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A response surface methodology for the use of MIL-101 as a catalyst for the one-step synthesis of lactide

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ABSTRACT Lactide is a vital monomer for producing high molecular weight polylactic acid (PLA) through ring-opening polymerization. This study synthesized crude lactide from L-lactic acid with MIL-101 as the catalyst. MIL-101 is a metal-based catalyst with organic ligands (MOF) that was prepared by reacting $Cr(NO_3)_3.9H_2O$ with terephthalic acid (BDC). The formation of MIL-101 was confirmed from Fourier-transform infrared (FTIR) analysis. The role of MIL-101 and the effect of temperature, time, and MIL-101 loading, as well as their interactions in the conversion of lactic acid to crude lactide, were then investigated using the response surface method (RSM). Crude lactide was analyzed using ^{1}H-nuclear magnetic resonance (NMR) spectroscopy to confirm the presence of lactide. The RSM results indicated that the highest conversion of 22.84% can be obtained using a temperature of 175 °C, 1.5% w/w MIL-101 loading, and a reaction time of 5 h. The RSM model showed that the interaction of MIL-101 loading and reaction time strongly affected the conversion of lactic acid to lactide, with a *P*-value of 0.0021 and an F-value of 50.45. In contrast, the interaction of catalyst loading and temperature did not significantly affect the conversion of lactic acid to lactide, with a *P*-value of 0.2565 and an F-value of 1.75.

KEYWORDS Lactic acid; Lactide; MIL-101; One-step synthesis; Polylactic acid (PLA)

1. Introduction

Studies on the development of biodegradable polymers, such as polyhydroxybutyrate (PHB) (Yuliastri et al. 2017) and polylactic acid (PLA) (Huang et al. 2014), are gradually increasing. PLA is an environmentally friendly and biodegradable polymer synthesized from renewable resources. Medical implant materials can be made from high molecular weight PLA (MW > 10^5 g/mol). PLA is commercially produced through ring opening polymerization (ROP) that requires L-lactide with high optical purity (Upare et al. 2014). The L-lactide is generally made from the polycondensation of L-lactic acid, followed by the prepolymer depolymerization process using a tin-based catalyst (Cunha et al. 2022). L-lactic acid polycondensation will produce oligo lactic acid (OLLA), and OLLA depolymerization will produce cyclic dimer lactide (Rahmayetty et al. 2015). The two-stage synthesis process with high temperature and the use of a tin catalyst which is challenging to purify, requires further research on other catalysts.

An environmentally friendly process can be achieved using a metal-organic framework (MOF) as it can catalyze lactide synthesis in one step self-esterification process (Gromov et al. 2018). It has been reported that a yield of 92% and an optical purity that reaches 99% can be produced using ZIF-8 with Cs_2CO_3 as a co-catalyst for one-step L-lactide synthesis (Ghadamyari et al. 2018). The MIL-101 is a type of MOF that has $Cr(NO_3)_3.9H_2O$ node with a benzene 1,4-dicarboxylic acid ligand. The catalyst's active site is Brønsted acid (Yang and Gates 2019). MIL-101 can be used as a catalyst at a reaction temperature of 55–120 °C (Niknam et al. 2018). It has large surface area of 4,500 m^2/g and pore size of 29–34 Å (Du et al. 2019). It was moderately active in cellulose depolymerization, hence, it can become a potential catalyst for L-lactide synthesis because it has the same bond-breaking process (Gromov et al. 2018).

In the synthesis of lactide, careful consideration of the operating conditions and several process variables is necessary, including reaction time, temperature, and the use of catalysts in the reaction process (Groot et al. 2022). The number of variables sometimes complicates the process of analyzing the resulting data. In such cases, the use of response surface methodology (RSM) can help analyze the relationship of each variable. The relationship of various variables can be evaluated using quantitative data of RSM. The stages in RSM include experimental design, statistical analysis, and variable optimization (Said and Amin 2015).

This study investigated the role of MIL-101, the effect of temperature, time, and MIL-101 loading, as well as the interactions of these variables on the conversion of lactic acid to crude lactide using the response surface methodology (RSM).

