CHAPTER III

THE SELECTIVE SEPARATION OF (*S*)-AMLODIPINE VIA A HOLLOW FIBER SUPPORTED LIQUID MEMBRANE: MODELING AND EXPERIMENTAL VERIFICATION

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3.1 ABSTRACT

A hollow fiber supported liquid membrane (HFSLM) containing the chiral selector *O,O'*-Dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) was characterized for the enantioseparation of (*R,S*)-amlodipine. The influence of various chemical parameters, including the concentration of feed and receiving phases, as well as the carrier concentration in the membrane, were also investigated. Valuable knowledge on the transport mechanisms within this system was thus attained. Furthermore, a mathematical model focusing on the extraction side of the liquid membrane system was presented in order to predict the concentration of (*S*)-amlodipine at different times. The extraction and recovery of (*S*)-amlodipine from feed phase were 77.50% and 72.50%, respectively. Extraction equilibrium constant (K_{ex}), distribution ratio (D), permeability (P) and mass transfer coefficients were determined. The aqueous-phase mass-transfer coefficient (k_f) and organic-phase mass-transfer coefficient (k_m) were reported to 2.74×10^{-2} and 2.52×10^{-2} cm/s, respectively. The results showed promising agreement with the experimental data.

3.2 INTRODUCTION

Cardiovascular disease is the major cause of death in Thailand and worldwide. Hypertension is the leading risk factor for cardiovascular and renal disease, increasing the risk of myocardial infarction, stroke and congestive heart failure. The benefit of drug treatment of hypertension to prevent major cardiovascular events is consistently demonstrated in a large series of clinical trials controlled by placebo [1]. The international clinical guidelines on antihypertensive treatment from the World Health Organization (WHO) [2] and the recently updated guidelines from the European Society of Hypertension (ESH) [3] both recommended the use of long-acting calcium channel blockers as one of the first-line antihypertensive drug classes. Calcium channel blockers can be used in combination with most of the other antihypertensive drug classes, including diuretics, producing the early and effective blood-pressure control that is essential for the cardiovascular protection of high-risk patients [4].

Amlodipine is a third generation dihydropyridine calcium channel antagonist. The drug selectively inhibits calcium ion influx across cell membranes selectively, with a greater calcium channel blocker effect on vascular smooth muscle cells than on cardiac muscle cells [5,6]. Essentially, the calcium channel blocking effect is confined to the (*S*)-amlodipine (Figure 3.1(a)) isomer [7], whereas (*R*)-amlodipine (Figure 3.1(b)) exhibits a much lower calcium channel blocking activity [8]. The (*S*)-amlodipine is the more potent calcium channel blocker showing about 2,000 times potency in *in vitro* evaluation in the rat aorta than the (*R*)-amlodipine [9].

