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ENZYMATIC MEMBRANE REACTOR FOR CHIRAL DRUGS SYNTHESIS

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Abstract. 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. Modern medicines often call for just one enantiomer of a stereo-isomer. The demand for these optically pure therapeutic agents is becoming more stringent due to its more-specific characteristic than racemic mixtures. However, conventional technologies yield a mixture of both isomers which are difficult to separate. In this context, enzymatic resolution is a subject of recent investigation, where high efficiency of heterogeneous and homogeneous catalyzed multiphase chemistries is being explored. Kinetic resolution is a method in which the residual substrate fraction can be obtained in high enantiomeric purity. Ideally one enantiomer reacts faster than the other with a chiral entity.

As a potential technology for the production of specific enantiomer, enzymatic membrane reactor (EMR) has been reported to overcome some of the limitations of the conventional system. Enzymatic membrane reactors combine selective mass transport with chemical reactions, and the selective removal of products from the reaction site increases the conversion of product-inhibited or thermodynamically unfavorable reactions. Of all the lipase available, lipase from *Candida rugosa* is given particular attention as an ideal biocatalyst for the resolution of racemic esters and alcohols, as it acts enantioselectively and prefers to catalyze the synthesis of one of the enantiomers using hydrolysis with higher preference. In this paper, the authors presented a review of unique potential application of lipase-immobilized EMR systems towards the development of chirotechnology that has been presented which mainly focuses on chiral drugs production.

Key words: Chiral drugs, optical purity, enantiomers, kinetic resolution, enzymatic membrane reactors

Abstrak. Kepentingan kekiralan dalam aktiviti farmaseutikal telah menuntut kaedah yang berproduktif tinggi dan ekonomik untuk mensintesis enantiomer tulen secara komersil. Ubat moden kerap menggunakan enantiomer daripada suatu campuran stereo-isomer. Permintaan terhadap agen terapeutik yang tulen secara optik menjadi semakin kritikal kerana cirinya yang lebih spesifik berbanding campuran rasemik. Walau bagaimanapun, teknologi konvensional yang dipraktikkan selama ini menghasilkan campuran kedua-dua enantiomer yang sukar dipisahkan. Dalam konteks ini, resolusi berenzim ialah suatu cara untuk mengatasi masalah ini. Resolusi kinetik ialah suatu kaedah yang membolehkan pecahan substratum baki dihasilkan dengan ketulenan enantiomer yang tinggi. Secara unggul, satu daripada enantiomer bertindak balas secara enantiopilihan dengan kadar yang lebih cepat bagi suatu entiti kiral.

Sebagai suatu teknologi yang berpotensi tinggi dalam penghasilan enantiomer spesifik, reaktor membran berenzim (EMR) berjaya mengatasi kekurangan yang dialami oleh sistem konvensional.

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Reaktor membran berenzim menggabungkan pengangkutan jisim memilih dengan tindak balas kimia, dan penyingkiran memilih produk daripada medium tindak balas. Ciri unggul yang ditunjukkan oleh reaktor membran berenzim ialah keupayaannya meningkatkan penghasilan tindak balas berenzim yang berbentuk perencat produk atau tindak balas yang tak sesuai secara termodinamik. Berbanding lipase lain yang ada, lipase daripada *Candida rugosa* dianggap sebagai suatu biomangkin yang unggul bagi resolusi campuran ester dan alkohol, kerana lipase ini bertindak secara enantiopilihan dan memangkin pensintesisan enantiomer melalui tindak balas hidrolisis. Dalam kertas kerja ini, penggunaan sistem EMR lipase tak boleh gerak terhadap perkembangan teknologi kiral dibincangkan secara umum, dengan tumpuan khusus diberikan terhadap penghasilan drug kiral.

Kata kunci: Drug kiral, ketulenan secara optik, enantiomer, resolusi kinetik, reaktor membran berenzim

1.0 INTRODUCTION: CHIRAL DRUGS AND THEIR CHEMISTRY

The discovery of isomers occurred about 150 years ago when Louis Pasteur noted that some organic molecules existed as two non-superimposable mirror images. These two images were enantiomers and named (S) for left and (R) for right. Racemates are 1:1 mixture of two enantiomers. In most cases, one enantiomer provides the desired therapeutic benefits, while the other enantiomer may be inactive or may cause side effects. The growing drug industry demands for enantiomerically pure compounds and specialty chemicals are the driver for many companies to pursue biocatalytic technology [1].

