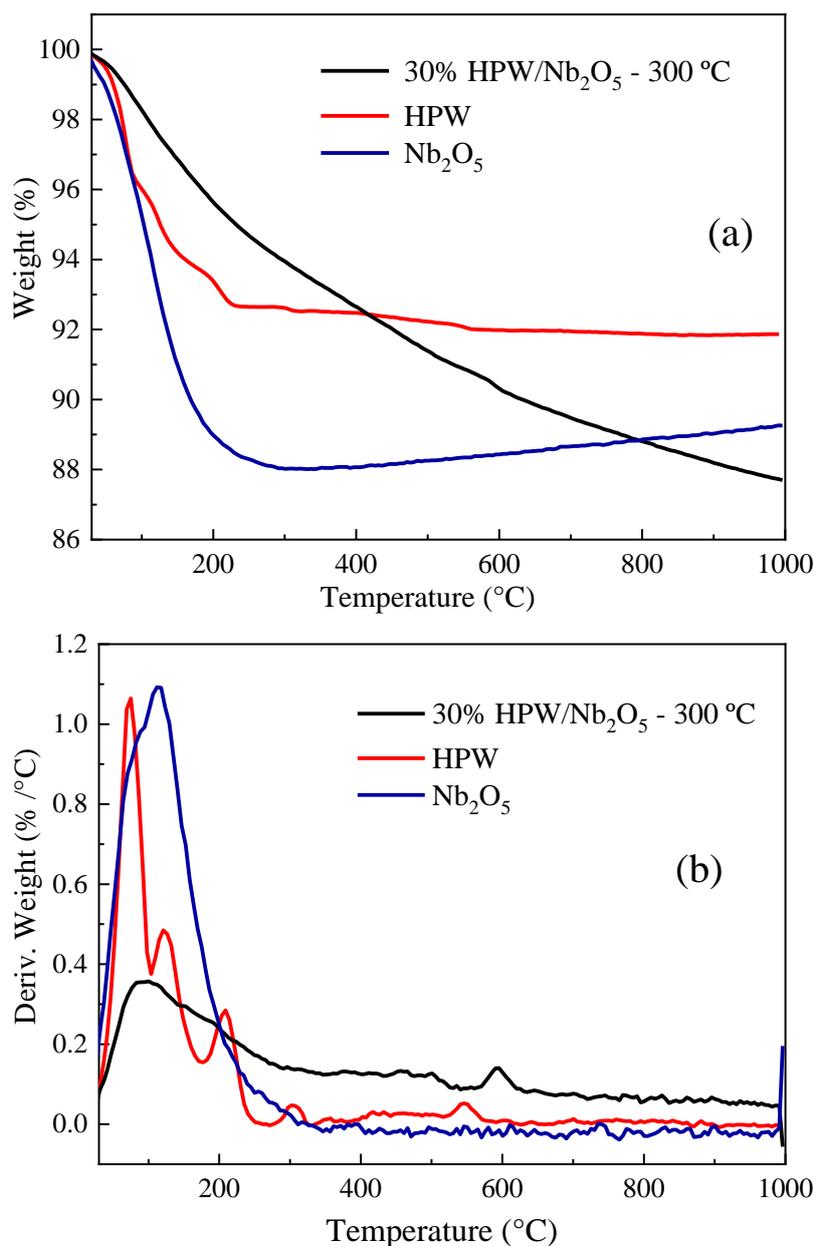


Figure 3. (a) Thermogravimetric analysis—thermogravimetric analysis (TGA) and (b) derivative thermogravimetry (DTG) of the HPW active phase, Nb₂O₅ support, and HPW/Nb₂O₅ catalyst calcined at 300 °C.

2.2. Evaluation of Reaction Conditions

An evaluation of reaction conditions capable of affecting the production of HMF from microcrystalline cellulose was carried out. For such a purpose, the reaction temperature (160 or 200 °C), acetone:water ratio (50:50 or 75:25 *v/v*), cellulose load (5% or 10% *w/v*) and catalyst (30% HPW/Nb₂O₅—300 °C) concentration (1% or 5% *w/v*) were assessed through a Taguchi's L₁₆ screening experimental design, where the HMF concentration (C_{HMF} , g/L) and HMF yield (Y_{HMF} , %) were considered as response variables (Table 1). In this study, HMF concentration of 16.0 g/L and yield of 20.6% were achieved. The best results were obtained in experiment 16, in which all the studied variables were used at the highest level (reaction temperature of 200 °C, acetone:water of 75:25 *v/v*, cellulose load of 10% *w/v* and catalyst concentration of 5% *w/v*, at 300 rpm in 30 min of reaction).

Table 1. Taguchi's L_{16} orthogonal array to evaluate the effects of temperature, acetone:water ratio, cellulose load and catalyst concentration on 5-hydroxymethylfurfural (HMF) production from cellulose.

Exp.	Experimental Conditions (Independent Variables and Interactions)														Response Variables		
	AT (°C)	B Acetone: Water (v/v)	AB	C ¹ C _{Cell} (% w/v)	AC	BC	CE	D Catalyst (% w/v)	AD	BD	CE	CD	BE	AE	² E	³ C _{HMF} (g/L)	⁴ Y _{HMF} (%)
1	160	50:50	1	5	1	1	1	1	1	1	1	1	1	1	1	0.0	0.0
2	160	50:50	1	5	1	1	1	5	2	2	2	2	2	2	2	0.7	1.8
3	160	50:50	1	10	2	2	2	1	1	1	1	2	2	2	2	0.0	0.0
4	160	50:50	1	10	2	2	2	5	2	2	2	1	1	1	1	1.0	1.3
5	160	75:25	2	5	1	2	2	1	1	2	2	1	1	2	2	0.0	0.0
6	160	75:25	2	5	1	2	2	5	2	1	1	2	2	1	1	2.0	5.0
7	160	75:25	2	10	2	1	1	1	1	2	2	2	2	1	1	0.0	0.0
8	160	75:25	2	10	2	1	1	5	2	1	1	1	1	2	2	2.6	3.3
9	200	50:50	2	5	2	1	2	1	2	1	2	1	2	1	2	2.1	5.3
10	200	50:50	2	5	2	1	2	5	1	2	1	2	1	2	1	3.6	9.3
11	200	50:50	2	10	1	2	1	1	2	1	2	2	1	2	1	3.2	4.2
12	200	50:50	2	10	1	2	1	5	1	2	1	1	2	1	2	6.2	8.0
13	200	75:25	1	5	2	2	1	1	2	2	1	1	2	2	1	6.8	17.5
14	200	75:25	1	5	2	2	1	5	1	1	2	2	1	1	2	7.3	18.8
15	200	75:25	1	10	1	1	2	1	2	2	1	2	1	1	2	8.4	10.8
16	200	75:25	1	10	1	1	2	5	1	1	2	1	2	2	1	16.0	20.6

¹ C_{Cell} (% w/v): cellulose load; ² E: Column for error estimation; ³ C_{HMF}: HMF concentration. ⁴ Y_{HMF}: HMF yield.

