

Scalable Reactor Design for Pharmaceuticals and Fine Chemicals Production. 3. A Novel Gas–Liquid Reactor for Catalytic Asymmetric Transfer Hydrogenation with Simultaneous Acetone Stripping

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Abstract:

For the asymmetric transfer hydrogenation of acetophenone to its chiral alcohols, in the presence of homogeneous catalyst (1*R*,2*S*-amino-indanol/pentamethylcyclopentadienylrhodium), with isopropanol as hydrogen donor, prior investigation revealed that removal of the byproduct acetone from the reaction system shortens the required reaction time to achieve high conversion and reduces enantiomeric excess erosion. Since acetone removal efficiency is different in different batch reactor scales, this issue poses a scalability problem. Regardless of scale, the stirred vessel operated as a gas/liquid batch reactor has limitations with regards to allowable gas flow rate through the vessel due to impeller flooding. Therefore, reactor systems where high gas/liquid flow rate ratio can be employed are advantageous. In this work, a continuous reactor that utilises a micromesh structure to stabilise the gas/liquid interface is presented. The reactor can operate with high gas/liquid flow rate, resulting in efficient acetone removal, low reaction time, and high enantiomeric excess.

Introduction

In our previous work¹ the main factors that inhibit fine chemicals and pharmaceuticals reactor scalability were reviewed. For scalable reactor design, it is suggested to first identify potential scale-up obstacles and then use shortcut calculations for their evaluation. This approach was demonstrated for the asymmetric transfer hydrogenation of acetophenone to its chiral alcohols, in the presence of the homogeneous catalyst, (1*R*,2*S*-amino-indanol/pentamethylcyclopentadienylrhodium) with isopropanol as hydrogen donor.² The investigation revealed that removal of the byproduct acetone from the reaction system by stripping could shorten the required reaction time to achieve high conversion and reduce enantiomeric excess erosion. It was further identified that one of the most influential factors that accelerates acetone removal is the ratio of stripping gas flow rate per liquid volume. Stirred vessels operated as gas/liquid batch reactors have limitations with regards to allowable gas flow rate due to impeller flooding. Therefore, reactor systems not constrained by limits in gas flow rate are advantageous. In Zafir et al.,³ a rotating disk reactor was investigated for this purpose, while in this work we focus on a micromesh

reactor, whose principles of operation are similar to those of gas/liquid membrane contactors.

Membrane contactors are devices that allow two phases to come into direct contact with each other, for the purpose of mass transfer between the phases, without dispersing one phase into the other.⁴ The concept of using membranes to bring two phases into contact covers many industrial processes such as reverse osmosis, filtration,⁵ extraction,⁶ pervaporation,⁷ evaporation,⁸ stripping,⁹ distillation,¹⁰ multiphase reactive systems,¹¹ absorption.¹² Their use is seen as part of process intensification trends boosting efficiency, saving energy, minimising environmental impact, and increasing safety. In this context, membrane operation has the potential to replace conventional energy intensive techniques, accomplishing selective and efficient transport of specific components and improving the performance of reactive processes.

Microfabricated meshes are the microengineered analogue of membranes. Recent developments in the area of microengineered structures for chemical processing¹³ have made it possible to manufacture micromeshes from various materials (i.e., steel, silicon nitride) by techniques such as standard mask lithography or laser interference lithography.¹⁴ Thin meshes with straight pores, micrometer-range pore size, and a regular arrangement can be obtained.¹⁵ Such micromeshes combine the advantage of minimising mass transfer resistance with high porosity and regular patterned pore structure having at the same time good mechanical strength. They can be easily incorporated in the design of microdevices for processing at microscale.

In the present paper acetone stripping and asymmetric hydrogenation of acetophenone with isopropanol as hydrogen donor and solvent in the presence of a homogeneous catalyst are investigated. Experimental studies showed that acetone presence in the reaction mixture limits conversion and erodes