2. Materials and Methods

2.1. The synthesis of MIL-101

The materials used were purchased from Sigma-Aldrich, which included benzene 1,4-dicarboxylic acid (BDC), $Cr(NO_3)_3.9H_2O$, ethanol, acetic acid; and demineralized water. The synthesis of the MIL-101 catalyst was performed based on the method carried out by Yulia et al. (2021). The solvothermal method was used to synthesize MIL-101 from $Cr(NO_3)_3.9H_2O$, benzene 1,4-dicarboxylic acid (BDC) as ligand, acetic acid, and demineralized water, producing a green liquid. The green liquid was dried and purified using 2-step purification with DMF and ethanol to produce a bluish-green powder that has the same color as the reference (Yulia et al. 2021). MIL-101 catalyst was analyzed using FTIR spectroscopy.

2.2. L-lactide synthesis

The materials for L-lactide synthesis were MIL-101 and L-lactic acid, with purity > 90%. The L-lactide synthesis was done by considering three process variables: temperature, reaction time, and MIL-101 catalyst loading. The L-lactide synthesis process begins by adding L-lactic acid and MIL-101 as catalysts at a predetermined ratio into a 100 mL round bottom flask connected to a condenser unit and a vacuum pump.

2.3. Modeling using response surface methodology

RSM analysis was performed using the Box-Behnken design on Design Expert V.11 software (Stat Ease Inc., Minneapolis, MN, USA), and the variations were analyzed using ANOVA. The type of ANOVA used is two-way ANOVA. It aims to know the effect of the independent variables on the dependent variables and the interaction between the independent variables and their significance. These values are presented as an F-value and a *p*-value. A large F-value with a *p*-value lower than 0.05 indicates that the model or the variable being tested is significant. In contrast, if the *p*-value is more than 0.05, it indicates that the model or the variable being tested is not significant. The first step of using RSM analysis was to select the test parameters according to the Box-Behnken design with 3 independent numerical variables (MIL-101 catalyst loading, temperature, and reaction time). The range of variables used in this study were reaction temperature 150–200 °C, reaction time 4–6 h , and MIL-101 catalyst loading 1–2% w/w. The number of center points per block selected was 2. The Box-Behnken design will duplicate a combination of categorical variables and will provide 14 variations of test variables. The relationship between variables and their interactions with the resulting conversion value can be obtained during data processing.

3. Results and Discussion

The synthesized MIL-101 was analyzed using FTIR to verify the functional groups (Figure 1). The bands at 3,700–2,500 cm^{-1} correspond to the hydroxyl (-OH) bond stretching from the carboxylic acid and adsorbed water. The band at 1631.64 cm^{-1} can be attributed to the bending of the hydroxyl groups. Whereas the band at 1509.11 cm^{-1} and the bands at 1135.57, 1017.28, 878.15, and 723.68 cm^{-1} can be related to the vibrations from (C=C) and (C-H) of benzene, respectively. Last, the band at 1400.48 cm^{-1} can be attributed to dicarboxylate's (O-C=O) vibration. All these confirm the presence of BDC (benzene 1,4-dicarboxylate) in the synthesized MIL-101 (Kayal et al. 2015; Yulia et al. 2021).

The condensation/dehydration and back-biting/end-biting reactions were involved during lactide synthesis. The latter are intramolecular reactions involving an ester bond and the terminal carboxylate group (Botvin et al. 2021). The back-biting reaction will produce cyclic dimers (lactides) and linear compounds (OLLA), while the end-biting reaction will produce a cyclic dimer (lactide) and water (Cunha et al. 2022). Water will be produced dur-

