Chemical Engineering Journal 166 (2011) 726–737

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

Conceptual design and simulation of a plant for the production of high purity (*S*)-ibuprofen acid using innovative enzymatic membrane technology

Sie Yon Lau, Fadzil Noor Gonawan, Subhash Bhatia, Azlina Harun Kamaruddin, Mohamad Hekarl Uzir*

School of Chemical Engineering, Engineering Campus, Universiti Sains Malaysia, Seri Ampangan, 14300 Nibong Tebal, Seberang Prai Selatan, Pulau Pinang, Malaysia

ARTICLE INFO

Article history:
Received 29 May 2010
Received in revised form 7 November 2010
Accepted 19 November 2010

Keywords:
Dynamic kinetic resolution
Lipase
Ibuprofen
Enzyme-mediated membrane reactor
Simulation

ABSTRACT

(*S*)-Ibuprofen is a low volume but high value pharmaceutical product which is categorized as non-steroidal anti-inflammatory drug (NSAID). This precious chiral drug may be produced using racemic ibuprofen as raw material through the dynamic kinetic resolution. In this work, a simulation of (*S*)-ibuprofen production is carried out using ASPEN PLUS® process simulation software. A pilot scale production with the capacity of 500 g/day of (*S*)-ibuprofen acid is considered in the present study. The product is synthesized through a three-step process: (i) substrate preparation via esterification; (ii) enzymatic dynamic kinetic resolution of substrate ester and (iii) product purification. Mass and energy balances of major equipment were calculated. The performance of the enzyme-mediated membrane reactor (EMR) was investigated by manipulating substrate and base concentrations as well as the flow rates. Besides, a number of issues related to the evaporation and crystallization of the product were identified and addressed. It was found that the optimum operating condition of EMR at 40 °C, 50–100 ml/min lumen flow rate with substrate and base concentrations, respectively at 10–20 mM and 60–100 mM, gave 0.92 conversion and 0.9 ee_p of the product. An overall yield of 82.5% product crystal was achieved by operating the cooling-crystallizer in the temperature range of 5–10 °C.

1. Introduction

An increase in the world's demand on single enantiomer therapeutic drugs has motivated the search for the production of enantiopure drugs, especially those of the non-steroidal anti-inflammatory drugs (NSAIDs) that belong to the family of propionic acid. Long term concern about the side effects of racemic drugs has triggered drug related regulatory agencies such as Foods and Drugs Administration (FDA) in the early 1990 to release guidelines or policy statements in the development of new stereoisomeric drugs [1]. After two decades, the concern on stereoisomeric drugs keeps increasing and the racemic drugs become undesired compared to the single enantiomer. In pharmacopeia research, obtaining high purity of enantiomeric form is a main interest in search for a comprehensive enantiomeric technology.

The emergence of new technologies in the 80s that allowed the production of pure enantiomers in significant quantities has increased the attention and interest in the use of stereochemistry drugs [2]. Statistics showed that an increase of single enantiomers launched between the period of 1985 and 2004 clearly indicated the rise of interest towards the single enantiomer in pharmaceutical industries rather than those of racemic mixture [3]. Single enantiomer therapeutic drugs have reported sales of $225 billion in 2005 [4]. This figure represents 37% of the total final formulation of pharmaceutical market worth $602 billion with 11% annual growth rate of single enantiomer products during the past 5 years which is on par with the pharmaceutical market as a whole [4].

In the anti-inflammatory class of pharmaceuticals, ibuprofen acid (2-(4-isobuthylphenyl) propionic acid) belongs to the family of propionic acid and is still widely marketed as racemic mixture. Since enantiomer does play a crucial role in pharmacokinetics and phamacodynamics [5], optically active ibuprofen which is also known as dexibuprofen ((*S*)-ibuprofen) should be used instead of the racemic type. Several methods have been developed to produce (*S*)-ibuprofen, among the popular ones are: chromatography [6,7], crystallization [8], and enzymatic resolution [9,10–13]. Among these methods, crystallization approach is widely applied in the pharmaceutical industry for the resolution of the enantiomers [14,15]. Enantioselective crystallization is favoured because the operation is easy and low manufacturing cost is required [16]. However, a major drawback of crystallization approach is that the selection of the ideal combination of resolving agents and solvents is a very time-consuming and labor-intensive process. In addition, the resolving agent is quite costly and results in low yield [17].

By considering other alternatives, enzymatic resolution is the most potent, effective and capable of producing very high enantiomeric excess of the desired enantiomers [16]. Based on the

* Corresponding author. Tel.: +60 4 5996464; fax: +60 4 5941013.
E-mail address: chhekarl@eng.usm.my (M.H. Uzir).

1385-8947/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.cej.2010.11.072

Nomenclature

E	enantiomeric ratio
ee_p	product enantiomeric excess
ee_s	substrate enantiomeric excess
k_d	deactivation constant
s_{alc}	alcohol concentration (mM)
s_{base}	base concentration (mM)
s_{T0}	initial racemic ester concentration (mM)
$t_{1/2}$	half time of enzyme activity (h)
T_r	reduced temperature (K)
ΔH_V	heat of evaporation (kJ/mol)
ΔH_R	heat of reaction (kJ/mol)
X	substrate fractional conversion

previous works related to the production of (*S*)-ibuprofen, enzymatic resolution was carried out either via kinetic resolution (KR) or dynamic kinetic resolution (DKR) [11,18,19]. Between these two enzymatic resolution techniques, DKR is more preferable since 100% conversion of the substrate could be achieved. The DKR of the (*R*,*S*)-ethoxyethyl-ibuprofen ester in an enzyme (*Candida rugosa* lipase) catalyzed system showed 86% conversion with 99.4% optical purity of (*S*)-ibuprofen [11]. In addition, a diffusion-reaction model has been developed to investigate the characteristics of the DKR in an enzymatic membrane reactor (EMR). The proposed model could predict the optimal reaction conditions during the design of immobilized enzyme systems using a particular membrane geometry [20]. Although the production of (*S*)-ibuprofen via KR and DKR has been studied in the past few years, the conceptual design for mass production has yet to become viable. Therefore, the investigation on the substrate preparation, integrated EMR and purification of the product is still needed in order to make the enzymatic resolution a competitive technology. The purpose of this article is to provide an innovative process design and simulations of the (*S*)-ibuprofen acid production as well as the product recovery and purification. The design of the pilot-scale (*S*)-ibuprofen production plant is discussed and the emphasis is made on the performance of the hollow fiber membrane reactor as well as product recovery and purification units including evaporator and crystallizer.

2. Process description of (*S*)-ibuprofen acid production

In this section, a conceptual design of (*S*)-ibuprofen acid production is discussed. The process is divided into three sections: (i) chemical esterification of (*R*,*S*)-ibuprofen acid; (ii) enzymatic dynamic kinetic resolution of (*R*,*S*)-ibuprofen acid, and (iii) purification of (*S*)-ibuprofen acid. The main objective of the process is to convert the racemic ibuprofen to an enantiomeric pure (*S*)-ibuprofen acid. In this novel process, only five main units are crucially involved. Among the unit operations, the EMR is described as the heart of the plant where the hydrolysis, by-product recovery as well as product separation occur simultaneously. Besides, simulations of the evaporator and crystallizer were carried out to investigate the effect of several process parameters on the product recovery and purification. A general process flow of each units operation is presented in a block flow diagram shown in Fig. 1.

2.1. Substrate preparation

Prior to the resolution process in the enzymatic membrane reactor (EMR), several units are required for the synthesis of racemic substrate ester. The fresh (*R*,*S*)-ibuprofen acid was converted into (*R*,*S*)-ibuprofen ester in a batch reactor with reflux system. The ester was prepared through chemical esterification in the presence of acid catalyst. 2-Ethoxyethanol was chosen as the substrate for the esterification due to the properties of electron-withdrawing alkyl group in the ester formed, which is highly reactive in the hydrolysis reaction. In addition, it has been reported that 2-ethoxyethyl-ibuprofen ester is a better substrate for the kinetic resolution process when comparing with 1-heptyl-ibuprofen ester [10]. The reaction for the esterification of ibuprofen acid with 2-ethoxyethanol is shown in Fig. 2.

A reflux system is designed to give high product yields in the production of racemic ibuprofen ester. Since the volatility of product esters is lower than those of the reactants, vapor-phase reflux stream is always rich in reactants such as isooctane and 2-ethoxyethanol. The reaction was maintained under reflux for 8–10 h with the temperature between 100 and 110 °C at atmospheric pressure. A steam-heated jacketing system is designed to supply heat to the reactor as well as maintaining the desirable operating temperature. In addition, an agitator arrangement of axial flow three-bladed impeller was centrally mounted in order to provide a uniform mixing inside the reactor. The subsequent steps include the neutralization of unconverted ibuprofen acid and acid catalyst, followed by the recovery of organic ester.

