CHAPTER I

INTRODUCTION

1.1 DESCRIPTION OF DISSERTATION

Chiral molecules are constituents of a large proportion of therapeutic agents. In nature, the chirality of a molecule is often as important as its chemical makeup. Biomolecules are mostly chiral molecules, for example, drugs, enzymes, proteins, hormones, nutrients, sugars, fats, and many others. Chiral molecules draw highly attention as they have two enantiomeric forms with identical molecular formula but different structural arrangement forms and non-superimposable mirror images. In the pharmacological viewpoint, it is necessary to mark the difference between the two enantiomers. The enantiomeric drug exhibits different pharmacological and toxicological activities which the human body can recognize. Hence, the enantiomeric separation is of great interest for the pharmaceutical industry since more than half of the pharmaceutically active ingredients are chiral molecules. Current perspective separation techniques such as crystallization, kinetic resolution, chiral chromatography, capillary electrophoresis, and membrane technology can successfully separate pure enantiomeric drugs [1, 2]. Recently, liquid membrane, especially the hollow fiber supported liquid membrane (HFSLM) becomes a promissing technique in the selective enantioseparation as it has high selectivity and efficiency of separation and uses less extractant (chiral selector) and organic solvent than the conventional solvent separation processes. It is practical for industrial applications in terms of scaling up [3].

This dissertation is devided into 8 chapters. CHAPTER I provides brief introduction. All chapters except CHAPTERS V are the research papers on the selective enantioseparation of (*S*)-amlodipine from chemical synthesis-based pharmaceutical wastewater as a feed solution by using a single-module HFSLM [4-10]. The feed and stripping solutions at equal flow rates flowed counter-currently in a batch operation. The overall concepts of the research originated from the state-of-the-art HFSLM technology for enantiomeric separation in a single unit operation.

The focus of this research is to find the possibility of using the HFSLM in selective enantioseparation of (*S*)-amlodipine. The various parameters on (*S*)-amlodipine extraction and recovery include the pH and the concentration of racemic amlodipine in the feed solution, types and concentrations of the extractants or carriers (chiral (+)-DBTA, achiral extractants D2EHPA and the synergistic extractant of (+)-DBTA and D2EHPA), types of the organic solvents, types and concentrations of the stripping solutions (benzenesulfonic acid and *β*-cyclodextrin), and the flow rates of feed and stripping solutions. The results demonstrate that HFSLM has high potential in the enantioseparation and the recovery of a relatively low concentration of (*S*)-amlodipine from pharmaceutical wastewater. In addition, the influence of temperature on mass transfer was studied because it was one of the variables that affected the enantioselectivity of (*S*)-amlodipine. The mathematical model to estimate the concentration of (*S*)-amlodipine in the feed solution with time was presented and verified with the experimental results. The publications in this dissertation are listed:

CHAPTER II: Enantioselective separation of racemic amlodipine by two-phase chiral extraction containing *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid as a chiral selector. Sep. Sci. Technol. (in-press) [4];

CHAPTER III: The modeling and the experimental verification of selective separation of (*S*)-amlodipine via hollow fiber supported liquid membrane. Chem. Eng. J. 180 (2012) 299-308. [5];

CHAPTER IV: The synergistic effect of selective separation of (*S*)-amlodipine via hollow fiber supported liquid membrane. Chem. Eng. J. 209 (2012): 201-214. [6];

CHAPTER V: The solubility and thermodynamic model of organic compound in aqueous and several organic solvents at different temperature solutions. This chapter is the summary of the contents that presented in APPENDIX A (Determination and modeling of aqueous solubility of 4-position substituented benzoic acid compounds in a high-temperature solution. Fluid Phase Equilib. 338 (2013): 217-223 [7]) and APPENDIX B (Thermodynamics of the solubility of 4-acetylbenzoic acid in different solvents from 303.15 to 473.15 K. J. Mol. Liq. 180 (2013): 252-259 [8]);

CHAPTER VI: The effects of thermodynamic parameters on mass transfer of selective separation of (*S*)-amlodipine via hollow fiber supported liquid membrane. Sep. Purif. Technol. 102 (2013): 50-61. [9]; and

CHAPTER VII: Enantioseparation of (*S*)-amlodipine from pharmaceutical industry wastewater by stripping phase recovery via HFSLM: polarity of diluent and membrane stability investigation. Sep. Purif. Technol. (in-press) [10].

The papers are in partial fulfilment of the requirements for the Degree of Doctor of Engineering Program in Chemical Engineering at Chulalongkorn University.

1.2 RATIONALE OF RESEARCH PROBLEM

To date, more than 90 percent of the active pharmaceutical ingredients (APIs) are imported in order to develop drug formulas for the finished products [11]. One of the major worldwide problems of the APIs and their intermediates are associated with the mixture of the enantiomers, namely effectiveness or ineffectiveness drugs [12]. In general, most drugs are used as a racemic mixture of (*R*)-and (*S*)-enantiomers; however, the pharmacological effects of these enantiomers might be different. One enantiomeric form may have a desired beneficial effect on pharmacology while another is likely to cause serious or undesired side effects. Some enantiomeric drugs have entirely different effects (desired and undesired effects), perhaps (*R*)-enantiomer is undesirable [13].

As a single enantiomer of the drug plays important pharmacological activity in the treatment and therefore many pharmaceutical firms have been trying by separating the chiral drugs to a single enantiomer, synthesizing pure single enantiomer or switching (*R*)-enantiomer in the racemic mixture to (*S*)-enantiomer. In a particular view of pharmacological studies of such drugs, the separation of the enantiomers contributes a major challenge from the stand point of the efficacy and safety of the drugs [14]. Outstanding advantages of single enantiomer products are simple structure, more selective pharmacodynamic profile, potential for an improved therapeutic index, less complex pharmacokinetic profile, less potential for complex

drug interactions, and less complex relationship between the plasma concentration and effect [15].

The therapeutic groups of drugs where more advances with regard to pure enantiomer have been described as chiral cardiovascular central nervous system, antiviral and anticancer drugs [16]. Cardiovascular disease is the major cause of death in Thailand and worldwide. Hypertension is the leading risk factor for cardiovascular and renal diseases. It increases the risk of myocardial infraction, stroke and congestive heart failure. The benefit of drug treatment of hypertension to prevent major cardiovascular disease is consistently demonstrated in a large series of clinical trials controlled by placebo [17]. According to the international clinical guidelines on antihypertensive treatment by the World Health Organization (WHO) [18] and the recent updated guidelines by the European Society of Hypertension (ESH) [19], the long-acting calcium channel blockers are recommended to use as the first-line for antihypertension. The calcium channel blockers are currently one of the major classes of cardiovascular drugs, and are widely used in the treatment of hypertension and angina [20]. They can be used together with most of the other antihypertensive drug classes, including diuretics of highly effective blood-pressure control and of essential for the cardiovascular protection of high-risk patients [21]. Many of the calcium channel blockers are the racemic mixtures; consequently, their pharmacological effects may be different. The (*S*)-(+)-nilvadipine, for example, is about 100 times more potent in relaxing potassium-induced contractions of isolated dog coronary arteries than the (*R*)-(-)-nilvadipine [22]. Amlodipine, the third-generation dihydropyridine derivative of the calcium channel blockers used in the present study, is demonstrated as follows,

1.2.1 Amlodipine

Amlodipine–3-ethyl-5-methyl-2-[-2-(aminoethoxymethyl)]-4-(2-chloro-phenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate is used in the treatment of hypertension and angina pectoris. Amlodipine selectively inhibits calcium ion influx across cell membranes and therefore it affects vascular smooth muscle and cardiac muscle cells [23, 24]. Like most other calcium blocker agents of the dihydropyridine type, amlodipine is therapeutically used as a racemic mixture. It contains

(*S*)-amlodipine (Figure 1.1(a)) and (*R*)-amlodipine (Figure 1.1(b)). (*S*)-amlodipine exhibits vasodilating properties [25]. (*R*)-amlodipine is inactive and is likely responsible for pedal edema observed with racemic amlodipine [26]. However, based on the pharmacological research, it remains uncertain if only (*S*)-amlodipine as the active moiety possesses therapeutic activity and fewer associated adverse effects compared with the racemic mixtures [27, 28]. (*S*)-amlodipine is more potent calcium channel blocker about 2,000 times in *in vitro* evaluation in the rat aorta than (*R*)-amlodipine [29]. In addition to its longer duration of action, (*S*)-amlodipine reduces the chances of reflex tachycardia, and its clearance is subject to much less inter-subject variation than (*R*)-amlodipine [30].