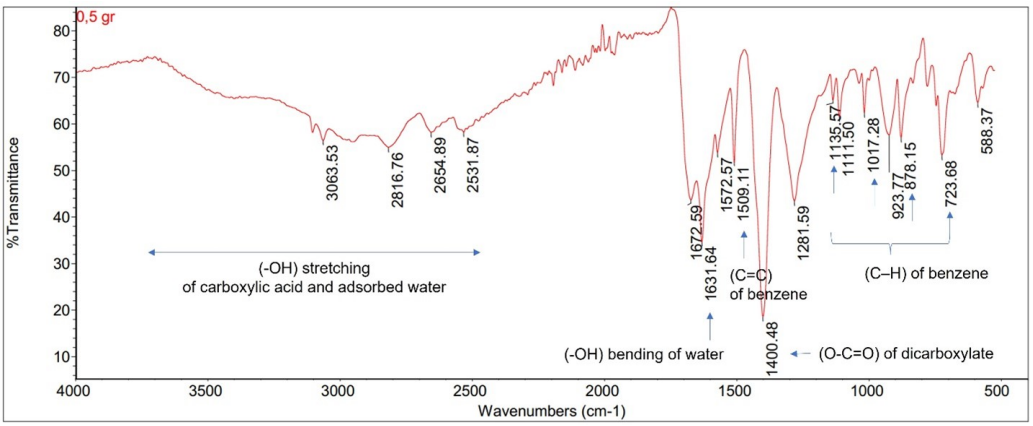


FIGURE 1 FTIR spectra of MIL-101.

ing the synthesis of lactide from lactic acid, either from the condensation/dehydration process or the back-biting/end-biting stage. The water resulting from the reaction must be separated immediately since it can disrupt the reaction equilibrium and limit the formation of lactide products (Ehsani et al. 2014). Therefore, a vacuum pump and condenser were used in this study to remove the formed water from the reaction system. Figure 2 illustrates the reaction of lactide synthesis from lactic acid using MIL-101 as the catalyst.

The lactide produced in this study is a hygroscopic solid crystal, so if exposed to free air for a long time, it could absorb water molecules. Such exposure could hydrolyze the lactide into lactic acid at room temperature (Cunha et al. 2022). The rate of hydrolysis from meso-lactide to lactic acid is higher than that of L-/D-lactide to lactic acid (Botvin et al. 2021). Due to the hygroscopic nature of lactide, proper storage handling is necessary to maintain the quality of lactide.

Figure 3 is the ^{1}H-NMR spectra of the obtained crude lactide. The spectra at 1.48 ppm, 1.55 ppm, and 4.37 ppm are the spectrum of OLLA (Nyiavuevang et al. 2022; Yoo et al. 2006). The doublet spectrum at 1.68 ppm and the quadruplet at 5.05 ppm belong to the (CH_3) and (CH) of lactide, respectively (Cunha et al. 2022), confirming the formation of lactide compounds. Although L-lactic acid was used as the raw material in this study, generally, traces of D-lactic acid may also be present (Botvin et al. 2021). If the lactide synthesis does not use a catalyst, the temperature and reaction time increase can also increase the racemization to meso-lactide (Tsukegi et al. 2007). However, without further analysis, the percentage of the formed L- and D-lactide isomers cannot be determined with certainty.

The effect of each variable and their interactions on the conversion of L-lactic acid to L-lactide was analyzed using Design Expert 11 software. Before this, a preliminary study using one variable at a time (OVAT) analysis was performed to determine the range of variables (temperature, catalyst loading, and reaction time) used in the Box-Behnken design. The effect of each variable, the interaction between variables, and the quadratic effect of the variables can be seen from the results of the ANOVA model. This model has 9 terms consisting of linear effects of the

