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Intensification of Carboxylic Acid Esterification using a Solid Catalyst in a Mesoscale Oscillatory Baffled Reactor Platform

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Abstract

Intensified production of carboxylic acid esters has been investigated using a mesoscale oscillatory baffled reactor (meso-OBR), operated in continuous multi-steady states, dynamic and multi-dimensional modes. This study was performed to investigate the suitability of the reactor for solid-liquid reactions, capacity for quality steady states and rapid process development. A heterogeneously catalysed hexanoic acid esterification with methanol was studied in a meso-OBR packed with AmberlystTM 70 resin as an acid catalyst. The esterification conditions investigated were feed molar ratios in the range of 1.5:1 - 30:1 and residence times in the range of 1min - 20min. The meso-OBR was operated at oscillatory conditions of 4.5Hz frequency and 8mm amplitude (centre-to-peak) and reaction temperature of 60°C. Clear steady states were achieved at all the residence times used, with maximum hexanoic acid to methyl hexanoate conversion of $95.4 \pm 1.0\%$ obtained at 20min residence time and 30:1 methanol to acid molar ratio. Methyl ester conversions were $98.5 \pm 1.5\%$ at 20min residence time and 30:1 methanol to acid molar ratio for dynamic screening, and $98.2 \pm 1.1\%$ at 14min residence time and 21:1 methanol to acid molar ratio for the multi-dimensional mode. Use of dynamic screening required 16% less time and reactant compared to the multi-steady states approach. A more significant reduction in the process development time and reactants requirement, approximately 30% compared to the multi-steady states approach, was achieved using the multi-dimensional approach. This demonstrates a substantial reduction in process development time, another major advantage of the meso-OBR platform as the choice reactor in process development for multiphase reactions. The AmberlystTM 70 entirely regained its catalytic activity after water spiking, and was not permanently deactivated by water.

Keywords: Continuous esterification, multi-steady states, dynamic mode, multi-dimensional approach, Amberlyst™ 70, process screening.

1. Introduction

The use of heterogeneous catalysts [1, 2] and process intensification strategies [3, 4] are becoming desirable process design routes for productions of valuable chemicals. Such processes reduce the materials requirement and save costs, and are at the heart of current drive for Green Chemistry processes. Use of heterogeneous catalysts in intensification reactors leads to more efficient utilisation of raw materials, energy efficiency and safer operation through smaller volume of reactors and lower system footprints [5]. The use of heterogeneous catalysts is advantageous due to reductions in the downstream purification stages and the costs of continual catalyst replacement. Acid catalysts are widely used in various chemical production processes such as alkylation, acylation, dehydration, condensation and esterification reactions. The esterification reaction is one of great importance due to its widespread application in the production of millions of tons of polyesters yearly, along with a large variety of esters for productions of fine and specialty chemicals used in fragrances, pharmaceuticals, and pesticides [6, 7]. Carboxylic acid esterification is also an important reaction in the productions of biodiesel from feedstock that contains high amount of free fatty acids (FFA). This is integral to current biodiesel technologies [8], as it allows for the use of lower quality feedstocks for biodiesel production, as these feedstocks typically contain large quantities of FFA. Another bio-energy related application of acid catalysts is in the areas of pre-treatments of bio-oils derived from fast pyrolysis of biomass, through esterification to improve the bio-oil stability through elimination of short chain acids and deoxygenation [9, 10].

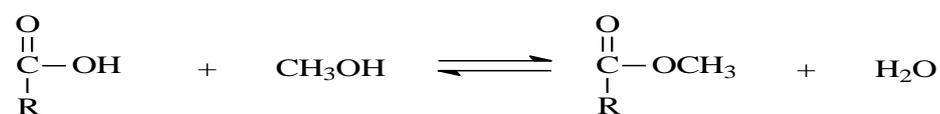


Figure 1: Carboxylic acid esterification

Esterification is an acid-catalysed reaction of organic acids with alcohol to produce carboxylic acid esters and water as by-product (Figure 1). This reaction is limited by the equilibrium which determines the conversion of the reactants. The water produced by the reaction should be continuously removed in order to allow for the reaction equilibrium to be driven in favour of the forward reaction. Generally, the esterification rate and ester yields are increased using higher alcohol to FFA molar ratios, catalyst concentration and pressure [11]. Continuous esterification of organic acids with methanol also reduces catalyst poisoning by water and improves the ester yield [2]. Further improvement in the heterogeneous acid-catalysed esterification processes could be achieved through the application of intensified reactors with multiphase mixing capabilities that would overcome the effects of mass transfer in the solid-liquid-liquid reactions, and allow for operations in continuous mode.

Many process intensification strategies have been considered for continuous esterification, such as reactive distillation [3, 12, 13], microchannel-flow reactors [14], fixed bed processes for fatty acids [15, 16], pervaporation methods [3, 17], and the use of meso-OBR [2]. The intensified continuous esterification reactors are designed to allow for utilisation of solid catalysts, ensure reduced reactor size and plug flow characteristics, and to achieve products of uniform composition at lower capital and running costs. The meso-OBR overcomes these problems through good multiphase mixing capability and plug flow behaviour arising from oscillating the reaction fluid through the orifices of equally spaced baffles [4]. Oscillatory baffled reactors have been widely investigated for application in multiphase fluid mixing, and their capacity for enhanced heat and mass transport and particle suspension [4, 18-22]. Net fluid flow in the OBR is decoupled from the oscillatory flow, which provides for independent control of the mixing intensity and residence time of the reaction [22]. This makes the reactors suitable for screening reactions that have long residence times, using reactors of greatly reduced length-to-diameter ratio. A mesoscale OBR is a millimetre scale version of the conventional OBR, typically consists of a 5mm inner diameter tube with equally spaced baffles. The meso-OBR has been designed particularly for screening of reactions because of their small volume [23]. It has a small

volume which allows for operation at low flow rates and reductions in the amount of reagent used and also the waste [24, 25]. Previous studies [2, 26, 27] have shown that the formation and cessations of vortices in the OBR is an effective and controllable method of uniform suspension of solid particles such as catalysts. These characteristics of OBRs makes them ideal for screening of multi-phase reactions, as well for suspension and screening of solid catalysts. Operation with solids is also very challenging for flow chemistry platforms based on microchannels, for the simple reason that representative catalyst particles do not fit in the channels. This work investigated the applications of the OBR as a reactor platform for rapid process development in solid-liquid reactions. Process parameters for heterogeneously catalysed carboxylic acid esterification with the Amberlyst™ 70 resin catalyst were screened in continuous multi-steady states, dynamic and multidimensional modes. Carboxylic acid esterification was selected for this study due to the importance of the process in industrial productions of fine chemicals and biofuels.

2. Materials and Methods

2.1. Materials

Materials used in the experiments were hexanoic acid (99%, Sigma-Aldrich), anhydrous methanol (99.8%, Sigma-Aldrich), methyl octanoate analytical standard (99.8%, Sigma-Aldrich), methyl hexanoate analytical standard (99.8%, Sigma-Aldrich), and Amberlyst™ 70 resin catalyst - consisting of sulphonic acid functionalised divinylbenzene/styrene copolymer. The Amberlyst™ 70 resin was supplied by Dow Chemical Company, Netherland. Physical and chemical properties of the Amberlyst™ 70 resin could be found in the chemical datasheet and in existing studies [28-30].