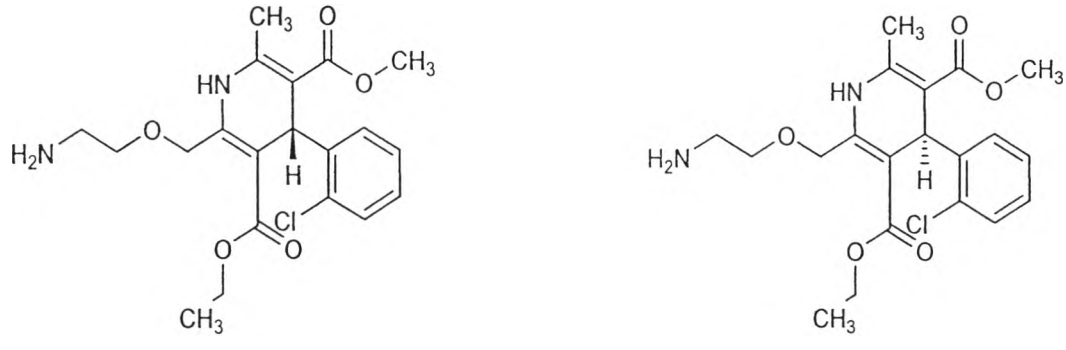

Figure 1.1 Structures of (a) (*S*)-amlodipine, (b) (*R*)-amlodipine [20, 23]

1.2.2 Enantioselective separation of (*S*)-amlodipine

The enantioselective separation of chiral compounds is a considerable challenge to the pharmaceutical industry. Many researchers have been trying to separate the enantiomeric drugs to a single enantiomer [31]. In particular, various sources from the literature and patents have reported the separation of (*S*)-amlodipine from its racemic mixture. The conventional methods such as crystallization [32], kinetic resolution [33], chromatography [34] and capillary electrophoresis [35] still have some constraints for most racemic compounds. The most often employed isolation of (*S*)-amlodipine involves selective diastereomeric salt crystallization but this technique is time-consuming and expensive, increases the complexity of the process, and leads to a considerable loss of products [36]. The application of kinetic

resolution is very costly due to its single operation and availability of enantiomerically differentiating materials [37]. In the case of chromatography and capillary electrophoresis, they are not suitable for a large production of chiral substances since they require a substantial amount of the solvents and high investment cost [38]. The techniques for the enantioseparation of racemic amlodipine are summarized in Table 1.1. Their merits and drawbacks were written elsewhere.

Table 1.1 The literature citations and patented methods for the separation of (*S*)-amlodipine

Author	Method	Chiral resolving agent	Ref.
Arrowsmith, J.E. *et al.*	Diastereomeric salt crystallization	Diastereotopic azide esters	[32]
Lee, H.W. *et al.*	Chemical kinetic resolution	*bis* (*S*-mandelic acid)-3-nitrophthalate	[33]
Luksa, J. *et al.*	Semi preparative purification	α-cyclodextrin	[34]
Arrowsmith, J.E. *et al.*	Diastereomeric salt crystallization	Cinchonidine salts	[39]
Gotrane, D.M. *et al.*	Diastereomeric salt crystallization	Naturally tartaric acid nitrophthalate	[40]
Goldman, S. *et al.*	Diastereomeric salt crystallization	*O,O'*-dibenzoyl tartaric acid	[41]
Goldman, S. *et al.*	Chromatographic separation	(1*S*)-camphanic acid and *S*-2-methoxy-2-phenylethanol	[42]
Zandkarimi, M. *et al.*	Capillary electrophoresis	Highly sulfated cyclodextrins	[43]
Streel, B. *et al.*	Chromatographic separation	α-acid glycoprotein coated	[44]
This work	Hollow fiber supported liquid membrane	*O,O'*-dibenzoyl tartaric acid andD2EHPA	

HFSLM combines liquid-liquid extraction and a membrane. Enantioseparation through liquid membranes was first reported in the 1970's [45]. Recently, enantioselection by membrane-supported liquid-liquid extraction has been a technology of interest for chemical engineers in a wide range of fields such as fine chemicals, pharmaceuticals and foods [46].

1.2.3 Enantioselective liquid-liquid extraction

Enantioselective liquid-liquid extraction (ELLE) is a promising technology to separate the two enantiomers of a racemate using a chiral extractant. Although the technique is already known since the late 1960's [47, 48], the ELLE is an attractive alternative for chromatography and crystallization. As far as we are aware, the ELLE has not been commercialized to date. Most previous studies in the literature deal with exploratory chemistry research and only a few engineering studies have been reported [49-51]. The ELLE combines the concepts of solvent extraction [52] and enantiomeric recognition in a single technique [53]. The principles of ELLE with the extractant in the organic phase and the racemate in the water phase are schematically displayed in Figure 1.2. The solute or guest transfers from the aqueous phase to the organic phase and interacts with an extractant or host in the organic phase. In this example, the interaction of the host with the (*S*)-enantiomer is favorable over the interaction with the (*R*)-enantiomer. As a result, the organic phase and the aqueous phase are enriched by the (*S*)-enantiomer and the (*R*)-enantiomer, respectively. The ELLE is an essential fundamental of HFSLM which has been developed to manage the limitation of liquid-liquid extraction and membrane separation. HFSLM is a simultaneous extraction and recovery of the target species at a dilute concentration in one single stage.

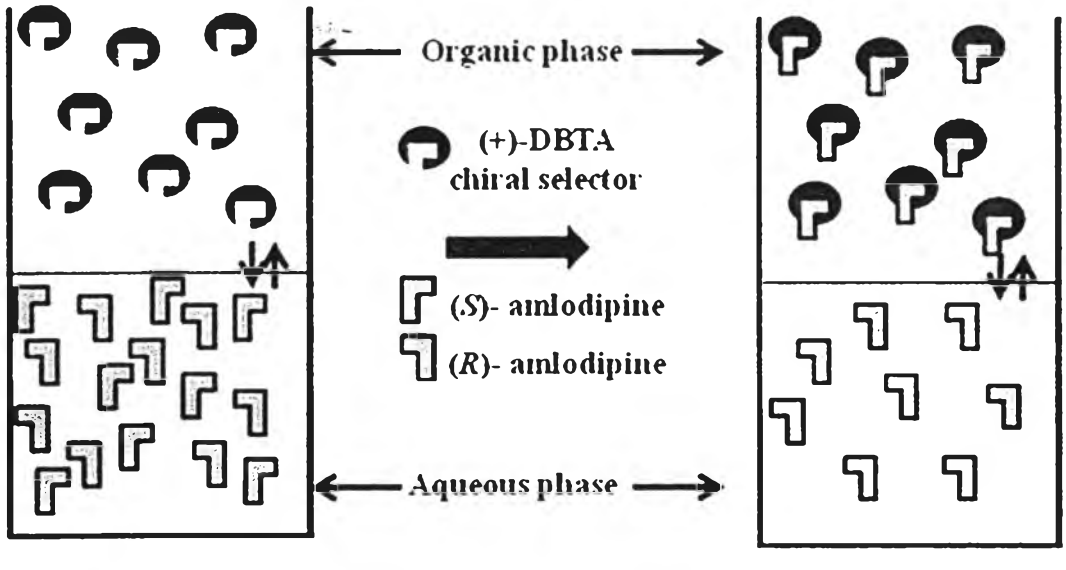

Figure 1.2 Distribution behavior scheme of enantioselective separation of racemic amlodipine by (+)-DBTA