In order to further evaluate HMF production herein obtained, the performance of HMF can be compared with some results obtained by other studies in the literature. The HMF yield found in the present study from microcrystalline cellulose (20.6%), even using an acetone/water system in a short reaction time (30 min), presented superior results in terms of HMF yield from cellulose than studies that used pure organic solvent under similar temperature conditions. For instance, Wang et al. [33] obtained HMF yield of 2%, i.e., approximately ten times less than herein achieved. The authors produced HMF from cellulose using a reaction medium composed by organic solvent (THF/DMSO—70:30 *v/v*), Sn–montmorillonite as catalyst, at 160 °C with a reaction time of 180 min. Tao et al. [13] obtained HMF yield of approximately 18%, which was closer to that achieved in the present study. However, this study used a more toxic and costly reaction medium, as well as longer reaction time. Tao et al. [13] evaluated HMF production from microcrystalline cellulose in a reaction medium composed of an ionic liquid, i.e., 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate and the organic solvent MIBK using a homogeneous catalyst (MnCl_2) at 150 °C for 150 min.

Still, regarding the performance of HMF production, in the studies of Tang and Su [16], Nandiwale et al. [17] and Li et al. [10], yields of up to 58.4%, 46% and 53.3%, respectively, were achieved. Although such yields are higher than those obtained in the present study, when comparing other parameters of great importance in the concept of viability of industrial processes, such as productivity in HMF ($\text{g/L}\cdot\text{h}$), HMF concentration (g/L) and specific activity of HMF in terms of the quantity of HMF produced per mass of catalyst and reaction time ($\text{g}_{\text{HMF}}/\text{g}_{\text{catalyst}}\cdot\text{h}$), the present results are clearly more promising. In the present study, a final HMF concentration of 14.1 g/L , productivity in HMF of 84 $\text{g/L}\cdot\text{h}$, and HMF produced per mass of catalyst and reaction time of 1.68 $\text{g}_{\text{HMF}}/\text{g}_{\text{catalyst}}\cdot\text{h}$ were achieved. In the studies of Tang and Su [16], the authors achieved around 7 g/L of HMF concentration, 3.5 $\text{g/L}\cdot\text{h}$ of HMF productivity, and 0.225 $\text{g}_{\text{HMF}}/\text{g}_{\text{catalyst}}\cdot\text{h}$, using $\gamma\text{-AlOOH}$ as catalyst, temperature of 160 °C, a 2 h reaction time, and a reaction medium composed of BMIMCl:DMSO:H₂O (4:2:1 *m/m*). Nandiwale et al. [17], who studied HMF production using water as reaction medium and bimodal-HZ-5 zeolite as catalyst, at 190 °C, within 4 h of reaction, obtained HMF concentration of 13 g/L , 2.25 $\text{g/L}\cdot\text{h}$ of HMF productivity, and 0.045 $\text{g}_{\text{HMF}}/\text{g}_{\text{catalyst}}\cdot\text{h}$. In addition, Li et al. [10], using niobium/carbon composite (Nb/C-50) at 170 °C, within 8 h in a biphasic system composed by an aqueous solution of NaCl/THF (1:3 *v/v*), achieved HMF concentration of 5.1 g/L , 0.64 $\text{g/L}\cdot\text{h}$ of HMF productivity, and 0.051 $\text{g}_{\text{HMF}}/\text{g}_{\text{catalyst}}\cdot\text{h}$. It is important to emphasize, for instance, that in the present study, HMF specific activity was around 37, 7.5 and 33-times higher than the results achieved by Nandiwale et al. [17], Tang and Su [16] and Li et al. [10], respectively. Furthermore, with the exception of Nandiwale et al. [17], who used only water as solvent, Tang and Su [16] (BMIMCl:DMSO:H₂O (4:2:1 *m/m*) and Li et al. [10] (aqueous solution of NaCl/THF 1:3 *v/v*) used solvents that are environmentally questionable. Therefore, the present study not only shows higher concentration (g/L), productivity ($\text{g/L}\cdot\text{h}$) and specific activity in HMF ($\text{g}_{\text{HMF}}/\text{g}_{\text{catalyst}}\cdot\text{h}$) compared to the mentioned studies, but also uses a greener and low-cost solvent, demonstrating the contribution of the present study to the establishment of technologies for HMF production from cellulose. It is worth mentioning that HMF production from cellulose, mainly using heterogeneous catalysis, remains scarce in the literature, which emphasizes the novelty of the present study. This fact can be confirmed through the bibliometric analysis presented in the Supplementary Materials section (Figure S1).

The statistical significance of the main effects and their interactions on HMF concentration and yield was evaluated by analysis of variance (ANOVA) (Table 2). For HMF concentration (C_{HMF}), the statistical analysis showed that all main independent variables (reaction temperature (A), acetone:water ratio (B), cellulose load (C) and catalyst concentration (D)), as well as the AB interaction, were significant at 95% confidence level. For HMF yield (Y_{HMF}), the variables A, B and D, as well as the interaction AB were significant at the same confidence level. High correlation coefficients (R^2), above 96%, were obtained for both responses.

Table 2. Analysis of variance of the main effects and their interactions on HMF concentration (C_{HMF}) and HMF yield (Y_{HMF}) based on Taguchi's L_{16} orthogonal array.

Source of Variation	Response Variables	
	<i>p</i> -Value for C_{HMF}	<i>p</i> -Value for Y_{HMF}
Temperature (A)	0.0004 *	0.0001 *
Acetone:water (B)	0.0055 *	0.0014 *
C_{Cel} (C)	0.0436 *	0.2515
C_{Cat} (D)	0.0202 *	0.0085 *
AB	0.0146 *	0.0043 *
AC	0.0662	0.5148
AD	0.3073	0.3478
BC	0.2808	0.6262
BD	0.3097	0.2940
CD	0.1537	0.4378
R^2	0.9648	0.9778

* Significant at 95% confidence level: *p* value < 0.05.

Figure 4 shows the signal-to-noise ratio (SN ratio) diagrams of HMF concentration (a) and HMF yield (b). According to Figure 4a, the highest HMF concentrations were obtained when all independent variables were used at the highest level, i.e., at reaction temperature of 200 °C, acetone:water ratio of 75:25 *v/v*, cellulose load of 10% *w/v* and catalyst concentration of 5% *w/v*. The same was observed for HMF yield (Figure 4b), with exception that the cellulose load was not significant in this case (within the range of values studied). Thus, for the subsequent experiments of HMF production from cellulose, it was decided to use the highest load of cellulose (10% *w/v*), given that this condition was able to provide the highest HMF concentrations.