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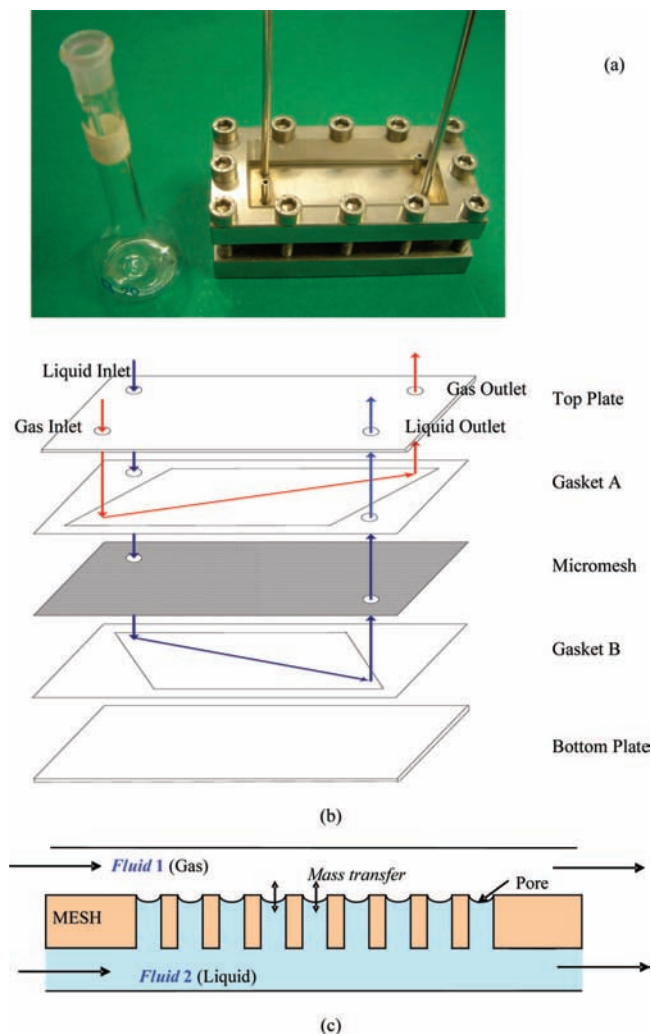


Figure 1. Micromesh reactor. (a) Assembled reactor. (b) Layer structure. (c) Gas/liquid flow configuration and interface.

selectivity.¹⁶ Efficient acetone removal from the liquid phase shortens the residence time required to achieve high conversion. Even though acetone vapour pressure is higher than isopropanol vapour pressure, simultaneous evaporation of isopropanol can take place. This becomes detrimental for reaction performance, since high substrate concentration leads to lower enantiomeric excess. The loss in solvent can be balanced by passing nitrogen gas through isopropanol before entering into the reactor system.

Experimental Setup

The heart of the experimental setup is the micromesh reactor (Figure 1a) which is built in a layer structure (Figure 1b). The reactor measures 3 cm × 8 cm in size. The gaskets utilised to define the gas and liquid flow channels are made from copper. The reactor is sealed by top and bottom stainless steel plates. The dimensions of the gaskets are 3 cm × 8 cm × 0.02 cm (W × L × H) outside and 2 cm × 6 cm × 0.02 cm (W × L × H) inside. The inlet and outlet of the gas and liquid are 1/8 in. stainless steel tubes connected to the top plate. The top gasket forms the gas flow channel, and the bottom gasket forms the liquid flow channel. The micromesh is placed between the two

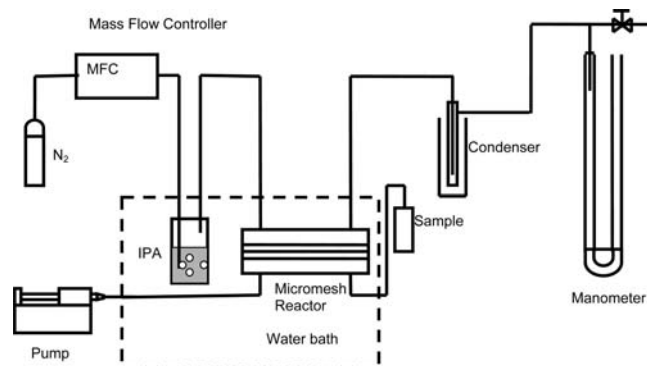


Figure 2. Experimental setup of the micromesh reactor. The configuration depicted was used for stripping experiments.

gaskets and defines the gas/liquid interface (Figure 1c). The gas/liquid interface is stabilized by applying a pressure difference across the phases. The stainless steel micromesh contains straight holes and is made by a chemical etching method; it is commercially available from Internetmesh. It has 76 μm average hole size, 100 μm maximum hole size, 50 μm thickness, and 23% open area. These pores are relatively large, and there was no indication of fouling during experiments. However, care should be exercised when this is not the case. Precautions, such as installing inline filters, can be taken to avoid fouling. Operation of the mesh reactor may be problematic in applications where particles form during reaction, unless they are small and do not adhere to the mesh and reactor walls.