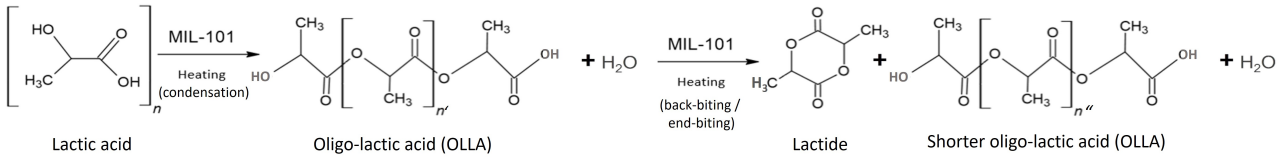


FIGURE 2 The synthesis of lactide from lactic acid catalyzed by MIL-101

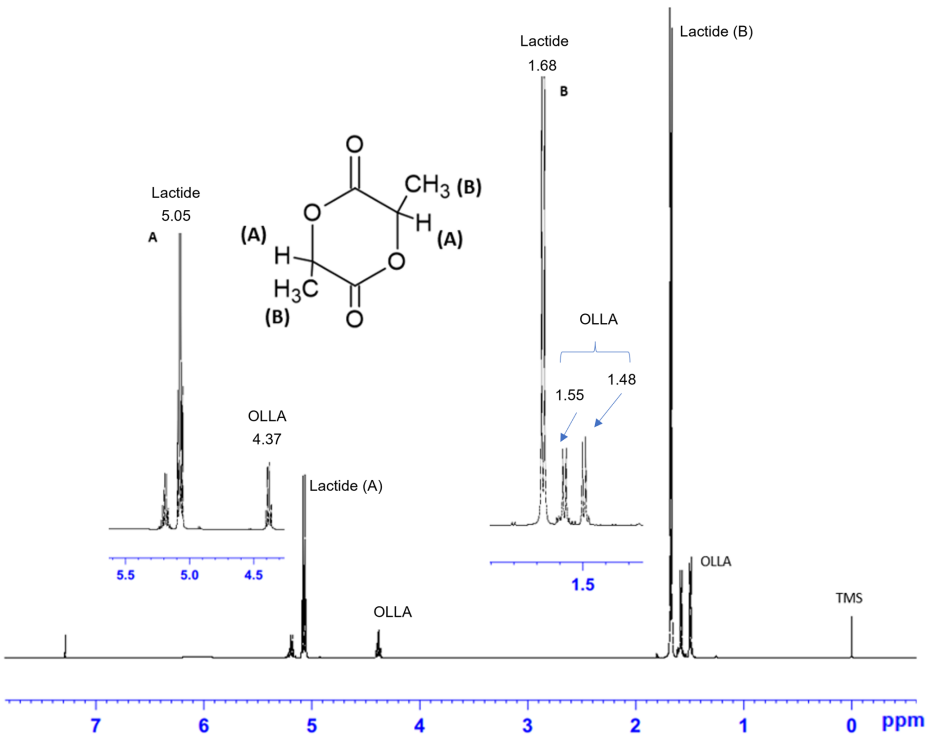


FIGURE 3 ^{1}H-NMR spectra of the crude Lactide. The ^{1}H-NMR spectroscopy was performed using Bruker Avance 500 MHz with $CDCl_3$ solvent.

3 variables, 3 interaction effects between variables, and quadratic effects of the 3 variables.

From the data in Table 1, A, B, and C are terms that express the linear effects. Variable A states the reaction temperature in the lactide synthesis process, B is the loading of the MIL-101 catalyst used, and C is the reaction time. The terms consisting of 2 letters showed the interaction effect of each variable, i.e., the interaction of A (temperature) and B (MIL-101 catalyst loading), A and C, as well as B and C. From the results of ANOVA modeling (Table 1), the terms AC, BC, B^2, and C^2 have *p*-value of less than 0.05. A *p*-value lower than 0.05 indicates that the term significantly affects the resulting response. This means that the interaction of temperature and time (AC) as well as MIL-101 loading and time (BC) had significant effects on the lactide produced. The respective quadratic effects of MIL-101 loading and reaction time are also significant to the resulting response. On the other hand, the linear effects of temperature, MIL-101 catalyst loading, and reaction time have no significant effect on the results obtained. This also applies to the interaction effect of temperature and MIL-101 catalyst loading (AB).

TABLE 1 F-value and *P*-value of each modeling term.

Term	F-Value	*P*-Value
A-Temperature	3.48	0.1354
B-Catalyst Loading	1.78	0.2534
C-Reaction Time	2.16	0.2153
AB	1.75	0.2565
AC	13.86	0.0204
BC	50.45	0.0021
A^2	1.30	0.3182
B^2	11.98	0.0258
C^2	64.99	0.0013

The resulting mathematical equation from the RSM is shown in Equation 1, where A, B, and C are temperature (°C), MIL-101 loading (% w/w), and time (hour), respectively. The predicted versus actual plot (Figure 4) implies that the developed model (Equation 1) could predict the lactic acid conversion well.