1.2.4 Chiral and achiral selectors

The extractant or selector is the most important chemical for the HFSLM system. The dominant of the selector in enantiomeric drug separation is the chiral selector. There are many types of chiral selectors such as crown ether [54], metal complexes [55], tartaric acid derivatives [56] and cyclodextrin derivatives [43]. According to the literature reporting the advantages of the tartaric acid derivative chiral selectors [57-59], they are acidic compound containing two carboxylic acid groups. The enantiomeric complex is formed 1:2 molar ratio of the tartaric acid derivatives and the enantiomer. The tartaric acid derivatives are normally distributed in the organic solvent such as alcohol, alkyl halide and hexane. The partitioning of the tartaric acid derivatives does not depend on the pH of the organic solvent because they are distributed predominantly only in the organic solvent [60]. Among the tartaric acid derivatives, the *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) is the most suitable chiral selector for enantioseparetion. Hence, in the present work we used *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA).

In the case of achiral selector, it is devided into three categories according to the functional groups in its structure [61]. The compounds such as di (2-ethylhexyl) phosphoric acid (D2EHPA) and LIX families are acidic extractant. The basic extractant, e.g., Aliquat 336 and TOA contains amine group. For the neutral extractant, TBP is widely used. The D2EHPA, an achiral extractant, has been studied and known for over 50 years. It is extensively used for racemic mixture as an achiral liquid-liquid extraction of metal cations [62] and amino acids [63]. D2EHPA is able to extract the amino acids as well as albeit even though it does not has enantioselectivity feature. D2EHPA with the addition of the tartaric acid derivatives becomes enantioselective extractant because of the synergy of the two extractants. The extracting species (+)-DBTA-D2EHPA is a complex between the chiral selector, ((+)-DBTA), and the achiral selector, D2EHPA.

1.2.5 Synergistic separation

The word "synergism" literally means "working together". It is a matter of fact that the two types of extractants or more are more successful in extraction when

they work together than when they work separately. Synergistic separation is the phenomenon in which mostly two extractants together extract a target species [64-66]. By using a mixture of the selected extractants with a particular chemical structure, the extracting power of the mixture exceeds the sum of the extracting power of the individual extractant. In synergism, one of the two extractants is a ligand or an organic acid which neutralizes the charge on the target species and the other solvating molecule. The synergistic extractant replaces the water molecule from the coordination sphere for less hydrophilic species. One of the most thoroughly investigated synergistic mixtures of the extractants is the ratio of the extractants and the synergistic coefficient [67].

1.2.6 Synergistic enantioseparation

The synergistic enantioseparation of (*S*)-amlodipine by a mixture of the chiral selector ((+)-DBTA) and the achiral selector (D2EHPA) occurred by two extraction reactions in the system. The first reaction is the reaction between a chiral selector ((+)-DBTA) and achiral selector (D2EHPA) to form the extractant complex (+)-DBTA-D2EHPA [68]. The second reaction is the reaction between the extractant complex and (*S*)-amlodipine. The latter reaction takes place in the presence of proton transfer-chiral interactions, i.e., (+)-DBTA-D2EHPA, and produces the derivative complex, namely (*S*)-amlodipine-(+)-DBTA-D2EHPA.

1.2.7 Diluent or organic solvent selection

The organic phase contains only the extractant or the extractant dissolved in a suitable diluent. It is worth to note the criteria to select the organic phase, i.e., it should be stable and immiscible with the aqueous phase [69]. A difference in densities of the contacting phases (feed phase and membrane phase) is important and should be as high as possible. Dissolution of the extractant(s) in low viscous diluent modifies the viscosity of the diluent itself to a high favourable degree [70]. Furthermore, the diluent should not be corrosive to common materials of construction for least equipment cost. The diluent should have low toxicity, high boiling point and flash point. It must avoid environmental pollution and fire hazards [71]. The desirable

properties of the diluent such as density, selectivity, recoverability and interfacial tension are essential to the extraction and must be considered.

1.2.8 Stripping solution selection

Another parameter that plays a significant role on the transport of the target species is type and concentration of the stripping solution. Since the extraction and the stripping reactions in the HFSLM system are simultaneously, it is significant to enhance the effective transport of the target species by driving the efficient stripping reaction at the interface between liquid membrane and the stripping solution [71]. The stripping solutions that were investigated in this work are benzenesulfonic acid (achiral molecule) and β-cyclodextrin (chiral molecule). β-cyclodextrin exhibited higher stripping results by creating a complex with (*S*)-enantiomer by various electrostatic forces and hydrogen bondings. The complex formation depends largely on the size, shape and polarity of (*S*)-enantiomer [72]. That means the configuration of (*S*)-amlodipine should compatible well with the cavity of β-cyclodextrin, and the stability of the generated complex is subject to shape, polarity and side groups of (*S*)-amlodipine.

1.2.9 Solubility

The solubility is the most fundamental physico-chemical properties. The solubility data of the substances are useful in the separation and a variety of applications in chemical manufacturing processes and product design, for example, in the biological, chemical and environmental industries [73, 74]. To achieve high extraction and high recovery by the HFSLM separation, the mass transport is attributed to the solubilities of all species in the HFSLM. Hence, it is necessary that the target species dissolve in the feed phase (mostly aqueous phase), the extractant in the organic solvent as well as its complex species with the target species dissolve in liquid membrane phase, and the complex species of the stripping solution dissolve in the stripping phase (mostly aqueous phase). The target species in feed phase must not dissolve in the selected organic solvent. The feed phase is insoluble in the liquid membrane phase. Likewise, the liquid membrane phase and the stripping phase are In

insoluble. In the present study, (*S*)-amlodipine is the target species; (+)-DBTA-D2EHPA is the synergistic extractant; *β*-cyclodextrin is the stripping solution; (*S*)-amlodipine-(+)-DBTA-D2EHPA and (*S*)-amlodipine-*β*-cyclodextrin are the complex species at the feed-liquid membrane interface and the liquid membrane-stripping phase interface, respectively.