A schematic of the experimental setup for acetone stripping is shown in Figure 2. In order to eliminate the hydrostatic pressure, the reactor was placed horizontally. A single-syringe infusion pump (RAZEL A-99.FJZ) was used to drive the liquid flow in the bottom of the micromesh through the reactor. Nitrogen gas controlled by a mass flow controller (Brooks 5850) was introduced into the contactor and flowed above the micromesh. The differential pressure between the gas and liquid phases was controlled at the outlet of the gas phase by a metering valve (Swagelok) to avoid phase breakthrough. The reactor operated at almost atmospheric pressure. Experiments identified that breakthrough of gas in the liquid phase occurred at a pressure difference $P_G - P_L$ of about 700–800 Pa. The gas phase pressure was measured by a manometer. The liquid phase pressure was calculated on the basis of the height difference of the liquid outlet and liquid layer inside the membrane reactor. In certain experiments, a 250 mL flask containing 150 mL of isopropanol (IPA) at 30 °C was placed between the mass flow controller and reactor inlet to saturate the nitrogen with IPA before it entered the reactor. A condenser was utilized to condense the vapor in the gas phase. Temperature control was by means of a water bath. For asymmetric transfer hydrogenation, 0.00028 M catalyst solution (prepared by 11.2 mg of rhodium complex and 5.6 mg of ligand in 125 mL of isopropanol) and substrate solution (containing 0.28 M acetophenone and 0.00224 M sodium isopropoxide in isopropanol) were pumped by two syringe pumps and mixed in a micromixer (Standard Slit Interdigital Micromixer SSIMM, IMM) before being fed to the micromesh reactor. Nitrogen flow rate was 70 mL/min and inlet liquid flow rate 0.026–0.4 mL/min. All experiments were performed at 30 °C. The analysis was carried out by gas chromatography as described elsewhere.¹⁶

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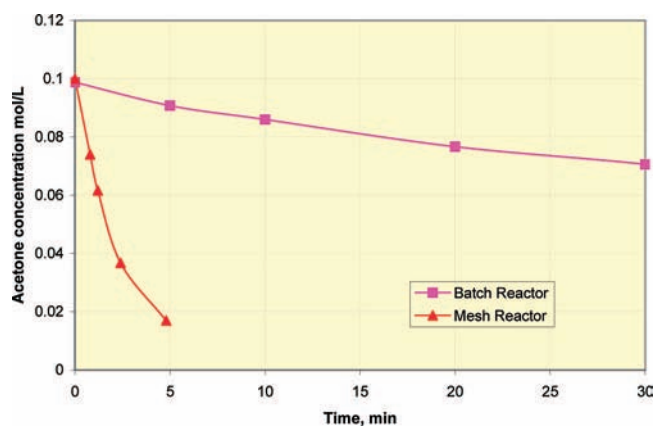


Figure 3. Acetone removal in batch and micromesh reactors as a function of real time for the former and residence time in the latter. (Micromesh reactor: Dry nitrogen flow rate: 70 mL/min. Batch reactor: Dry nitrogen flow rate: 800 mL/min; liquid volume: 250 mL).

Results

Acetone Stripping in Batch and Micromesh Reactors.

For batch experiments, a 500 mL flask was initially filled with 250 mL of 0.1 M acetone solution in isopropanol. Temperature was controlled at 30 °C by means of water bath. Nitrogen at 800 mL/min was introduced into the system through a frit; 70 mL/min nitrogen flow rate was chosen for the micromesh contactor due to gas phase breakthrough to liquid phase at higher nitrogen flow rate. Figure 3 shows the comparison of the micromesh reactor and batch reactor experiments. Within 5 min about 90% of acetone was removed in the former, while only about 10% acetone was removed in the latter. Furthermore, in the batch reactor it took 30 min to remove only 30% acetone. This more efficient acetone removal in the micromesh reactor is due to the fact that a much higher gas flow rate/liquid volume ratio is employed. For 5 min contact time, the gas/liquid volume ratio is 1400 in the micromesh reactor which is 2 orders of magnitude higher than 16 in the batch reactor.

Acetone Stripping with Nitrogen Bubbled in IPA in the Micromesh Reactor. When acetone evaporated and was removed by nitrogen, isopropanol evaporated and was removed by nitrogen as well. The loss of IPA results in a more concentrated solution. For the asymmetric transfer hydrogenation, enantiomeric excess decreases faster at high substrate concentration.¹⁶ Therefore, it is important to top-up the reaction solution with isopropanol to keep the solution concentration constant. In order to avoid IPA evaporation, the nitrogen can be passed through an IPA container (Figure 2) before it flows into the micromesh reactor.