2.2. Experimental Procedures

The Amberlyst™ 70 resin was screened for catalysis of hexanoic acid esterification using the meso-OBR platform. The reactor was a jacketed integrally baffled glass tube of about 770mm length, 8mm outer diameter, 5mm inner diameter and periodic constrictions of 2.5mm diameter along the length of the tube at 7.5mm spacing (Figure 2). The baffled tube was fully packed with 400 – 500µm beads of the Amberlyst™ 70 resin which had been conditioned by washing it several times using methanol.

The base and top of the packed baffled tube were sealed with 5mm discs of stainless steel wire mesh (#60) of 160 µm wire diameter and 263µm apertures to constrain the catalyst beads from leaving the reactor. The reactor was then assembled with the base, connected through Swagelok fittings to three Confluent syringe pumps (Eurodyne Ltd). One of these pumps was used to provide the oscillations at 2Hz - 4.5Hz frequency and 4mm - 8mm amplitude, and the other two to provide the net flows of hexanoic acid and methanol (Figure (2b)). The syringe pump used for oscillation was connected to the base of the reactor, and the fluid mixing inside the reactor provided by adjusting the speed of the piston movement (frequency) and the oscillation amplitude (centre-to-peak) of the pump [31]. The syringe pumps were controlled via a PC interface. Prior to each experiment, the pumps were initialised, and set at the required mixing intensity (amplitude and frequency) and reactants net flow rates.

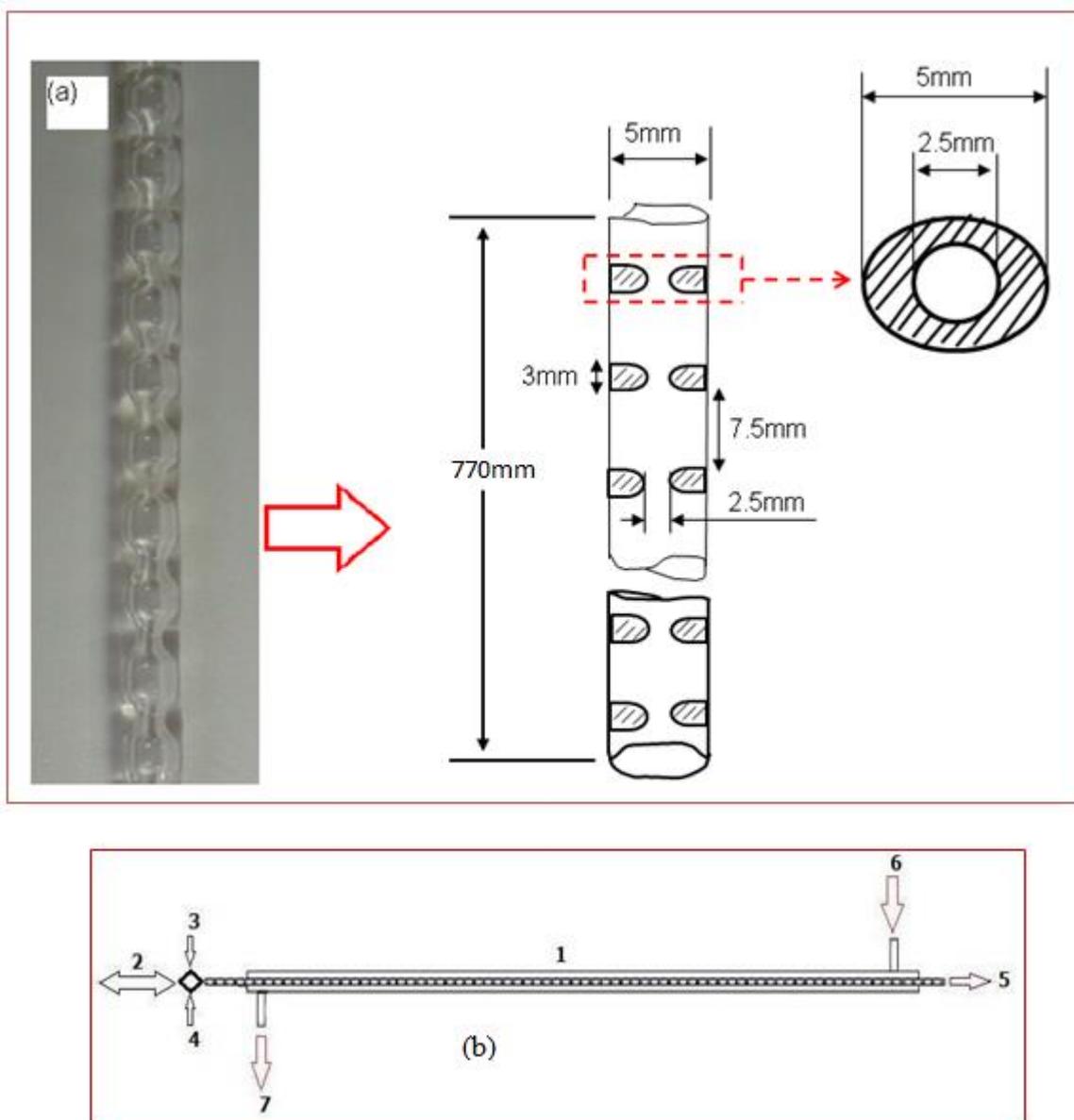


Figure 2: (a) Integrally baffled meso-OBR and the schematics of the internal configuration, (b) diagrammatic view of the meso-OBR used in the reaction: jacketed meso-OBR (1), oscillation line (2), Feed lines (3 & 4), product/sampling point (5), hot water in (6), and hot water out (7).

The volume of the reactor after packing with 9g of Amberlyst™ 70 resin was 8.3mL, and the volume of the reactor without packing was 15.2mL. The reaction temperature was maintained by the circulation of heated water through the jacket of the meso-OBR using a temperature-control water bath (Ecoline, LUADA E100). Hexanoic acid and methanol feed were dispensed from reservoirs maintained at the reaction temperatures inside the water bath. Prior to each experiment, continuous

circulation of methanol over the Amberlyst™ 70 resin packed bed was carried out to swell the resins and make the pores accessible to the reactants [32, 33]. The reactor was operated at atmospheric pressure for all the experiments.

The effect of oscillation conditions was investigated at 4mm - 8mm amplitude and 2Hz – 4.5Hz to ensure that the meso-OBR was operated at mixing independent region. Mixing intensity had no effect in the hexanoic acid esterification at 30:1 molar ratio of methanol to acid and 10 min residence time (Figure 3). The reaction was not dependent on mixing intensity at oscillation conditions of ≥ 4 mm amplitude and ≥ 4.5 Hz, corresponding to oscillatory Reynolds numbers $Re_o \geq 1300$. Mass transfer and external resistances were minimal at these oscillation conditions. The net flow Reynolds numbers (Re_n) and Re_o were calculated as shown in equations (1) and (2).

$$Re_n = \frac{\rho U D}{\mu} \quad (1)$$

$$Re_o = \frac{\omega x_o \rho D}{\mu} = \frac{2\pi f_o x_o \rho D}{\mu} \quad (2)$$

Where:

ρ : density of the fluid (kg.m^{-3}); U : superficial net flow velocity (m.s^{-1})

ω : angular oscillation frequency (rad.s^{-1}); μ : dynamic viscosity of the fluid (Pa.s).

