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ENCAPSULATED ACIDIC ASPIRIN-BASED EUTECTIC SOLVENTS FOR ESTERIFICATION OF FREE FATTY ACID

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ABSTRACT

The combination of high free fatty acid (FFA) palm oil and non-edible microalgae oil presents a promising avenue for sustainable biodiesel production. Efficient catalyst development and innovative technologies are crucial, particularly for the esterification reaction in feedstock pre-treatment processes. In this study, two novel active pharmaceutical ingredients (API)-based deep eutectic solvents (DESs) were introduced. They derived from p*-toluenesulfonic acid monohydrate (PTSA) and benzenesulfonic acid (BZSA) combined with aspirin (ASA), encapsulated within medical capsules for safe handling and storage. These DESs effectively reduce FFA content from 11% to less than 2% under optimum conditions (1 wt% of DES catalyst dosage, 10:1 methanol-to-oil molar ratio, 60°C esterification reaction temperature and 60 min reaction time). The activation energies of the reaction using ASA:PTSA and ASA:BZSA based DES were determined as 53.11 and 39.20 kJ mol^{-1}, respectively, according to the pseudo first order reaction rate. Furthermore, FFA to fatty acid methyl ester (FAME) conversion rates remained above 50% for both DESs even after three consecutive recycling runs. The utilisation of API-based DESs enhances catalyst physical properties, recyclability for FFA esterification reactions, underscoring their potential in advancing biodiesel production processes.*

Keywords: deep eutectic solvent, encapsulation, esterification, free fatty acid, microalgae oil.

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INTRODUCTION

In the continuous efforts to reduce carbon emissions and advance renewable energy, diesel fuel derived from depletable fossil fuel sources may be substituted with renewable and environmentally benign biofuels such as biodiesel (Wang et al., 2023). Edible, refined oil crops such as soybean, rapeseed and palm oil are the primary feedstocks used in the present biodiesel production market. The utilisation of edible oil crops for biodiesel manufacturing may pose threats to food supply competition and create an economic imbalance (He et al., 2024; Mukhtar et al., 2022). Consequently, there has been a notable increase in research attention towards non-edible second-generation oil crops, such as jatropha oil, *Koelreuteria integrifolia* oil, mahua oil and *Pongamia pinnata* seed oil as alternative sources of feedstock for biodiesel production (Brahma et al., 2022;

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Sangeetha & Baskar, 2024; Zheng et al., 2024). Low commercial oil sources, such as waste cooking oil, animal fats and sludge oils have similarly been explored and demonstrated for biodiesel generation (Pongraktham & Somnuk, 2023; Rocha-Meneses et al., 2023; Singh et al., 2024). However, the lack of well-established waste oil reusability efforts, for example, collecting systems and supply chains, in many countries impedes waste oils from being fully utilised as raw materials for sustainable biodiesel. Thus, non-edible microalgae oil has emerged as a potential raw material to produce third- and fourth-generation biodiesel (Huang et al., 2023; Patnaik & Mallick, 2021).

Catalyst development and technologies play a significant role in the efficient conversion of the feedstocks, particularly for the esterification reaction in the feedstock pre-treatment process for biodiesel production. The use of mineral acids (such as sulphuric acid and hydrochloric acid) as homogeneous catalysts is required in the esterification reaction process due to the high free fatty acids (FFA) nature of the low-value feedstocks. However, their use is associated with high costs for separation and purification, along with concerns about equipment corrosion and the inability to recycle the catalyst (Dai et al., 2020). A viable alternative in homogeneous catalysts for the esterification reactions may be through the development of ionic liquids (ILs) and deep eutectic solvents (DESs) as catalysts (Bian et al., 2021; Li et al., 2021; Zhou et al., 2023). Compared to ILs, DESs offer several valuable advantages such as cost-effectiveness, biodegradability, environmental friendliness and can potentially incorporate natural ingredients (Mamtani et al., 2021). DESs are usually prepared as a homogeneous mixture by combining the hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) where the melting point is reduced significantly when combining the HBA and HBD. Generally, DESs are composed of organic halide salts and complexing organic agents such as amines, alcohols, carboxylic acids and amides (Al-Farsi & Hayyan, 2023). Due to their unique properties, DESs have received increased research focus and have been investigated for applications in biomass conversion and bioenergy production, such as for the esterification and transesterification of low-value feedstocks for biodiesel production, conversion and synthesis of 5-hydroxymethylfurfural and lignocellulosic treatment/valorisation (He et al., 2023; Liu et al., 2020; Tan et al., 2023; Zhou et al., 2023). Additionally, using *p*-toluenesulfonic acid monohydrate (PTSA) and benzenesulfonic acid (BZSA) as eutectic mixtures for acid-catalysed esterification offers several benefits and can reduce the hygroscopicity of the acid and the potential to reuse the catalyst. Moreover, PTSA is readily available and has been effectively used as a catalyst in protein and biodiesel production.