Recently, there have been increasing interests for process involving the enzyme-catalysed kinetic resolution of racemates [2,3,4]. Efforts are being made to produce low-volume but yet high-value products. Over the years, a number of reports have been published on enantiopure epoxides, which are versatile chiral synthons in organic synthesis. For example, chiral glycidol (**1**) and its derivatives are important intermediates in the synthesis of S(-)-propranolol (**2**) (β-blocker [5,6,7]), among which (R)-glycidyl butyrate (**3**) is the most useful intermediate for β-blocker cardiovascular drugs. Effort has also been centered on the production of (S)-2-hydroxy alkanoic acids (**4**) [8], (R)-2-chloro- (**5**) and (R)-2-bromoalkanoic acids (**6**) [9,10], (S)-2-alkylalkanoic acids [11], (S)-arylpropionic acids, and (R)-2-aryloxypropionic acids [12] due to their important role as intermediates or products in synthesizing drugs or herbicides. The α-arylpropionic acids, typified by ibuprofen (**7**) and naproxen (**8**) constitute the largest single group of drugs used in the treatment of rheumatoid arthritis and as general analgesics [13]. Ibuprofen (**7**) and naproxen (**8**) are chiral molecules and it is the (S)-enantiomer that is responsible for the desired therapeutic effect. Their respective structures of (S)-enantiomers are shown in Figure 1. Current research interest focuses on the application of enzymatic membrane reactor (EMR) in the production of optically pure compounds [5,6].

The objective of this review is to highlight the unique potential application of lipase-immobilized EMR systems towards the development of chirotechnology for the

No. of Structures

(These structures are not grouped as a single illustration. In fact, each structure is to be quoter in the text **throughout**).

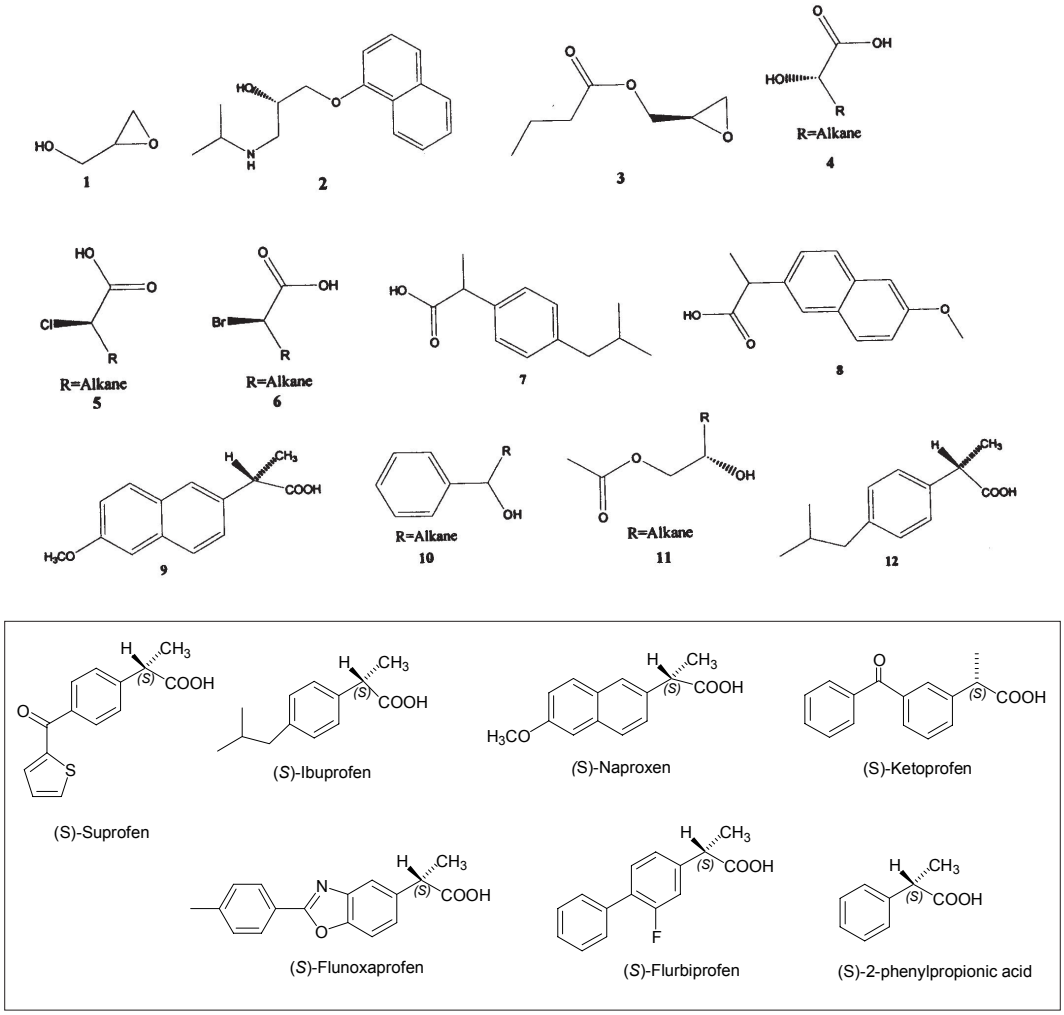


Figure 1 Non-steroid anti-inflammatory drugs: the (S)-enantiomers

production of drugs. The effort towards environmentally friendly technologies makes the membrane reactors particularly interesting since they are able to function at moderate temperature and pressure while no additives are required and no by-products are being produced.

2.0 ROLE OF ENZYME IN SYNTHESIS

The role of enzyme in fine chemical industries is crucial due to new technologies coming into play in the biological sciences [14]. Its use is very much preferred for

reason of its high activity at room temperature. Current pharmaceutical and fine chemical compounds are derived from sensitive raw materials like glycerine, fats, sugars, amino acids derivatives, and highly reactive acrylates which require high reaction temperatures and they are always associated with products with color and smell to be removed.