1.2.10 Influences of the temperature and thermodynamic parameters on the mass transfer

A few works about the effect of temperature on the transport of the enantiomers through the HFSLM have been reported [75-77]. However, no report involving the activation energy (E_a) for the permeation of enantioseparation is available. As a matter of fact, the temperature plays a significant role on the separation including the enantioseparation. The partition coefficient of the target species increases with the temperature. In other words, the distribution ratio increases with temperature. Generally, the complexation of the target species (metal ions or enantiomers) in the interface of the feed solution and the liquid membrane depends on the temperature and therefore their selectivity depends on the temperature. In contrast to the selectivity of metal ions, the enantioselectivity decreases with higher temperature. High temperature decreases the stability of the (*S*)-amlodipine-(+)-DBTA-D2EHPA complex and also decreases the activity of the chiral selector in a way. For the separation by the HFSLM, the E_a proposed by the Arrhenius equation [78] is the indicator to identify if the transport in the hollow fiber module is the diffusion-limited or the chemical reaction transport because the E_a has a strong effect on the actual rate constants. The E_a less than 20 kJ/mol indicate pure diffusion-limited transport while the E_a higher than 40 kJ/mol indicates the chemical reaction transport [79, 80]. From this work, the E_a of the (*S*)-amlodipine extraction reaction is 71.10 kJ/mol, which indicates that the extraction and recovery of (*S*)-amlodipine through the HFSLM should be controlled by the chemical reaction. The extraction equilibrium constant ($K_{ex(S)}$) for (*S*)-amlodipine extraction depending on the temperature was calculated by the slope of [(*S*)-amlodipine-(+)-DBTA-D2EHPA] as a function of [(*S*)-amlodipine]^2[(+)-DBTA][D2EHPA]. According to the Van't Hoff equation, the $K_{ex(S)}$ is correlated closely to the Gibb's free-energy change (ΔG) [81, 82]. The Gibb's free-

energy change (ΔG) is related to the molar enthalpy and molar entropy changes (ΔH and ΔS) through the Gibbs–Helmholtz equation. The standard enthalpy (ΔH) value indicates that the process is an endothermic or exothermic system. The positive value of ΔH indicates that the extraction process is an endothermic system. The value of molar entropy (ΔS) and Gibb's free-energy change (ΔG) indicated the total direction of reaction process. The thermodynamic parameters are important information for the design the enantioseparation system and controlling of the separation temperature.

1.2.11 Hollow fiber supported liquid membrane

According to the many literature review, HFSLM is a challenging and the great interest as a promising system for the efficient enantioseparation and high recovery of chiral drugs with very low concentrations from aqueous solutions by the use of a suitable extractant for the transport mechanism. HFSLM is an effective simultaneous process to extract and recover compounds from a very dilute solution of interested components in the feed by a single-unit operation [83-86]. Great progress has been made in such applications, as in metal ion extraction [87, 88], organic extraction [89], pharmaceutical extraction [90], and enzymatic transformation [91]. The simultaneous process of extraction and stripping in a single unit operation of HFSLM system is very interesting. The advantages of HFSLM over traditional separation techniques include high selectivity, lower operating costs, lower energy consumption, and low organic diluent [92-95]. Besides some other advantages of HFSLM over the conventional separation techniques, the high selectivity and rapid transportation of the desired enantiomeric isomer, (*S*)-amlodipine, make the HFSLM suitable for the enantioseparation and recover of racemic amlodipine for the pharmaceutical application. Table 1.2 exhibits the examples of using the HFSLM in enantioseparation.

Table 1.2 The examples of using hollow fiber supported liquid membrane in enantioseparation

Year	Feed solution	Extractant	Organic solvent	Stripping solution	Membrane material	Ref.
2002	(*RS*)-lactic acid and(*RS*)- alanine	*N*-3,5-dinitrobenzoyl-(*L*)-phenylalanine-octylester	Toluene	DI water	Polypropylene hollow fiber	[96]
2003	(*RS*)-ofloxacin	(*DL*)- dibenzoyltartaric acid	1-octanol	DI water	Polysulfone hollow fiber	[97]
	(*RS*)-terbutaline	(*L*)- dibenzoyl tartaric acid	1-octanol	DI water	Polysulfone hollow fiber	[98]
2004	(*RS*)-propanolol	*N*-hexadecyl-(L)-hydroxyproline	Propan-2-yl tetradecanoate	DI water	Polytetrafluoro ethylene hollow fiber	[99]
2005	(*RS*)-lactic acid	*N*-3,5-dinitrobenzoyl-(*L*)-phenylalanine-octylester	Toluene	DI water	Polypropylene hollow fiber	[100]
2006	(*RS*)-salbutamol	DBTA,DTTA	Toluene	DI water	Polyvinylidene fluoride hollow fiber	[101]
2008	(*RS*)-phenylalanine	Copper(II) *N*-decyl-(*L*)-hydroxyproline	1-hexanol: 1-decanol (1:1 v/v)	DI water	Polyvinylidene fluoride hollow fiber	[102]
	(*RS*)-α-cyclohexyl-mandelic acid	Copper(II) *N*-decyl-(*L*)-hydroxyproline	1-octanol	DI water	Polyvinylidene fluoride hollow fiber	[103]
2009	(*RS*)-ofloxacin	(*L*)- tartarate	1,2-choroetahane	DI water	Polyvinylidene fluoride hollow fiber	[104]
2011	(*RS*)-ketoconazole	(*L*)- IPT and SBE-*β*-CD	1-hexanol	DI water	Polyvinylidene fluoride hollow fiber	[105]
2012	(*RS*)-phenylalanine	(+)DBTA) +(D2EHPA)	1-octanol	DI water	Polypropylene hollow fiber	[106]
This work	(*RS*)-amlodipine	*O,O'*-Dibenzoyl-(2*S*, 3*S*)-tartaric acid+ di(2-ethylhexyl) phosphoric acid (D2EHPA)	1-decanol	Benzene sulfonic acid and *β*-cyclo dextrin	Polypropylene hollow fiber	

1.3 OBJECTIVES OF THE DISSERTATION

The main objective of this dissertation is the extraction and recovery of racemic amlodipine from the chemical synthesis-based pharmaceutical wastewater via HFSLM. The HFSLM is one of the promising methods for the enantioseparation due to its simplicity, low energy and chemicals consumed. The specific objectives of each chapter relating to the publication are described below:

CHAPTER II: Enantioselective separation of racemic amlodipine by two-phase chiral extraction containing *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid as chiral selector [4]. The two-phase chiral extraction system containing *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) in 1-decanol organic phase, and the aqueous phase for the enantioselective separation of racemic was discussed. The effects of the concentration of the chiral extractant ((+)-DBTA), the equilibrium time, and the pH of the aqueous phase on the percentage of separation were investigated.

CHAPTER III: The modeling and experimental verification of selective separation of (*S*)-amlodipine via hollow fiber supported liquid membrane [5]. The selective enantioseparation of (*S*)-amlodipine via the HFSLM by using *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) as the chial extractant was studied. The mathematical model was developed for the prediction of the concentration of (*S*)-amlodipine with time.

CHAPTER IV: The synergistic effect of selective separation of (*S*)-amlodipine via hollow fiber supported liquid membrane [6]. The novel synergistic chiral-to-achiral extractant dissolved in 1-decanol for the selective enantioseparation of (*S*)-amlodipine from chemical synthesis-based pharmaceutical wastewater by using the HFSLM was demonstrated.

CHAPTER V: The solubilities and thermodynamic model of organic compounds in aqueous and several organic solvents at different temperature solutions [APPENDICES A-B]. The solubility data of the solid–liquid equilibrium of the organic compounds in the aqueous solvent and several organic solvents at different temperature solutions were investigated. The thermodynamic correlation was developed. The effect of temperature on the solubilities of the organic compounds was investigated.

CHAPTER VI: The effects of thermodynamic parameters on mass transfer of selective separation of (*S*)-amlodipine via hollow fiber supported liquid membrane [7]. The effect of temperature on mass transfer in a single-module HFSLM extraction was investigated. Van't Hoff analysis of enantioselectivity of (*S*)-amlodipine was derived from variable temperatures for the thermodynamic functions. The thermodynamic parameters, i.e., the activation energy (E_a), the Gibb's free-energy change (ΔG), the molar enthalpy (ΔH), and the molar entropy (ΔS) were determined. We can identify if the transport in the hollow fiber module is the diffusion-limited or the chemical reaction transport from the E_a.