A similar study was conducted previously using glucose as feedstock for HMF production [32]. In a study carried out using glucose, the best results were observed in reactions performed at 160 °C, while the present study was carried out using cellulose as feedstock, and the highest temperature evaluated (200 °C) provided the greatest HMF concentrations and yields. This temperature difference is probably because cellulose conversion into HMF requires an additional reaction stage, i.e., cellulose hydrolysis, which increases the energy demand.

A similar result was reported in the literature by Kawamura et al. [18], who studied the production of HMF from glucose and cellulose using heterogeneous catalysts in an aqueous media at temperatures ranging from 120 to 250 °C. In that study, the authors observed that HMF yields from cellulose at 200 °C were higher than those obtained from glucose at the same temperature range, while at lower temperatures (120 or 150 °C), HMF yields from glucose were higher than those from cellulose. These authors also attributed the low HMF yield from glucose at high temperatures to further HMF degradation, therefore forming carboxylic acids, aldehydes and other by-products.

In summary, based on the results of the statistical analysis, the reaction temperature and acetone:water ratio were the variables with the greatest influence on the HMF production, and were therefore selected for further optimization in the subsequent experiments.

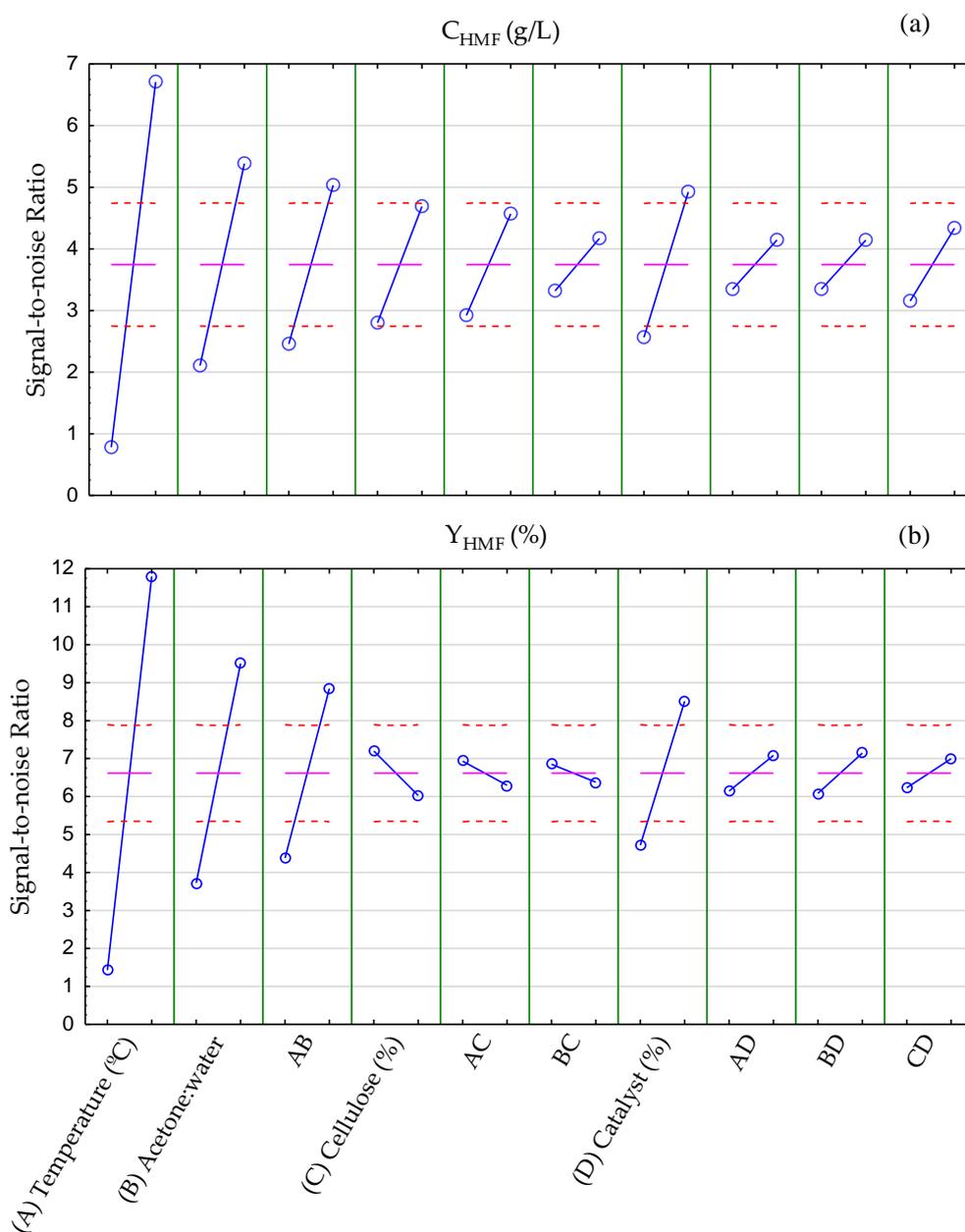


Figure 4. Signal-to-noise ratio (SN ratio) of (a) HMF concentration (C_{HMF} g/L) and (b) HMF yield (Y_{HMF} %) as response variables.

2.3. Reaction Conditions Optimization

In order to optimize temperature and acetone:water levels, a central composite rotatable design (CCRD) was used. For such purpose, the reaction temperature (160 to 240 °C) and acetone:water ratio (60:40 to 90:10 *v/v*) were combined using a factorial 2^2 rotation matrix comprising four tests in axial conditions and three repetitions at the central point totaling eleven experiments (Table 3). Since the catalyst concentration was the variable with less influence on HMF production in the previous experiments, it was then fixed at 5% *w/v*, which gave the best results.

Table 3. Central composite rotatable design (CCRD) matrix for optimizing reaction conditions of cellulose conversion into 5-hydroxymethylfurfural (HMF).

Experimental Conditions (Independent Variables)			Response Variables		
Exp.	A: T (°C)	B: Acetone:Water (v/v)	Y _{HMF} ¹ (%)	S _{HMF} ² (%)	X _{Cel} ³ (%)
1	160	60:40	2.2	9.3	24.2
2	240	60:40	2.1	2.1	99.6
3	160	90:10	4.2	14.3	29.4
4	240	90:10	1.2	1.2	100.0
5	143	75:25	0.0	0.0	47.6
6	257	75:25	0.0	0.0	100.0
7	200	54:46	10.0	18.9	53.0
8	200	96:4	5.0	9.1	55.2
9	200	75:25	21.5	24.8	86.5
10	200	75:25	15.2	19.6	77.7
11	200	75:25	17.7	20.7	85.7

¹ Y_{HMF}: HMF yield. ² S_{HMF}: HMF selectivity. ³ X_{Cel}: cellulose conversion.