Enzymatic process can help to avoid by-products and other problems from the very beginning [14]. The catalytic behavior of enzymes is highly selective as compared to chemical catalyst; these enzymes demonstrate higher reaction rate, milder condition, and greater stereospecificity. Efforts are being made by experts from applied enzymology especially in the manipulation of enzyme activity to improve enzymatic reaction rate. Steve Taylor from Chrom Tech [1] admitted that bioresolution of (S)-naproxen (**9**) with recycle of unwanted enantiomer could compete with chemical route. For an enantioselective catalyst to be effective, it must possess two qualities, first it must be able to accept a broad range of substrates, and second it must be able to retain high enantioselectivity.

Lipase (triacylglycerol hydrolases) is among the few catalysts that fulfill both criteria, and for this reason, organic chemists often use lipase for the synthesis of enantiomerically pure compounds. Lipase accepts wide range of substances and its stability in non-aqueous media allows its use in various conditions. Some chiral compounds prepared by lipase-catalysed resolutions have been found to be intermediates to β-blockers, therapeutic, and chiral drugs used for the treatment of hypertension and angina pectoris [5]. This review, however, focuses on lipase (acyglycerol hydrolases EC 3.1.1.3) only, which plays an important role in the synthesis processes of hydrolysis, esterification, and transesterification. Of all the lipase available, *Candida cylindracea* (also known as *Candida rugosa*) has been given particular attention as an ideal catalyst for the resolution of racemic esters and alcohols [8–11, 15–17].

3.0 LIPASE IMMOBILIZATION

The restriction of enzyme mobility in an enclosed channel is known as enzyme immobilization. Enzyme immobilization offers advantages which include re-utilization, increase in reactor stability and productivity, improve in product purity and quality, and reduction in waste. Enzyme attachment can be done by: (1) ionic binding to ion-exchanger supports (*e.g.* carboxymethyl cellulose), (2) adsorption through van der Waals interactions to hydrophobic supports (*e.g.* polypropylene) or (3) covalent binding between the carboxyl or amino groups of amino acids and the membrane.

The covalent bond is usually formed by active bridge molecules, such as CNBr and bi- or multifunctional reagents. This immobilization is highly stable but it has the disadvantage of denaturing the native enzyme during the binding process. Immobilization process does not alter the stereoselectivity of the biocatalyst, among which, membrane entrapment is the gentlest approach available owing to the absence of chemical agents or harsh conditions. Physical entrapment has an added advantage

that once the enzyme is deactivated, it can be flushed from the system, by reversing the pressure difference and back flushing, and replacing with fresh enzyme. In all cases, a semi permeable membrane is employed to retain high molecular weight compounds (enzyme), while allowing small molecular weight compounds (substrates or product) access to the enzyme. Membranes also provide *in-situ* separation of the enzyme from the product, thereby obviating the need for this downstream step. Enzyme can be immobilized either onto the asymmetric sponge layer or in the inner dense layer of the membrane. Such immobilization methods are suitable mainly for enzymes that can be deactivated by shear stress. For example, immobilization of lipase on hollow fiber asymmetric membrane pore was carried out by circulating the lipase solution in the shell side [18]. The lipase was immobilized into the sponge layer by cross-flow filtration of the lipase solution. However, while these immobilized systems establish significant advantages in enzymatic resolution, they also suffer from reductions in effective enantioselectivity of the enzyme. It was reported that diffusional limitations in immobilized enzyme systems can result in reduced stereospecificity [19].

4.0 ENZYMATIC MEMBRANE REACTOR

A membrane reactor is a flow reactor within which membranes are used to separate cells or enzymes from the feed or product streams. Enzymatic membrane reactor (EMR) is referred to any enzyme-catalyzed process which takes place in membrane-mediated reactor. The feed is continuously fed into the reactor where the reaction is taking place and product is discharged. Enzymatic membrane reactor is particularly attractive when the substrate has different solubility from the product. An example for this resolution is enzymatic hydrolysis reaction in an EMR system, which is shown in Figure 2. Suppose that (S)-acid is the desired pure product of a racemic mixture in the enzymatic hydrolysis reaction. Enzyme with high selectivity catalyzes only the (S)-ester producing the (S)-acid, which then diffuses through the membrane into the aqueous phase due to its water-solubility behavior, thus separating it from the (R)-acid. This EMR system does not require downstream product separation. The membrane can be flat-sheet shaped, assembled in a plate and flame module, tubular-like assembled in tube-shell modules, or a spiral-wound. Membranes of symmetric or an asymmetric structure are made of a variety of materials including cellulose acetate and nitrate, polyvinylidene difluoride, polysulfone, polypropylene, polytetrafluoroethylene (PTFE) and polyacrylonitrile and aromatic polyamide. Membranes are classified into microfiltration (MF) with pore size in the range of 0.1 to 10 mm, ultrafiltration (UF) with a molecular weight cut off (MWCO) between 0.5 and 500 kD, and reverse osmosis (RO) membrane suitable for low-molecular weight solute such as salts. Enzymes with sizes between 10 and 500 kD are not retained by MF but by UF membranes with a typical MWCO of 10kD of commercial membranes. Polymeric microfiltration or ultrafiltration membranes are most commonly employed for the construction of