CHAPTER VII: Enantioseparation of (*S*)-amlodipine from pharmaceutical industry wastewater by stripping phase recovery via HFSLM: polarity of diluent and membrane stability investigation [8]. The selective enantioseparation of (*S*)-amlodipine from chemical synthesis-based pharmaceutical wastewater as a feed solution by the HFSLM was examined. The effect of polarity index of the diluents and the stability of the HFSLM system were investigated.

APPENDIX A: Determination and modeling of aqueous solubility of 4-position substituented benzoic acid compounds in a high-temperature solution [9]. The aqueous solubility of the organic compounds in a high-temperature solution and the temperature effect dependence of the aqueous solubility were investigated. The correlations of the aqueous solubilities of the organic compounds were established.

APPENDIX B: Thermodynamics of the solubility of 4-acetylbenzoic acid in different solvents from 303.15 to 473.15 K [10]. The solubility data of the solid–liquid equilibrium of the organic compounds in different organic solvents and the influence of temperature were investigated. Thermodynamic model of the solubility data of 4-acetylbenzoic acid was developed.

1.4 SCOPE OF THE DISSERTATION

This dissertation reports on the exploration of the new and efficient HFSLM in enantioseparation and pharmaceutical wastewater treatment. The scope of this dissertation is based on each research chapter as follows:

1. Optimization of parameters affecting the selective chiral resolution method for (*S*)-amlodipine by using the two-phase chiral extraction system containing *O*,*O*'-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) in 1-decanol organic phase and aqueous phase. The effects of extractant concentration, equilibrium time and pH of the aqueous phase on the performance of (*S*)-amlodipine extraction were investigated.

2. Investigation of parameters affecting the selective enantioseparation method for (*S*)-amlodipine by using HFSLM system based on *O*,*O*'-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) as chiral extractant and validation of the proposed method based on acceptable performance criteria for further applications. The mathematical model of the HFSLM system was presented in order to predict the concentration of (*S*)-amlodipine at different times.

3. Development of the novel synergistic enantioseparation of (*S*)-amlodipine from racemic amlodipine from pharmaceutical wastewater by using the mixture of chiral selective extractant, *O*,*O*'-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) and achiral extractant, di (2-ethylhexyl) phosphoric acid (D2EHPA). The new enantioseparation system was investigated.

4. Evaluation of the effect of temperature on mass transfer in a single HFSLM extraction. Van't Hoff equation of enantioselective separation was derived from variable temperatures to assess thermodynamic functions of enantioselective separation. The derived Van't Hoff equation was validated for possible routine applications.

5. Application of HFSLM process for amlodipine pharmaceutical wastewater pretreatment and (*S*)-amlodipine recovery. The effect of polarity index of diluents was investigated. The polarity of the diluents is the main factor influencing the separation performance and the stability of HFSLM system.

6. Measurement of the aqueous solubility of (*S*)-amlodipine in a high-temperature solution. The temperature effect on the aqueous solubility of (*S*)-

amlodipine was investigated. The correlation between temperature and the aqueous solubility of (*S*)-amlodipine was proposed.

7. Determination and thermodynamic model of (*S*)-amlodipine solubility in different solvents. The influence of temperature on molar solubility was investigated.

1.5 EXPECTED RESULTS

Due to the drawbacks of the traditional enatioseparation processes, this study aimed to assess the applicability of HFSLM system in enantioseparation and pharmaceutical wastewater treatment. The HFSLM system has many beneficial features in simultaneous extraction and stripping processes of low concentration of target species. The advantages of the HFSLM system over traditional separation techniques include high selectivity, lower capital and operating costs, lower energy consumption and low organic diluent. A more effective overall approach was established to achieve the highest enantioseparation and industrial needs with acceptable results in reasonable time and cost. Other expected results are listed as follows:

1. A simple and effective system for enantioseparation and pharmaceutical wastewater treatment is established.
2. The simultaneous and low cost system for enantioseparation and pharmaceutical wastewater treatment is demonstrated.
3. The HFSLM system and the mathematical model of the HFSLM system were presented in order to predict the concentration of (*S*)-amlodipine at different times.

1.6 REFERENCES

[1] Aboul-Enein, H.Y., Wainer, I.W. The Impact of Stereochemistry on Drug Development and Use. New York: Wiley 1997.

[2] Sekhon, B.S. Enantioseparation of Chiral Drugs - An Overview Int. J. Pharm Tech Res. 2(2) (2010): 1584-1594.

[3] Lothongkum, A.W., Pancharoen, U., Prapasawat, T. Roles of Facilitated Transport Through HFSLM in Engineering Applications, in Markoš J. (Ed.), Mass Transfer in Chemical Engineering Processes, pp. 177-204. InTech, India, 2011.

[4] Sunsandee, N., Pancharoen, U., Rashatasakhon P., Ramakul, P., Leepipatpiboon, N. Enantioselective separation of racemic amlodipine by two-phase chiral extraction containing *O*,*O*'-dibenzoyl-(2*S*,3*S*)-tartaric acid as chiral selector. Sep. Sci. Technol. (in-press).

[5] Sunsandee, N., Leepipatpiboon, N., Ramakul, P., Pancharoen, U. The selective separation of (*S*)-amlodipine via a hollow fiber supported liquid membrane: modeling and experimental verification. Chem. Eng. J. 180 (2012): 299-308.

[6] Sunsandee, N., Ramakul, P., Thamphiphit, N., Pancharoen, U., Leepipatpiboon, N. The synergistic effect of selective separation of (*S*)-amlodipine from pharmaceutical wastewaters via hollow fiber supported liquid membrane. Chem. Eng. J. 209 (2012): 201-214.

[7] Sunsandee, N., Suren, S., Leepipatpiboon, N., Hronec, M., Pancharoen, U. Determination and modeling of aqueous solubility of 4-position substituted benzoic acid compounds in a high-temperature solution. Fluid Phase Equilib. 338 (2013): 217-223.

[8] Sunsandee, N., Hronec, M., Štolcová, M., Leepipatpiboon, N., Pancharoen, U. Thermodynamics of the solubility of 4-acetylbenzoic acid in different solvents from 303.15 to 473.15 K. J. Mol. Liq. 180 (2013): 252-259.

[9] Sunsandee, N., Leepipatpiboon, N., Ramakul, P., Wongsawa, T., Pancharoen, U. The effects of thermodynamics on mass transfer and enantioseparation of (*R*,*S*)-amlodipine across a hollow fiber supported liquid membrane. Sep. Purif. Technol. 102 (2013): 50-61.

[10] Sunsandee, N., Ramakul, P., Pancharoen, U., Leepipatpiboon, N. Enantioseparation of (*S*)-amlodipine from pharmaceutical industry wastewater by stripping phase recovery via HFSLM: polarity of diluent and membrane stability investigation. Sep. Purif. Technol. (in-press).

[11] Srikun, O. Chiral drugs in pharmaceutical industry J. Res. Develop. Govern. Pharm. Org. 14(1) (2007): 4-8.

[12] Li, B.Y., Haynie, D.T. Chiral Drug Separation, in Lee, S.G. (Ed.), Encyclopedia of Chemical Processing, pp. 449-458. Oxford: Taylor & Francis, 2006.

[13] Porter, W.H. Resolution of chiral drugs. Pure Appl Chem 1991; 63: 1119-1122.

[14] Vermeulen, N.P.E., Koppele, J.M. Stereoselective biotransformation: toxicological consequences and implications in Wainer, W.I. (Ed.), Drug Stereochemistry: Analytical Methods and Pharmacology. 2nd ed, pp. 245–280. NewYork: Marcel Dekker, Inc, 1993.