Recently, active pharmaceutical ingredients (APIs) such as paracetamol, ibuprofen and phenylacetic acid have been reported to be effective HBAs/HBDs in the formation of DESs, enabling the multifunctional applications of DESs such as in drug delivery, drug solubilisation and catalysts (Abbott et al., 2017; Hayyan et al., 2023; Shah et al., 2023). The use of APIs in the formation of DESs may have the potential to address the issues of highly abundant unused or expired drugs by repurposing their active ingredients. The increase in the production and consumption of pharmaceuticals has generated high volumes of pharmaceutical waste in the form of unused, unwanted or expired medicines (Freitas & Radis-Baptista, 2021). Improper disposal of excess medicine causes water resource contamination and toxicity exposure to the environment and public health (Aluko et al., 2022). To solve the negative impacts of excess waste drugs, studies have suggested several viable applications, such as the recovery and reutilisation of active pharmaceutical contents in waste drugs as reagents for organic syntheses (Pratama et al., 2020; Puzanova et al., 2019). Hence, the development of API-based DESs is prospective in advancing the applications of DESs while enabling the recovery of resources.

In this study, acidic API-based DESs were prepared from aspirin mixed with PTSA and BZSA for acid-catalysed esterification. The high-viscosity DESs were encapsulated in medical capsules to ensure safe handling and storage. Incorporating a catalyst within a confined space such as medical capsules can induce reagent molecules to interact under specific geometric constraints. This can result in reaction products exhibiting regio- and stereoselectivity that differs from typical solution conditions. The blending of microalgal oil with palm oil was performed to produce a non-edible oil with lower viscosity and cost. The resulting oil mixture underwent pre-treatment through acid-catalysed esterification to decrease the FFA content and convert it into FAME. Through batch esterification, the optimum conditions for each variable, in particular, DES catalyst dosage, methanol molar ratio to oil, esterification reaction temperature and esterification reaction times were investigated. Additionally, reaction kinetic studies were conducted to examine the reaction order, and recyclability studies were carried out to assess the catalyst's reusability.

MATERIALS AND METHODS

Materials and Chemicals

As raw material to produce FAME, an untreated high acidity oil mixture was prepared by blending

15 wt% microalgal oil with low grade palm oil (denoted as LGPO-MO). Acetylsalicylic acid (aspirin) (≥99%) and two types of acidic catalysts, including *p*-toluenesulfonic acid monohydrate (PTSA) (≥98.5%), 8-hydroxyquinoline-5-sulfonic acid monohydrate (98%), 1-amino-2-hydroxy-4-naphthalenesulfonic acid (≥96%) and benzenesulfonic acid (≥90%) were purchased from Merck (Malaysia) Sdn. Bhd., for the analysis of FFA, potassium hydroxide pellets (>85%) were procured from Merck (Malaysia) Sdn. Bhd.

Preparation of Aspirin-based DESs

Aspirin-based DES were prepared by adding aspirin to PTSA or BZSA at a molar ratio of 1:3 (denoted as ASA:PTSA and ASA:BZSA respectively in this study). The DESs were prepared under a moisture controlled environment, where the mixture was stirred at 400 rpm at temperatures of 80°C-90°C for 2 hr. The resultant DESs were viscous liquids at elevated temperatures and formed a gel-like appearance when cooled down to room temperature (28°C). The visual appearances of the ASA:PTSA and ASA:BZSA DESs were brownish-purple and chalk white, respectively.

Encapsulation of DES Catalysts

The prepared API-based DES catalysts with the desired dosage were transferred and encapsulated in the medical capsules using a syringe as represented in *Figure 1* (Hayyan et al., 2023). To reduce viscosity, DESs were pre-heated to 45°C prior to encapsulation. Then, the encapsulated DES catalyst was stored for use in the esterification. Gelatine-based medical capsules have limited solubility in non-aqueous solvents like methanol due to their protein-derived nature from collagen. Heating accelerates the dissolution of gelatine capsules by breaking down their structure, allowing the encapsulated DES catalysts to be released into the oil within 20-30 min. As a result, before initiating the esterification reaction, the encapsulated DES catalyst was added to untreated oil and preheated to 60°C to fully release the catalysts. Methanol was subsequently added, and the batch esterification was performed under magnetic stirring.