A comparison of acetone removal with dry nitrogen and with IPA-enriched nitrogen is summarised in Table 1. The outlet liquid flow rate was measured by collecting the outlet flow for 35 min after starting the experiments. The sample vial was placed in an ice bath to prevent acetone evaporation. The amount of acetone removed was calculated by a mass balance. The outlet liquid flow rate could also be calculated based on the assumption that

nitrogen was saturated after it flowed through the micromesh reactor.

IPA mole fraction in the gas phase is:

$$y = \frac{P^{\text{VAP}}}{P^{\text{Total}}} = \frac{8157}{101325} = 0.0805$$

IPA lost into the nitrogen stream is calculated from:

$$F_{\text{N}_2} \cdot \frac{P}{RT} \cdot y = 70 \times 10^{-6} \times \frac{101325}{8.314 \times 303} \times 0.0805 = 0.227 \times 10^{-3} \text{ mol/min} = 0.017 \text{ mL/min}$$

Therefore, the outlet liquid flow rate is:

$$F_{\text{L-out,cal}} = 0.1 - 0.017 = 0.083 \text{ L/min}$$

which is close to the experimental value 0.079 mL/min.

It can be seen that outlet acetone concentration is slightly higher, corresponding to less acetone being removed by using nitrogen bubbled in isopropanol. This may be due to the fact that with dry nitrogen, liquid flow rate decreases because of IPA evaporation, and this leads to higher residence time. When the nitrogen was saturated with IPA, there was no IPA concentration gradient, and hence no driving force for IPA mass transfer. The experimental results show that, when using nitrogen bubbled in isopropanol, the inlet and outlet liquid flow rates are almost the same, which indicates that solvent loss is avoided and the concentration of the reactant + products will be kept constant during asymmetric transfer hydrogenation. However, from an economic point of view, recycle of IPA in the nitrogen flow has to be considered for operation in the large scale.

Asymmetric Transfer Hydrogenation in Batch and Micromesh Reactors. The experimental results for the batch and micromesh reactor are compared in Figure 4. Batch experiments were performed in a stirred 500 mL flask with a reaction solution volume of 250 mL into which nitrogen was bubbled at a flow rate of 800 mL/min, as described elsewhere.¹⁶ Figure 4a shows conversion as function of reaction or residence time. In the micromesh reactor, the reaction reached almost 100% conversion within 15 min. In the batch reactor, only 88% conversion was obtained in 60 min, and it takes more than 3 h to complete the reaction. The fact that a higher reaction rate was obtained in the micromesh reactor is due to more efficient acetone removal. This can be confirmed from Figure 4b and c. Figure 4c shows acetone concentration at reactor outlet for the micromesh and the batch reactors as function of conversion. In the batch reactor, the acetone concentration keeps increasing before reaching 85% conversion; it decreases afterwards and reaches almost zero concentration in 3 h. The peak acetone concentration in the batch reactor is about 0.23 M which happens at about 85% conversion. The possible reason for such behaviour is that the reaction rate is very fast in the beginning of the reaction and acetone removal rate is relatively slow; therefore, acetone concentration increases. As the reaction continues, the decrease of reactant concentration and increase

Table 1. Effect of nitrogen bubbled in IPA on acetone removal in the micromesh reactor^a

N ₂	F _{L,in} (mL/min)	F _{N₂} (mL/min)	ΔP (mm H ₂ O)	C _{Ac,in} (M)	C _{Ac,out} (M)	F _{L,out} (mL/min)	acetone removed (mol/min)
dry	0.1	70	30	0.107	0.037	0.079	0.0077
	0.1	70	30	0.108	0.038	0.078	0.0079
bubbled in IPA	0.1	70	30	0.102	0.044	0.098	0.0059
	0.1	70	30	0.102	0.045	0.097	0.0058

^a T = 30°C; solvent: isopropanol; F_{L,in}: liquid inlet flow rate, F_{N₂}: N₂ flow rate; ΔP: pressure difference (P_{gas} - P_{liquid}); C_{Ac,in}: acetone concentration in the liquid inlet; C_{Ac,out}: acetone concentration in the liquid outlet of the reactor; F_{L,out}: liquid outlet flow rate.