Table 3 shows the results obtained from the CCRD matrix, HMF yield (Y_{HMF} %), HMF selectivity (S_{HMF} %) and cellulose conversion (X_{Cel} %). The highest HMF yield was 21.5%, obtaining a maximum selectivity of 24.8%, while cellulose conversion ranged from 24.2% to 100%. Moreover, it is possible to observe that the highest cellulose conversions (close to 100%) were linked to the highest reaction temperatures (as in the assays 2 and 4, performed at 240 °C, and in assay 6, performed at 257 °C). However, the HMF yield reached only 2.1% and 1.2% in assays 2 and 4, respectively, and no yield was observed in assay 6. Such behavior may be associated with a higher formation of by-products, which may occur in reactions carried out at elevated temperatures. The highest values of HMF yield and selectivity were obtained under the conditions of the central points (assays 9, 10 and 11), which have been performed at 200 °C and acetone:water ratio of 75:25 v/v.

These results are similar to those reported by Yan et al. [2] and Cao et al. [28]. Yan et al. [2] studied the conversion of microcrystalline cellulose into HMF at 180, 200, 220 and 240 °C, using several catalysts (FeCl₃, RuCl₃, VCl₃, TiCl₃, MoCl₃ e CrCl₃) in aqueous reaction media. These authors noted that, for all the catalysts studied, a raise in reaction temperature from 200 to 220 °C increased the production of levulinic acid (by-product of HMF rehydration). The same was observed for lactic acid (by-product of glucose retro-aldol degradation) when MoCl₃ and CrCl₃ were used as catalysts. However, an increase in reaction temperature to 240 °C resulted in a reduction of levulinic acid and lactic acid concentration due to the formation of humin and/or other by-products. Cao et al. [28] also evaluated microcrystalline cellulose conversion into HMF at different temperatures varying from 145 to 205 °C, with a step at 15 °C using HfO(PO₄)_{2.0} as catalyst in a time reaction of 240 min and a biphasic medium (aqueous solution of NaCl and THF). These authors noted that, up to 190 °C, cellulose conversion, HMF yield and selectivity enhanced with the temperature increase. However, at 205 °C, an increase in cellulose conversion was accompanied by HMF yield and selectivity reduction, which may be related to the presence of side reactions, such as HMF condensation and/or polymerization into humin.

The statistical significance of the linear and quadratic effects and their interactions on both responses was verified using a Pareto chart. For HMF yield (Figure 5a), quadratic effects of reaction temperature (A²) and acetone:water ratio (B²) were significant at 95% confidence level; while for HMF selectivity (Figure 5b), only the quadratic effect of reaction temperature (A²) was significant at the same confidence level. Concerning cellulose conversion (Figure 5c), the linear effect of temperature (A) and the quadratic effect of acetone:water ratio (B²) were significant at the 95% confidence level.

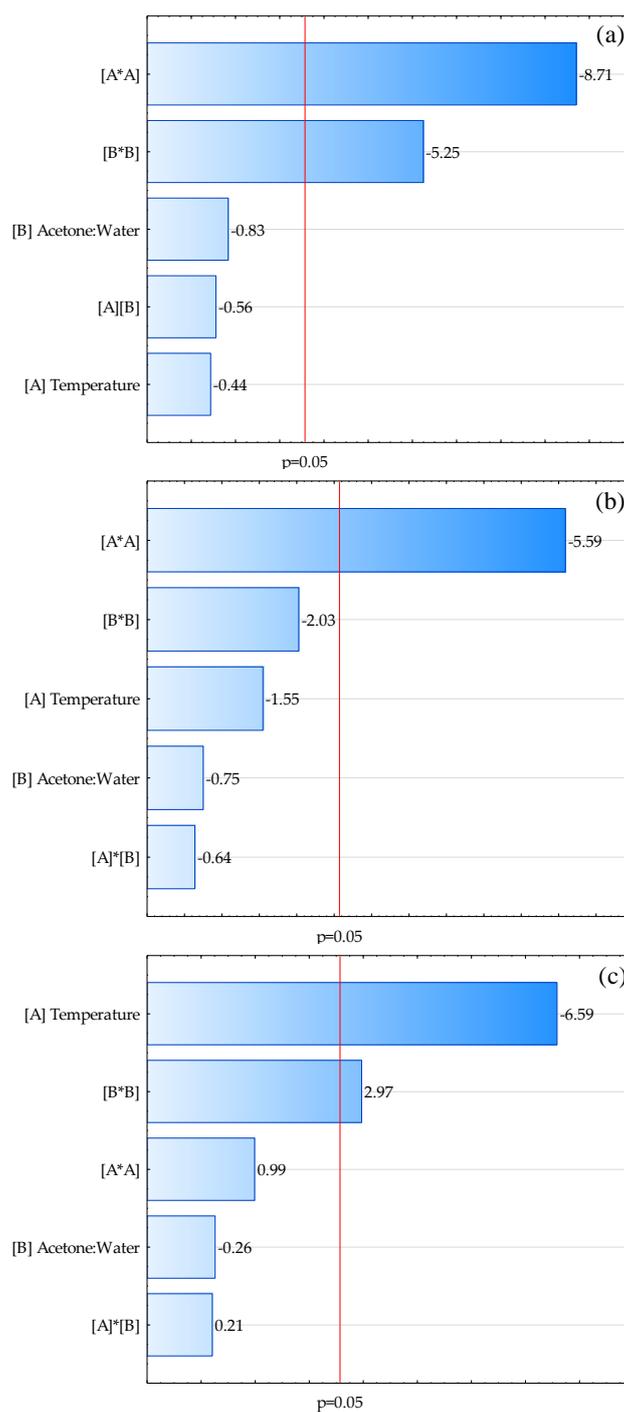


Figure 5. Pareto chart of estimated effects (blue bar) of the variables temperature (A) and acetone:water ratio (B) on HMF yield (a), HMF selectivity (b) and cellulose conversion (c).

According to these results, mathematical models were proposed to describe the HMF yield, HMF selectivity and cellulose conversion (Equations (1)–(3), respectively), where A is the temperature and B the acetone:water ratio to be used for reaction. Terms with little influence on the adjustment of the regression models were not considered for the equations. Moreover, the models were determined for real values of the variables (uncoded levels).

$$Y_{\text{HMF}}(\%) = -352.343 + 2.340 \cdot A - 0.006 \cdot A^2 + 3.716 \cdot B - 0.025 \cdot B^2 \quad (1)$$

$$S_{\text{HMF}}(\%) = -330.450 + 2.666 \cdot A - 0.007 \cdot A^2 + 2.531 \cdot B - 0.017 \cdot B^2 \quad (2)$$

$$X_{\text{Cel}}(\%) = -397.275 + 0.668 \cdot A - 8.951 \cdot B - 0.059 \cdot B^2 \quad (3)$$

The ANOVA of models, which describe HMF yield, HMF selectivity and cellulose conversion as a function of reaction temperature and acetone:water ratio (v/v), are presented in Table 4. In general, all response variables presented at least one significant quadratic term, which indicates that quadratic models are able to better describe the behavior of the responses. In addition, the adjusted correlation coefficient (R^2_{adjust}) was above 90% for HMF yield, and above 77% for HMF selectivity and cellulose conversion, and the lack of fit of the models was not significant at the 95% confidence level.