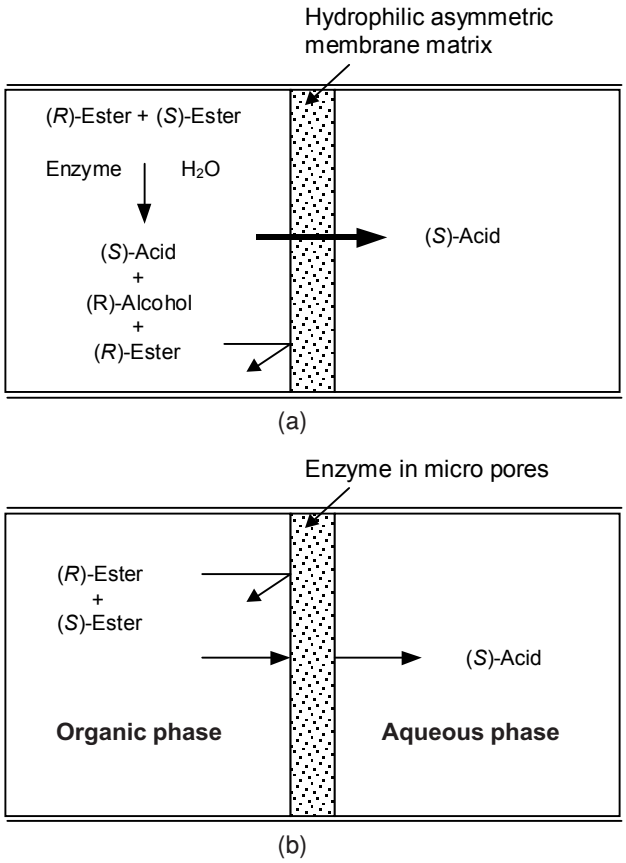


Figure 2 Membrane acts as a semipermeable barrier with a selective enzyme in EMR:
(a) Enzyme in direct contact with the substrate in the reaction medium
(b) Enzyme immobilized in the membrane matrix

membrane bioreactors, although other types of membranes have been used, including ceramic, silicone rubber, and ion exchange membranes [20]. There have been a number of excellent reviews on various types of membrane reactors reported in the literature [21].

4.1 Classification of EMR

Enzymatic membrane reactors (EMRs) are generally classified into: (1) biocatalyst with microencapsulation, (2) dialysis reactor, (3) immobilization on membranes, and (4) recycle reactors. This review focus on the third type only, *i.e.* immobilization on membranes, which is more commonly known as EMRs.

Enzymatic membrane reactors can be further categorized into two types. In the first type, the reactor is divided into two compartments by a permselective membrane. Besides being a selective barrier, the membrane itself can provide structural support for the enzyme,

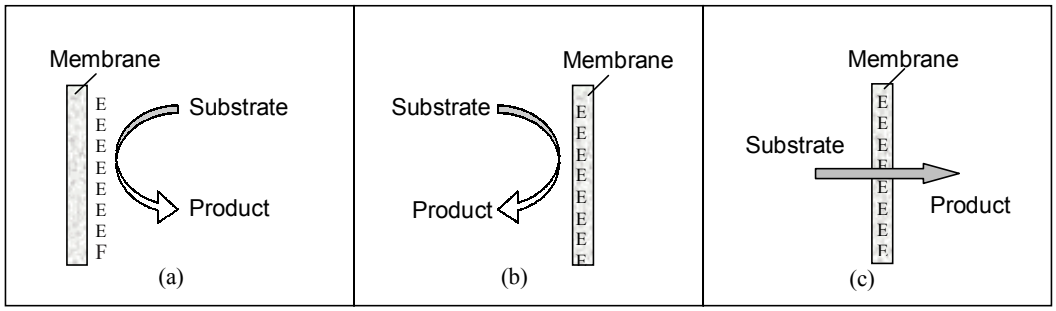


Figure 3 Enzyme immobilized on the membrane
(a) enzyme immobilized on the membrane at which it is in contact with substrate
(b) enzyme entrapped within the membrane matrix, substrate and product are in the same phase
(c) enzyme immobilized in the membrane pores, enzyme-substrate react at membrane interface and the product diffuses into another phase

in which the enzyme can be loaded within the porous structure or on the surface of the membrane. In the second type, the enzyme is physically entrapped within a microporous membrane (usually an asymmetric hollow fiber membrane). Figure 3 illustrates three ways of enzyme immobilization on the membrane, at which a slight pressure gradient on the outside of the membrane maintains the organic/aqueous phase boundary at the outside of the hydrophilic membrane surface. However, in another way, membrane reactors can also be (either enzymatic or non-enzymatic) classified according to: (a) driving force, (b) pore structure, (c) pore size, and (d) direction of flux.

Convective and diffusive mass transports are two different driving forces to be accounted. When a pressure difference, ΔP, is imposed across the membrane, the main separation power stems from the convective forces. Diffusive mass transfer is based on a concentration difference, ΔC, approach. High flux can be achieved sooner and more practicable with enforced convective flow across the membrane, which is superior than diffusive mass transfer. The membrane can be a barrier for diffusive flux only, thus separation is based on the ΔC only.