Analysis of FFA Content

The initial FFA content of the untreated LGPO-MO was recorded as 11%. The acceptable FFA concentration in the treated product was limited to below 2%. According to the American Oil Chemists' Society Ca 5a-40 method, the standard method for determining FFA in untreated oil and treated oil is the acid-base titration technique with KOH as the base component and phenolphthalein as an indicator. The initial FFA concentration was calculated from the titrated volume of KOH and the weight of oil as detailed by the Ca 5a-40 method (AOCS, 2017). Subsequently, the FFA conversion was calculated using Equation (1).

$$\text{Conversion} = \frac{\text{FFA}_{\text{initial}} - \text{FFA}_{\text{final}}}{\text{FFA}_{\text{initial}}} \times 100\% \qquad (1)$$

where, $\text{FFA}_{\text{initial}}$ and $\text{FFA}_{\text{final}}$ are the initial and final FFA contents (%), respectively.

Experimental Setup for FFA Esterification Reaction

Before the esterification pre-treatment process, the LGPO-MO which appears in a semi-solid

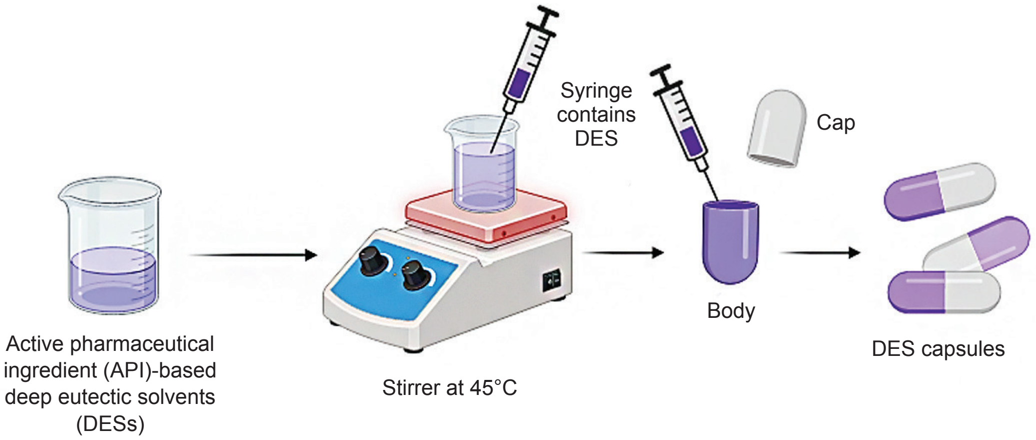

Figure 1. Preparation of active pharmaceutical ingredient (API)-based deep eutectic solvent (DES) catalysts with the desired dosage and encapsulated in medical capsules using a syringe.

state at room temperature was preheated until a homogeneous phase was achieved. Methanol and an untreated LGPO-MO were then added into a conical flask, forming a solution of not more than 50 mL based on the molar ratio required. The esterification reaction of the oil was conducted with a magnetic stirrer at 400 rpm over a specific reaction time period whilst restricting the temperature to below 80°C.

Using single-factor optimisation, the optimum operating condition of esterification was studied using different values of parameters. The experiment was repeated by varying the catalyst dosage (0.25-1.50 wt%), methanol-to-oil mixture molar ratio (4:1-12:1), reaction temperature (40°C-80°C), and reaction time (40-80 min). At the optimum conditions, validation experiments were carried out by repeating the esterification reaction three times to validate the optimum operating conditions. Furthermore, the recyclability of the DESs as catalysts was studied. The separation and recovery of the DESs were carried out by centrifugation for 5 min at 3,000 rpm. After centrifugation, the product mixture underwent phase separation by gravity, forming two distinct layers: The top layer consisted of excess methanol mixed with the DES catalyst, while the bottom layer consisted of the treated oil. The top layer was recovered and transferred to treat a fresh batch of LGPO-MO mixture under the optimal conditions for esterification reaction without purification. The reaction was performed repeatedly, employing the recycled DES catalyst, to evaluate its reusable effectiveness.