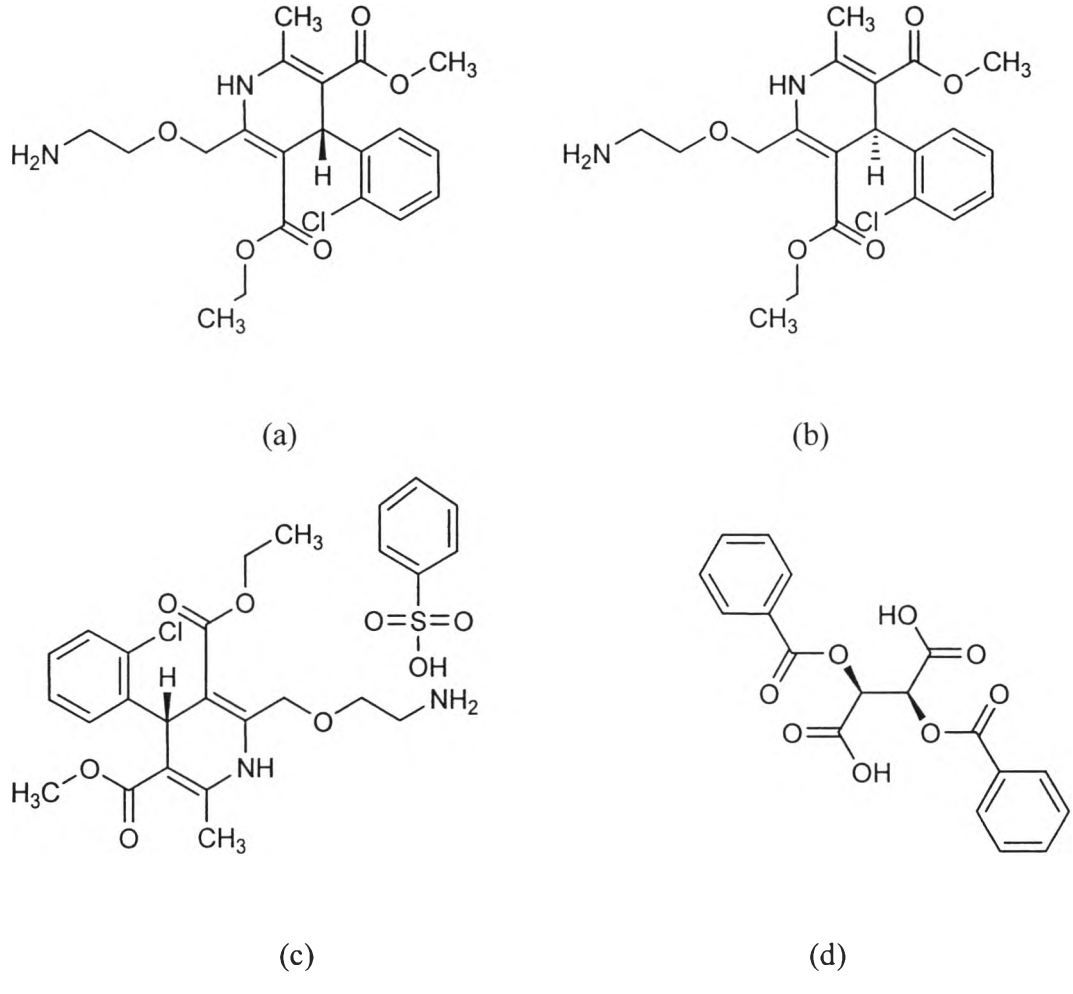


Figure 3.1 Structures of (a) (*S*)-amlodipine, (b) (*R*)-amlodipine
(c) (*S*)-amlodipine benzenesulfonate, (d) *O,O'*--dibenzoyl-(2*S*, 3*S*)-tartaric acid

The enantioselective separation of chiral compounds poses a considerable challenge to the pharmaceutical industry such that, historically, countless attempts have been made to develop efficient resolutions of racemic mixtures [10, 11]. In particular, various sources in the literature and patents have reported the separation of (*S*)-amlodipine from its racemic mixture, using crystallization, kinetic resolution, chromatography and capillary electrophoresis [12]. The most often employed isolation of (*S*)-amlodipine involves selective diastereomeric salt crystallization but this technique requires many time-consuming and expensive steps [13]. Kinetic resolution is very costly due to its single operation while chromatography and capillary electrophoresis are not suitable for gram-quantity scale up [14]. Whereas Hollow fiber supported liquid membrane is renowned as an effective simultaneous process to extract and recovery compound from very dilute solution of interested component in the feed by a single unit operation [15]. The merits and drawbacks of several enantioseparation techniques previously attempted for the resolution of racemic amlodipine are summarized in Table 3.1.

Table 3.1 Literature citations and patented methods for the isolation of (*S*)-amlodipine

Author	Method	Chiral resolving agent	Reference
J.E. Arrowsmith *et al.*	diastereomeric salt crystallization	diastereotopic azide esters	[16]
J.E. Arrowsmith *et al.*	diastereomeric salt crystallization	cinchonidine salts	[17]
H.W. Lee *et al.*	chemical kinetic resolution	*bis* (*S*-mandelic acid)-3-nitrophthalate	[18]
D.M. Gotrane *et al.*	diastereomeric salt crystallization	naturally tartaric acid nitrophthalate	[19]
S. Goldman *et al.*	diastereomeric salt crystallization	*O,O'*-dibenzoyl tartaric acid	[20]
S. Goldman *et al.*	chromatographic separations	(1*S*)-camphanic acid and *S*-2-methoxy-2-phenylethanol	[21]
M. Zandkarimi *et al.*	capillary electrophoresis	highly sulfated cyclodextrins	[22]
B. Streel *et al.*	chromatographic separations	α-acid glycoprotein coated	[23]
J. Luksa *et al.*	semi preparative purifications	α-cyclodextrin	[24]
This work	hollow fiber supported liquid membrane	*O,O'*-dibenzoyl tartaric acid	