D : internal diameter of the tube (m); f_o : oscillatory frequency (Hz)

x_o : centre-to-peak amplitude of oscillation (m)

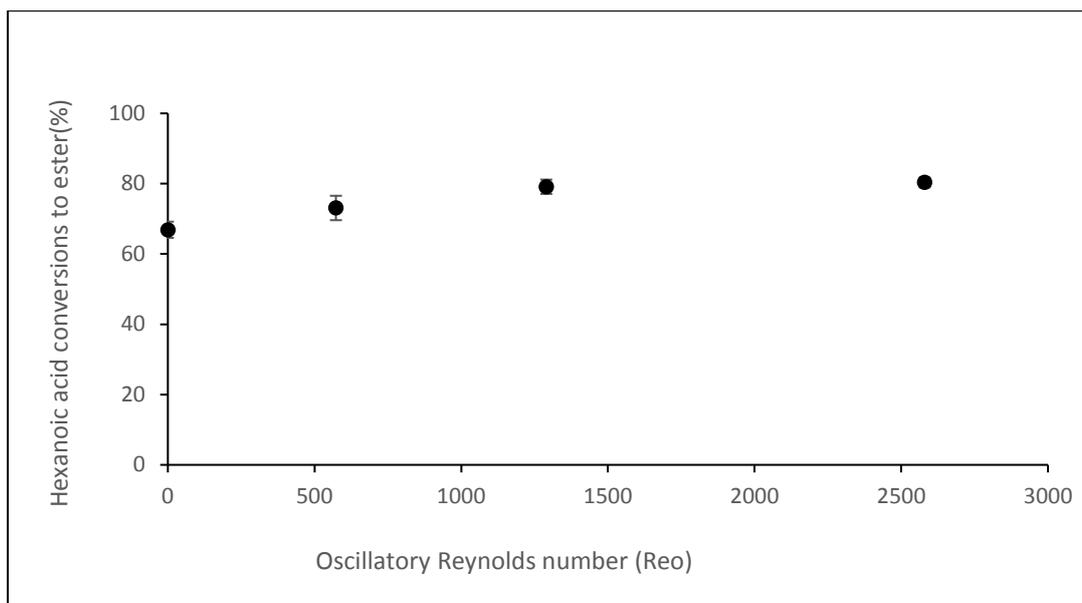


Figure 3: Effects of oscillatory mixing intensity for hexanoic acid esterification at 30:1 methanol to acid molar ratio, 10min residence time and meso-OBR packed with 9g of Amberlyst™ 70 catalyst.

2.2.1. Multi-Steady States Study of Continuous Esterification Parameters for Hexanoic Acid

Process parameters for the hexanoic acid esterification were investigated through continuous screening in multi-steady states mode. The reaction conditions studied were methanol to hexanoic acid molar ratios of 1:1 to 30:1, residence times (τ) of 1 - 20min and reaction temperature of 60°C. Effects of residence times, methanol to hexanoic acid molar ratios and water were investigated in multi-steady states mode. The multi-steady states study of the reaction time was performed at methanol to hexanoic acid molar ratio of 30:1, with the residence time linearly ramped from 2.5min, 5min, 10min to 20min, followed by a “downward” ramp from 20min, 10min, 5min to 2.5min. The effects of feed molar ratio was studied through linear ramp of methanol to hexanoic acid molar ratio from 1:1, through 2:1, 4:1, 15:1 to 30:1, at fixed residence time of 10min.

Water tolerance of the Amberlyst™ 70 was investigated via exposure to methanol containing 2.5vol% water for the continuous esterification, and by controlled spiking the system with water (1mL water spike for reactions using anhydrous methanol and 0.5mL spike for reactions using non-anhydrous methanol with 2.5vol% water) after enough time was allowed for the reactor to attain steady state.

2.2.2. Dynamic and multidimensional Study of the Continuous Esterification Parameters

The hexanoic acid esterification parameters were investigated in a dynamic mode by continuously varying the residence time linearly at constant methanol to hexanoic acid molar ratio of 30:1, from 2.5min to 20min at the interval of 2.5min. Each residence time was held for 2.5min which allowed high throughput of the reaction screening. In the multi-dimensional parametric screening of the hexanoic acid esterification, the residence time and the methanol to acid molar ratio were continuously varied linearly: residence time varied at an interval of 2.5min in the range of 2.5min - 20min, and the methanol molar ratio varied at the interval of 1.5 in the range of 1.5:1 - 30:1. The multi-dimensional screening was designed to investigate any possible combination of reaction conditions that allows for maximum hexanoic acid conversion at shorter time and less cost.

2.2.3. Samples Collections and Analysis

Several samples were collected in a 2mL screw cap vials at predetermined real times, depending on the residence times, and stored at -20°C in a freezer. About 20 – 50mg of each sample was measured into a 2ml GC vial and diluted with 500µL of methanol in order to bring the sample within the range of the FID detector on the GC. This was followed by the addition of 500µL of methyl octanoate (8mg/mL of methanol) into the diluted sample. GC responses of the methyl octanoate internal standard and the methyl hexanoate were calibrated before the sample analysis. About 0.5µL of the sample mixture was injected into the column manually using a 5µL GC syringe (SGE). The syringe was rinsed thoroughly with clean methanol before sample injection to avoid any contamination. The samples were analysed for their methyl hexanoate esters content with a 5890 Hewlett Packard Series II gas chromatography equipped with CP Wax Capillary column (BPX70). The GC oven temperature was programmed as follows: starting temperature at 50°C held for 3min, ramped at 30°C/min to 150°C and held for 2min, and finally ramped at 30°C/min to 210°C and held for 5min. The total running time was approximately 15.3min per injection. Methyl hexanoate contents of the samples were obtained

based on the BS EN 14103:2011 method for quantification of methyl esters, from where the hexanoic acid conversions were calculated.

3. Results and Discussions

3.1. Multi-steady states Screening

The methanol to hexanoic acid molar ratio of 30:1 was used over a range of 2.5min to 20min residence time. These consisted of 7 consecutive residence times imposed on the meso-OBR system through linear ramping. Steady states were achieved for the multi-steady states screening at all the ramped residence times of 2.5 – 20min (Figure 4). The results clearly showed that a step change occurred between residence times, similar to that reported elsewhere [34]. The flows inside the meso-OBR were therefore at a high degree of plug flow at these experimental conditions, resulting in a tight control of residence time and effective mixing, which allowed steady states to be achieved quickly with little variation in hexanoic acid conversion.