In this case, a hybrid neutralizing-settling tank is designed so as to meet the requirement of carrying out the neutralization and settling in a single unit. A two-phase liquid was formed upon neutralizing the excess amount of acid in the system. Both the organic

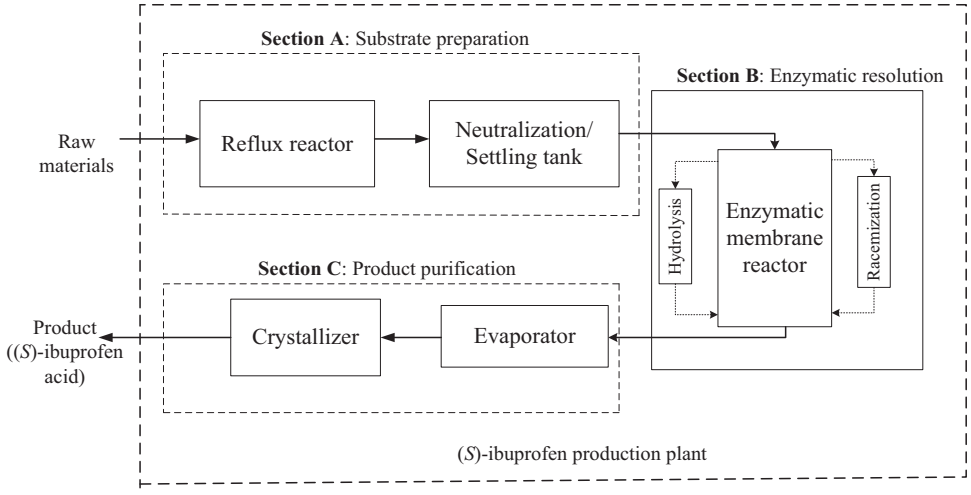
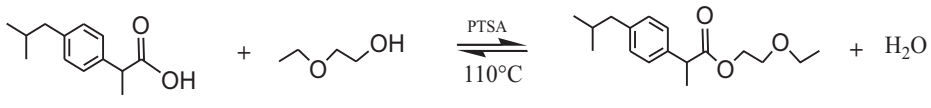


Fig. 1. Block flow diagram of the (*S*)-ibuprofen production plant.



2-(4-isobutylphenyl)propanoicacid ((*R*,*S*)-ibuprofenacid) + 2-ethoxyethanol ⇌ 2-ethoxyethyl2-(4-isobutylphenyl)propanoate ((*R*,*S*)-ibuprofenester) + H_2O

Fig. 2. Esterification of (*R*,*S*)-ibuprofen acid with 2-ethoxyethanol at reflux temperature of 110 °C.

and aqueous phases are then separated based on the density difference. The aqueous phase settled at the bottom of the tank due to the larger density compared to the organic phase. Consequently, the aqueous phase was removed and the organic phase was left for further purification. Then, the recovered ester was stored in the storage tanks as a feedstock for DKR process in the EMR.

2.2. Dynamic kinetic resolution via enzymatic membrane reactor

EMR refers to any enzyme-catalyzed process which takes place in a membrane mediated reactor. The reactant is continuously fed into the lipase-immobilized membrane matrix where the reaction is taking place and at the same time, the product is discharged. The main advantage in enantiomers separation by adopting the membrane technology is that continuous mass production is guaranteed. The proposed EMR is a combination of separation and enzymatic reaction occurred in a single unit operation. The enzyme was immobilized on the sponge side of the fiber membrane as a biocatalyst for enantioselective resolution. The wall of the porous membrane functions as a selective barrier, creates two distinct compartments inside the membrane reactor, namely luminal side and shell side [20]. On the outer side of the fiber membrane, there is an organic phase where the substrate dissolved in organic solvent. Inside the fiber lumen is an aqueous phase where the product will be collected. Three membrane modules are configured in parallel to provide membrane surface of 18 m^2 for the lipase-immobilized hydrolysis of racemic substrate. The membrane modules are incubated in a closed oven in order to maintain the operating temperature inside the modules.

Two agitated tanks namely organic tank and aqueous tank are designed with the provision of hot water jacket to heat up the solution inside the tanks. Both tanks are connected, respectively to the shell and lumen sides of the membrane modules. The organic tank consists of fresh substrate esters which keep circulating within the membrane shell loop. During the same instance, the base-catalyzed ketol–enol tautomerism also occurs simultaneously to recover the unreacted (*R*)-esters. On the other hand, buffer in the aqueous tank circulates within the membrane lumen and brings out the (*S*)-ibuprofen acid from the system. Thus, by employing the EMR with the DKR, the product in the aqueous media could be obtained easily without any contamination of the reactants.

2.3. Crystallization and purification

The effort of separating the (*S*)-ibuprofen from aqueous solution leads to a major challenge. High temperature purification process needs to be avoided since (*S*)-ibuprofen might degrade and reduce its therapeutic effect. In this work, vacuum evaporator followed by a batch cooling crystallizer was used in order to obtain an optically pure product. The vacuum evaporator is capable to evaporate 80–100 L of the water within 2 h without affecting the quality of the active ingredient. The vacuum condition (100–150 mmHg) inside the evaporator has reduced the water boiling point to approximately 50 °C. The evaporated water was collected in a condensate tank while the product concentrate remained in the bottom of evaporator.

It was reported that the lipase only catalyzes the (*S*)-ester and forms a polar product ((*S*)-acid) which diffuses into the aqueous stream due to its water-soluble behaviour [19]. As a result, the

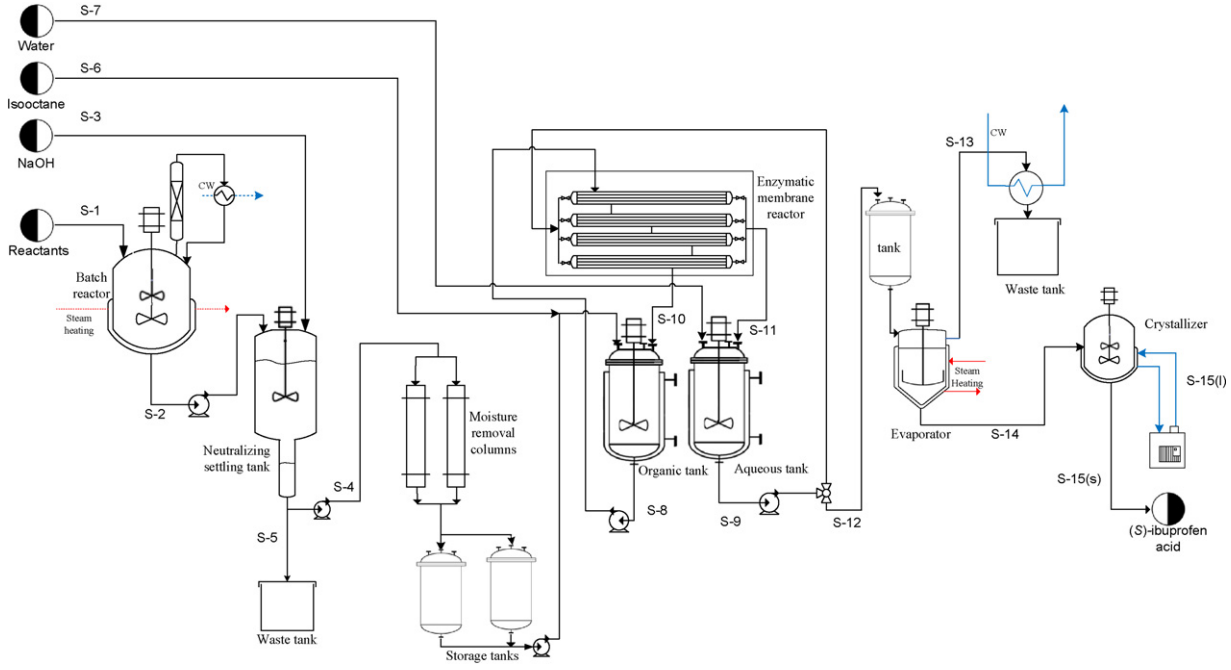


Fig. 3. Process flow diagram of the (*S*)-ibuprofen production plant.

concentrated product solution only consists of (*S*)-ibuprofen acid and a small amount of phosphate buffer salt. The buffer salt is commonly used in biological research due to the osmolarity and the ion concentrations of the buffer solution usually match those of the human body (isotonic). Since the product solution is free of chiral resolving agent, the selective crystallizer of ibuprofen/lysine salt, which was described in the literature, is not appropriate in the present work [15]. Therefore, direct cooling crystallization without converting into the salt form is preferred. This method has several advantages compared to that of the preferential crystallization method, where there is no addition of salt and acid which could reduce the purity of the products formed. Additionally, with a single crystallizer unit, the product loses and energy consumptions could also be minimized. The overall process is illustrated in a simplified process flow diagram (PFD). Fig. 3 shows a proposed PFD of the (*S*)-ibuprofen acid production plant.