[15] Reddy, I.K, Mehvar, R. Chirality in Drug Design and Development. New York: Marcel Dekker, Inc, 2004.

[16] Maier, N.M., Franco, P., Lindner, W. Review Separation of enantiomers: needs, challenges, perspectives. J. Chromatogr. A. 906 (2001): 3-33.

[17] Thompson, A.M., Hu, T., Eshelbrenner, C.L., Reynolds, K., He, J., Bazzano, L.A. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: A meta-analysis. JAMA 305(9) (2011): 913-922.

[18] Guidelines Subcommittee, World Health Organization International Society of Hypertension Guidelines for the management of hypertension, J .Hypertens. 17 (1999): 151–183.

[19] Mancia, G., De, G.B., Dominiczak, A., Cifkova, R., Fagard, R., Germano, Grassi, G.G., Heagerty, A.M. Guidelines for the management of arterial hypertension. J .Hypertens. 25 (2007): 1105–1187.

[20] Hardman, J.G., Limbird, L.E. Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. New Delhi: McGraw Hill, 2001. pp. 853-860.

[21] Schachter, M. Calcium antagonists and atherosclerosis. Int. J. Cardiol. 62 Suppl. 2 (1997): S9–S15.

[22] Tokuma, Y., Noguchi, H. Review Stereoselective pharmacokinetics of dihydropyridine calcium antagonists. J. Chromatogr. A. 694 (1995) 181-193.

[22] Abernethy, D.R. The pharmacokinetic profile of amlodipine. Am. Heart. J. 118 (1989): 1100-1103.

[24] Mason, R.P., Walter, M.F., Trumbore, M.W., Olmstead Jr., E.G., Mason, P.E. Membrane antioxidant effects of the charged dihydropyridine calcium antagonist amlodipine. J. Mol. Cell. Cardiol. 31 (1999): 275–281.

[25] Cheng, Y.Z., Wu, X.G., Chen, X.Y. Clinical trial of therapeutic effects and adverse drug reaction of S-amlodipine. Chin J Med Guide. 4 (2002) 198–200.

[26] Wang, R.X., Jiang, W.P., Li, X.R., Lai, L.H. Effects of (*S*)-amlodipine and (*R*)-amlodipine on L-type calcium channel current of rat ventricular myocytes and cytosolic calcium of aortic smooth muscle cells. Pharmazie. 63(6) (2008): 470-4.

[27] Liu, G.S. Wang, K. Zhang M.H. Comparative effect of amlodipine and levamlodipine on nocturnal hypertension in hypertensive patients. J. Med. Postgrad. 14 (2001): 496–499.

[28] Park, J.Y., Kim, K.A., Park, P.W., Lee, O.J., Ryu. J.H., Lee, G.H., Ha, M.C., Kim, J.S., Kang, S.W., Lee, K.R. Pharmacokinetic and pharmacodynamic characteristics of a new *S*-amlodipine formulation in healthy Korean male subjects: a randomized, open-label, two-period, comparative, cross over study. Clin. Ther. 28 (2006): 1837-1847.

[29] Yinghua, S., Liang, F., Meng, Z., Wei, L., Ping, M., Li, L., Zhonggui, H. A drug-in-adhesive transdermal patch for *S*-amlodipine free base: In vitro and in vivo characterization. Int. J. Pharm. 382 (2009): 165-171.

[30] Liu, F., Qiu, M., Zhai, S.D. Tolerability and effectiveness of (S)-amlodipine compared with racemic amlodipine in hypertension: A systematic review and meta-analysis. Current Therapeutic Research. 71 (1) (2010) 1-29.

[31] Fumio T (Ed.). Enantiomer Separation: Fundamentals and Practical Methods, Springer, 2004.

[32] Arrowsmith, J.E., Campbell, S.F., Cross, P.E., Stubbs, J.K., Burges, R.A., Gardiner, D.G., Blackburn, K.J. Long-acting dihydropyridine calcium antagonists 1,2-alkoxymethyl derivatives incorporating basic substituents. J. Med. Chem. 29 (1986): 1696-1702.

[33] Lee, H.W., Shin, S.J., Yu, H., Kang, S.K., Yoo, C.L. A novel chiral resolving reagent, bis ((*S*)-mandelic acid)-3-nitrophthalate, for amlodipine racemate resolution: Scalable synthesis and resolution process. Org. Process Res.Dev. 13 (2009): 1382-1386.

[34] Luksa, J., Josic, D.J., Podobnik, B., Furlan, B., Kremser, M. Semi-preparative chromatographic purification of the enantiomers *S*-(-)-amlodipine and *R*-(+)-amlodipine. J. Chromatogr. B. 693 (1997): 367-375.

[35] Zandkarimi, M., Shafaati, A., and Foroutan, S.M. Chiral separation of basic and zwitterionic drugs by highly sulfated cyclodextrins using short-end injection capillary electrophoresis. Iran. J. pharm. Res. 7(4) (2008): 275-281.

[36] Gotrane, D.M., Deshmukh, R.D., Ranade, P.V., Sonawane, S.P., Bhawal, B.M., Gharpure, M.M., Gurjar, M.K. A novel method for resolution of amlodipine. Org. Process Res. Dev. 13 (2010): 640-643.

[37] Tang, K., Chen, Y.Y., Liu, J.J. Resolution of Zopiclone enantiomers by biphasic recognition chiral extraction. Sep. Purif. Technol. 62 (2008): 681-686.

[38] Maftouh, M., Granier-Loyaux, C., Chavana, E., Marini, J., Pradines, A., Heyden, Y.V., Picard, C. Screening approach for chiral separation of pharmaceuticals: Part III. Supercritical fluid chromatography for analysis and purification in drug discovery. J. Chromatogr. A. 1088 (2005): 67-81.

[39] Arrowsmith, J.E., Campbell, S.F., Cross, P.E., Stubbs, J.K., Burges, R.A., Gardiner, D.G. Long acting dihydropyridine calcium antagonists. 2. 2-[2-aminoheterocycloethoxy] methyl derivatives. J. Med. Chem. 32 (1986): 562-568.

[40] Gotrane, D.M., Deshmukh, R.D., Ranade, P.V., Sonawane, S.P., Bhawal, B.M., Gharpure, M.M., Gurjar, M.K., A novel method for resolution of amlodipine. Org. Process Res.Dev. 13 (2010): 640–643.

[41] Goldmann, S., Stoltefuss, J., Born, L., 1,4-Dihydropyridines: Effects of Chirality and Conformation on the Calcium Antagonist and Calcium Agonist Activities. J. Angew. Chem., Int. Ed. Engl. 30 (1991): 1559–1578.

[42] Goldmann, S., Stoltefuss, J., Born, L., Determination of the absolute configuration of the active amlodipine enantiomer as (-)-*S*: A correction. J. Med. Chem. 35 (1992): 3341-3344.

[43] Zandkarimi, M., Shafaati, A., Foroutan, S.M., Lucy, C.A. Rapid enantioseparation of amlodipine by highly sulfated cyclodextrins using short-end injection capillary electrophoresis. DARU 17(4) (2009): 269- 276.

[44] Streel, B., Laine, C., Zimmer, C., Sibenaler, R., Ceccato, A. Enantiomeric determination of amlodipine in human plasma by liquid chromatography coupled to tandem mass spectrometry. J. Biochem. Biophys. Methods 54 (2002): 357-368.

[45] Newcomb, M., Toner, J.L., Helgeson, R.C., Cram, D.J., Host-Guest Complexation. 20. Chiral recognition in transport as a molecular basis for a catalytic resolving machine. J. Am. Chem. Soc. 101 (1979): 4941–4947.