Recently, membrane processes have been highlighted as promising alternatives to conventional resolution methods [25]. Many researchers have attempted and have been undertaken, using bulk liquid membranes [26], supported liquid membranes [27], emulsion liquid membranes [28], liquid membrane contactors [29] and carrier membranes [30]. Liquid membrane extraction has received considerable attention due to the advantages of combining liquid–liquid extraction with membranes in one single process. Furthermore, most membrane separations can be performed at room temperature, which makes them energy economical. Among these processes, supported liquid membranes (SLM) in particular show considerable potential, as only a very small amount of the expensive chiral carrier is needed to accomplish resolution of large quantities of the desired racemic mixture [31].

Hollow fiber supported liquid membrane (HFSLM) draws considerable interest due to its industrial applications. These include the removal of dilute heavy metals from waste waters (to meet stringent environment quality standards) as well as a simple design amenable to scaling up in industry [32]. The hollow fiber supported liquid membrane (HFSLM) technique has specific characteristics of simultaneous extraction and stripping processes of low-concentration of target species in one single stage [33]. Some other advantages of the hollow fiber contactor over traditional separation techniques include lower capital and operating costs [34], lower energy consumption [35], low solvent used and high selectivity [36]. These advantages of the hollow fiber contactor is suitable to used hollow fiber contactor to apply to treatment of chemical synthesis-based pharmaceutical wastewater more than previous works listed Table 3.1. A summary of the many examples of using HFSLM in industrial, biomedical and analytical fields is given in Table 3.2.

Table 3.2 The examples of using HFSLM in enantioseparation

Year	Feed solution	Extractant	Organic solvent	Stripping solution	Membrane material	Reference
2002	(*RS*)-lactic acid and(*RS*)- alanine	*N*-3,5-dinitrobenzoyl-(*L*)-phenylalanine-octylester	Toluene	DI water	Polypropylene hollow fiber	[37]
2003	(*RS*)-ofloxacin	(*DL*)- dibenzoyltartaric acid	1-octanol	DI water	Polysulfone hollow fiber	[38
	(*RS*)-terbutaline	(*L*)- dibenzoyl tartaric acid	1-octanol	DI water	Polysulfone hollow fiber	[39]
2004	(*RS*)-propanolol	*N*-hexadecyl-(L)-hydroxyproline	Propan-2-yl tetradecanoate	DI water	Polytetrafluoro ethylene hollow fiber	[40]
2005	(*RS*)-lactic acid	*N*-3,5-dinitrobenzoyl-(*L*)-phenylalanine-octylester	Toluene	DI water	Polypropylene hollow fiber	[41]
2006	(*RS*)-salbutamol	DBTA,DTTA	Toluene	DI water	Polyvinylidene fluoride hollow fiber	[42]
2008	(*RS*)-phenylalanine	Copper(II) *N*-decyl-(*L*)-hydroxyproline	1-hexanol: 1-decanol (1:1 v/v)	DI water	Polyvinylidene fluoride hollow fiber	[43]
	(*RS*)-α-cyclohexyl-mandelic acid	Copper(II) *N*-decyl-(*L*)-hydroxyproline	1-octanol	DI water	Polyvinylidene fluoride hollow fiber	[44
2009	(*RS*)-ofloxacin	(*L*)- tartarate	1,2-choroetahane	DI water	Polyvinylidene fluoride hollow fiber	[45]
2011	(*RS*)-ketoconazole	(*L*)- IPT and SBE-*β*-CD	1-hexanol	DI water	Polyvinylidene fluoride hollow fiber	[46]
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	

This work discusses the racemic resolution of amlodipine. A selective separation method for (*S*)-amlodipine by using HFSLM technology based on *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid (+)-DBTA) as chial extractant is shown in Figure 3.1(d). HFSLM contactors were evaluated considering two parameters. The separation factor (α), a measure of the separation efficiency of the process, and the percentage enantiomeric excess (% *e.e.*) were first recorded, followed by evaluation of the product's purity. The product recovery ratio (defined as the ratio of the quantity of enantiomer recovered over its initial quantity) was also calculated and this value serves to indicate the overall productivity of the process.