Table 4. Analysis of variance of estimated HMF yield (Y_{HMF}), HMF selectivity (S_{HMF}) and cellulose conversion (X_{Cel}) based on a central composite rotatable design matrix.

Source of Variation	Response Variables		
	<i>p</i> -Value for Y_{HMF}	<i>p</i> -Value for S_{HMF}	<i>p</i> -Value for X_{Cel}
Temperature (A)	0.6672	0.1533	0.0002 *
Acetone:Water (B)	0.4175	0.4619	0.7864
AA	0.0001 *	0.0010 *	-
BB	0.0015 *	0.0782	0.0192 *
Lack of fit	0.815	0.243	0.135
R^2 adjust.	0.9005	0.7746	0.8505

* Significant at 95% confidence level: *p* value < 0.05.

Through the models contour plots (Figure 6), the optimal conditions for HMF production from cellulose were determined. For HMF yield (Figure 6a), the contour plot indicated that the central conditions (in red) are ideal to maximize the yield, and any conditions that are displaced from this region result in HMF yield reduction. The response surface methodology analysis revealed the following as optimum condition for obtaining maximum HMF yield: temperature of 200 °C and acetone:water ratio of 74:26 v/v , which are very close to the central point conditions of the experimental design. With respect to HMF selectivity (Figure 6b), the contour plot was very similar to that obtained for HMF yield and also indicated the central conditions as optimal for maximum selectivity.

Regarding the cellulose conversion (Figure 6c), the contour plot suggests that the temperature increase at the central region of acetone:water ratio (75:25 v/v) has led to higher cellulose conversions. This result is in agreement with those obtained by the ANOVA, since the quadratic temperature term was not significant, thus indicating that it was unable to reach optimal values of this variable within the range studied. According to the response surface methodology analysis, the optimal conditions to obtain maximum cellulose conversion are as follows: temperature of 257 °C and acetone:water ratio of 75:25 v/v . Therefore, it is possible to infer that increased cellulose conversion is associated with higher reaction temperatures, which is also associated with by-product formation.

In light of these results, the optimal conditions for HMF production from cellulose were defined as 200 °C and acetone:water ratio of 75:25 v/v . These conditions were then used to determine the kinetic parameters of HMF production in the subsequent step.

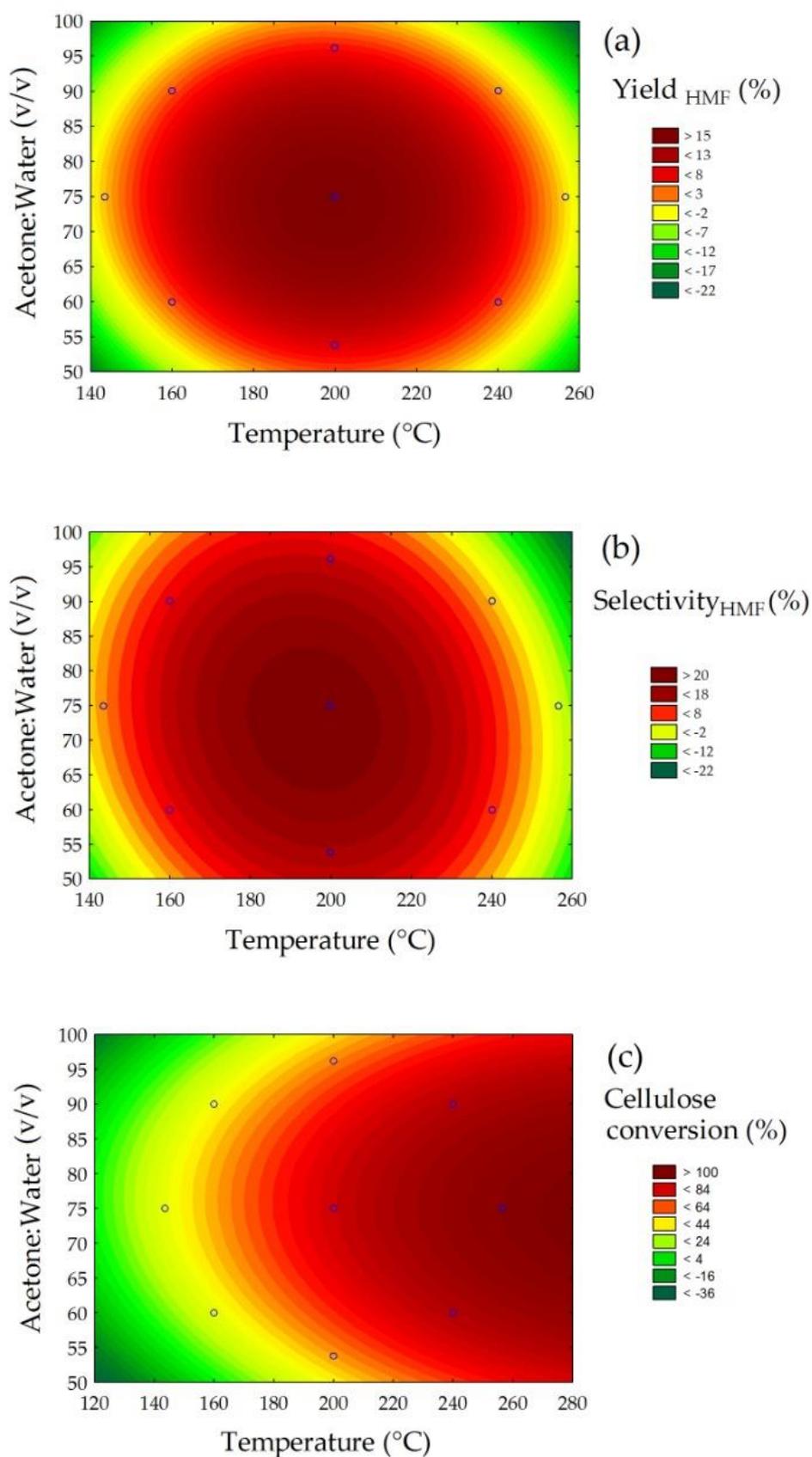


Figure 6. Contour plots of reaction temperature and acetone:water ratio (v/v) as a function of HMF yield (a), HMF selectivity (b) and cellulose conversion (c).

2.4. Kinetic Modeling Results

The behavior of the chemical reaction obtained with the two different modeling approaches: power law and Langmuir–Hinshelwood–Hougen–Watson (LHHW) with HMF adsorption, as shown in Figures 7 and 8, respectively (the results of cellulose concentration (g/L) and conversion (%), HMF concentration (mol/L and g/L) and yield (%) obtained in the kinetic study are shown in Table S2, Supplementary Materials).