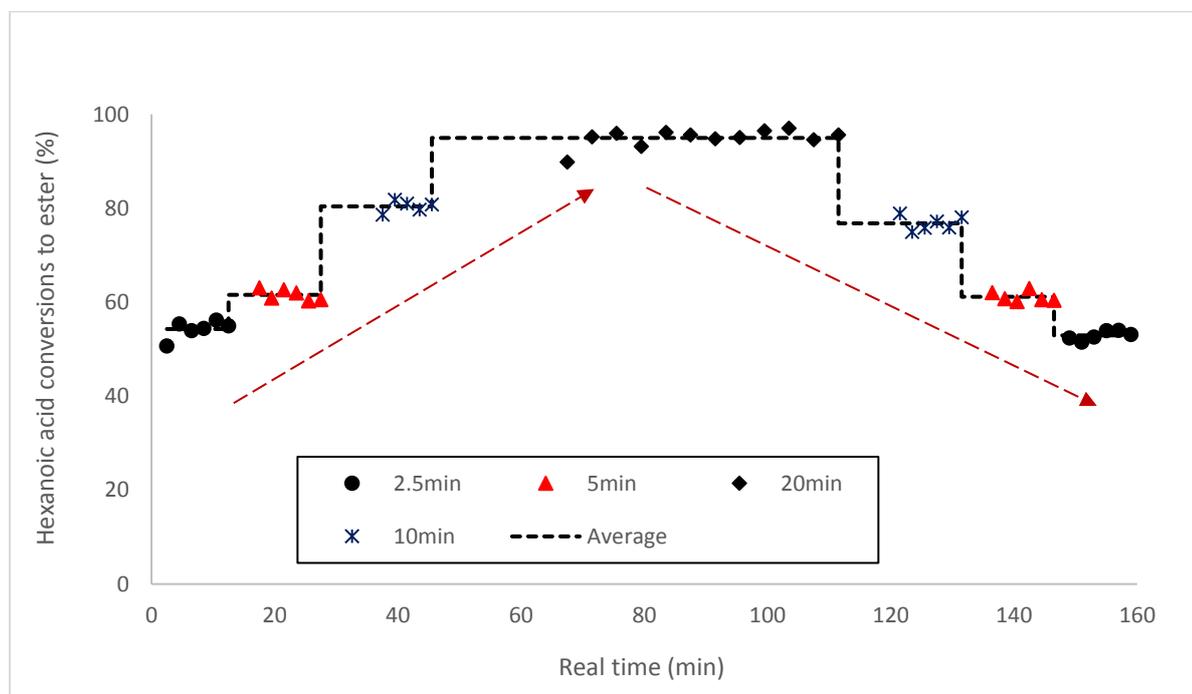


Figure 4: Effects of residence time on esterification reaction at 30:1 molar ratio, 60°C, oscillation conditions of 8mm and 4.5Hz, 9g Amberlyst™ 70 catalyst packing in meso-OBR.

The induction times for the various steady states achieved were in the range of $1.2 - 1.4\tau$, which are consistent with induction period of 1.5τ reported for the integrally baffled meso-OBR in homogeneous base-catalysed transesterification of rapeseed oil [31]. Generally, the hexanoic acid conversions increased with residence times from $55.0 \pm 0.9\%$ at 2.5min, $61.6 \pm 1.2\%$ at 5min, $80.1 \pm 1.4\%$ at 10min, to $95.4 \pm 1.0\%$ at 20min, for the multi-steady states screening at 30:1 methanol to hexanoic acid molar ratio and 60°C reaction temperature. The hexanoic acid conversions were consistent and reproducible for the “upward” and “downward” residence times ramping as shown in the Figure 4. The increases in hexanoic acid conversions with residence times were due to the longer contact time between the reagents and the catalyst, which was expected. There was no visible hysteresis in the hexanoic acid conversion, an indication of plug flow behaviour and good mixing in the meso-OBR. The AmberlystTM 70 resin was found to possess a high degree of catalytic stability and reusability, consistent with what has been reported [29].

In the multi-steady states reactions, the data points in each clear and consistent step are consistent with numerous batch reactions conducted in series. This is one of the advantages of the meso-OBR system: it allows reaction parameters be screened rapidly in a much more efficient manner.

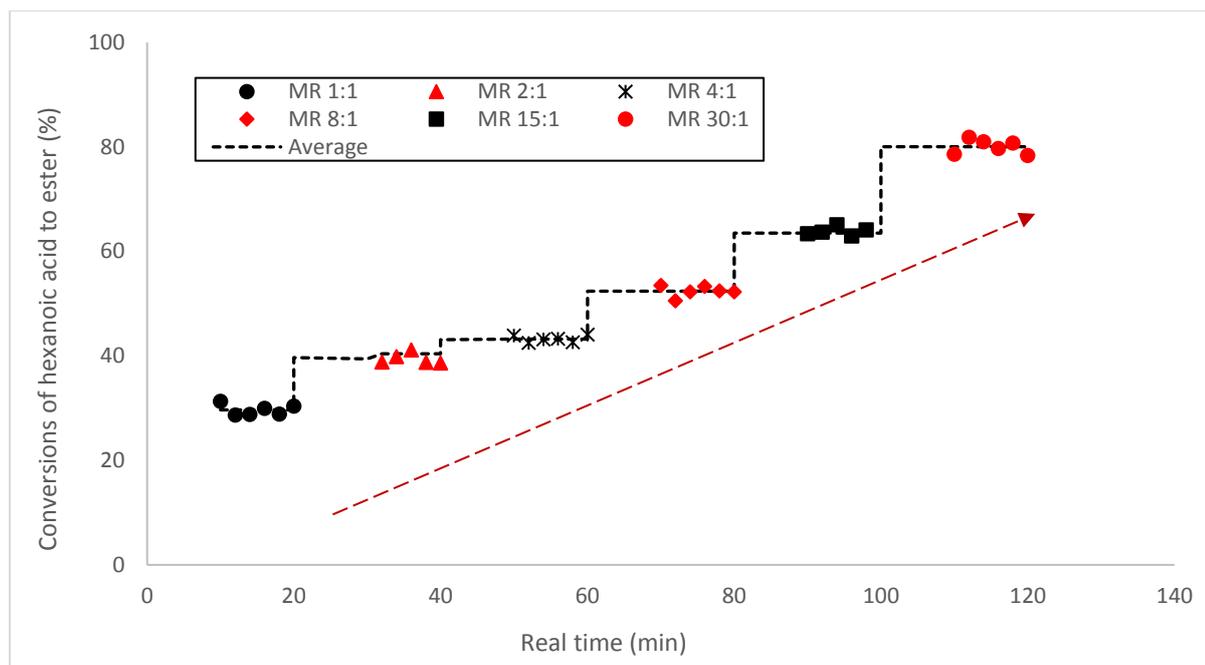


Figure 5: Effect of feed molar ratios for hexanoic acid esterification at 60°C, oscillation conditions of 8 mm and 4.5 Hz, and 9g Amberlyst™ 70 catalyst packing in meso-OBR.

Figure 5 also shows the results of the multi-steady states screening at the ramped feed molar ratios for the hexanoic acid esterification at 60°C and 10min residence time. The meso-OBR equally achieved steady states at all feed molar ratios studied with no hysteresis. There was a positive correlation between the hexanoic acid conversion and methanol molar ratio. This trend was expected due to the requirement of excess methanol to drive the reaction equilibrium to favour methyl hexanoate ester production. The average conversions of hexanoic acid to ester at the various methanol -to-acid molar ratios were $29.7 \pm 1.1\%$ at 1:1, $43.3 \pm 0.7\%$ at 4:1, $52.4 \pm 1.0\%$ at 8:1, $63.5 \pm 1.1\%$ at 15:1 and $81.2 \pm 1.3\%$ at 30:1. These results show that the extent of increase in hexanoic acid conversion diminished as the methanol molar ratio increased. Therefore, an optimisation between the cost of methanol versus hexanoic acid conversion or product yield would be required to minimise reagent use.