3. Process simulation and validity studies

In order to monitor the progress of (*S*)-ibuprofen production via enzymatic DKR, ASPEN PLUS® was used as a tool for simulations. The CONVEN stream class has been used throughout the simulation except for crystallization process where MIXCIPSD stream class was employed. The CONVEN stream class is appropriate for system containing vapor, liquid and salts, whereas the MIXCIPSD is suitable for the system where conventional solids are present with a particle size distribution. The main models incorporated within ASPEN PLUS® such as the NRTL and ELECNRTL were used for chemical and crystallization process, respectively. Normally, the common components are well-defined in ASPEN PLUS® database. However, the definition of rare components such as the (*R*,*S*)-ethoxyethyl-ibuprofen ester and (*S*)-ibuprofen acid were estimated via the property estimation software such as Chemdraw Ultra®. Table 1 shows several important properties of the racemic ester and (*S*)-ibuprofen acid which are employed in the simulation.

This study addresses on how process development could be greatly improved with the use of ASPEN PLUS®. The simulation of batch reactor is focused on the effect of reactant fed to the ester conversion. The process conditions involved in the simulation are presented in Table 2. In addition, the simulator is also used to predict the unforeseen parameters which could affect the production of (*S*)-ibuprofen acid during the DKR in an EMR. In the present study, four crucial effects of DKR such as initial ester concentration, base concentration, alcohol (inhibitor) concentration, and lumen loop flow rates were investigated. Since the EMR was operated at mild conditions, the temperature and pressure changes give no significant effect to the (*S*)-ibuprofen production. Therefore, the performance of the EMR was investigated by manipulating the parameters presented in Table 3.

In order to run an accurate simulation, it is important to select the appropriate boundary condition of the particular system. The boundary condition for EMR was assumed to be the inlet and outlet

Table 1
Chemical properties of (*S*)-ibuprofen acid and ibuprofen ester obtained via Chemdraw Ultra®.

Properties	(*S*)-Ibuprofen acid	(*R*,*S*)-Ibuprofen ester
Molecular weight (g/mol)	206.28	278.19
Boiling point (K)	673.33	699.98
Melting point (K)	405.31	354.35
Critical temperature (K)	789.46	783.59
Critical pressure (bar)	23.91	15.62
Heat of formation (kJ/mol)	−447.42	−629.21
Log *P* value	1.75	4.20

Table 2
Process parameter used in the batch reactor simulation.

Process parameter	Range of study
Operating pressure (atm)	1–5
Operating temperature (°C)	80–110
Ibuprofen:alcohol ratio	1–5
Reflux time (h)	8–10

Table 3
Process parameter used in the EMR simulation.

Parameter	Range of study
Substrate initial concentration (mM)	10–100
2-Ethoxyethanol concentration (mM)	20–200
Base concentration (mM)	10–100
Lumen loop flow rate (L/min)	20–200

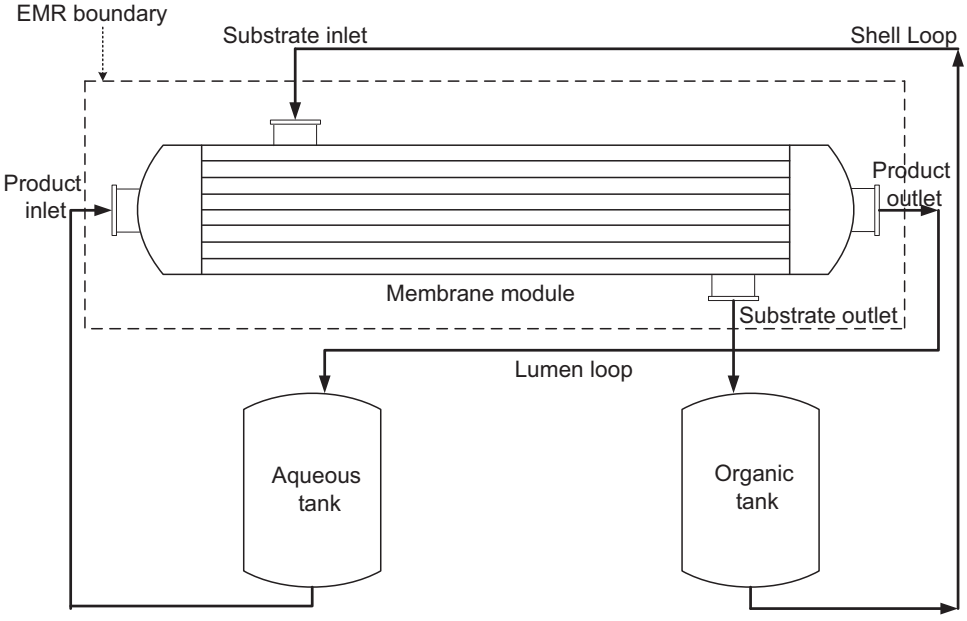


Fig. 4. The simulation boundary of the EMR unit.

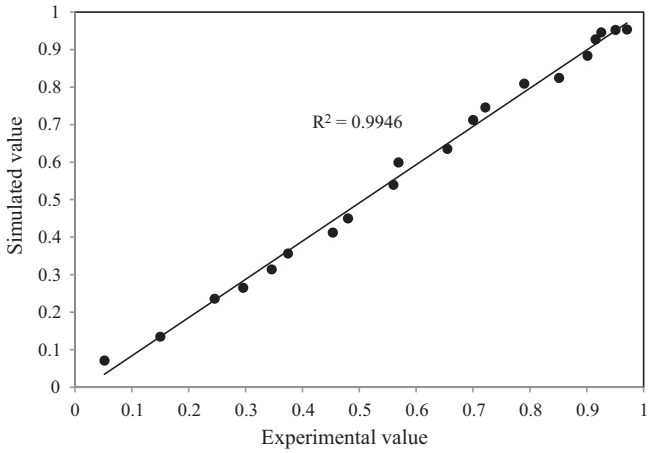


Fig. 5. Plot of experimental values in comparison with the simulated values of ester conversion.

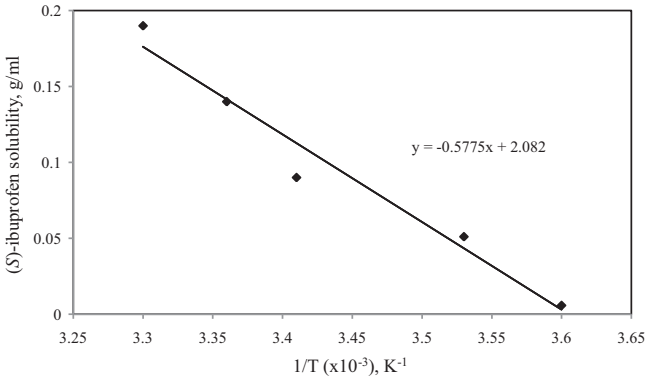


Fig. 6. Solubility curve of (*S*)-ibuprofen acid in phosphate buffer at pH = 8.

of both the shell and lumen loop as depicted in Fig. 4. The results of the simulation are presented in terms of conversion as well as the enantiomeric excess of the product and substrate which are denoted as ee_s and ee_p, respectively. In the DKR system, ee_s is defined as the amount of unreacted enantiomer remained after the dynamic resolution. Conversely, ee_p represents the excess amount of desired enantiomer obtained after the process. A successful DKR system should have low ee_s value and maintain high ee_p in order to achieve 100% optically pure product [20].

To date, most of the findings reported in the literatures were performed in bench scale either in batch bioreactors or membrane reactors [10,11,18] and none of these reactors were operated above 50 L working volume. However, two major assumptions were made during the simulation of EMR prior to ASPEN PLUS® simulation which include: (i) negligible mass diffusion characteristics of the substrate and product and (ii) constant enzyme activity and production rate throughout the process. In this case, the validity of the proposed hollow fiber EMR was tested by comparing the simulated conversion profile with the results obtained from experimental work at an alcohol concentration of s_{alc} = 50 mM with the initial concentration, s_{T0} = 80 mM. The parity plot depicted in Fig. 5 shows good agreement between the simulation and experimental results. The coefficient of determination of the plot, R^2 = 0.9946 confirmed that the capability of the proposed flow sheet to predict the theoretical results for DKR in the preceding sections. Owing to the flexibility of the proposed process, it is expected that the system is suitable for handling the DKR at different process conditions. In this present work, it is also important to demonstrate that the reactor is practical under target operation with particular emphasis on enzyme loading, lipase activity and biocatalyst life span.

On the other hand, several issues on the evaporator and crystallizer have also been addressed through the simulations. The effects of the operating pressure and temperature were investigated in order to determine the optimum productivity rate of (*S*)-ibuprofen crystals. For an aqueous (*S*)-ibuprofen acid, the solubility curve obtained from the lab-scale experiment is within the range of 0.005–0.2 g/ml at room temperature. Fig. 6 shows a negative-sloped linear solubility curve of the (*S*)-ibuprofen acid in phosphate buffer solution. The simulation of crystallizer unit is based on the lab-scale solubility data. The process of crystallization in pilot scale is assumed to obey the same solubility characteristics.