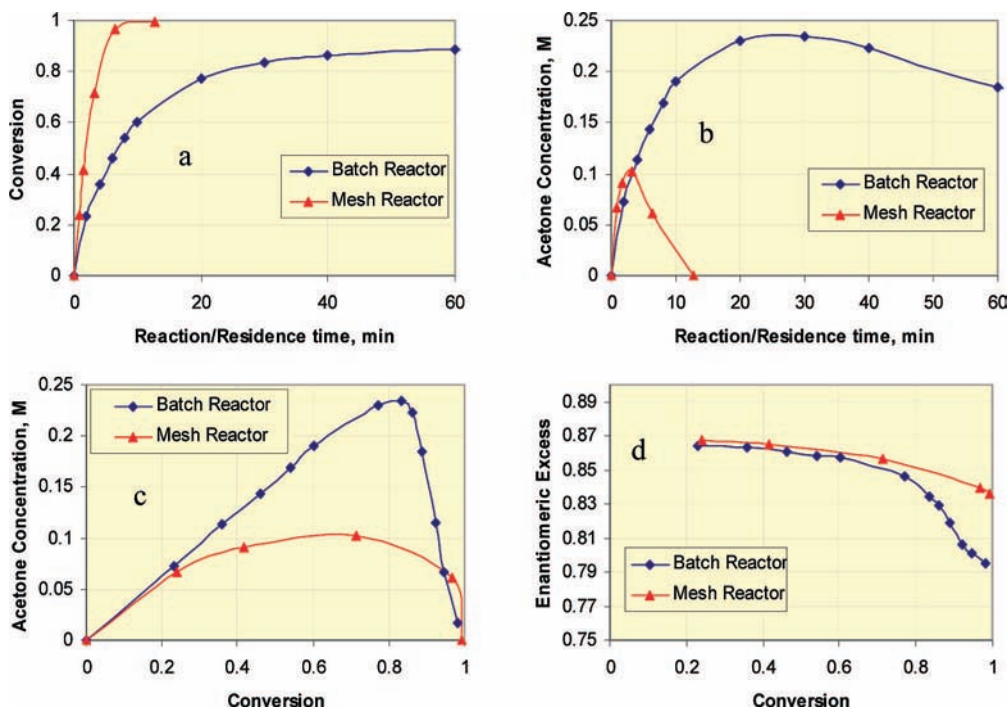


Figure 4. Comparison of batch reactor and micromesh reactor performance for asymmetric transfer hydrogenation. (a) Conversion as function of reaction/residence time. (b) Acetone concentration as function of reaction/residence time. (c) Acetone concentration as function of conversion. (d) Enantiomeric excess as function of conversion ([substrate]: 0.33 M, [substrate]/[catalyst] = 1000, N₂ bubbled in IPA in micromesh reactor).

of product concentration results in a decrease of the reaction rate. The increase in the amount of acetone produced results in a higher driving force for the acetone removal rate. When the acetone removal rate is faster than acetone production rate, acetone concentration decreases. Therefore, a maximum in acetone concentration occurs. In the micromesh reactor acetone concentration increases up to 0.1 M and decreases afterwards. In less than 15 min, acetone concentration reaches zero (Figure 4b). The peak acetone concentration has been significantly reduced from 0.23 to 0.1 M, and it has been brought forward to about 70% conversion in the micromesh reactor.

Figure 4d shows enantiomeric excess as function of conversion. The same initial enantiomeric excess is obtained in both reactors, which is probably because in the beginning of the reaction acetone concentration is too low to affect initial enantiomeric excess. Furthermore, no products are available in the beginning of the reaction, and thus, a backward reaction with acetone that would erode enantiomeric excess is minimal. The enantiomeric excess decreases with conversion in all cases, especially after 80% conversion. However, the final enantiomeric excess varies between the two reactors. Higher final enantiomeric excess is obtained in the micromesh than in the batch reactor. The possible reason is that, in the micromesh

reactor where acetone is removed more efficiently, the forward reaction is encouraged (acetone reacting with isopropanol to give phenylethanol and acetone) and the backward reaction is prevented (acetone reacting with phenylethanol to give isopropanol and acetophenone). Moreover, because the reaction is complete in 15 min in the micromesh reactor, there will not be enough time for the backward reaction to take place.