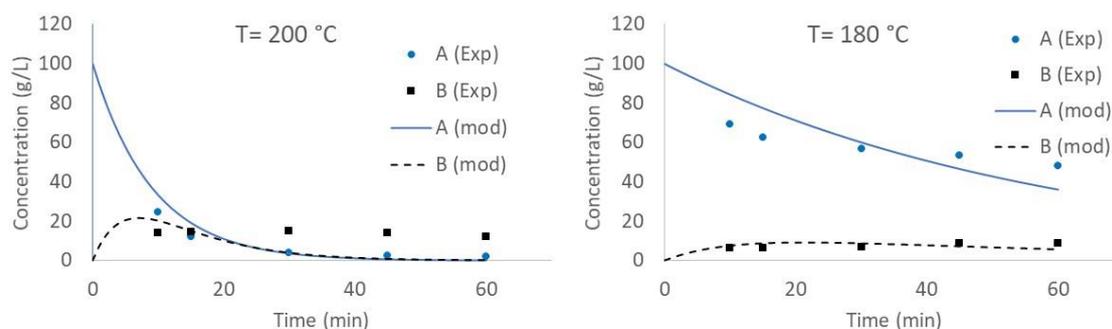


Figure 7. Fittings through power law modeling. (A) Cellulose concentration experimental and modeling (g/L); (B) HMF production experimental and modeling (g/L).

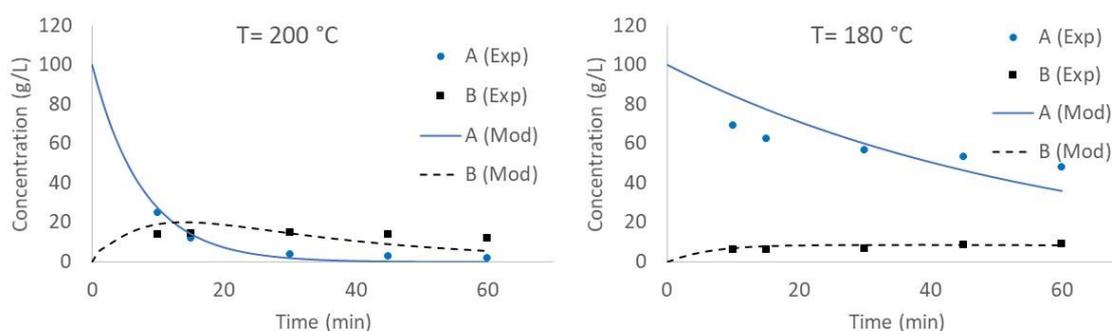


Figure 8. Fittings through the Langmuir–Hinshelwood–Hougen–Watson (LHHW) model concerning HMF adsorption. (A) Cellulose concentration experimental and modeling (g/L); (B) HMF production experimental and modeling (g/L).

The kinetic parameters obtained for all studied models are depicted in Table 5.

Table 5. Kinetic parameters.

Parameter	PL Model		LHHW Model	
	T = 200 °C	T = 180 °C	T = 200 °C	T = 180 °C
k_1 (min ⁻¹)	0.110	0.180	0.120	0.016
k_2 (min ⁻¹)	0.017	0.100	2.100	0.120
k_c (L mol ⁻¹)	-	-	66.000	2.300

PL: power law; LHHW: Langmuir–Hinshelwood–Hougen–Watson.

It can be observed that the LHHW model was coherent with the dependence of rate parameters on temperature. Conversely, the power law model did not provided the expected temperature dependence for the parameters under evaluation. Reasonable agreements between the model and the experimental data have been obtained by both approaches. In order to assess the predictability of models as a function of the number of fitting parameters, the Akaike information criterion adjusted for small samples (AICC) was applied [34]. Table 6 shows the AICC calculated values.

Table 6. Akaike information criterion (AICC) for model selection.

Model	AICC	Δ
PL	−111.03	4.44
LHHW	−115.47	0.00

The low value of AICC ($\Delta = 0$) indicated that LHHW is optimal between the models being tested. A study conducted by Lacerda et al. [35] achieved results in which the values of k_1 and k_2 were found in the ranges of 0.25–0.44 and 0.005–0.009, respectively, at temperatures between 180 and 200 °C. Despite using different catalyst systems, Lacerda et al. [35] has not considered adsorption/desorption phenomena in HMF consumption, which might be the cause of a discrepancy in k_2 in comparison with the values found in the present study. On the other hand, the k_1 values obtained herein are in agreement with literature data.

2.5. HMF Production from Different Sources of Cellulose

In this section, HMF production from cellulose obtained from different biomass sources is evaluated. Commercial eucalyptus cellulose pulp (Suzano Pulp and Paper Industry) and brewer's spent grain cellulose pulp [36,37] were employed as feedstock for HMF production, and the results were compared to HMF production from microcrystalline cellulose. Assays were performed under the experimental conditions previously optimized: 200 °C, acetone:water ratio of 75:25 *v/v*, 10% *w/v* cellulose, and 5% *w/v* catalyst at 300 rpm for a duration of 10 min.

Table 7 presents the results of HMF concentration, yield and selectivity, and cellulose conversion for the assays carried out using different sources of cellulose. HMF production from commercial eucalyptus cellulose pulp and brewer's spent grain cellulose pulp was higher than 8 g/L, with HMF yields of over 11%. For microcrystalline cellulose, HMF concentration and yield reached 14.1 g/L and 18.1% respectively, i.e., nearly 28% and 55% higher than HMF yields achieved from commercial eucalyptus cellulose pulp and brewer's spent grain cellulose pulp, respectively. This lower HMF production from eucalyptus and brewer's spent grain cellulose pulp may be associated with their higher particle size and polymerization degree, which could hinder cellulose hydrolysis into glucose due to accessibility to the substrate. In addition, contaminants that are usually found in these feedstocks, such as lignin residues and hemicellulose, might also have reduced the HMF yield. In general, even though there was a lower performance of HMF production from commercial eucalyptus cellulose pulp and brewer's spent grain cellulose pulp compared to microcrystalline cellulose, the HPW/Nb₂O₅—300 °C catalyst was also demonstrated to be suitable for use on the production of HMF from different sources of cellulose.

Table 7. Assays results carried out with feedstock from different sources of cellulose.

Feedstock	Purity (%)	C_{HMF}^1 (g/L)	Y_{HMF}^2 (%)	S_{HMF}^3 (%)	X_{Cel}^4 (%)
Microcrystalline cellulose	>99	14.1	18.1	24.0	75.2
Commercial eucalyptus cellulose pulp	89.7	9.8	14.1	17.6	80.4
Brewer's spent grain cellulose pulp	90.4	8.2	11.7	15.1	77.4

¹ C_{HMF} : HMF concentration. ² Y_{HMF} : HMF yield. ³ S_{HMF} : HMF selectivity. ⁴ X_{Cel} : cellulose conversion.