By applying all the process data obtained from estimation and lab-scale work, simulations based on the mass and energy balances were performed for different process conditions. The mass and energy balances simulated via the ASPEN PLUS® are important for the detail equipment design. In order to simulate a process in ASPEN PLUS®, it is necessary to assemble each unit operation into

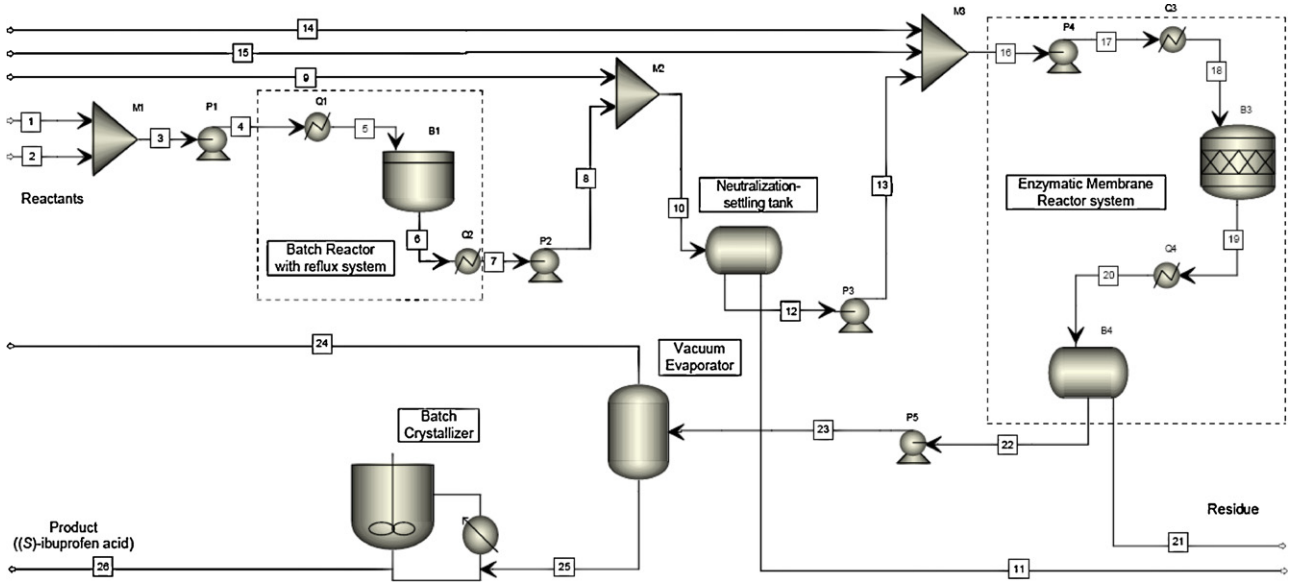


Fig. 7. Process flow sheet implemented in ASPEN PLUS® for the simulation of (*S*)-ibuprofen acid production plant.

Table 4
The summarized input–output data of (*S*)-ibuprofen production pilot plant by referring to the PFD in Fig. 3.

Component (kg)	Stream no.							
	S-1	S-2	S-3	S-4	S-5	S-6	S-7	S-8
Isooctane	22.9	22.8	0.0	22.8	0.0	97.1	0.0	119.9
(*R*,*S*)-Ibuprofen	0.8	0.1	0.0	0.0	0.1	0.0	0.0	0.0
2-Ethoxy ethanol	0.5	0.2	0.0	0.0	0.2	0.0	0.0	0.0
Water	0.0	0.1	17.6	0.0	17.6	0.0	108.0	0.0
Ibuprofen Ester	0.0	1.0	0.0	1.0	0.0	0.0	0.0	1.0
Sodium hydroxide	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0
(*S*)-Ibuprofen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total mass (kg)	24.2	24.2	17.7	23.8	18.0	97.1	108.0	120.9
Temperature (K)	298.15	383.15	298.15	298.15	298.15	298.15	298.15	318.15
Enthalpy (J/s)	0.0	1351.6	0.0	0.0	0.0	0.0	0.0	1086.5

Component (kg)	Stream no.							
	S-9	S-10	S-11	S-12	S-13	S-14	S-15 (l)	S-15 (s)
Isooctane	0.0	119.9	0.0	0.0	0.0	0.0	0.0	0.0
(*R*,*S*)-Ibuprofen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2 Ethoxy-ethanol	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0
Water	108.0	0.0	107.9	107.9	85.1	22.8	22.8	0.0
Ibuprofen Ester	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Sodium hydroxide	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
(*S*)-Ibuprofen	0.0	0.0	0.7	0.7	0.0	0.7	0.1	0.6
Total mass (kg)	108.0	120.3	108.6	108.6	85.1	23.5	23.0	0.6
Temperature (K)	318.15	318.15	318.15	303.15	320.15	320.15	273.15	273.15
Enthalpy (J/s)	1759.8	1124.3	1763.0	582.5	73463.8	35.7	−664.3	−5.7

a flow sheet and resolve the material and energy balances. Fig. 7 shows a complete flow sheet of the (*S*)-ibuprofen production.

4. Results and discussion

The simulation results provide the input–output mass and energy requirement of the (*S*)-ibuprofen plant. Table 4 shows an example of mass and energy stream table of each component that involved in the overall process at 100 °C temperature, pressure of 1 atm with reactant ratio of 3. The simulation shows that 1.0 kg of feedstock ester could be produced from the esterification of 0.8 kg of (*R*,*S*)-ibuprofen acid as starting material. The ester was diluted with isooctane from 96 mM to 40 mM and fed to the EMR as a substrate. The result of the simulation gives a total of 0.68 kg (*S*)-ibuprofen acid (or equivalent to the 82.5% of overall conversion) at optimum process condition. The result also shows that most of the product loss occurred during the reaction where 7.5% and 5.7% losses were detected in the esterification and enzymatic hydrolysis, respectively.

Table 5 summarizes the heat duties of the entire plant which indicates the amount of total energy required for all the equipment. The heat duties of the equipment were obtained from the overall simulation. The net energy requirement simulated for the production of (*S*)-ibuprofen acid is 72.25 kJ/s during a full-capacity operation. Most of the unit operations showed low energy consumption, except for the vacuum evaporator which gave a value of 72.92 kJ/s. The transition state of water from liquid to vapor phase which involved high heat of evaporation (2389 kJ/kg) caused an increase in the energy consumption. The heat of evaporation (ΔH_V) of water at a desired temperature can be estimated using Eq. (1) [22];

$$\Delta H_V = C_1 \times (1 - T_r)^{C_2 + C_3 T_r + C_4 T_r^2} \quad (1)$$

where $T_r = T/T_C$ is the reduced temperature in Kelvin, while C_1, C_2, C_3 and C_4 are constants with values of 5.2053×10^{-7}, 0.3177, 0.212 and 0.25795, respectively for water. Other units operations do not require excessive amount of energy because no phase change is involved. As for the batch reactor, even the process was operated at 110 °C the energy consumption is less than the evaporator. This is because only a small amount of energy is required to vaporize the low boiling point reactants. For instance, both isooctane and 2-ethoxyethanol gave low specific heat of evaporations (ΔH_V = 263 kJ/kg and 516 kJ/kg, respectively) in the reactor. Therefore, it is apparent that the result obtained from the process simulation contributed to low enthalpy and energy consumption especially for the reactor unit.

Table 5
Heat duty of major equipment in (*S*)-ibuprofen production pilot plant.

Unit operation	Enthalpy (kJ/s)
Batch reactor	1.35
Neutralization/settling	−1.35
EMR	0.04
Evaporator	72.92
Crystallizer	−0.71
Net energy requirement	72.25

4.1. Esterification in a batch reactor

The simulated result in Fig. 8 shows that the amount of substrate ester synthesized is proportional to the fractional conversion. This implies that the lower conversion results in a higher reactant loss. Therefore, the effective method of chemical esterification should be

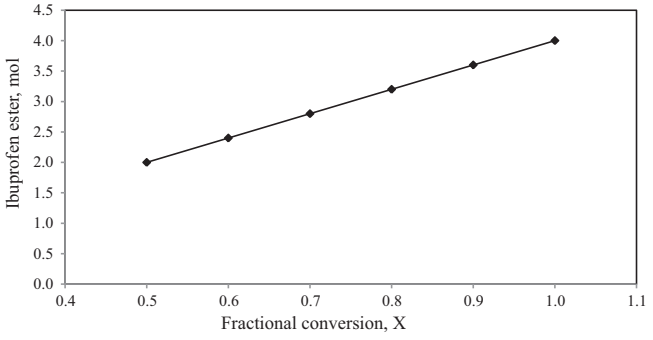


Fig. 8. Ibuprofen ester produced against esterification conversion in a batch reactor.

Table 6
Operating conditions for batch esterification reactor.