Effect of Nitrogen Enrichment with Isopropanol in Transfer Hydrogenation in the Micromesh Reactor. During acetone evaporation, a portion of IPA is simultaneously evaporated if the IPA partial pressure in the sweeping gas is lower than IPA vapour pressure. Isopropanol evaporation concentrates the reaction solution which will lead to reduction of the enantiomeric excess. Therefore, hindering solvent loss can keep the concentration constant and improve reaction performance. Using nitrogen bubbled in IPA prevents this solvent loss. In this series of experiments, dry nitrogen and nitrogen bubbled in IPA were used as the sweeping gas. The results are summarized in Figure 5. Conversion as function of time is plotted in Figure 5a. Conversions obtained with dry nitrogen and nitrogen bubbled in IPA are almost the same. The possible reason is the following. The residence time in Figure 5 is calculated as reactor volume divided by liquid inlet flow

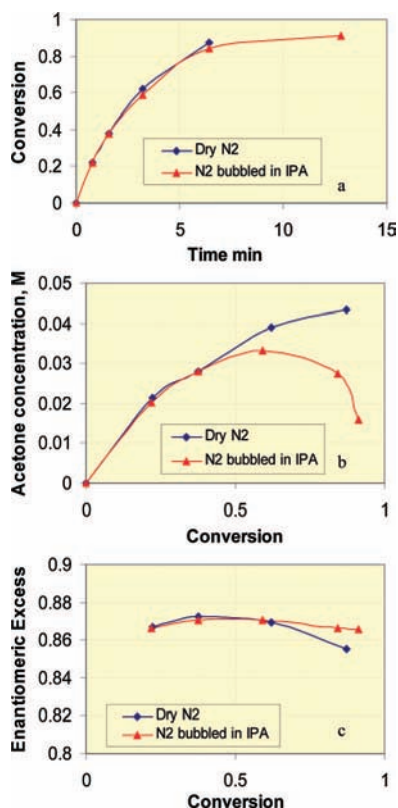


Figure 5. Effect of IPA enrichment of nitrogen during asymmetric transfer hydrogenation in the micromesh reactor. (a) Conversion as function of residence time. (b) Acetone concentration as function of conversion. (c) Enantiomeric excess as function of conversion ([substrate]: 0.14 M, [substrate]/[catalyst] = 1000).

rate. In the experiment with dry N₂, some IPA is consumed to saturate the dry N₂, which results in longer real residence time in the reactor. Longer residence time favours higher conversion. The loss of IPA concentrates the reaction solution which results in higher concentration of products. This aids backward reactions and thus favours lower conversion. These effects may offset each other, so that ultimately similar conversion/time profiles are observed for both cases. Figure 5b shows acetone concentration against conversion. Higher acetone concentration is obtained with dry nitrogen as sweeping gas. In the experiments using nitrogen bubbled in IPA, acetone concentration increased to a maximum and then decreased. The acetone concentration kept increasing in the experiments using dry nitrogen, which is expected due to the fact that IPA loss

concentrated the reaction solution. Higher enantiomeric excess was obtained by using nitrogen bubbled in IPA than by using dry nitrogen (see Figure 5c). This can be explained by the final reaction solution concentration. Using dry nitrogen and nitrogen bubbled in IPA, although the initial concentration is 0.14 M for both cases, the final reaction solution concentrations (acetophenone + phenylethanol) are 0.25 M and 0.14 M, respectively. Because high product concentration favours the backwards reactions, enantiomeric excess drops at high conversion.

Conclusions

The micromesh reactor is an efficient device for stripping acetone from isopropanol. In 5 min, about 90% of acetone was removed in the micromesh reactor, while only 10% was removed in the batch reactor under the conditions investigated. This is attributed to the higher gas/liquid ratio employed. Efficient acetone removal leads to a higher reaction rate and shifts the reaction equilibrium which results in higher conversion for the asymmetric transfer hydrogenation of acetophenone in the micromesh reactor. The lower level of acetone concentration in the reaction solution prevents backward reactions, thus achieving higher final enantiomeric excess. Using nitrogen bubbled in isopropanol before entering the reactor is a convenient method to avoid solvent loss from the reaction mixture, and this further improves the final enantiomeric excess. The hydrodynamic properties of the micromesh reactor can be maintained at higher production rate by piling up a larger number of micromeshes. In this way hydrodynamic behaviour and hence reaction performance will remain the same, provided care is taken to ensure flow equidistribution to all the liquid and gas channels and to avoid phase breakthrough. In that respect, scalability of the micromesh reactor is expected to be better than that of the batch reactor, in which hydrodynamic characteristics cannot necessarily be kept the same and maximum gas flow rates are limited by impeller flooding.

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