[46] Schuur, B., Verkuijl, B.J., Minnaard, A.J., de Vries, J.G., Heeres, H.J., Feringa, B.L., Chiral separation by enantioselective liquid-liquid extraction, Org. Biomol. Chem. 9 (2011): 36–51.

[47] Romano, S.J., Wells, K.H., Rothbart, H.L., Rieman, W. Resolution of racemic substances by liquid ion-exchange. Talanta 16 (1969): 581–590.

[48] Schweitz, G.K., Supernaw, I.R., Bowman, N.S. Solvent extraction resolution of some optically-active neutral chelates. J. Inorg. Nucl. Chem. 30 (1968): 1885-1890.

[49] Viegas, R.M.C., Afonso, C.A.M., Crespo,J.G., Coelhoso,I.M., Modelling of the enantio-selective extraction of propranolol in a biphasic system. Sep. Purif. Technol. 53 (2007): 224-234.

[50] Steensma, M., Kuipers, N.J.M., de Haan, A.B., Kwant, G. Modelling and experimental evaluation of reaction kinetics in reactive extraction for chiral separation of amines, amino acids and amino-alcohols. Chem. Eng. Sci. 62 (2007): 1395-1407.

[51] Steensma, M., Kuipers, N.J.M., de Haan, A.B., Kwant, G. Analysisand optimization of enantioselective extraction in a multi-product environment with a multi stage equilibrium model. Chem. Eng. Proc. 46 (2007): 996-1005.

[52] Breuer, M., Ditrich, K., Habicher, T., Hauer, B., Kesseler, M., Sturmer, R., Zelinski, T., Industrial methods for the production of optically active intermediates. Angew. Chem. Int. Ed. 43 (2004): 788–824.

[53] Pirkle, W.H., Pochapsky, T.C. Considerations of chiral recognition relevant to the liquid chromatography separation of enantiomers. Chem. Rev. 89 (1989): 347-362.

[54] Pedersen, C.J. Cyclic polyethers and their complexes with metal salts. J. Am. Chem. Soc. 89 (26) (1967): 7017-7019.

[55] Larrow, J.R., Jacobsen, E.N. Asymmetric processes catalyzed by chiral (salen) metal complexes. Top. Organomet. Chem. 6 (2004) 123–152.

[56] Jiao, F.P., Chen, X.Q., Jiang, X.Y. Enantioselective extrction of ofloxacin enantiomers using ester alcohol L-tartarate as chiral selector. Iran. J .Chem. Chem. Eng. 28 (2006): 7-11.

[57] Andrisano, V.; Gottarelli, G.; Masiero, S.; Heijne, E. H.; Pieraccini, S.; Spada, G.P. The enantioselective extraction of dinitrophenyl amino acids mediated by lipophilic deoxyguanosine derivatives: an example of chiral discrimination via self-assembly and anion recognition. Angew. Chem. Int. Ed. 38 (1999): 2386-2388.

[58]. Dzygiel, P., Monti, C., Piarulli, U., Gennari, C. Efficient resolution of racemic N-benzyl beta 3-amino acids by iterative liquid-liquid extraction with a chiral (salen)cobalt(III) complex as enantioselective selector. Org Biomol Chem. 5 (2007): 3464-3471.

[59]. Dzygiel, P.; Reeve, T. B.; Piarulli, U.; Krupicka, M.; Tvaroska, I.; Gennari, C. Resolution of racemic *N*-benzyl α-amino Acids by liquid-liquid extraction: a practical method using a lipophilic chiral cobalt(III) salen complex and mechanistic studies. Eur. J. Org. Chem. 7 (2008): 1253-1264.

[60] Jiao, F.P., Chen, X.Q., Yang, L., Hu, Y.H. Enantioselective extraction of mandelic acid enantiomers using ester alcohol l-tartarate as chiral selector. Latin. Am. Appl. Res. 38 (2008): 249-252.

[61] Lothongkum, A.W., Pancharoen, U., Prapasawat, T. Roles of Facilitated Transport Through HFSLM in Engineering Applications, in Markoš J. (Ed.), Mass Transfer in Chemical Engineering Processes, pp. 177-204. InTech, India, 2011.

[62] Van de Voorde, I., Pinoy, L., Courtijn, E., Verpoort, F. Equilibrium studies of nickel(II), copper(II), and cobalt(II) extraction with aloxime 800, D(2)EHPA, and Cyanex reagents. Solvent Extr. Ion Exch. 24 (2006): 893-914.

[63] Teramoto, M.; Yamashiro, T.; Inoue, A.; Yamamoto, A.; Matsuyama, H.; Miyake, Y. Extraction of amino acids by emulsion liquid membranes containing di (2-ethylhexyl)phosphoric acid as a carrier biotechnology; coupled, facilitated transport; diffusion. J. Membr. Sci. 58 (1991): 11-32.

[64] Lothongkum, A.W., Suren, S., Chaturabul, S., Thamphiphit, N., Pancharoen, U. Simultaneous removal of arsenic and mercury from natural-gas-co-produced water from the Gulf of Thailand using synergistic extractant via HFSLM. J. Membr. Sci. 369 (2011): 350-358.

[65] Mathur, J.N., Khopkar, P.K. Extraction of trivalent actinides with some substituted pyrazolones and their synergistic mixtures with tri-n-octylphosphine oxide in chloroform. Solvent Extr. Ion Exch. 3 (1984): 1125-1129.

[66] Ramakul, P., Supajaroon, T., Pancharoen, U., Prapasawat, T., Lothongkum, A.W. Synergistic separation of yttrium ions in lanthanide series from rare earths mixture via hollow fiber supported liquid membrane. J. Ind. Eng. Chem. 15 (2009): 224-228.

[67] Luo, F., Li, D., Wei, P. Synergistic extraction of zinc (II) and cadmium (II) with mixtures of primary amine N1923 and neutral organophosphorous derivatives. Hydrometallurgy 73 (2004): 31-40.

[68] Tan, B., Luo, G.S., Qi, X., Wang, J.D. Extractive separation of amino acid enantiomers with co-extractants of tartaric acid derivative and aliquat-336. Sep. Purif. Technol. 53 (2007): 330-336.

[69] Yaws, C.L., Chemical Properties Handbook. New York: McGraw-Hill, 1999.

[70] Schulz, G., Separation Techniques with Supported Liquid Membrane. Desalination 68 (1988): 191- 202.

[71] Chitra, K.R., Gaikwad, A.G., Surender, G.D., Damodaran, A.D. Studies on ion transport of some rare earth elements through solvating extractants immobilised on supported liquid membrane. J. Membr. Sci. 125 (1997) 257-268.

[72] O'Brien, T., Crocker, L., Thompson, R., Thompson, K., Toma, P.H., Conlon, D.A., Feibush, B., Moeder, C., Bicker G., Grinberg, N., Mechanistic aspects of chiral discrimination on modified cellulose. Anal. Chem. 69 (1997): 1999–2007.

[73] Mullin, J.W. Solution and Solubility, in Mullin, J.W. (Ed.), Crystallization, 4th ed., pp. 86–134. Oxford: Butterworth-Heinemann, 2001.

[74] Kislik, V.S. Carrier-Facilitated Coupled Transport Through Liquid Membranes: General Theoretical Considerations and Influencing Parameters, in Kislik V.S. (Ed.), Liquid Membranes, pp. 16–71. Amsterdam: Elsevier, 2010.

[75] Kazusaki, M., Kawabata H., Matsukura, H. Influence of temperature on enantioseparation employing an amylase-derivative stationary phase. J. Liquid Chromatogr. Relat. Technol. 23 (2000): 2937–2946.