Parameter	Operating condition
Temperature (°C)	100–110
Pressure (atm)	1
Reflux (h)	8–10
Heat of reaction (kJ/mol)	88

used in order to prepare a premium grade feedstock without wasting any precious raw materials. It was reported that the conversion of nearly 100% with equimolar reactant could be achieved using diarylammonium pentafluorobenzenesulfonates [23], hafnium (IV) salt and zirconium (IV) salt as catalysts [24].

Nevertheless, the simulations have also determined several important parameters that could give at least 65% conversion of product. Table 6 shows the desired operating conditions needed in order to ensure high conversion of racemic ibuprofen ester. The simulated result shows that the esterification of racemic ibuprofen acid is an endothermic process with heat of reaction, ΔH_R of 88 kJ/mol. This implies that a continuous heat supply is needed for the esterification process. This can be achieved by maintaining the temperature at a range between 100 and 110 °C and controlling the operating pressure at atmospheric level so that the excess 2-ethoxyethanol is kept refluxing within the system.

4.2. Enzymatic dynamic kinetic resolution via membrane reactor

In the experimental work, the enzyme loading on membrane sponge layer was found to be 0.23–3.02 g-enzyme/m^2. The values are within the same order of magnitude (0.4–2.85 g-enzyme/m^2) as reported in the literature [19]. The specific activity (mmol/h g-enzyme) of lipase was reported for optimal operation condition, i.e. at 20 mM initial substrate concentration, 60 mM base concentration, 50 mM phosphate buffer solution (pH 8) at 45 °C reaction temperature. Fig. 9 shows the effect of enzyme loading on specific activity on the sponge layer. The specific activity was found to decrease when lipase loading was increased on the sponge layer, from 30.12 mmol/h g-enzyme at 0.23 g/m^2 lipase loading to 2.97 mmol/h g-enzyme at 3.02 g/m^2 lipase loading. Mass transfer limitation might occur at high lipase loading due to the lower effective diffusivity at higher lipase loading, causing a decrease in the specific activity to a greater extent. The half time ($t_{1/2}$) of lipase activity is defined as the time taken for the activity to reduce by

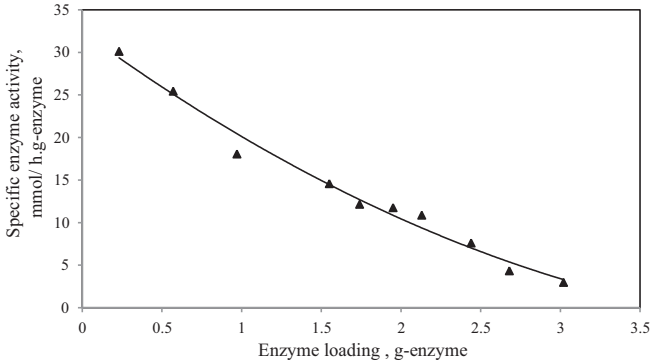


Fig. 9. Specific activity of immobilized lipase for hydrolysis reaction at different enzyme loading.

half of its initial activity. This is given by

$$t_{1/2} = \frac{0.693}{k_d} \quad (2)$$

where k_d is the deactivation constant. In the experimental study, k_d value for immobilized lipase on the spongy layer at 45 °C is 0.00478 h^{-1}. Therefore, the half time calculated from Eq. (2) for the immobilized lipase on spongy layer is 145 h at 45 °C reaction temperature. The observed lipase half-life is greater than that of the reported result in the literature [10] which implies that the DKR involving trioctylamine could increase the enzyme's half life compared to that of the KR system. The role of the trioctylamine as racemization catalyst and lipase activator in the EMR contributed to this particular result [9].

The performance of the EMR was studied as a function of the initial substrate concentration. The simulation results in Fig. 10 show that the product enantiomeric excess, ee_p and conversion, X decreases with the increase in the initial racemic substrate concentrations. This phenomenon was due to the occurrence of the enzyme inhibition by the uncompetitive inhibitor. The modified Michaelis–Menten rate equation used in the process simulation apparently involved the inhibition terms. The substrate (*R*)-ibuprofen ester acts as an uncompetitive inhibitor in the hydrolysis of racemic ester [19] and it tends to attack the allosteric sites and reduces the hydrolysis rate due to the changes of the enzyme conformation. Since the complex formed is reversible, it then further dissociates to form the products. On the other hand, by reducing the ester concentration in the organic phase, the chances of substrate inhibition are mitigated. The active sites bind easily

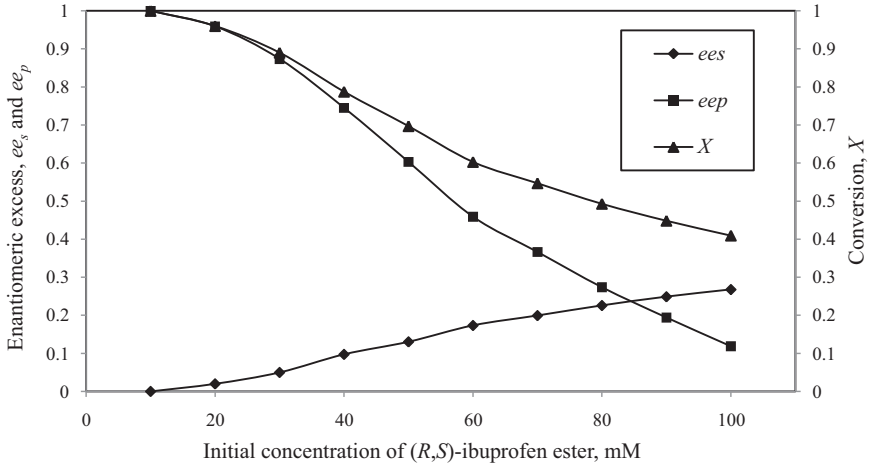


Fig. 10. Effect of initial racemic ester concentration on ee_p, ee_s and X at reaction time, t = 240 min; base concentration, s_{base} = 10 mM; alcohol concentration, s_{alc} = 50 mM.

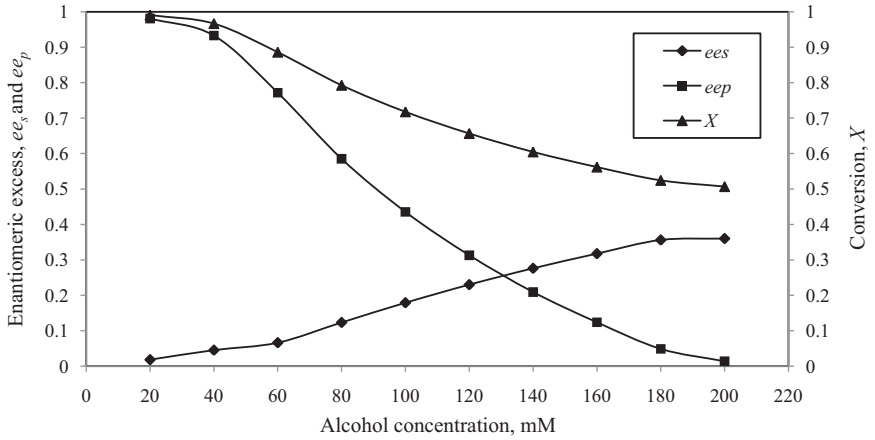


Fig. 11. Effect of alcohol concentration on ee_s, ee_p and conversion at reaction time, t = 240 min; base concentration, s_{base} = 50 mM; initial concentration, s_{T0} = 80 mM.

with the (*S*)-substrate and enhances the hydrolysis reaction. Meanwhile, the enzyme activity is maintained at a high level. However, the equimolar properties of a unique racemic compound lead to a problem where the increased level of initial substrate concentration would also increase the amount of the uncompetitive inhibitor. This not only adds the uncompetitive inhibitor to the system, but also eventually increases the amount of non-competitive alcohol after the hydrolysis. Hence, the ee_p value and conversion were reduced while the amount of unreacted substrate increased with an increasing amount of initial (*R*,*S*)-ibuprofen ester concentration.

The effect of the non-competitive inhibition was investigated by manipulating the alcohol concentration in the organic phase. The simulation result presented in Fig. 11 shows that higher amount of alcohol in the system gave lower substrate conversion and product enantiomeric excess. The process exhibited low productivity in the presence of alcohol when it bound to the enzyme–substrate complex and caused the active sites to be unavailable to the substrate. The hydrolysis of (*R*,*S*)-ibuprofen ester gave 0.5 conversion and presumably, zero product (ee_p = 0.01) at 200 mM alcohol concentration. On the other hand, it was also observed that high value of both conversion and ee_p (X = 0.99, ee_p = 0.99) were obtained at the lowest alcohol concentration, i.e. 20 mM. An acceptable range of the alcohol present in the bulk substrate was also observed. The organic phase with 20–60 mM alcohol could still provide high conversion and ee_p. This implies that the organic phase of the EMR should be controlled at the lowest alcohol concentration so as to provide a maximum (*S*)-ibuprofen acid productivity. However, the simulated results show that the initial substrate concentration exhibited stronger inhibition effect than the alcohol concentration. The hydrolysis of ibuprofen ester gave ee_p of 0.12 and conversion of 0.41 at maximum initial substrate concentration of 100 mM while the enantiomeric excess maintained at the same value with conversion of 0.56 when the system contains 160 mM of alcohol.