3.3 THEORY

A liquid membrane consists of an organic solution of chiral selector as the extractant, which is held in polymeric micropores by capillary action [47]. The supported liquid membrane lies between the aqueous solution initially that contains the racemic feed solution and the aqueous stripping solution. Transportation of (*S*)-amlodipine occurs as a consequence of the concentration driving force between the two opposite side of aqueous phase.

In this study, the enantioselector *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) resided in the liquid membrane, trapped in the hydrophobic microporous hollow fiber module. (+)-DBTA forms enantioselective complexes with (*S*)-amlodipine by hydrogen bonding. Previous partitioning experiments [48] indicate that (*R*)-amlodipine prefers to remain in the feed phase whereas the (*S*)-amlodipine-(+)-DBTA complex dissolves in the membrane phase. However, the equilibrium constant (K_{ex}) of complex is far bigger than the distribution coefficient, so the influence on mass transfer is small and can be neglected generally. The transport mechanism of (*S*)-amlodipine through the liquid membrane is shown in Figure 3.2.

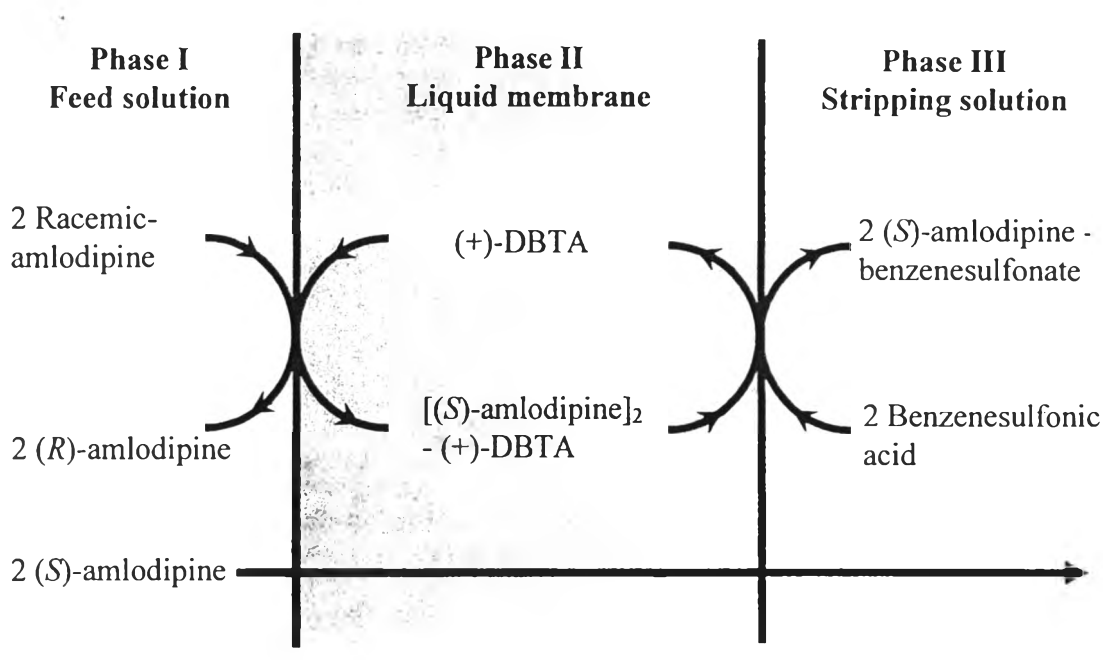


Figure 3.2 Transport scheme for chiral extractant

The mechanism and the enantioselective transport kinetics scheme of amlodipine enantiomers through hollow fiber supported liquid membrane are schematically described in Eq. (3.1)-(3.2):

$$2[(S)\text{-amlodipine}]_f + [(+)\text{-DBTA}]_m \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}]_m \quad (3.1)$$

where k_1 and k_2 are the apparent rate constants of feed membrane interfacial and membrane strip interfacial transport of amlodipine enantiomer, respectively. Define F and M suffixes as feed phase and membrane phase, respectively.