Enzymatic membrane reactors have an added advantage due to the flexibilities of their modes of operation. For instance, the continuous processes can exclusively be classified into: (1) immobilized enzymatic reactor, usually as a fixed bed plug flow reactor (PFR) containing immobilized enzyme on a support as a catalyst, and (2) the EMR, or commonly known as a continuous stirred-tank reactor (CSTR). In the normal case, there are distinctive differences between the continuous and batch operation. However, a continuous operation can be modelled as or mimic to an ideal batch process by means of model approximation under some circumstances. For example, the continuous operation of a membrane reactor can be modified to a recycle CSTR by circulating the solutions in both the substrate and product channels. This recycle

CSTR system is accomplished only when the conversion per pass is limited to less than 5%, to achieve satisfactory substrate resolution [6].

Membrane reactor can also be operated as CSTR with dead-end filtration, or with tangential (crossflow) filtration. Mostly tangential and crossflow filtration is employed within a loop reactor rather than dead-end filtration, in which the fluid travels tangentially to the membrane surface, rejected material is swept away, and thus it can no longer block the membrane surface.

4.2 Reaction Media in EMR

The reaction media in the EMR can be of non-aqueous (total organic), two-liquid phases (organic-aqueous), or multiphase (for an enzymatic reaction taking place in an aqueous-organic medium, being the enzyme present as the solid form). For an EMR in which the operation carried out in at least two different phases, the system is called multiphase membrane reactor system. The membrane acts as a phase contactor, phase separator, and interfacial catalyst in multiphase membrane reactor.

In the operation of flat membrane reactor, there are cases where soluble enzyme is suspended in the reaction medium composed only of organic solvent, and it is simply named as single-phase reaction. Rosell [22], Giorno [18,23,24,25], Ceynowa [26,27,28] and their co-workers have used the EMR for reactions involving aqueous and organic phases for both fine chemicals and fatty acids production. In multiphase membrane reactor, two types of membrane are being used, namely hydrophilic and hydrophobic membrane. The distinctive differences between both types of membranes are presented in the following section.

4.3 Differences between Hydrophilic and Hydrophobic Membrane

The permeability of a membrane is dependent not only on pore size and structure but also on characteristics such as hydrophobicity and hydrophilicity. A major difference between hydrophobic and hydrophilic membranes is the thickness of the reaction layer [29], which is much smaller in hydrophobic membranes making enzyme loading and overloading threshold high in the membrane. There may be significant advantages in employing relatively thin membranes with high enzyme loading for enzymatic resolution system, at which a membrane thickness limit was found critical for optimum enzyme loading [6].

Hydrophilic membrane is capable of increasing the enzyme activities, as the immobilized lipases could retain their full activity [29]. This is attributed by the fact that there is no diffusion limitation of the reactants or enzyme deactivation, and more importantly, the contact zone between the organic and aqueous phases must be extended over the entire membrane, whereas in hydrophobic membranes, the immobilized lipase lost 86-99% of its activity.

4.4 Advantages and Disadvantages of EMR

The EMR has reaction and downstream processing combined together and therefore *in-situ* separation of substrate and products from the biocatalyst/enzyme after reaction. Convenient scale up by adapting membrane area and the ease to counteract enzyme deactivation at constant interval are major advantages. However, despite its many promising features, the enzymatic approach is still in its formative stage.

Table 1 Advantages and disadvantages of membrane reactors

Advantages	***Disadvantages***
No mass transfer limitation: *in situ* product separation	Pre-filtration necessary
Scale up simple: convenient scale up by adapting membrane area and flux data	No polymeric products
Potentially more stable enzyme with different techniques of enzyme immobilization	Immobilization adds extra cost
Co-immobilization simple	

Table 2 Strategies for improving enantioselectivity

	Strategies for Improving Enantioselectivity
Recycling of the product	In kinetic resolution processes, the residual substrate fraction can be obtained in high enantiomeric purity even for biocatalytic systems that possess low E value. That is, the optical yield can be enhanced at the expense of chemical yield. The reaction must be terminated prior to 50% conversion to maximize the optical yield of the product fraction. For biocatalyst with moderate E values (E = 5-10), the product may be recycled to enhance the optical purity (ee_p), which is for hydrolytic enzymes the product may be easily re-esterified.
Modification of the substrate	The enantioselectivity of a biocatalytic system can frequently be improved by manipulating the structural features of the substrate molecule.
Protection of enzymes from the environment	Mechanical stress may have significant effects on the activity of cells and enzymes. An additional cause of inactivation is the protein denaturation. The use of membrane reactors can solve the problem as the enzymes are immobilized in the micro pores, thus they are protected from mechanical damage. Another approach to overcoming convective and gravitational polarization is to immobilize the proteins chemically.

A major limitation of this method is the lack of an arsenal of enzymes with well-defined enantioselectivities to enable chemists to resolve enantiomers with predictability. Diffusional limitations in immobilized enzyme systems can result in reduced stereospecificity. Membrane fouling is a problem which must be solved in the industrial utilization of the membrane reactor. Table 1 presents the advantages

and disadvantages of membrane reactors, while Table 2 presents the strategies for improving process enantioselectivity.