The effect of the *in situ* racemization in the DKR process has also been studied. The racemization was carried out in the presence of base, i.e. trioctylamine as a catalyst. The product and substrate enantiomeric excess as well as conversions were studied at variable base concentrations. As depicted in Fig. 12, the trioctylamine concentration gave very significant effect on the product yield where the ee_p and conversion obtained were 0.2 and 0.6, respectively at 10 mM trioctylamine. Both values increased rapidly until they reached a steady state at ee_p = 0.9 and X = 0.95. The steady state of the DKR maintained after achieving the concentration of 60 mM. However, the substrate enantiomeric excess remained at ee_s = 0.04 regardless of any changes of the base concentration. This implies that the DKR is sufficient to provide high ee_p and conversion at moderate base concentrations even with high initial substrate concentration, i.e. s_{T0} = 80 mM. The base concentration is vital in

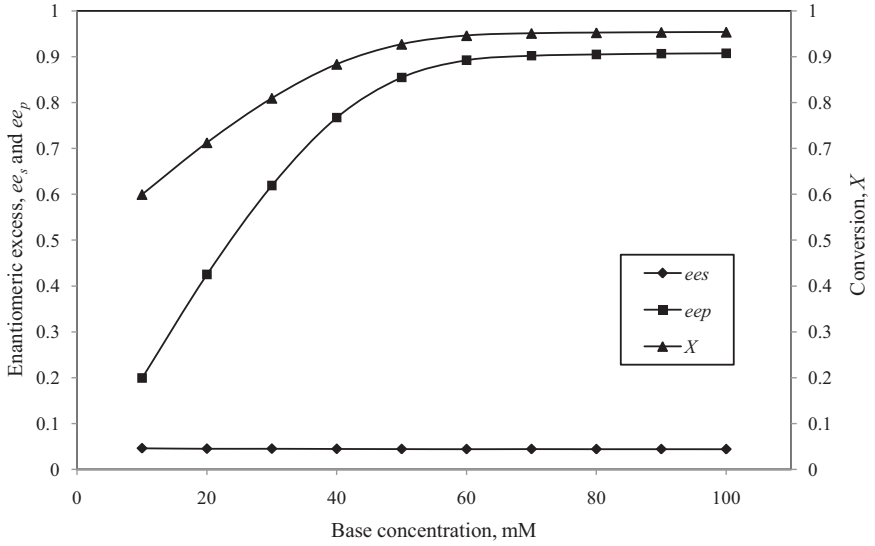


Fig. 12. Effect of base concentration on ee_s, ee_p and X at reaction time, t = 240 min at alcohol concentration, s_{alc} = 50 mM; initial concentration, s_{T0} = 80 mM.

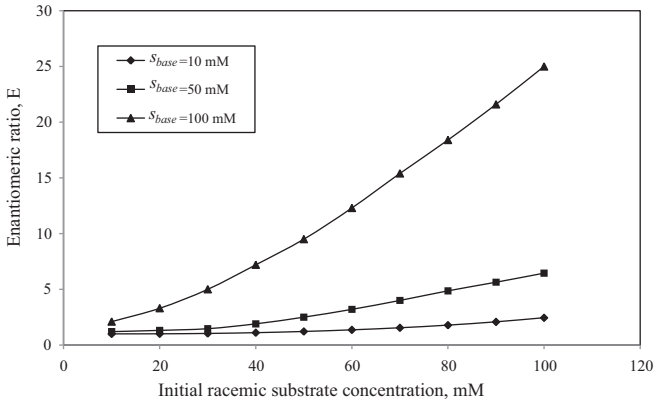


Fig. 13. Profile of the enantiomeric ratio at various base concentrations; reaction time, t = 240 min; alcohol concentration, s_{alc} = 50 mM.

controlling the dynamic equilibrium among (*R*,*S*)-esters and enolate molecules. In addition, the literature also reported that the rate of the dynamic equilibrium of the tautomerism leading to racemization is proportional to the base concentration [21]. Simultaneously, the amount of (*S*)-ester in the system is decreasing due to the hydrolysis with a (*S*)-specific lipase. The shift of equilibrium can be explained using the Le Chatelier's principle where the position of equilibrium will move to a direction such that the concentration of (*R*)-ibuprofen ester will decrease. Hence, the enolate formed will convert the (*S*)-ibuprofen ester and consequently reduce the uncompetitive inhibitor in the system.

Moreover, the base concentration also affects the enantiomeric ratio, *E* which characterizes the enantioselectivity of a particular enzyme of a reaction in which the (*S*)-isomer selectively reacts. Fig. 13 shows that the enantiomeric ratio increased dramatically with the increase in the base concentration. The enantiomeric ratio also steeply increased at s_{base} = 100 mM while nearly constant at s_{base} = 10 mM. Generally, it can be observed that the value of *E* will increase when the initial concentration of racemic ester in the organic phase increases. In the resolution process, high enantiopurity of the product is only obtainable at a very high *E* value. This is due to the fact that the *E* value is ee_p and conversion dependent. This is represented by Eq. (3) [19];

$$E = \frac{\ln[1 - X(1 + ee_p)]}{\ln[1 - X(1 - ee_p)]} \quad (3)$$

A similar theory to that of the effect of base concentration applies to the enantiomeric ratio. High tendency of uncompetitive inhibitor that converts the (*S*)-substrate has reduced the inhibition effect towards the immobilized enzyme. Therefore, the enzyme activity is maintained throughout the DKR process and contributed to a high productivity. These results could provide a guideline to select the suitable EMR operating condition based on the desired productivity. For instance, the EMR should be operating at s_{base} = 100 mM and s_{T0} = 85 mM in order to achieve a resolution with enantiomeric ratio of 20.

The (*S*)-ibuprofen acid diffuses through the membrane pores into the aqueous phase at lumen side. Due to this particular reason, the effect of the lumen loop flow rate was studied. It was observed in Fig. 14 that the lumen flow rate showed an insignificant effect on the conversion and enantiomeric excess. There were very little changes among the ee_s, ee_p and conversion despite of the high lumen flow rate. The ee_p and conversion profiles remained at 0.8 and 0.9, respectively. On the other hand, the ee_s profile decreased gradually from 0.1 to 0.08 with the increase of lumen flow rate. The reason is probably due to the batch-wise operation of the EMR as well as the continuous circulation of the aqueous phase in the lumen side. Eventually, the process reaches steady state after 4 h of continuous operation. In addition, the constant enzyme activity during the hydrolysis process produces equal amount of product along the hollow fiber and diffuses slowly into the lumen side. Since the production of (*S*)-ibuprofen does not get affected much by the lumen flow rate, the EMR should then operate at low to moderate flow rate so as to reduce the energy consumption.

4.3. Product recovery and purification

The special feature of chiral resolution via EMR is that the product could be directly collected in the aqueous solution. The characteristic of the hydrophilic membrane as a support for the biocatalyst has created film boundary between organic and aqueous phase. Thus, the contamination of the desired product is reduced to a minimum level and the costly downstream processing steps are eliminated. Since the polar (*S*)-ibuprofen acid highly dissolves in aqueous buffer, the process for product purification and recovery become simple. Two unit operations such as evaporator and crystallizer would be sufficient to recover the product. A vacuum evaporator was proposed in order to remove the excess water in the product solution. The evaporator was simulated in

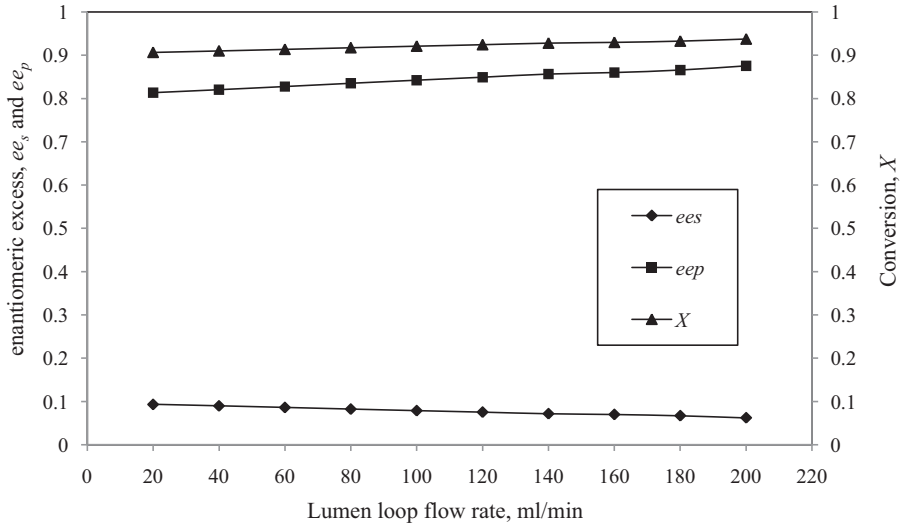


Fig. 14. Effect of lumen flow rates on ee_s, ee_p and *X* at reaction time, t = 240 min at alcohol concentration, s_{alc} = 50 mM; base concentration, s_{base} = 50 mM and initial concentration, s_{T0} = 80 mM.