$$\begin{aligned} &Conversion\ of\ lactic\ acid\ to\ crude\ lactide\ (\%) \\ &= -90,1223 + 0,2556A + 21,8283B + 29,5761C \\ &+0,0223AB - 0,0315AC - 3,2752BC - 0,0004A^2 \\ &-3,2752B^2 - 1,9071C^2 \end{aligned} \quad (1)$$

The interactions of each variable on the conversion of lactic acid to lactide are shown in Figure 5. The graphs formed positive quadratic parabola so that the highest conversion of lactic acid to lactide can be obtained from the peak point of each curve. The curvature of Figure 5a is less visible than in Figures 5b and 5c, which is in line with the ANOVA result. In other words, the interaction of reaction temperature and time (AC) (Figure 5b), as well as the interaction of MIL-101 loading and time (BC) (Figure 5c), are more significant in affecting the conversion of lactic acid to lactide. From Figure 5, the highest conversion of 22.84% can be obtained at a temperature of 175 °C, a MIL-101 loading of 1.5% w/w, and a reaction time of 5 h.

The higher the reaction temperature, the reaction product will increase, but at an optimum point, the conversion will decrease with the higher temperature used. Increasing the temperature beyond this optimum temperature can also cause the quality of lactide to decrease, indicated by the formation of lactide with a more yellowish color. Studies of the two-step lactide synthesis process have also shown that the crude lactide produced will increase with increasing depolymerization temperature (Yoo et al. 2006). Still, increasing temperature will increase the possibility of racemization/isomeric change from lactide to meso-lactide (Botvin et al. 2020). This is also explained in the study conducted by Ehsani et al. (2014), that the rate of lactide synthesis will increase with the rise in the operating temperature, but increasing the temperature will also increase the chemical impurities in the crude lactide produced. At a temperature of < 215 °C, meso-lactide has been found and increases significantly at 230 °C (Ehsani et al. 2014). This was not expected to be occured here since the temperature used is < 200 °C. Hence, selection of the appropriate reaction temperature is important as it affects the conversion as well as the quality of the lactide product.

The catalyst used strongly influenced the reaction time in lactide synthesis (Hu et al. 2017). Figure 5c showed the interactions of MIL-101 loading and time form a positive quadratic parabola. The longer the reaction time, the con-