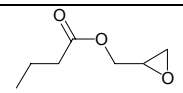
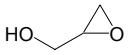
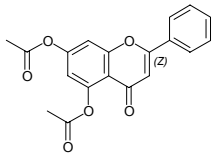
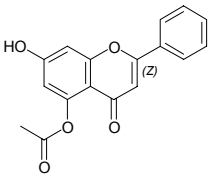
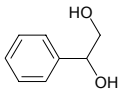
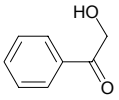
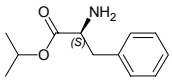
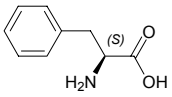
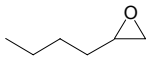
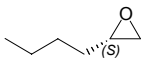
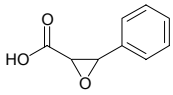
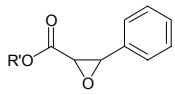
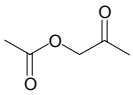
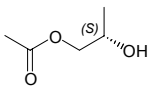
5.0 USE OF EMR IN SYNTHESIS OF CHIRAL DRUGS

Among various methods available for the synthesis of chiral drugs, EMR configuration has been used to increase the reactor inventory of reactant and to reduce potential reactant/product inhibition. Membranes with immobilized enzyme were used earlier in processes carried out in bi phasic systems, such as the hydrolysis of achiral oils [26], as well as in the enantioselective hydrolysis of chiral acids esters, alcohols, and glycidol derivatives [5,7]. This is attributed by the fact that emulsion formation presents a difficult downstream separation problem, as a result of the presence of surface active biological materials combined with the high intensity of mixing [22,30,31,32]. In addition, conventional packed bed reactors often cause problems due to mass transfer limitations of the reactants and products in the support matrix. All these drawbacks bring to the discovery of an alternative method using EMR.

Ultrafiltration is a separation process in which large molecules or colloidal particles are filtered from the solution by means of suitable membranes. Online ultrafiltration membrane reactor is a replacement of downstream operations into one ultrafiltration unit to isolate the product and separate from the enzyme as reaction is taking place. Ultrafiltration of the heterogeneous reaction mixture at the end of the enzymatic hydrolysis could essentially circumvent the 'emulsion problem'. For instance, the ultrafiltration by polyacrylonitrile membrane has been used for the *in-situ* removal of the product [33], in which the application of the on-line ultrafiltration leads to a two-fold increase in the overall productivity, due to the reduced inhibition of the enzyme by the product. In this context, the product is removed continuously from the system as permeate or by the aqueous sweeper stream. Use of enzyme membrane reactors in enantioselectivity of 1-phenyl alcohols (**10**) by sequenced processes of ester hydrolysis and transesterification had been documented [28]. Excellent results have been obtained by performing the processes in reactors with lipase chemically immobilized within the membranes.

Membrane reactor has also been practiced for the effective production and extraction of (S)-1-acetoxy-2-alkanol (**11**) using a Bakers' yeast cell-free extraction [34]. The specificity of the system was that the reactor system required neither the isolation of the enzyme for the reduction of the substrate nor the addition of the enzyme participating in the cofactor of the NADPH regeneration. The following sections address the role of EMRs towards the development of two types of chiral drugs. Table 3 summarizes the work reported in the literature on enzymatic chiral resolution of fine chemicals using membrane reactors.

Table 3 Enzymatic chiral resolution

Racemic mixture	Enzyme/ Microorganisms	Reaction Type	Optically pure product	Applications	Ref
 (R,S)-Glycidyl butyrate	Lipase from *porcine pancreas*	Multiphase membrane reactor	 Glycidol	Intermediates in the synthesis of s(-)-propanolol, a β-blocker	6
 (R,S)-5,7-diacetoxyflavon	Lipase *Pseudomonas cepacia*	Monophasic nonaquoeus membrane reactor	 5,acetoxy-7,hydroxyflavon	Anti-inflammatory, antitumor,antivival. antioxidant reagent	24
 1-phenyl-1,2-ethanediol	Glycerol dehydrogenase (GDH)	Continuous extraction in HFMR	 2-hydroxyacetophenone	Pharmaceutical uses	41
 (R,S)-phenylalanine isopropylester	Esterase	Hollow fiber supported liquid membrane	 (S)-phenylalanine	Intermediates for pharmaceutical & agrochemical	42
 1,2-epoxyhexane	*Rhodotorula glutinis*	Cascade HFMR	 (S)-1,2-epoxyhexane	Chiral building blocks for pharmaceuticals	33
 3-phenylglycidic acid	*Serratia Marcescens*	HFMR	 3-phenylglycidic acid ester	Pharmaceutical uses	36
 (R,S)-1-acetoxy-2-propanone	Bakers' yeast	Bakers' yeast cell-free Extract membrane reactor	 (S)-1-acetoxy-2-propanol	Pharmaceutical product	34

HFMR : Hollow fiber membrane reactor
Cascade membrane reactor: Two identical hollow fiber membrane reactor were employed in cascade for hydrolysis and subsequent diol extraction