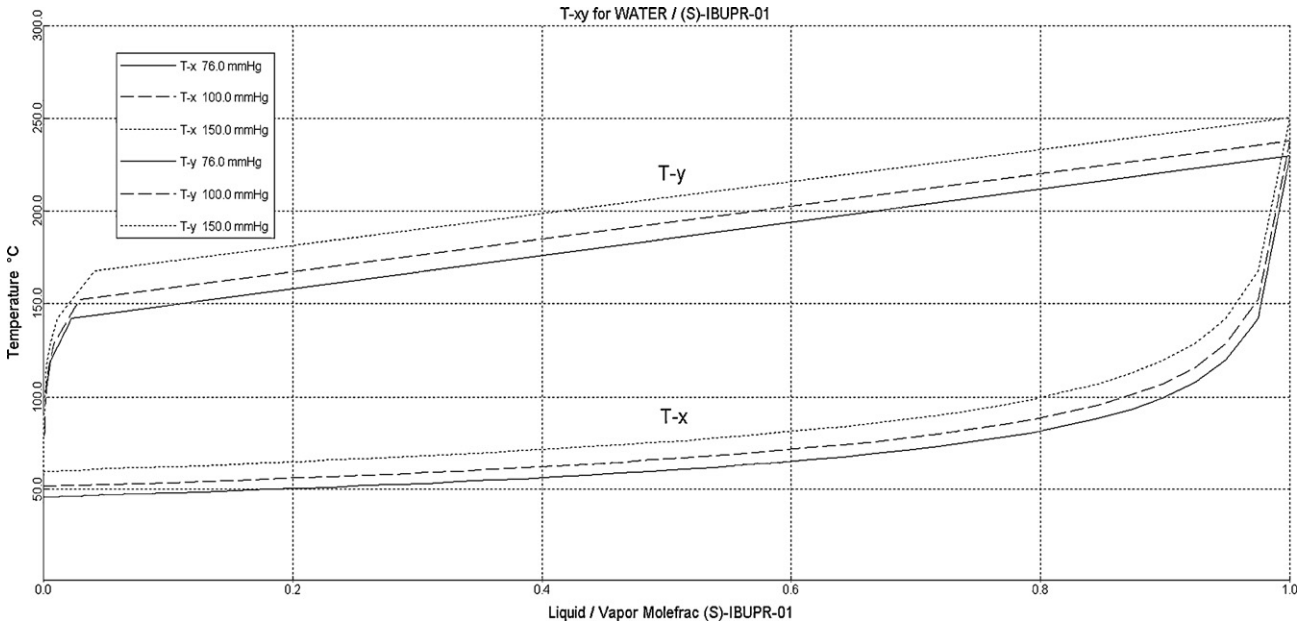


Fig. 15. Binary mixture VLE diagram for water-(*S*)-ibuprofen at vacuum pressure of 76 mmHg, 100 mmHg and 150 mmHg.

order to investigate the effect of operating pressure so that the product degradation could be avoided during water evaporation. Fig. 15 shows the vapor–liquid equilibrium for binary mixture of ibuprofen–water at vacuum pressure. For temperature less than 60 °C with a vacuum pressure of 150 mmHg, it might be necessary to preserve the therapeutic value of (*S*)-ibuprofen. In addition, at this particular pressure, the boiling point of water and (*S*)-ibuprofen are at 60 °C and 250 °C, respectively, which indicate that binary mixture of (*S*)-ibuprofen–water has high relative volatility. Hence, the quality of the concentrated product solution could be assured. In order to avoid degradation of optically pure (*S*)-ibuprofen acid, the temperature of the evaporator needs to be operated slightly higher than the bubble point curve. This might reduce the evaporation rate of water since less energy is supplied to the system. However, for the sake of preserving the product, temperature control inside the evaporator is crucially required. The evaporator should be designed in such a way to provide high surface area so that efficient heat transfer rate could be achieved.

Fig. 16 shows that the fraction of water removed from the product solution increases with the increase of the operating temperature at 100 mmHg. At high vacuum condition, the boiling point of water reduces to approximately 50 °C and any temperature above the boiling point could cause the water to evaporate. However, it was observed that there is only a very small fraction of water removal when the operating temperatures varied from 47 °C to 57 °C. The large relative volatility of vapor phase inside the vacuum evaporator is believed to result in this phenomenon. This result shows that high water removal could be achieved without operating at high temperature. In order to attain a saturated condition with low energy consumption, the evaporator should be operated slightly lower than the boiling point of (*S*)-ibuprofen. Besides, the simulation at 50 °C and 100 mmHg gave approximately 1.42 kg/min of water evaporation rate. Table 7 summarizes the optimum operating conditions extracted from the simulation. This information is particularly useful as a guideline during the operation of the evaporator.

Table 7
Operating conditions for vacuum evaporator.

Parameter	Operating condition
Temperature (°C)	50–60
Pressure (mmHg)	100–150
Energy of evaporation (kJ/kg of H_2O)	3084
Evaporation rate (kg H_2O/min)	1.42

The final stage of (*S*)-ibuprofen production is to obtain solid crystals of the compound. For the ease of crystallization process, the product solution should be concentrated by removing up to 80% of

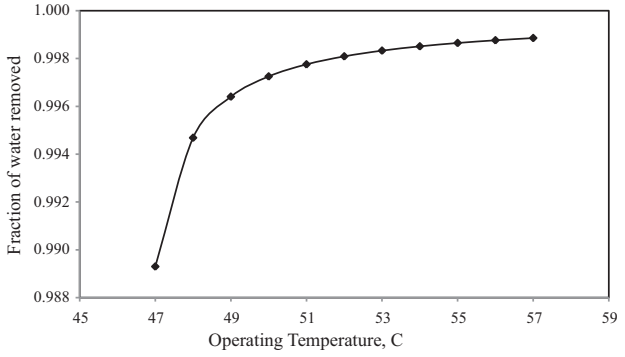


Fig. 16. Fraction of water removed against operating temperature of vacuum evaporator at 100 mmHg.

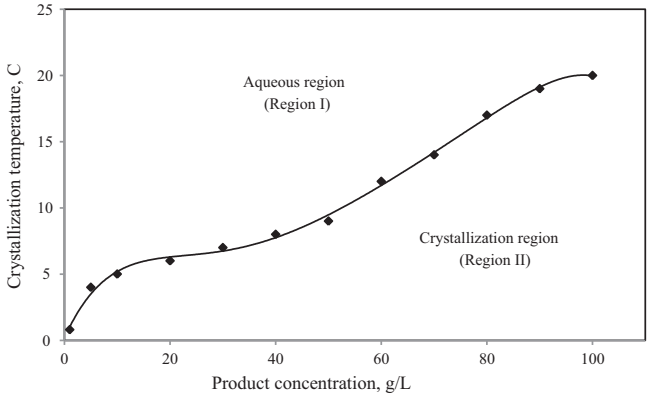


Fig. 17. The crystallization temperature against (*S*)-ibuprofen acid concentration in the cooling crystallizer.

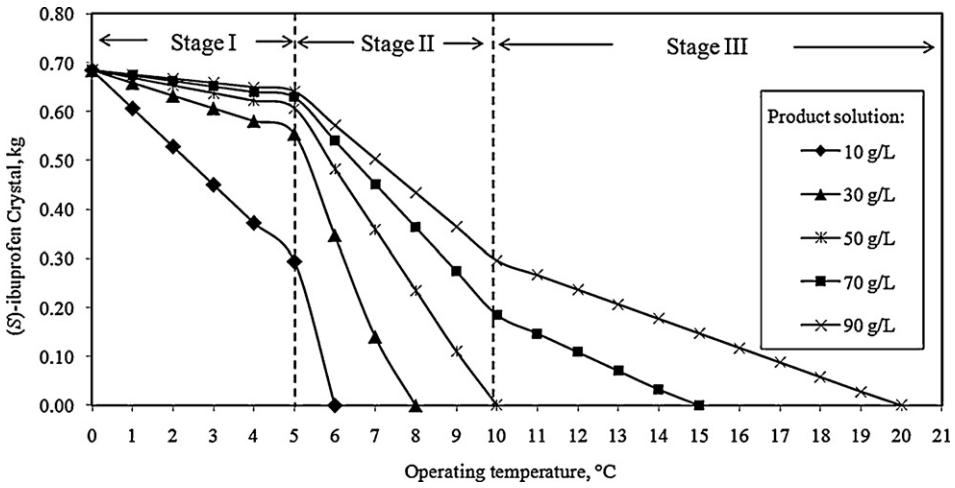


Fig. 18. Amount of (*S*)-ibuprofen crystal obtained at various operating temperatures for different product solutions.

water content. After reaching the supersaturation limit, there is a high possibility of spontaneous crystallization within the evaporator. In this present work, the crystallization process was simulated base on the solubility curve of (*S*)-ibuprofen in the aqueous system. The final concentration of the product solution obtained from the evaporation process should not exceed 100 g/L in order to prevent the formation of crystal inside the evaporator. In this context, a simulation of crystallization process at lower product concentrations (10–100 g/L) is important so as to determine the temperature induced crystallization profile in the cooling crystallizer. Fig. 17 shows a minimum crystallization curve which separates the crystallization diagram of the (*S*)-ibuprofen acid into aqueous region (region I) and crystallization region (region II). The crystallization of (*S*)-ibuprofen initiated spontaneously within the crystallization region. In addition, rapid crystal growth is also observed in region II. However, there was no crystal formed in the aqueous region. In order to crystallize the product in region I, the solution should either increase the product concentration or further cool down to the minimum crystallization point on the curve.