RESULTS AND DISCUSSION

Screening of Acidic Catalyst

The FFA content of the treated oil at the end of the esterification reaction using different types of acidic catalysts were demonstrated in *Table 1*. The use of PTSA and BZSA as catalysts led to a significant reduction in FFA in the treated oil, decreasing from 11.00%-0.87% and 0.66%, respectively. This demonstrates that both catalysts have high catalytic activity while 1-amino-2-hydroxy-4-naphthalenesulfonic acid and 8-hydroxyquinoline-5-sulfonic acid monohydrate did not show any significant reduction in the FFA content.

PTSA and BZSA are strong organic acids that have high solubility in organic solvents such as methanol, making them effective for serving as HBDs in the formation of DESs. Besides, they are considered homogeneous catalysts, leading to a more uniform distribution and interaction with the reactant compared to the heterogenous catalysts. Additionally, homogeneous PTSA and BZSA with a low melting point (38°C and 51°C, respectively) can easily be prepared as DES. Therefore, PTSA and BZSA catalysts are selected for the formation of the DES due to their promising properties and high efficacy in reducing FFA levels to below 1%.

Effect of DES Catalyst Dosage

Catalyst loading is crucial for completing a chemical reaction and generating the desired product. To study the optimal amount of catalyst required, the dosage of DESs as acid catalysts was investigated at 0.25-1.50 wt%. As shown in *Figure 2*, the increase in DES catalyst dosage promotes a higher reduction and conversion of FFA, which is attributed to the larger area of contact between the reactants and catalysts provided by a higher catalyst dosage facilitating the esterification reaction. At 1.00 wt% of ASA:PTSA and ASA:BZSA DES catalyst dosages, the FFA content was decreased from 11.00% to final levels of 1.77% and 1.71%, respectively. Hence, the optimum dosage of DES catalyst using ASA:PTSA and ASA:BZSA DES in FFA esterification reactions was observed at 1.00 wt%, aiming to achieve FFA levels below 2.00%, which serves as a benchmark for FFA reduction. This consideration also takes into account the associated costs related to catalyst consumption if the DES catalyst dosage is further increased. In comparison, the optimal catalyst dosage for pre-treating highly acidic crude palm oil using methanesulfonic acid as the homogeneous acid for FFA esterification was determined at 1.00 wt%, while requiring a reaction temperature of 60°C and a 30 min reaction time (Hayyan et al., 2012).

TABLE 1. SCREENING OF DIFFERENT TYPES OF ACIDIC CATALYST

Catalyst	Phase in oil	FFA (%)	Conversion (%)
1-amino-2-hydroxy-4-naphthalenesulfonic acid	Homogeneous	8.10	25.24
8-hydroxyquinoline-5-sulfonic acid monohydrate	Homogeneous	6.20	42.78
PTSA	Homogeneous	0.87	91.97
BZSA	Homogeneous	0.66	93.88

Note: PTSA - p-toluenesulfonic acid monohydrate; BZSA- benzenesulfonic acid.

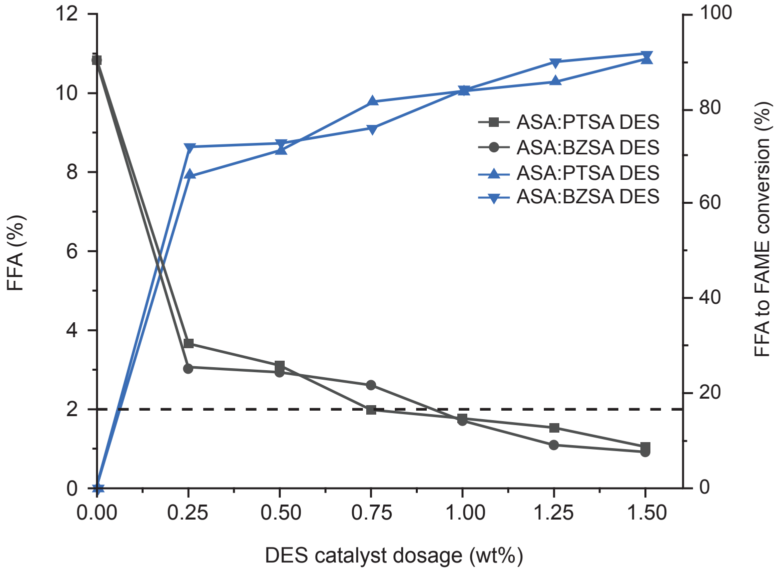

Figure 2. Effect of DES catalyst dosage on FFA content reduction at a temperature of 60°C and a 30 min reaction time for the esterification of LGPO-MO.