5.1 Synthesis of a-Arylpropionic Acids (NSAIDs)

Various methods for producing optically active S-ibuprofen (**12**) have been reported [9]. The most common being the aqueous/organic system, either by membrane-mediated reactors or heterogeneous emulsion systems without membrane assistance. Several configurations of EMR have been developed for hydrolysis reactions involving

chiral centers, *e.g.* a packed bed column with immobilized *Candida cylindracea* lipase has been used for the resolution of naproxen by hydrolysis [35], and for other hydrolysis reactions using hollow fiber membrane reactors [36]. *Candida cylindracea*-catalyzed (S)-specific hydrolysis of ibuprofen esters in an EMR has been described by Sepracor [12]. Enzymatic hydrolytic resolution of naproxen esters by *Candida cylindracea* was addressed in which high enantioselectivity for the S-form of the racemate was observed [18,23,24,25]. Besides, the enantioselective hydrolysis of methyl ester of 2-acryl- and aryloxypropionates has been carried out by high enantioselective *Bacillus subtilis* using pressure-driven membrane reactor [18], in which the *Carboxyesterase NP* was derived from a *Bacillus subtilis* strain. A schematic diagram of pressure-driven membrane reactor is shown in Figure 4.

A comparison of bi phasic membrane reactor performance between hollow fiber and flat-sheet membrane had been carried out for enzymatic stereoselective hydrolysis of (R,S)-1-phenylethyl propionate [36]. It was reported that the productivity of a hollow-fiber membrane reactor was more stable than that of the flat sheet enzyme membrane reactor. The use of a high recirculation ratio of substrate feed rate through the capillary fibers to the entire system, was reported to allow the system to be modeled as a continuous-flow stirred-tank reactor (CSTR), as shown in Figure 5 [27]. The recycle CSTR membrane system was more flexible as the reaction and the separation zones were physically separated.

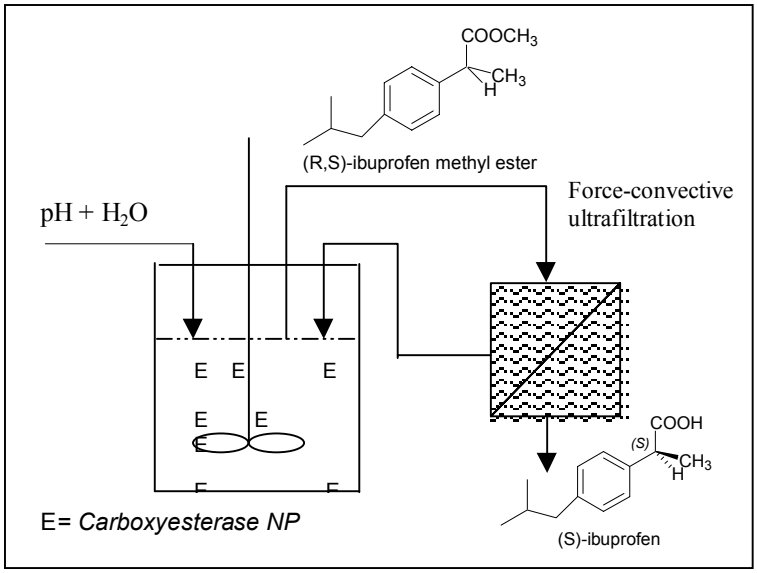


Figure 4 Pressure-driven membrane reactor

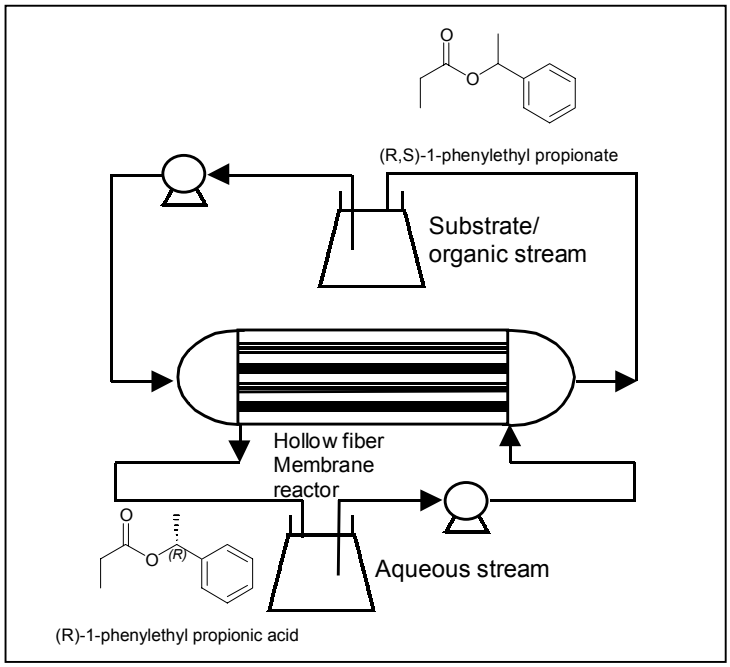


Figure 5 Hollow fiber enzymatic membrane reactor

5.2 Synthesis of Chiral Glycidol and its Derivatives

The conventional lipase-catalyzed racemic resolution employs the normal heterogeneous organic medium for hydrolysis, such as the hydrolysis of chiral epoxy alcohols and esters [37] and the preparation of enantioselective glycidyl acetate from glycidyl butyrate by sequential enzymatic resolution [28]. Despite the high enantiomeric excess attainable from this lipase-catalyzed reaction system, such heterogeneous emulsion systems are associated with difficult separation in downstream processes [30,31]. In this situation, the process enhancement was attained by the use of flat sheet enzymatic membrane reactor in the lipase-catalyzed kinetic resolution of racemic glycidyl butyrate. Figure 6 shows a flat sheet enzymatic reactor used for production of (R)-glycidol.