Fig. 18 clearly shows the amount of (*S*)-ibuprofen acid crystal formed at various saturated product solutions at atmospheric pressure. Among the simulated profiles, the range of preferable product solutions is within 30–90 g/L. The concentrations within this range are able to contribute high crystal productivity, which is above 0.5 kg at 5 °C. However, the same temperature only produces 0.29 kg crystals at low product solution, i.e. 10 g/L. It can be clearly observed that at the product solution of 70 g/L and 90 g/L, there are three visible cooling stages. Both solutions give low crystal formation at temperature above 10 °C (stage III). The results at temperatures within 5–10 °C (Stage II) show rapid increment of crystal formation for the product solution of 30 g/L, 50 g/L, 70 g/L and 90 g/L, respectively. At this stage, small changes in the cooling temperature will bring significant effect on the crystal formation. Eventually, when the temperature is further reduced to 1–5 °C (Stage I), nearly all the solute will be crystallized.

The optimum operating conditions of the crystallizer shown in Table 8 were determined from the simulated result. The yield of the (*S*)-ibuprofen is more than 90% with the 99% enantiopurity.

Table 8
Operating conditions for cooling crystallizer.

Parameter	Operating condition
Temperature (°C)	5–10
Pressure (atm)	1
Feed concentration (g/L)	30–60

The results obtained from ASPEN PLUS® could be used as guidance in order to monitor the operating conditions of the process. These results could evaluate the performance of the EMR as well as determine the amount of product obtained at the specified optimum condition.

5. Conclusion

The increasing popularity of chirality in pharmaceutical activity has stimulated an increasing demand for economical and high productive methods for commercial synthesis of pure enantiomers. The demand for those optically pure therapeutic agents is becoming more stringent due to its more target-specific therapeutic effect than racemic mixtures. The optically active (*S*)-ibuprofen acid crystal could be obtained via the proposed plant. The conceptual design of pharmaceutical product plant is the first step for better understanding of the process and help in the development of PFD of the entire plant. The information of the PFD is converted into ASPEN PLUS® flow sheet in order to simulate the effect of several process conditions. The mass stream and heat duty of the equipment were determined. The simulation showed that the performance of the EMR is affected by the initial substrate and base concentrations. Meanwhile, the vacuum evaporator should be operated at 60 °C with vacuum pressure of 100–150 mmHg. The cooling type agitated-crystallizer was suggested with operating temperature range of 5–10 °C in order to get the productivity above the designed plant capacity. Besides, 82.5% overall yield of product crystal was achieved through the overall process. The use of enzymatic biphasic membrane reactor for dynamic kinetic resolution becomes more potent and viable as the innovative technology which contributed to the achievement of 100% theoretical yield when it is combined with racemization process.

Acknowledgements

The authors would like to acknowledge the Malaysian Technology Development Corporation (MTDC) for providing research fund (304/PJKIMIA/6053010/M130) which resulted in this article. The financial support (USM-RU-PGRS 1001/PJKIMIA/8033041), USM Fellowship and research facilities provided by Universiti Sains Malaysia (USM) are also duly acknowledged.

References

[1] C.G. Sahajwalla, New Drug Development 141 (2004) 421–426.
[2] H. Caner, E. Groner, L. Levy, I. Agranat, Trends in the development of chiral drugs, Drug Discovery Today 9 (3) (2004) 105–110.

[3] H. Murakami, From racemates to single enantiomers—chiral synthetic drugs over the last 20 years, Novel Optical Resolution Technologies (2007) 273–299.
[4] S. Erb, Single-enantiomer drugs poised for further market growth, Pharmaceutical Technology 30 (Suppl.) (2006) s14–s18.
[5] A.M. Evans, Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs, European Journal of Clinical Pharmacology 42 (3) (1992) 237–256.
[6] P. Molnár, E. Székely, B. Simándi, S. Keszei, J. Lovász, E. Fogassy, Enantioseparation of ibuprofen by supercritical fluid extraction, Journal of Supercritical Fluids 37 (3) (2006) 384–389.
[7] S. Peper, M. Johannsen, G. Brunner, Preparative chromatography with supercritical fluids, comparison of simulated moving bed and batch processes, Journal of Chromatography A 1176 (1–2) (2007) 246–253.
[8] W.H. Lam, K.M. Ng, Diastereomeric salt crystallization synthesis for chiral resolution of ibuprofen, AIChE Journal 53 (2) (2007) 429–437.
[9] C.H. Lu, Y.C. Cheng, S.W. Tsai, Integration of reactive membrane extraction with lipase-hydrolysis dynamic kinetic resolution of naproxen 2,2,2-trifluoroethyl thioester in isooctane, Biotechnology and Bioengineering 79 (2) (2002) 200–210.
[10] W.S. Long, P.C. Kow, A.H. Kamaruddin, S. Bhatia, Comparison of kinetic resolution between two racemic ibuprofen esters in an enzymic membrane reactor, Process Biochemistry 40 (7) (2005) 2417–2425.
[11] H. Fazlena, A.H. Kamaruddin, M.M.D. Zulkali, Dynamic kinetic resolution: alternative approach in optimizing S-ibuprofen production, Bioprocess and Biosystems Engineering 28 (4) (2006) 227–233.
[12] W.J. Choi, K.Y. Lee, S.H. Kang, S.B. Lee, Biocatalytic enantioconvergent separation of racemic mandelic acid, Separation and Purification Technology 53 (2) (2007) 178–182.
[13] Y. Liu, F. Wang, T. Tan, Cyclic resolution of racemic ibuprofen via coupled efficient lipase and acid–base catalysis, Chirality 21 (3) (2009) 349–353.
[14] A.I. Stankiewicz, J.A. Moulijn, Process intensification: transforming chemical engineering, Chemical Engineering Progress 96 (1) (2000) 22–33.
[15] A. Bhattacharya, D. Murphy, Temperature selective diastereo-recognition (TSD): enantiomeric ibuprofen via environmentally benign selective crystallization, Organic Process Research and Development 7 (5) (2003) 717–722.
[16] J.E. Rekoske, Chiral separations, AIChE Journal 47 (1) (2001) 2–5.
[17] K. Uhm, S. Lee, H. Kim, H. Kang, Y. Lee, Enantioselective resolution of methyl 2-chloromandelate by *Candida antarctica* lipase A in a solvent-free transesterification reaction, Journal of Molecular Catalysis B: Enzymatic 45 (1–2) (2007) 34–38.
[18] W.S. Long, S. Bhatia, A. Kamaruddin, Modeling and simulation of enzymatic membrane reactor for kinetic resolution of ibuprofen ester, Journal of Membrane Science 219 (1–2) (2003) 69–88.
[19] W.S. Long, A. Kamaruddin, S. Bhatia, Chiral resolution of racemic ibuprofen ester in an enzymatic membrane reactor, Journal of Membrane Science 247 (1–2) (2005) 185–200.
[20] S.Y. Lau, M.H. Uzir, A.H. Kamaruddin, S. Bhatia, Lipase-catalyzed dynamic kinetic resolution of racemic ibuprofen ester via hollow fiber membrane reactor: modeling and simulation, Journal of Membrane Science 357 (1–2) (2010) 109–121.
[21] X. Yuchun, L. Huizhou, C. Jiayong, Kinetics of base catalyzed racemization of ibuprofen enantiomers, International Journal of Pharmaceutics 196 (1) (2000) 21–26.
[22] R.H. Perry, D.W. Green, J.O. Maloney, Perry's Chemical Engineer's Handbook, The McGraw-Hill Companies, Inc., New York, 1999.
[23] K. Ishihara, M. Nakayama, S. Ohara, H. Yamamoto, Direct ester condensation from a 1:1 mixture of carboxylic acids and alcohols catalyzed by hafnium (IV) or zirconium(IV) salts, Tetrahedron 58 (41) (2002) 8179–8188.
[24] K. Ishihara, S. Nakagawa, A. Sakakura, Bulky diarylammonium arenesulfonates as selective esterification catalysts, Journal of the American Chemical Society 127 (12) (2005) 4168–4169.