Effect of Methanol-to-oil Molar Ratio

Methanol requirement is commonly expressed as a molar ratio to the raw material (untreated oil) used in biodiesel production. Although the stoichiometric equation requires a 1:1 methanol to oil molar ratio in the esterification reactions, an excess amount of methanol is usually used in practice to ensure continuous reaction and to maximise the yield. The experiments were repeated by testing the methanol to oil molar ratio from 4:1 to 12:1, whilst keeping other variables constant. As presented in *Figure 3*, at the low methanol molar ratio of 4:1, both the ASA:PTSA and ASA:BZSA DES catalysts exhibit low catalytic activity, resulting in a low reduction of FFA content to 7.19% and 3.41%, respectively. The FFA content of LGPO-MO mixture was decreased to below 2% when utilising a 10:1 molar ratio for both DES catalysts. There was no significant change in FFA conversion and reduction observed when the amount of methanol used exceeded a 10:1 molar ratio, suggesting that the optimal molar ratio for the esterification pre-treatment process of FFA was determined. Likewise, an optimal methanol-to-oil molar ratio of 10:1 was reported for the acid-catalysed esterification of acidic crude palm oil at a catalyst dosage of 3 wt% MTPB:PTSA DES (Hayyan et al., 2022).

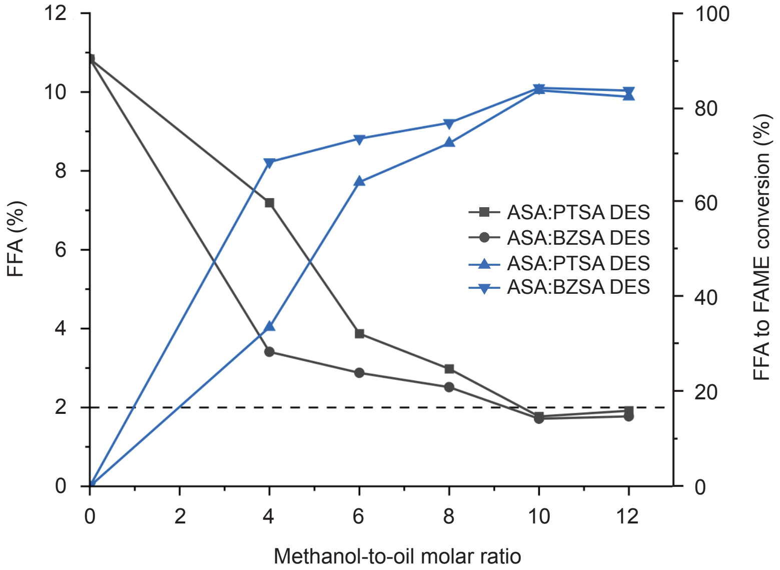

Figure 3. Effect of methanol to oil molar ratio on FFA content reduction at a temperature of 60°C and a 30 min reaction time for the esterification of LGPO-MO at DES dosage of 1 wt%.

Effect of Reaction Time

Esterification reaction time is a crucial factor in kinetic analyses and the reactor design, and optimal contact time between the catalyst and the reactant should be provided to ensure an effective esterification reaction. Thus, the duration for batch esterification reactions is important in achieving an efficient process and cost-effective scaling up in an industrial application. The optimal reaction time was investigated within the range of 20-80 min and presented in *Figure 4*. The increase in reaction time improves the FFA conversion and reduction as a prolonged reaction time allows the protonation during the reaction, aiding in overcoming the activation energy required for the esterification process to take place. The FFA concentration of the treated LGPO-MO product drops to below 2% within the 60 min reaction time mark achieved by the ASA:PTSA and ASA:BZSA DESs. Hence, the optimal esterification reaction time for the pre-treatment process employing ASA:PTSA-DES and ASA:BZSA-DES were found to be 60 min to ensure the maximum formation of the desired product within a minimal timeframe.

Effect of Reaction Temperature

Methanol as a key component in the esterification reaction, tends to have a high evaporation rate at a higher temperature. When reaction temperatures rise, energy consumption for industrial-scale manufacturing will also increase, driving up overall process running costs. To conduct the optimisation test for the reaction temperature, the optimised catalyst dosage of 1 wt%, methanol to oil molar ratio of 10:1 and esterification reaction time of 60 min (determined previously) were performed constantly while the reaction temperature was adjusted from 40°C to 80°C. As illustrated in *Figure 5*, at a reaction temperature of 60°C, the FFA levels decrease to the acceptable level of <2%. However, beyond 60°C, the FFA conversion rate decreases for both the DESs. Elevating the temperature resulted in decreased formation of FAME due to the production of gaseous methanol above its boiling point of 65°C. This caused a decline in the amount of methanol adsorbed on the catalyst surface. Therefore, a 60°C esterification reaction temperature is selected as the optimum for the esterification process with a yield of 84.50%. For comparison, the esterification of sludge palm oil using sulphuric acid catalyst resulted in a yield of 83.72% under the same optimum process conditions of a 10:1 molar ratio of methanol to oil, a reaction temperature of 60°C, and a reaction time of 60 min (Hayyan et al., 2011).