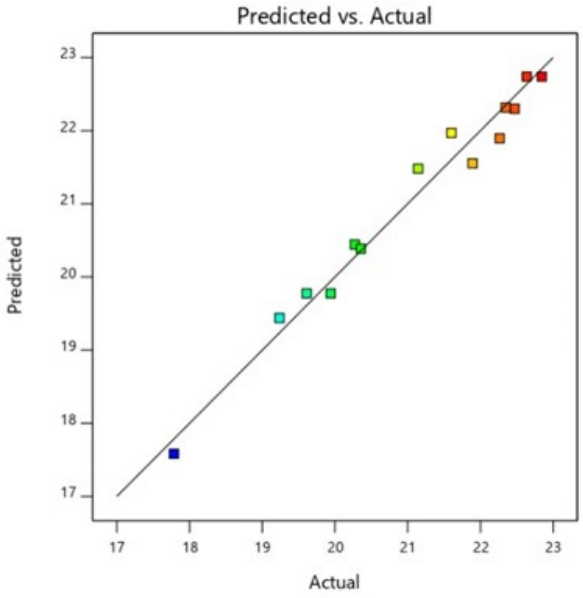
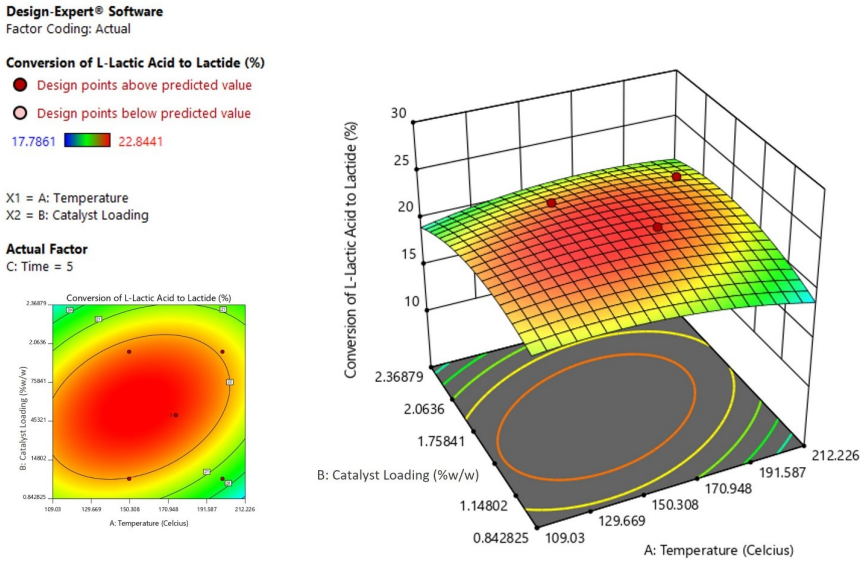
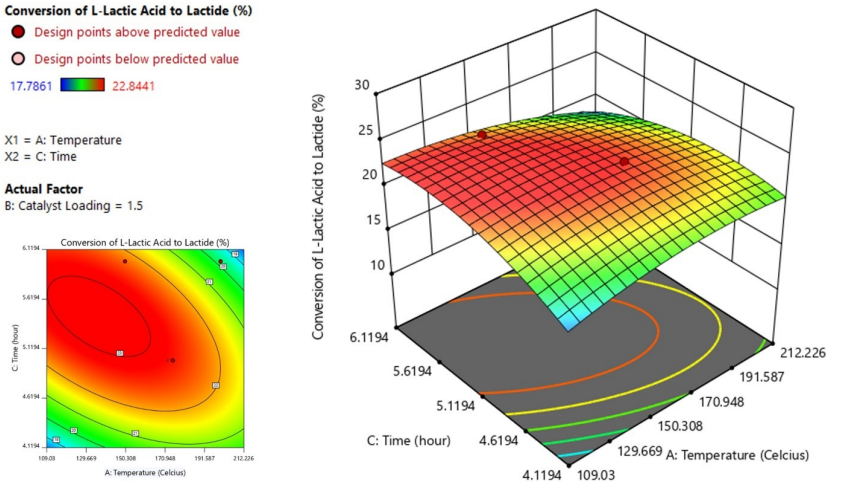


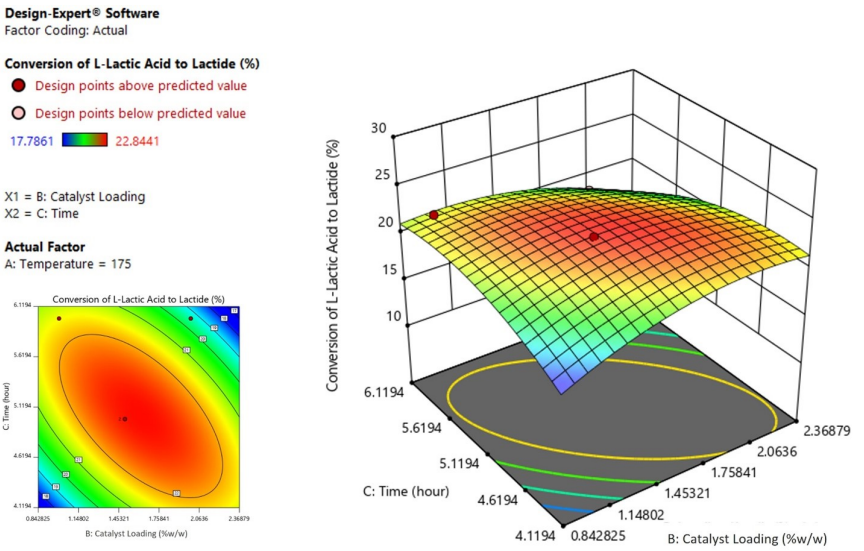
FIGURE 4 Predicted versus actual plot from the RSM analysis. The blue, green, yellow and red squares indicate the data points sorted by value (blue: the lowest, green: moderately low, yellow: moderately high, red: the highest value, relative to the experimental results).