Hollow fiber membrane reactors were also employed in lipase-catalyzed resolution of racemic glycidyl butyrate [5,6]. Besides applying a single hollow fiber reactor unit, an aqueous/organic two-phase cascade hollow fiber membrane reactor had been practiced in large-scale resolution of epoxide by the yeast *Rhodotorula glutinis* [33]. The cascade hollow fiber membrane reactor had succeeded in minimizing the toxicity of organic solvents towards the epoxide hydrolase of *Rhodotorula glutinis* as well as to remove inhibitory amounts of formed diol from the yeast cell containing aqueous phase. This EMR system is a potential method for large-scale resolution of chemically unstable and water insoluble epoxides.

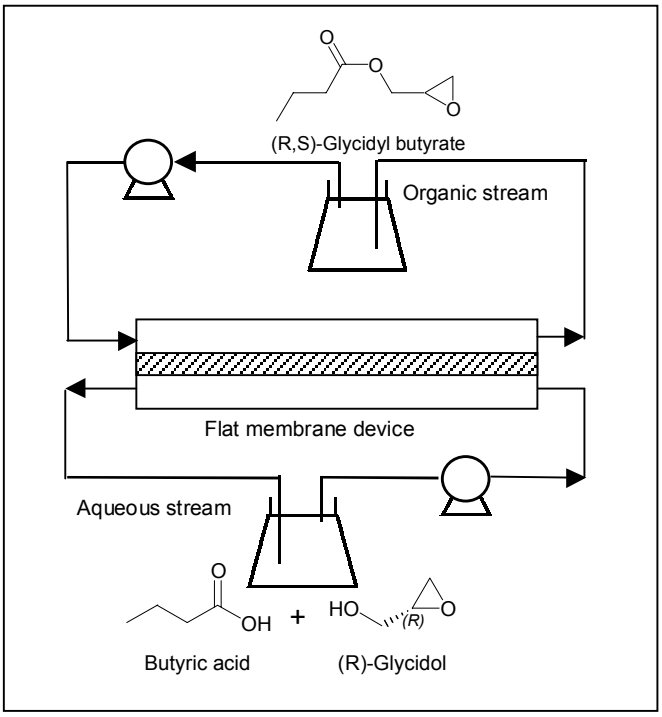


Figure 6 Flat sheet enzymatic membrane reactor

6.0 FUTURE PROSPECTS

Enzyme is the key success for most ecologically feasible production route. Enzymatic operation requires less energy and produces less waste than chemical processes. This makes enzymatic membrane technology gaining a good prospect in the agrochemical and pharmaceutical industries. However, there is still a lot more to be understood about the compatibility between the lipase stereoselectivity and the functioning of EMR towards the production of specialty chemicals with obtainable high optical purity.

The major technological difficulties of using EMR system include process-dependent and not fully reliable, as each system requires individual consideration in order to function practically. This is attributed by the problems encountered in membrane processing such as concentration polarization and fouling problem, which often restrict the performance of membrane reactor. Efforts are being made to improve fluid dynamic conditions and membrane reactor design. While the role of organic chemist is essential in pharmaceutical process development, the role of chemical engineers is also greatly needed to provide the expertise in the application of chemical technology in pharmaceutical process economics.

7.0 CONCLUSIONS

Highly enantioselective stable enzyme and membrane reactor technology are two basic reaction engineering tools which increasingly dominate the enzymatic processing technology, especially in the enzymatic kinetic resolution of enantiomers. Membrane technology has become prominent at a point where possible control of membrane thickness and pore structure can be done. The unique strength established by EMR, together with numerous commercial availabilities of membrane shapes, modules, and materials at reduced costs have made it a compatible and preferable alternative to the conventional reactor. To achieve highest productivity with most economical operation, factors such as membrane reactor costs, fine chemicals properties, energy requirement, product purification, and enzyme recovery shall be taken into account, and yet a compromise has to be found in the process between gaining high productivity and retaining environmental friendly and sustainable processes at the same time.

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ABBREVIATION

EMR	Enzymatic membrane reactor
PTFE	Polytetrafluoroethylene
MF	Microfiltration
MWCO	Molecular weight cut off
UF	Ultrafiltration
RO	Reverse osmosis
PFR	Plug flow reactor
CSTR	Constant stirred-tank reactor
NADPH	Nicotinamide adenine dinucleotide phosphate
NSAIDs	Non-steroid anti-inflammatory drugs

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