The catalytic activity of the Amberlyst™ 70 was evaluated in terms of the Turnover Number (TON) and Turnover Frequency (TOF) to allow for comparison of its performance with other solid catalysts. Cumulative TON of 31, corresponding to TOF of 93 h^{-1} , was calculated from Figure 4 at 20 min

residence times for the hexanoic acid esterification at 30:1 molar ratio, 60°C, oscillation conditions of 8mm and 4.5Hz and catalyst packing of 9g Amberlyst™ 70 catalyst. The turnover frequency was calculated as TON of the catalyst per unit time, whereas TOF is the number of moles hexanoic acid converted to methyl ester per mole of the catalytic active sites, i.e. $TOF = TON/time$. This TOF is higher than the values previously reported for hexanoic acid esterification in using PrSO₃H-SBA-15 catalyst, which were 57 h⁻¹ in meso-OBR [2] and 31 h⁻¹ in stirred tank batch reactors [35]. When compared with other studies that applied Amberlyst™ 70 resin as catalyst, the TOF calculated from this study was higher than 69 h⁻¹ reported for Amberlyst™ 70 in esterification of mixed succinic and acetic acid with ethanol [28], and about 85h⁻¹ for acetic acid and 12h⁻¹ for butyric acid in a batch esterification of the acids with methanol in a 75ml capacity 316 Stainless Steel autoclave reactors at 60°C and mixing speeds in the range of 0–1400 rpm [36].

The lower TOF in the above works [28, 36] for the Amberlyst™ 70 catalyst is perhaps due to mass transfer limitations arising from poor mixing. Another factor that probably contributed to the lower TOF could be the competitive adsorption of water on the active sites of the Amberlyst™ 70. This is important considering that those experiments were carried out in a batch mode; where reactively-formed water remained in the reaction mixture and in contact with the catalyst. Operation in continuous plug flow mode should prevent accumulation of water on the catalyst surface. Generally, there is a decrease in carboxylic acid esterification rate with alkyl chain length as reported for C₂-C₈ acid esterification catalysed by H₂SO₄ and SAC-13 [37], and C₃ – C₁₆ acid esterification by PrSO₃H-SBA-15 [2]. Such decreases are attributed to a combination of polar and steric influences of the alpha substituent on the carboxylic group. Therefore, inductive effects were responsible for the lower TOF reported for butyric acid as compared to acetic acid [36]. Inductive effects may lead to increase in carboxylate electron density with alkyl chain length which favours initial protonation; however, the electrophilicity of the carbonyl simultaneously decreases, resulting in reductions of the subsequent rate of alkoxy insertion [37].

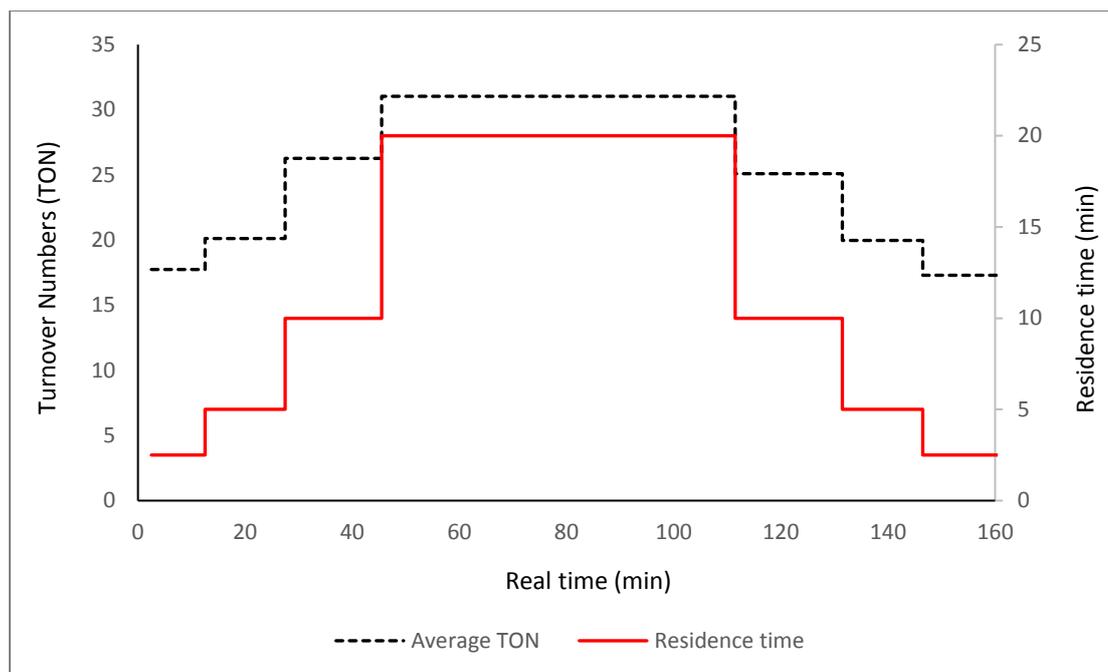


Figure 6: Cumulative TON of the Amberlyst™ 70 catalyst at various ramped residence times for hexanoic acid esterification at 30:1 molar ratio, 60°C, 8mm and 4.5Hz oscillation conditions and Amberlyst™ 70 catalyst packing of 9g in meso-OBR.

Figure 6 shows that similar TON were obtained at corresponding residence times for the upward and downward ramps. This suggests that there was no loss in the catalytic active sites, and that the Amberlyst™ 70 has good stability. Previous work [2] indicated that there was gradual deactivation of PrSO₃H-SBA-15 in esterification of hexanoic acid with methanol, which was attributed to leaching of the active sites into the reaction mixture and poisoning by water accumulation at the active site, displacing the equilibrium towards the hexanoic acid formation. Such deactivation was not observed with Amberlyst™ 70 catalyst. Further investigation on the effects of water on the Amberlyst™ 70 catalysed esterification carried out through esterification with water-laden methanol and controlled water spiking of the methanol feed are discussed in the section 3.2.

3.2. Effects of Water on the Hexanoic Acid Esterification

The investigations on the effects of water on Amberlyst™ 70 resin catalysed hexanoic acid esterification showed that the system was not permanently poisoned by water. Adsorption of water on

the catalytic active sites was reversible. Steady state conversion of the hexanoic acid was restored within 1.4 to 1.6 times the residence time after spiking with 1.0mL of water for esterification with anhydrous methanol and 0.5mL of water for the reaction using methanol that contained 2.5vol% of water, as shown in the Figure 7(a). This was probably due to the removal of any water adsorbed on the catalyst surface by the continuous inflow of fresh methanol into the packed bed of Amberlyst™ 70 in the meso-OBR. In batch esterification processes, any water introduced into the system may adsorb irreversibly and poison the catalyst. This would lead to a permanent deactivation of the affected active sites of the catalyst. Catalysts used in esterification processes should ideally be water-tolerant to prevent catalyst deactivation. Presence of water in an esterification reactor could also lead to hydrolysis of the produced esters as the reaction equilibrium would favour the reverse reaction.

The most significant effects of the water spike on the Amberlyst™ 70 packed meso-OBR were observed at 28min running time, corresponding to 12min after the water spiking, for both anhydrous methanol and non-anhydrous methanol. Considering the fact that the residence time of the reactor was 10 minutes, it is sensible for the effect of water on the system to occur at this point. At a mean residence time of 10 minutes, the system had a response time of approximately 2 minutes. The hexanoic acid conversions dropped from the average values of about 80% for the anhydrous methanol and 75% for the water-laden methanol, to minimum conversions of 43.5% and 56.3% respectively, after 12min of water spiking.