In general, HMF concentrations and yields found in the present study (9.8 g/L and 14.1% for commercial eucalyptus cellulose pulp and 8.2 g/L and 11.7% for brewer's spent grain cellulose pulp) are superior to most studies reported in literature for HMF production from different sources of cellulose

using a heterogeneous catalyst (Table 8). Oysel et al. [38], for instance, evaluated the production of HMF from cellulose from corn straw and cotton linter and obtained concentrations of about 0.4 and 0.2 g/L, respectively, using an aqueous medium at 200 °C and a heterogeneous catalyst derived from sulfonated biomass (BT300S—sulfonated solid acid carbonaceous catalyst). Li et al. [39] also obtained lower HMF yields from sugarcane bagasse conversion using microwave heating, although this method has the ability to improve heating uniformity of the reaction medium. The results obtained by these authors reveal the complexity of working with different sources of cellulose for HMF production.

Zhang et al. [15] and Zhang et al. [40] obtained HMF yields of approximately 13% and 10%, respectively, which were similar to those obtained in the present study using commercial cellulose. However, in the present study, shorter times were used, and higher cellulose load was also employed (C_{cel}), which allows obtaining higher concentrations of HMF and facilitates the subsequent step of HMF separation. Hence, the reaction conditions used in the present study by applying HPW/ Nb_2O_5 —300 °C as catalyst are quite promising for HMF production from different sources of cellulose, which can contribute to increase the possibilities for processing biomass in biorefineries and developing technologies aimed at obtaining HMF, which is such an important building block.

Table 8. Comparison of HMF production results carried out using feedstock from different sources of cellulose in the present study with a few recent studies reported in literature.

Feedstock	Cellulose (%)	Catalyst	Solvent	C _{Cel} ¹ (%w/v)	T (°C)	t (min)	C _{HMF} (g/L)	Y _{HMF} (%)	Ref.
Raw sugarcane bagasse	42.62	D001-cc ion-exchange resin	Water	5	140	25 (MWH) ²	3.42	8.8	[39]
Ball-milling cellulose	-	SO ₄ ²⁻ /TiO ₂ —450 °C	Water: ethanol (1:1 v/v)	3.33	200	30	3.37	13.0	[15]
Corn cob	30.2	SPTPA—porous polytriphenylamine—SO ₃ H solid acid	γ-valerolactone (GVL)	1.25	175	85	0.97	10	[40]
Corn straw	49.9	BT300S—sulfonated solid acid carbonaceous catalyst	Water	0.2	200	60	0.4	-	[38]
Cotton linter	82.2	BT300S—sulfonated solid acid carbonaceous catalyst	Water	0.2	200	240	0.23	-	
Commercial eucalyptus cellulose pulp	89.7	HPW/Nb ₂ O ₅ —300 °C	Acetone: water (3:1 v/v)	10	200	10	9.8	14.1	Present study
Brewer's spent grain cellulose pulp	90.4	HPW/Nb ₂ O ₅ —300 °C	Acetone: water (3:1 v/v)	10	200	10	8.2	11.7	

¹ C_{Cel}—initial cellulose concentration. ² MWH—microwave heating.

3. Materials and Methods

3.1. Catalyst Preparation (HPW Supported on Nb₂O₅)

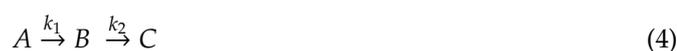
The catalyst was prepared using the incipient wetness impregnation method [32]. The support (Nb₂O₅) was impregnated with a 70% ethanol solution containing the active phase (HPW) solubilized. This step was performed in triplicate until the catalyst reached metal concentration of 30%. Then, the catalyst was dried at 100 °C for 2 h and calcined at 300 °C for 3 h. The support (Nb₂O₅ HY-340) was supplied by Companhia Brasileira de Metalurgia e Mineração (CBMM, Minas Gerais, Brazil).

3.2. HMF Production

All catalytic tests were performed in pressurized stainless-steel reactors (Parr series 4566). In the first stage, the reaction conditions able to influence HMF production from microcrystalline cellulose were evaluated. Thus, the influences of the following variables: temperature (160 or 200 °C), acetone:water ratio (50:50 or 75:25 *v/v*), cellulose load (5% or 10% *w/v*) and catalyst concentration (HPW/Nb₂O₅—300 °C; 1% or 5% *w/v*) were evaluated based on a Taguchi L₁₆ experimental design (Table 1). Column “E” had no variable associated with experimental design error. These reactions were carried out using 100 mL of reaction medium at stirring speed of 300 rpm for 30 min.

For optimization of the reaction conditions, the variables temperature (160 to 240 °C) and acetone:water ratio (60:40 to 90:10 *v/v*) achieved the greatest statistical significance in the conversion of cellulose into HMF, and were therefore evaluated using the central composite rotatable design (CCRD) (Table 3). These reactions were carried out using 100 mL of reaction medium, 5% *w/v* catalyst, 10% *w/v* cellulose at 300 rpm for 30 min.

In the kinetic study, reactions were carried out at temperatures of 180 and 200 °C and lasted from 10 to 60 min using 100 mL of reaction medium, acetone:water ratio of 75:25 *v/v*, catalyst concentration of 5% *w/v*, and cellulose load of 10% *w/v* at 300 rpm. Kinetic parameters were determined using the HMF and cellulose concentrations obtained during the time mentioned above by considering three approaches, as described in Table 9. The series of reactions described in Equation (4) was considered to describe the process and balance of Equations (5)–(7) which were written for the three models.



where:

A: cellulose;

B: HMF;

C: other products.

$$\frac{dC_A}{dt} = -r_1 \quad (5)$$

$$\frac{dC_B}{dt} = r_1 - r_2 \quad (6)$$

$$\frac{dC_C}{dt} = r_2 \quad (7)$$

Table 9. Modeling approaches.

Model	Rate Equations
Power law	$r_1 = k_1 C_A$ $r_2 = k_2 C_B$
LHHW	$r_1 = k_1 C_A$ $r_2 = \frac{k_2 C_B}{1 + K_C C_C}$

Scilab 6.1 was used to solve the system of differential equations and treat data by comparing the experimental results to the proposed kinetic models. The most suitable model among those proposed in Table 9 was selected based on Akaike information criterion [34], according to Equations (8)–(10).

$$AIC = N \ln \left(\frac{SSE}{N} \right) + 2K \quad (8)$$

$$AIC_C = AIC + \frac{2K(K+1)}{N-K-1} \quad (9)$$

$$\Delta_i = AIC_{Ci} - \min AIC_C \quad (10)$$

where:

AIC: Akaike information criterion;

AIC_C: Akaike information criterion corrected for small samples;

minAIC_C: smallest *AIC_C* among all candidate models;

N: number of data points;

K: number of model parameters;

SSE: error sum of squares;

Δ_i : *AIC_C* differences.