Validation of Reaction Conditions and Catalyst Recyclability

The recyclability performances of the DESs were investigated at the optimal operating conditions. The catalysts were reused without adding fresh catalysts for multiple successive runs. Results in *Figure 6* indicated that both catalysts maintained good catalytic performance in the first run, achieving a reduction of FFA content down to 1.58% and 2.02% using ASA:PTSA and ASA:BZSA, respectively. In the second and third runs, lower but considerable catalytic activity was observed, with FFA content ranging from 3.00%-5.00%. However, during the fourth run, the recycled catalyst's effect was insignificant. Thus, the acceptable reusability cycle of both DESs as catalysts were three cycles. Losses of DES catalyst during recycling and unseparated catalyst remaining in the treated oil

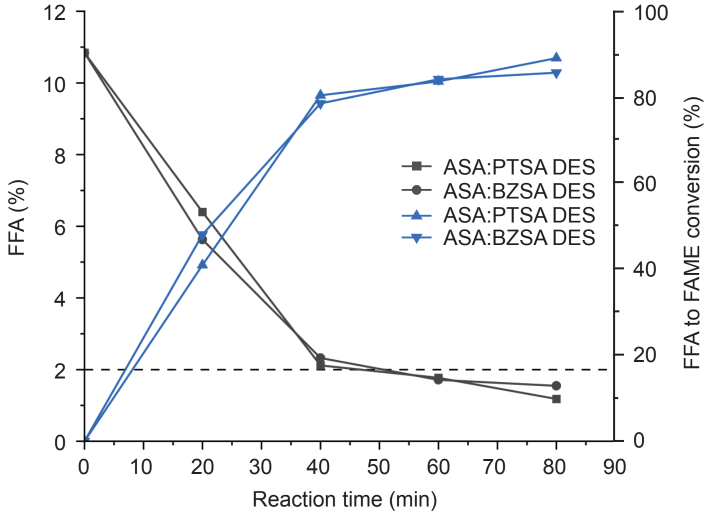

Figure 4. *Effect of reaction time on FFA content reduction at a temperature of 60°C with 10:1 molar ratio for the esterification of LGPO-MO at a DES dosage of 1 wt%.*

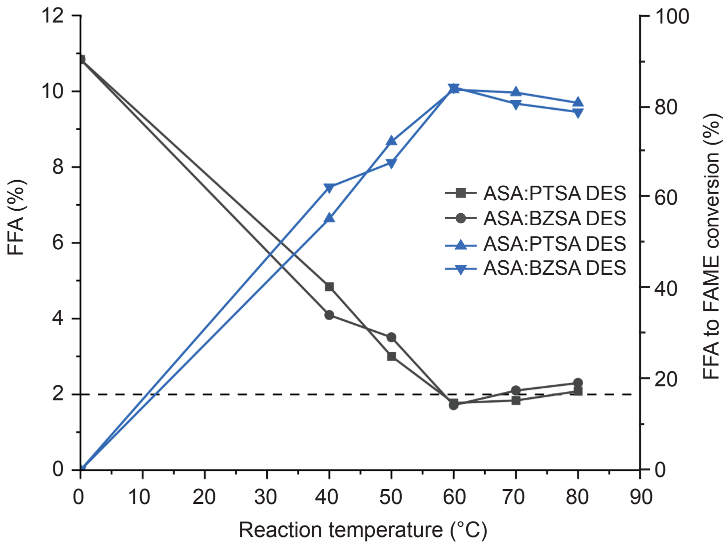

Figure 5. Effect of reaction temperature on FFA content reduction at 30 min reaction time, 10:1 molar ratio for the esterification of LGPO-MO at a DES dosage of 1 wt%.

were potential reasons for the reduced conversion rates. To achieve desired FFA levels, extending the reaction time or increasing methanol concentration in each reuse of the DES catalyst could be explored. In comparison, the recyclability of choline chloride-based DESs employed for the esterification treatment of high acidic crude palm oil was similarly recorded for a maximum recyclability of three cycles (Hayyan et al., 2013).