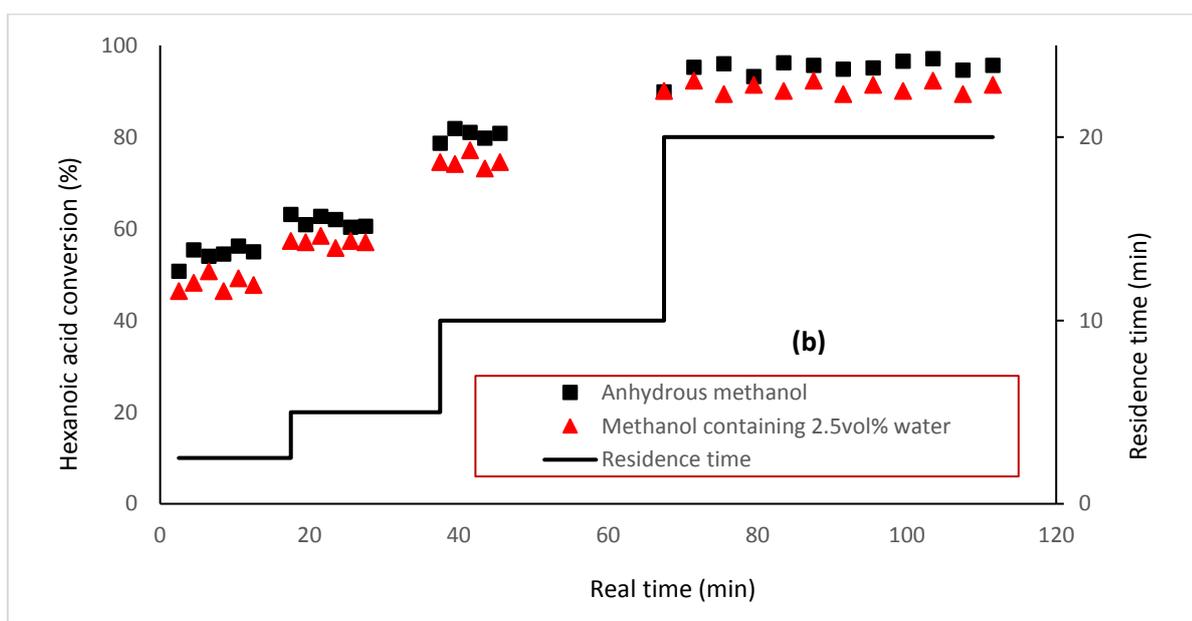
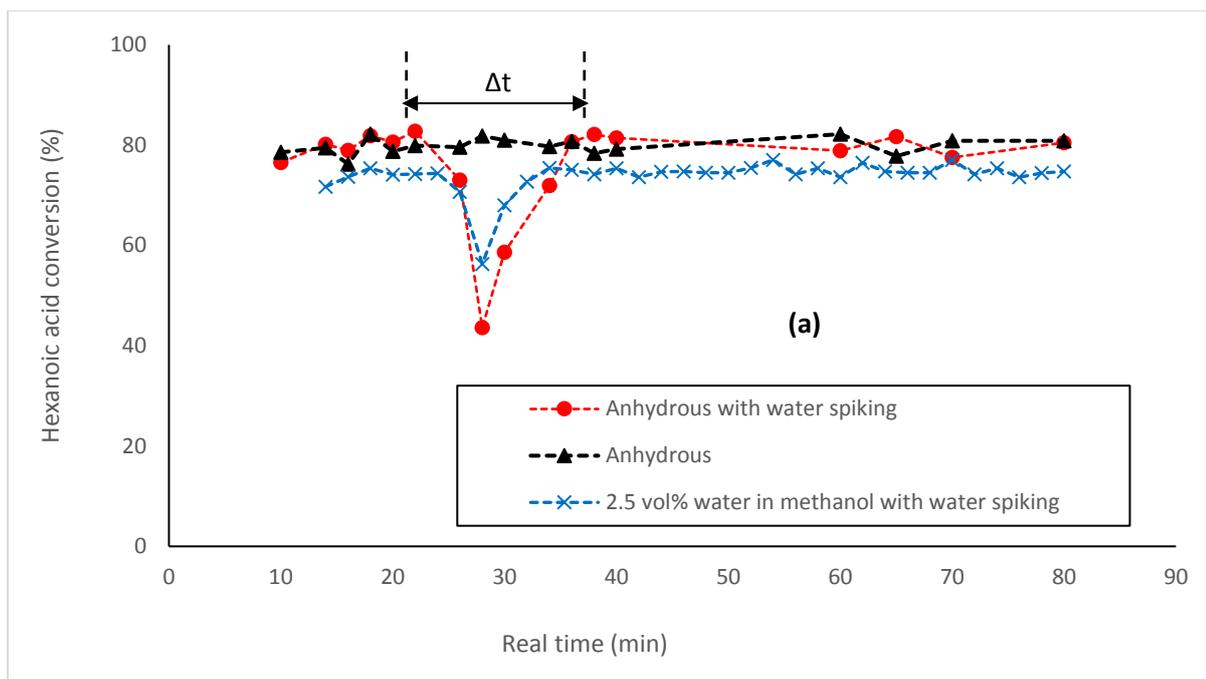


Figure 7: Hexanoic acid esterification at 30:1 molar ratio, 60°C, oscillation conditions of 8mm amplitude and 4.5Hz, and catalyst packing of 9g in meso-OBR: (a) with water spiking for reactions using anhydrous methanol and methanol containing 2.5vol% water, (b) steady states conversions for anhydrous methanol and methanol containing 2.5vol% water (Δt = catalyst recovery time).

The calculated maximum decreases in the hexanoic conversions were approximately 46% for injections of 1mL of water into the anhydrous methanol system and 25% for the injections of 0.5mL of water into the non-anhydrous methanol system. The decrease in the hexanoic acid conversions in

both cases were proportional to the amount of water injected. This decrease could be due to dilution of the methyl hexanoate concentration by the slug of injected water as it flows through the reactor, hydrolysis of methyl hexanoate due to reverse esterification reaction, and competitive adsorptions of the injected water on the active sites of the Amberlyst™ 70 catalyst.

The results in the Figure 7(a) clearly showed that the Amberlyst™ 70 packed meso-OBR system had recovered after 36 – 38min running time; therefore, the system took approximately 14min to 16min to recover from the water spike, corresponding to 1.4 - 1.6 times the residence time. Recovery times for the reactor after water spiking were similar to the induction time (time to reach steady state) for the Amberlyst™ 70 packed meso-OBR. The system reverted to the original average hexanoic acid conversion showing that the catalytic activity is entirely regained and that water was not permanently adsorbed on the active sites of Amberlyst™ 70 catalyst. More studies on the effects of water on the Amberlyst™ 70 through continuous esterification of hexanoic acid using methanol that contained 2.5vol% of water is shown in the Figure 7(b). The results followed the expected trend: theoretically, the conversion of the hexanoic acid was expected to be lower when the methanol contained water. This result allowed us to evaluate further whether continuous flow of water into the reactor was capable of permanently deactivating the catalyst. Although the anhydrous methanol system achieved approximately 5% higher hexanoic conversion than the methanol that contained water, no evidence of complete loss of activity was found after prolonged esterification of hexanoic acid using methanol that contained water.