[76] Tang, K.W., Song, L.T., Liu, Y.B., Jiang, X.Y., Pan, C.Y. Separation of flurbiprofen enantiomers by biphasic recognition chiral extraction. Chem. Eng. J. 158 (2010): 411-417.

[77] Schuur, B., Hallett, A.J., Winkelman, J.G.M., de Vries, J.G., Heeres, H.J. Scalable enantioseparation of amino acid derivatives using continuous liquid–liquid extraction in a cascade of centrifugal contactor separators. Org. Process Res. Dev. 13 (2009): 911–914.

[78] Scheuplein, R.J. Analysis of permeability data for the case of parallel diffusion pathways. Biophysical J. 6 (1966): 1–17.

[79] O'Hara, P.A., Bohrer, M.P. Supported liquid membranes for copper transport, J. Membr. Sci. 44 (1989): 273–281.

[80] Peng, P., Fane, A.G., Li, X.D. Desalination by membrane distillation adopting a hydrophilic membrane. Desalination 173 (2005): 45–54.

[81] Greiner, W., Neise, L., Stöcker, H. Thermodynamics and Statistical Mechanics. Berlin and Heidelberg: Springer-Verlag, 1995. pp. 101-111.

[82] Angulo-Brown, F., Arias-Hernández, L.A., Van't Hoff's Equation for endoreversible chemical reactions. J. Phys. Chem. 100 (1996): 9193–9195.

[83] Pancharoen, U., Somboonpanya, S., Chaturabul, S., Lothongkum, A.W. Selective removal of mercury as $HgCl_4^{2-}$ from natural gas well produced water by TOA via HFSLM. J. Alloy Compd. 489 (2010): 72-79.

[84] Pancharoen, U., Lothongkum, A. W., Chaturabul, S. Mass transfer in hollow fiber supported liquid membrane for As and Hg removal from produced water in upstream petroleum operation in the Gulf of Thailand, in El-Amin, M. (Ed.), Mass Transfer in Multiphase Systems and Its Applications, pp. 499-524. India: InTech, 2011.

[85] Wannachod, P., Chaturabul, S., Pancharoen, U., Lothongkum, A.W., Patthaveekongka, W. The effective recovery of praseodymium from mixed rare earths via a hollow fiber supported liquid membrane and its mass transfer related. J. Alloy. Compd. 509 (2011): 354-361.

[86] Cui, Z. F., Jiang, Y., Field, R.W. Fundamentals of pressure-driven membrane separation processes, in Cui, Z.F. and Muralidhara H.S. (Eds), Membrane Technology: A Practical Guide to Membrane Technology and Applications in Food and Bioprocessing, pp. 12, 16. Elsevier: Butterworth-Heinemann, 2010.

[87] Lothongkum, A.W., Panchareon, U., Prapasawat, T. Treatment of heavy metals from industrial wastewaters using hollow fiber supported liquid membrane, in Demadis, K. (Ed.), Water Treatment Processes, pp. 299-332. New York: Nova Science Publishers, 2012.

[88] Ramakul, P., Songkun, E., Pattaweekongka, W., Hronec, M., Pancharoen, U. Permeation study on the hollow-fiber supported liquid membrane for the extraction of cobalts (II). Korean J. Chem. Eng. 23 (1) (2006): 117-123.

[89] Ren, Z.Q., Zhang, W.D., Li, H.S., Lin, W. Mass transfer characteristics of citric acid extraction by hollow fiber renewal liquid membrane. Chem. Eng. J. 146 (2009): 220–226.

[90] Vilt, M.E., Winston Ho, W.S. Supported liquid membranes with strip dispersion for the recovery of Cephalexin. J. Membr. Sci. (2009): 80–87.

[91] Rios, G.M., Belleville, M.P., Paolucci, D., Sanchez, J. Progress in enzymatic membrane reactors - a review. J. Membr. Sci. 242 (2004): 189–196.

[92] Suren, S., Wongsawa, T., Pancharoen, U., Prapasawat, T., Lothongkum, A.W. Uphill transport and mathematical model of Pb(II) from dilute synthetic lead-containing solutions across hollow fiber supported liquid membrane. Chem. Eng. J. 191 (2012): 503-511.

[93] Lothongkum, A.W., Ramakul, P., Sasomsub, W., Laoharochanapan, S., Pancharoen, U. Enhancement of uranium ion flux by consecutive extraction via hollow fiber supported liquid membrane. J. Taiwan Inst. Chem. Eng. 40 (2009): 518-523.

[94] Rogers, J.D., Long, R. Modeling 686 hollow fiber membrane contactors using film theory, Voronoi tessellations, and facilitation factors for systems with interface reactions. J. Membr. Sci. 134 (1997): 1-17.

[95] Giorno, L., Drioli, E. Enantiospecific membrane processes. Membrane Technol. 106 (1999): 6-11.

[96] Hadik, P., Szabó, L.P., Nagy, E. D,L-lactic acid and D,L-alanine enantioseparation by membrane process. Desalination 148 (2002): 193-198.

[97] Tang, K.W., Zhou, C.S., Jiang, X.Y., Racemic ofloxacin separation by supported-liquid membrane extration with two organic phase, Science in China (Series B). 46 (2003): 96-103.

[98] Tang, K.W., Zhou, C.S. Enantioselective extraction of terbutaline enantiomers by lipophilic tartaric acid, J. Cent. South Univ. Technol. 10 (2003): 44-48.

[99] Gumía, T., Valientea, M., Paleta, C. Characterization of a supported liquid membrane based system for the enantioseparation of *SR*-propanolol by *N*-hexadecyl-*L*-hydroxyproline. Sep. Sci. Technol. 39 (2004): 431-477.

[100] Hadik, P., Kotsis, L., Eniszné-Bódogh, M., Szabó, L.P., Nagy, E., Lactic acid enantioseparation by means of porous ceramic disc and hollow fiber organic membrane. Sep. Purif. Technol. 41 (2005): 299-304.

[101] Jiao, F.P., Huang, K.L., Peng, X.H., Zhao, X.H., Yu, J.G. Hollow fiber liquid-supported membrane technology for enantioseparation of racemic salbutamol by combinatorial chiral selector. J. Cent. South Univ. Technol. 13 (2006): 39-43.

[102] Huang, D.S., Huang, K.L., Chen, S.P., Liu, S.Q. Rapid reaction diffusion model for the enantioseparation of phenylalanine acrooss hollow fiber supported liquid membrane. Sep. Sci. Technol. 43 (2008): 259-272.

[103] Huang, D.S., Huang, K.L., Chen, S.P., Liu, S.Q., Yu, J.G. Enantioseparation of racemic α-cyclohexyl-mandelic acid acrooss hollow fiber supported liquid membrane. J. Braz. Chem. Soc. 19 (2008): 557-562.

[104] Jiao, F.P., Chen, X.Q., Jiang, X.Y. Enantioselective extrction of ofloxacin enantiomers using ester alcohol L-tartarate as chiral selector. Iran. J. Chem. Chem. Eng. 28 (2006): 7-11.

[105] Wang, Z., Cai, C., Lin, Y., Bian, Y., Guo, H., Chen, X. Enantioselective separation of ketoconazole enantiomers by membrane extraction. Sep. Purif. Technol. 79 (2011): 63–71.

[106] Naksang, C., Sunsandee, N., Thamphiphit, N., Pancharoen, U., Ramakul, P., Leepipatpiboon, N. Synergistic Enantioseparation of rac-Phenylalanine via Hollow Fiber Supported Liquid Membrane. Sep. Sci. Technol. 48, (2013): 867–876.