Evaluation of Reaction Kinetics

The FFA esterification reaction kinetics of the ASA:PTSA and ASA:BZSA DES catalysts were evaluated by correlating the empirical data with the pseudo first order model according to prior literature, where the reverse rate of reaction could be neglected due to the excess use of methanol in enhancing the forward reaction (Chai et al., 2014). The linearised pseudo first order model is presented in Equation (2).

$$In\ [FFA]_t = (-k)(t) + In\ [FFA]_0 \qquad (2)$$

where, k is the reaction rate constant, t is the reaction time, $[FFA]_t$ is the FFA concentration at a specific time and $[FFA]_0$ is the initial FFA concentration. The experimental data was fitted to Equation (2) to yield the corresponding k values at the specific temperatures with a satisfactory coefficient of determination (R^2) as presented in *Figure 7*.

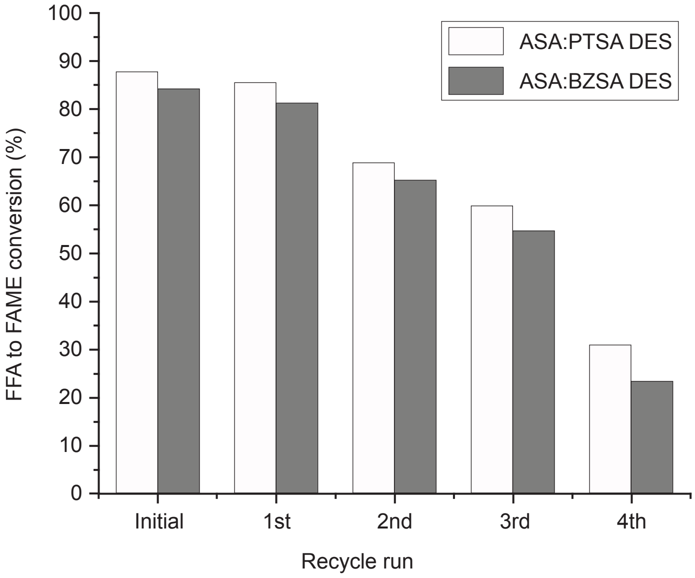

Figure 6. FFA conversion at different recycle run at a temperature of 60°C, 30 min reaction time with 10:1 molar ratio for the esterification of LGPO-MO at a DES dosage of 1 wt%.

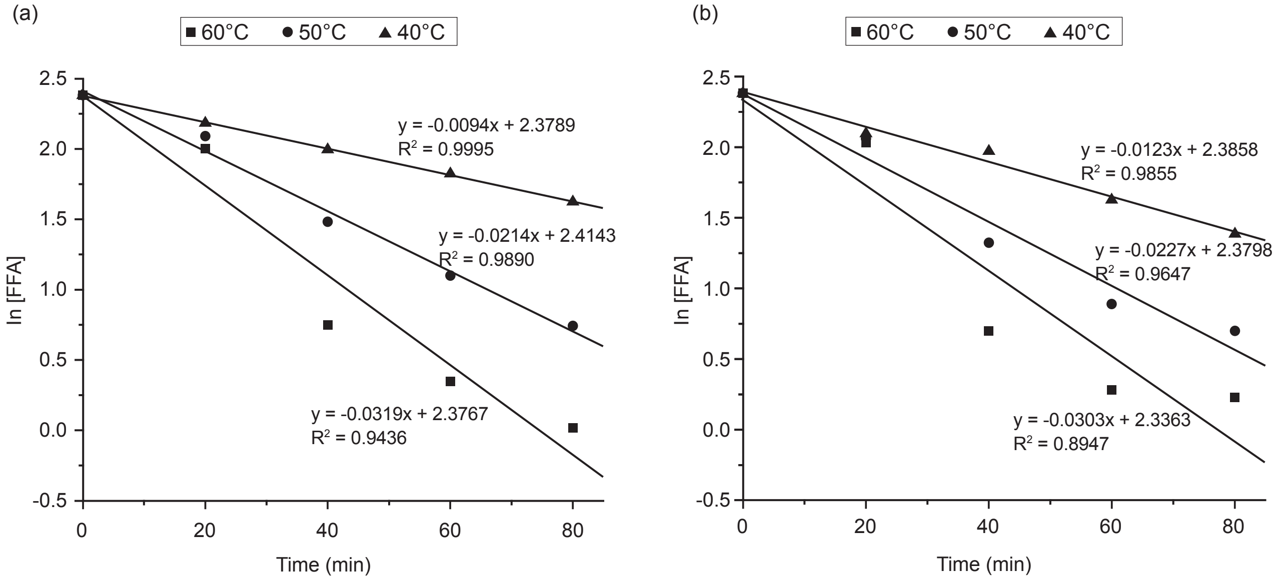

Figure 7. Temperature plot of the first order kinetic modelling using (a) ASA:PTSA DES, and (b) ASA:BZSA DES.