(a)



(b)



(c)

FIGURE 5 Interaction of (a) Temperature and MIL-101 Catalyst Loading, (b) Temperature and Reaction Time, and (c) MIL-101 Catalyst Loading and Reaction Time on the Conversion of L-Lactic Acid to L-Lactide.

TABLE 2 Comparison of research results.

No	Method	Yield (%)	Catalyst	Reference
1	One-step synthesis of lactide	19.61–22.84	MIL-101	This Research
2		41–90	ZIF-8	Ghadamyari et al. (2018)
3	Condensation and Depolymerization of Lactic Acid	60–64	$Sn(Oct)_2$	Hu et al. (2017)
4		67.5–77.5	SnO	Yoo et al. (2006)
5		39–97	$SnCl_2$	Ehsani et al. (2014)
6		69.5	Creatin	Groot et al. (2022)
7		76	$Pb(NO_3)_2$	Upare et al. (2014)
8		77	PbO	Upare et al. (2014)
9		78.8	$SnCl_2$	Rahmayetty et al. (2015)
10		82	$Sn(Oct)_2$	Upare et al. (2014)

version of lactic acid to lactide will also increase, but at one point, it happens the other way around. With the addition of reaction time, the results obtained will decrease. In this synthesis, the lactide may react to form OLLA or turn back into lactic acid, depending on the operating conditions. It has also been reported in other study of D, L-lactide synthesis that the highest conversion was reached in 180 minutes, after which the results were stagnant (Moravek 2008). Reaction time needs to be considered to see the productivity of the process being carried out. If the reaction time is too short, the expected product may not have been formed, while if it is too long, the reaction process may not be effective anymore.

To observe the possible conversion that can be achieved by slightly reducing the temperature, MIL-101 loading, and reaction time, we optimized the variables further around the optimum point generated by the RSM (175 °C, 1.5% w/w MIL-101 loading, and reaction time of 5 h). This can be performed using the RSM optimization feature in the Design Expert 11 software. It was obtained that a lactic acid conversion of 21.83% can be achieved using a temperature of 150 °C, MIL-101 loading of 1.2%, and reaction time of 4.73 h. This means a high enough conversion, only 1% less than the optimum point, can be reached using more efficient operating conditions. To validate this finding, lactide synthesis was performed at this operating condition (150 °C, 4.73 h, and MIL-101 loading of 1.2%). The ^{1}H-NMR spectra shown in Figure 3 is indeed the spectra of the product obtained at this adjusted optimum operating condition. However, as seen in Table 2, the conversion of lactic acid to lactide from this study is still relatively low compared to other studies. Further research is needed to improve the conversion obtained. Nonetheless, this study has shown that MIL-101 can be used as the catalyst for one-step synthesis of lactide, which is a more efficient route to synthesize lactide than through the 2 steps condensation-depolymerization of lactic acid.

4. Conclusions

In this study, MIL-101 has been successfully synthesized and confirmed by the FTIR spectra. The obtained MIL-101 can be used as the catalyst for one-stage lactide synthesis from lactic acid. The formation of lactide was evidenced by the appearance of peaks at the typical chemical shift of lactide in the ^{1}H-NMR spectra of the product. Based on the RSM analysis, the quadratic effect of MIL-101 catalyst loading, the quadratic effect of reaction time, the interaction of reaction temperature and reaction time, as well as the interaction of MIL-101 catalyst loading and reaction time significantly affect the conversion of lactic acid. These are shown by the p-value of these modeling terms, which are less than 0.05. According to the model, the highest conversion that can be achieved is 22.84% at an operating condition of 175 °C, 5 h, and MIL-101 loading of 1.5% w/w. Nonetheless, by adjusting the optimization feature in the Design Expert 11 software, it was obtained that performing the lactide synthesis at a milder condition of 150 °C, 4.73 hours, and MIL-101 loading of 1.2% could result in a lactic acid conversion of 21.83%. This is only 1% lower than the highest possible conversion. Hence, this milder operating condition is considered as the optimum operating condition for one-step lactide synthesis using MIL-101 as the catalyst.

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Authors' contributions

CN, CAC, MG designed the study. CN carried out the laboratory work. CN, CAC, MG analyzed the data. CN, CAC, MG wrote the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

We declare that there are no competing interests.

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