Water poisoning is a common problem in esterification processes. This has been reported for esterification of acetic acid with methanol at 60°C in the presence of H₂SO₄ and SAC-13 catalysts [38, 39]. Another study has also shown that water has deleterious effect on acrylic acid esterification by butanol over Cs_{2.5}H_{0.5}PW₁₂O₄₀, SO₄/ZrO₂, Amberlyst-15, Nafion-H and H₃PW₁₂O₄₀, where the equilibrium conversions decreased by 24 %, 99 %, 69 %, 48 %, and 42 % respectively upon addition of one equivalent of water [40]. The sulphated zirconia was the most severely affected, probably due

to permanent deactivation through adsorption of water on the active sites. In esterification reactions, water is the major by-product, so water poisoning is particularly problematic to the catalytic system. Irreversible water adsorption at the active sites is widely believed to cause deactivation of hydrophilic solid acid catalysts, necessitating the search for hydrophobic catalysts which are able to expel water from catalyst surface [41].

The AmberlystTM 70 packed meso-OBR was found to be tolerant to presence of water even at a reasonable concentration. For instance, only a 5% decrease in the hexanoic acid conversion was observed when 1 mmol/min of water was added continuously through the methanol feed. Generally, the thermodynamic equilibria of the esterification and hydrolysis reactions determine the extent of carboxylic acid conversion to esters. For instance, here, hexanoic acid and methanol in the feed reach equilibrium with the produced esters and water, when the reaction is carried out in batch. At this condition, there is a constant competitive adsorption and desorption of water on the active sites of the catalyst. The AmberlystTM 70 resin is resistant to permanent deactivation by water; therefore, adsorption of water on the surface of the catalyst is reversible.

In the continuous hexanoic acid esterification with water spiking, the constant flow of hexanoic acid and anhydrous methanol into the meso-OBR system enhanced removal of water molecules adsorbed on the -SO₃H active sites. Use of the continuous meso-OBR prevents any water that was introduced into the system from accumulating on the surface of the catalyst. Therefore, complete recovery of the catalyst after water-spiking was attributed to resistance of AmberlystTM 70 resin to permanent deactivation by water, and the continuous flow of anhydrous methanol. The continuous flow of methanol into the system prevents water accumulation on the surface of the catalyst, minimising the rate of ester hydrolysis, thereby enhancing the esterification reaction. This agrees with a previous study showing that water-spiking has a lower effect on carboxylic acid esterification in continuous flow reactors than in batch [2].

The meso-OBR platform lends itself to rapid process screening, as the reactor allowed a wide range of experimental parameters to be investigated in a single experiment, particularly through dynamic and multi-dimensional screening which are discussed in the section 3.3. This is in contrast to batch reactions where separate experiments must be conducted to compare initial rates under different conditions. This is challenging in this case, as the size of the catalyst particles dictates that the experiment must be a certain minimum size (to contain enough particles to be valid), thereby ruling out screening in 96-well plates or similar. Operation with solids is also very challenging for flow chemistry platforms based on microchannels, for the simple reason that representative catalyst particles do not fit in the channels. In this case the OBR allows the investigation of the activity of catalyst particles in the form in which they are used.

3.3. Dynamic and Multi-dimensional Screening of Hexanoic Acid Esterification Parameters

Dynamic and multi-dimensional screening of the hexanoic esterification parameters appeared feasible, given the consistency of the multi-steady-state conversions of the hexanoic acid, lack of hysteresis in the conversions and the stability of AmberlystTM 70. In the dynamic screening program (Figure (8a)), the residence time was varied linearly at constant methanol to hexanoic acid molar ratio of 30:1, from 2.5min to 20min at the interval of 2.5min, throughout the duration of the experiments. Each set of residence times was held for only 2.5min, allowing high throughput of the reaction screening. The results showed that the hexanoic acid conversions to methyl hexanoate increased from about $61.9 \pm 0.4\%$ at 5min residence time to $80.7 \pm 1.3\%$ at 10min residence, and finally to $98.5 \pm 1.1\%$ conversion at 20min residence time.

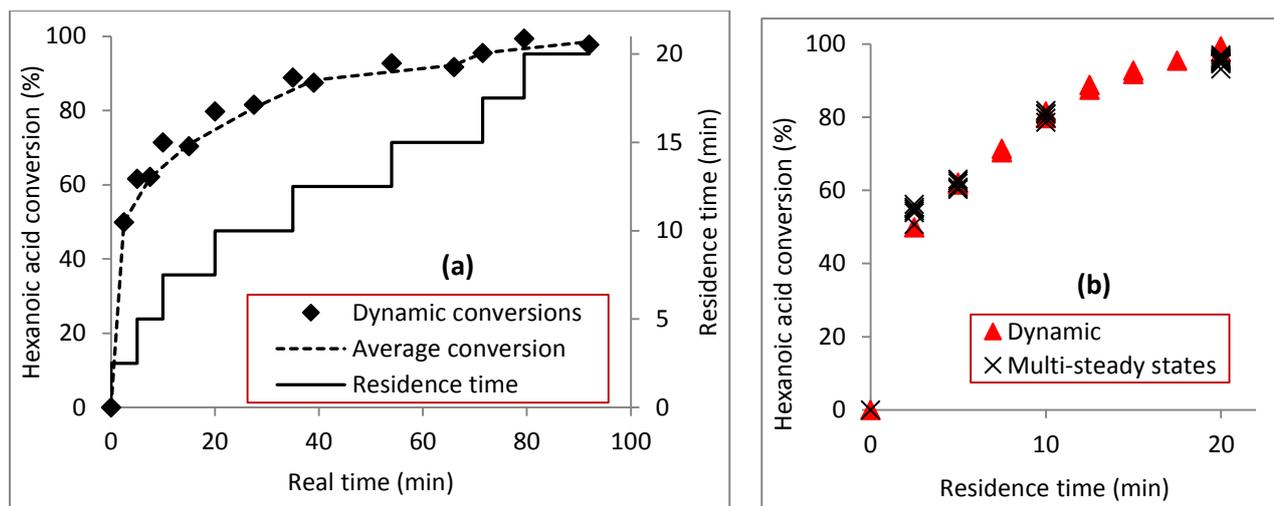


Figure 8: Hexanoic acid esterification at methanol to acid molar ratio of 30:1, 60°C, oscillation conditions of 8mm amplitude and 4.5 Hz, and 9g Amberlyst™ catalyst packing in the meso-OBR, (a) dynamic mode at 2.5min – 20min residence time, (b) comparison of results for dynamic mode and multi-steady states.

As shown in Figure 8(b), the hexanoic acid conversions achieved for the dynamic screening were consistent with the results obtained from the multi-steady state mode at similar residence times. This clearly suggests that the meso-OBR can be used for rapid screening in dynamic mode, which results in a substantial reduction in processing time by about 16% compared to the multi-steady state experiments. The hexanoic acid conversions of $61.9 \pm 0.4\%$ at 5min residence time, $80.7 \pm 1.3\%$ at 10min residence and $98.5 \pm 1.5\%$ at 20min residence time for the dynamic mode, agree well with $61.6 \pm 1.2\%$ at 5min and $80.1 \pm 1.4\%$ at 10min and $95.4 \pm 1.0\%$ at 20min for the multi-steady states. As expected, there was a positive relationship between increasing residence time and hexanoic acid conversion in the dynamic screening, similar to that observed in the multi-steady states ramping. The maximum conversions for the dynamic ($98.5 \pm 1.5\%$) and multi-steady states ($95.4 \pm 1.0\%$) were obtained at 20min residence time.