Subsequently, the k values were fitted to the linearised form of the Arrhenius equation [Equation (3) and Equation (4)] to compute the activation energy (E_a) and frequency factor (A) values. In the Arrhenius equation, R is the gas constant (8.314 J mol^{-1}·K) and T is the absolute temperature (K).

$$k = Ae^{-\frac{Ea}{RT}} \tag{3}$$

$$ln\ k = -\frac{E_a}{RT} + ln\ A \tag{4}$$

As presented in *Figure 8*, the activation energy was calculated as 53.11 and 39.20 kJ mol^{-1} with frequency factor values of 7.32 and 4.48 min^{-1} for ASA:PTSA and ASA:BZSA DESs, respectively. The results imply that higher energy input is required to overcome the activation energy for the reaction to occur when using ASA:PTSA-DES compared to ASA:BZSA-DES. Additionally, the frequency factor of the reaction using ASA:PTSA-DES is significantly higher than that of ASA:BZSA-DES, suggesting that ASA:PTSA-DES promotes a greater number of successful collisions between reactant molecules (LGPO-MO and methanol). The activation energies of the DES catalysts were comparable to existing values reported in the literature (38.82-59.58 kJ mol^{-1}) for the esterification of various low value oils such as animal fats, non-edible seed oils and waste cooking oils (Encinar et al., 2021; Guo et al., 2021; Nayak et al., 2021).

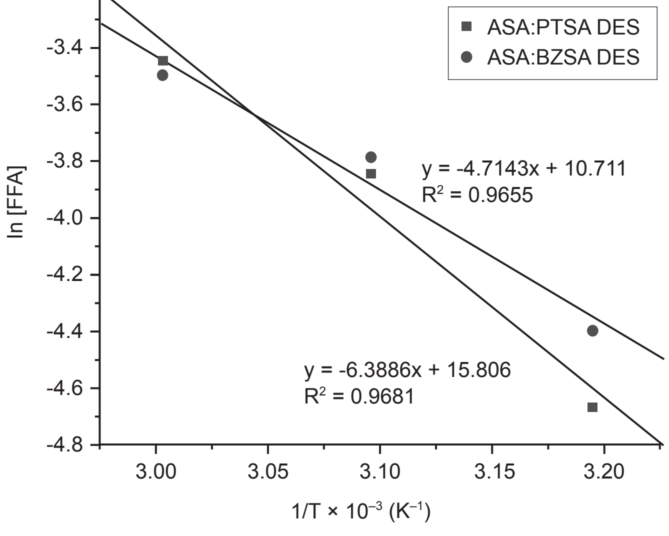

Figure 8. Arrhenius plot for FFA esterification using ASA-based DESs.

CONCLUSION

In this study, two novel encapsulated API-based DESs catalysts (ASA:PTSA and ASA:BZSA) were prepared for the acid-catalysed esterification pre-treatment of LGPO-MO mixture with high FFA content. Under optimised conditions, both DES catalysts exhibited high catalytic activity in the acid-catalysed esterification reaction, leading to a significant reduction in the FFA content of the LGPO-MO mixture from 11% to below 2%. Both the ASA:PTSA-DES and ASA:BZSA-DES gave the optimal performance with the following reaction conditions: DES catalyst to oil ratio of 1 wt%, methanol to oil molar ratio of 10:1, reaction temperature of 60°C, and reaction time of 60 min. The DESs were successfully recycled and reused three times with considerable catalytic activity. The reaction kinetics of the DESs were examined where the activation energies for ASA:PTSA-DES and ASA:BZSA-DES were 53.11 and 39.20 kJ mol^{-1} with frequency factor values of 7.32×10^6 and 4.48×10^4 min^{-1}, respectively. Overall, the introduced encapsulated ASA:PTSA and ASA:BZSA DES catalysts in this study offered benefits and superior catalytic activity performance in terms of safe handling during pre-reaction procedures. Thus, the formation of DESs from API is worth being investigated for the pre-treatment process of high acidity feedstock and for advancing biodiesel production.

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