In the final stage, HMF production using cellulose from different biomass sources was also evaluated. In this regard, HMF production from microcrystalline cellulose was compared to that from commercial eucalyptus cellulose pulp (Suzano Pulp and Paper Industry) and brewer's spent grain cellulose pulp [36,37]. Before the catalytic test, commercial eucalyptus cellulose pulp and brewer's spent grain cellulose pulp were milled and sifted, and only a grain size fraction of less than or equal to 0.841 mm was used in the reaction. HMF production was carried out under optimal reaction conditions: 100 mL of reaction medium, 200 °C, acetone:water ratio of 75:25 (*v/v*), 5% *w/v* catalyst, and 10% *w/v* cellulose at 300 rpm for a duration of 30 min.

3.3. Analytical Methods

The presence of Keggin structure was determined by Fourier-transform infrared (FTIR) spectroscopy using a Frontier PerkinElmer equipment. The samples were prepared by diluting 2 mg of catalyst in 200 mg of KBr. The spectra were recorded in the range of 450 to 4000 cm^{-1} , at resolution of 4 cm^{-1} after 16 scans accumulation. The active phase (HPW), support (Nb_2O_5) and catalyst (HPW/ Nb_2O_5 —300 °C) were also evaluated by thermogravimetry (TGA) and derivative thermogravimetry (DTG) analysis using a Netzsch equipment (model STA 443 Jupiter, with 100 mL/min of nitrogen flow, heating rate of 10 °C/min and temperature ranging from 30 to 1000 °C).

Cellulose concentration was determined by converting cellulose into glucose and determining glucose concentration by high-performance liquid chromatography (HPLC). The first step was performed according to a procedure adapted from Gouveia et al. [41]. After the HMF production reaction, the remaining cellulose was separated from the reaction medium by centrifugation and dried at 105 °C until constant mass was reached. Then, 25 mL of 72% *w/w* H_2SO_4 preheated at 45 °C was added to the beaker containing dry cellulose and the mixture was kept in a thermostatic bath at 45 °C for 7 min under constant agitation. The mixture was diluted in 275 mL of distilled water in an Erlenmeyer flask of 500 mL, which was capped with aluminum foil and autoclaved at 121 °C for 45 min. After autoclaving, the material was filtered and diluted in a 500 mL volumetric flask. Then, glucose concentration was determined by HPLC analysis using a calibration curve ranging from 0.2 to 4.0 g/L and a Waters chromatograph equipped with an isocratic pump, a refractive index detector and a Bio-Rad Aminex HPX-87H column (300 × 7.8 mm). Operational conditions were 45 °C, 0.005 mol/L of sulfuric acid as eluent at a flow rate of 0.6 mL/min and sample volume of 0.02 mL. HMF concentration was also determined by HPLC, but using a UV detector (at 276 nm), a Waters Spherisorb

C18 5 μm column (100 \times 4.6 mm) at room temperature, 1:8 *v/v* acetonitrile-to-water ratio with 1% of acetic acid as eluent at flow rate of 0.8 mL/min, and sample volume of 0.02 mL. Cellulose conversion (X_{Cel}), HMF yield (Y_{HMF}) and HMF selectivity (S_{HMF}) were calculated according to Equations (11)–(13), where all concentrations are expressed in mol/L.

$$X_{\text{Cel}}(\%) = \frac{[\text{Cellulose}]_{\text{initial (based on glucose unit)}} - [\text{Glucose}]_{\text{after conversion}}}{[\text{Cellulose}]_{\text{initial (based on glucose unit)}}} \cdot 100 \quad (11)$$

$$Y_{\text{HMF}}(\%) = \frac{[\text{HMF}]_{\text{produced}}}{[\text{Cellulose}]_{\text{initial (based on glucose unit)}}} \quad (12)$$

$$S_{\text{HMF}}(\%) = \frac{\text{HMF yield}}{\text{Cellulose conversion}} \cdot 100 \quad (13)$$

4. Conclusions

This study showed that the catalyst HPW/Nb₂O₅—300 °C was effective for use on the direct conversion of microcrystalline cellulose into HMF. Optimization of the reaction conditions indicated that maximum HMF yield from cellulose was 20% and was obtained by using an acetone:water ratio of 75:25 (*v/v*), cellulose load of 10% *w/v*, catalyst concentration of 5% *w/v*, at 200 °C. The kinetic study revealed that only 10 min of reaction is sufficient to achieve 18.1% of HMF yield, which is equivalent to 90% of the yield obtained at the end of the reaction after 30 min (20% HMF yield). Moreover, the Langmuir–Hinshelwood–Hougen–Watson modeling approaches applied to the present catalytic system provided excellent fittings to the experimental data. The optimal reaction conditions using the catalyst HPW/Nb₂O₅—300 °C were also effective in the conversion of different cellulose sources (commercial eucalyptus cellulose pulp and brewer's spent grain cellulose pulp) into HMF, although reaction yields were lower. This was the first time that a catalyst based on HPW and Nb₂O₅ was used for direct HMF production from cellulose. The obtained results infer that the heterogeneous catalyst developed in the present study is quite able to be applied in HMF production from different feedstock sources. These results are promising and contribute for the establishment of new technologies for HMF production from cellulose.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/12/1417/s1>, Bibliometric analysis and kinetic study results. Figure S1: Number of documents published per year referring to the occurrence of the term “Hydroxymethylfurfural” in studies from 2011 to 2020. Bibliometric analysis was carried out on the Scopus search platform on 23 June 2020. Table S1: Search criteria and number of documents found in the bibliometric analysis of the Scopus search platform on 23 June 2020. Table S2: Cellulose concentration (mol/L) and conversion (%), HMF concentration (mol/L e g/L) and yield (%) obtained in the HMF production from cellulose at 180 and 200 °C with time ranging from 10 to 60 min.

Author Contributions: Conceptualization, J.P.A.S., S.I.M. and L.M.C.; methodology, J.S.M.N., J.P.A.S. and L.M.C.; software, J.S.M.N., L.G.d.A., J.P.A.S. and L.M.C.; validation, J.S.M.N., S.I.M., J.P.A.S. and L.M.C.; formal analysis, J.S.M.N., V.T.S., P.V.H., L.G.d.A., J.P.A.S. and L.M.C.; investigation, J.S.M.N., V.T.S., P.V.H., S.I.M. and L.M.C.; resources, J.P.A.S., S.I.M. and L.M.C.; data curation, J.S.M.N., J.P.A.S. and L.M.C.; writing—original draft preparation, J.S.M.N., V.T.S., P.V.H., L.G.d.A. and L.M.C.; writing—review and editing, J.P.A.S., S.I.M. and L.M.C.; visualization, J.S.M.N. and L.M.C.; supervision, L.M.C.; project administration, J.P.A.S. and L.M.C.; funding acquisition, J.P.A.S., S.I.M. and L.M.C. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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