Another method of continuous process screening applied in the study was a “multi-dimensional” approach as shown in Figure 9. In this parametric screening, the residence time and the methanol to hexanoic acid molar ratio were simultaneously continuously varied linearly. The residence time was varied at intervals of 2.5min over the residence time range 2.5min - 20min, and the methanol molar

ratio varied at the interval of 1.5 in the range of 1.5:1 - 30:1. The average hexanoic acid conversions to methyl ester (for two experiments) increased rapidly from about $13.0 \pm 0.9\%$ at 1min residence time and 1.5:1 methanol to acid molar ratio to $57.6 \pm 2.2\%$ at 5min and 7.5:1 molar ratio, and finally to the maximum value of $98.2 \pm 1.1\%$ at 14min and 21:1 molar ratio. These results clearly demonstrate that multi-dimensional screening of the esterification parameters is significantly more economical in terms of time-saving and judicious utilisation of resource in process development.

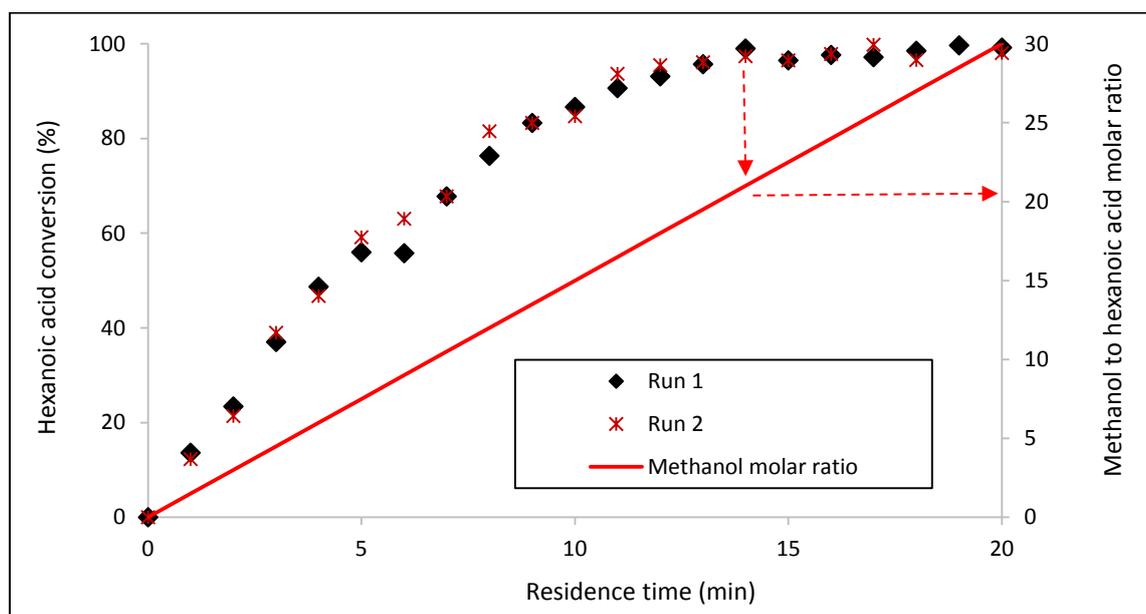


Figure 9: Multi-dimensional screening of hexanoic acid esterification at 60°C , oscillation conditions of 8mm amplitude and 4.5 Hz, 9g Amberlyst™ 70 catalyst packing in the meso-OBR. The residence time was increased from 1min to 20min at 1min interval and the methanol to hexanoic acid molar ratio from 1.5:1 to 30:1 at intervals of 1.5.

As shown in Figure 9 above, a much more effective optimal feed composition and reaction time for the reactor could be determined from the multi-dimensional screening results. There was a substantial reduction, approximately 30%, in the amount of methanol required to achieve the maximum possible conversion using the multi-dimensional approach. Although here methanol is inexpensive, in other applications the cost savings could be significant. It was found that 14min reaction time was required at the reduced methanol molar ratio (21:1) to achieve the maximum hexanoic acid to ester conversion, instead of 20min residence time observed in the multi-steady states and dynamic modes. This implies

a 30% reduction in the reaction time compared to multi-steady states and dynamic modes. Considering that the reaction parameters were investigated simultaneously, a great deal of time and resources would be saved in process development using the meso-OBR platform in multi-dimensional mode. The meso-OBR has an advantage over batch reactors due to its capability for continuous rapid process screening in multi-steady states, dynamic and multi-dimensional modes. Among other continuous flow reactors, the meso-OBR combined its small volume for reduced reagents requirements and ease of compatibility with the ability to work with heterogeneously catalysed reactions (without alteration of those catalysts to fit the reactor platform). The meso-OBR can be predictably scaled up, and can be operated as a plug flow reactor which results in products of uniform composition and high degree of reproducibility.

4. Conclusion

A heterogeneously catalysed carboxylic acid esterification was investigated using a meso-OBR as a screening platform. The reactor was operated continuously in multi-steady states, dynamic and multi-dimensional modes for hexanoic acid esterification with methanol using a meso-OBR packed with a sulphonic acid functionalised divinylbenzene/styrene copolymer (Amberlyst™ 70). The meso-OBR was operated at oscillatory conditions of 4.5Hz frequency and 8mm amplitude (centre-to-peak) and the reaction temperature of 60°C, to demonstrate the capacity of this reactor for screening solid-liquid reactions in a rapid process development. The Amberlyst™ 70 resin catalyst had high turn-over frequency (93.1hr⁻¹) for the hexanoic acid esterification in the meso-OBR. The catalyst was found to be 100% recoverable from water poisoning within 1.4 - 1.6 times the residence time. The system reverted to the original average hexanoic acid conversion showing that the catalytic activity is entirely regained and that water was not permanently adsorbed on the active sites of Amberlyst™ 70 catalyst. Complete recovery of the catalyst after water-spiking was attributed to resistance of Amberlyst™ 70 resin to permanent deactivation by water, and the continuous flow of anhydrous methanol to prevent water accumulation on the surface of the catalyst and enhance the equilibrium-limited esterification

process. A large excess of methanol was therefore required to shift the equilibrium towards methyl hexanoate production.

Clear steady states were achieved at each residence time for all the multi-steady states screened at ramped residence times of 2.5min – 20min and ramped methanol to hexanoic acid ratios in the range of 1:1 – 30:1. This indicates a high degree of plug flow behaviour by the meso-OBR. The hexanoic acid conversions at the “upward” and “downward” ramped residence times were similar, evidencing high degree of reproducibility and catalyst reusability. Induction times of the packed meso-OBR for the various steady states were in the range of 1.2 – 1.4 residence times, which are consistent with 1.5 residence times achieved using the reactor in a homogeneously catalysed liquid-liquid biodiesel reaction. The maximum hexanoic acid to methyl hexanoate conversion at 20min residence time and 30:1 methanol to hexanoic acid molar ratio were $95.4 \pm 1.0\%$ for the multi-steady states, and $98.5 \pm 1.5\%$ for the dynamic mode. A more significant reduction in the process development time and reactants requirement was obtained using the multi-dimensional mode, with hexanoic acid conversion of $98.2 \pm 1.1\%$ at 14min residence time and 21:1 methanol to acid molar ratio. The hexanoic acid conversions were similar and repeatable for the continuous multi-steady states, dynamic and multi-dimensional modes in the meso-OBR. Use of dynamic screening required 16% less time and reactant compared to the multi-steady states approach. Process screening in multi-dimensional mode was even more efficient, resulting in approximately 30% reduction in the process development time and reactants requirement compared to the multi-steady states mode. As demonstrated in this study, a substantial reduction in process development time was possible using the reactor in this mode. This could be a major advantage of the meso-OBR platform in process development for multiphase reactions.

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