In the presence of benzenesulfonic acid in the stripping phase, benzenesulfonic acid reacts with $[[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}]_m$ to recovery (*S*)-amlodipine into the stripping phase:

$$[[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}]_m + 2[\text{benzenesulfonic acid}]_s \quad (3.2)$$

$$\underset{k_4}{\overset{k_3}{\rightleftharpoons}} 2[(S)\text{-amlodipine-benzenesulfonate}]_s + [(+)\text{-DBTA}]_m$$

where k_3 and k_4 are the apparent rate constants of feed membrane interfacial and membrane strip interfacial transport of amlodipine enantiomer, respectively. Define M and S suffixes as membrane phase and stripping phase, respectively.

3.3.1 Extraction equilibrium constant and distribution ratio

The extraction equilibrium constant (K_{ex}) of (*S*)-amlodipine extracted by [(+)-DBTA in Eq. (3.1) was derived from the experimental data and calculated from the following equation:

From the extraction reaction described in Eq. (3.1), the extraction equilibrium constant (K_{ex}) can be expressed as

$$K_{ex} = \frac{[[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}]_m}{[(S)\text{-amlodipine}]_f^2[(+)\text{-DBTA}]_n} \tag{3.3}$$

The distribution ratio (*D*) for (*S*)-amlodipine, was given by

$$D = \frac{[[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}]_m}{[(S)\text{-amlodipine}]_f} \tag{3.4}$$

According to Eq. (3.4), the distribution ratio could then be derived to a function of the extraction equilibrium constant as follows:

$$D = K_{ex}[(S)\text{-amlodipine}]_f[(+)\text{-DBTA}]_n \tag{3.5}$$

From the stripping reaction described in Eq. (3.2), the stripping equilibrium constant (K_{st}) can be expressed as

$$K_{st} = \frac{[(S)\text{-amlodipine - benzenesulfonate}]_s^2[(+)\text{-DBTA}]_m}{[[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}]_m[\text{benzenesulfonate}]_s^2} \tag{3.6}$$

where the value of K_{ex} for (*S*)-amlodipine extracted with (+)-DBTA and K_{st} for (*S*)-amlodipine stripped with benzenesulfonic acid were found to be 1.3160 $L^2/mmol^2$ and 1.2508, respectively. The results of experiment were showed in section 3.5.8.

3.3.2 Permeability coefficient

The permeation of (*S*)-amlodipine can be expressed in terms of the permeability coefficient (*P*) as proposed by Danesi [49] in Eq. (3.7).

$$-V_f \ln\left(\frac{C_f}{C_{f,o}}\right) = AP\frac{\beta}{\beta+1}t \tag{3.7}$$

$$\beta = \frac{Q_f}{PL\varepsilon\pi Nr_i} \tag{3.8}$$

where P is the permeability coefficient (cm/s), V_f is the volume of the feed (cm^3), $C_{f,0}$ is the (*S*)-amlodipine concentration (mol/L) in initial time (t = 0), C_f is the (*S*)-amlodipine concentration at time t (mol/L), A is the effective area of the hollow fiber module (cm^2), t is the time (min), Q_f is the volumetric flow rate of feed solution (cm^3/s), L is the length of the hollow fiber (cm), ε is the porosity of the hollow fiber (%), N is numbers of hollow fibers in the module and r_i is the internal radius of the hollow fiber (cm). $AP(\beta/(\beta+1))$ is the slope of the plot between $-V_f \ln (C_f / C_{f,0})$ versus time (t) in Eq. (3.7), and P can be obtained by Eq. (3.8). To determine mass transfer coefficients for (*S*)-amlodipine enantioseparation by HFSLM, the mass transfer model and permeability coefficient (P) are employed. The permeability coefficient depends on mass transfer resistance which is the reciprocal of the mass transfer coefficients as follows.

$$\frac{1}{P} = \frac{1}{k_f} + \frac{r_i}{r_{lm}}\frac{1}{P_m} + \frac{r_i}{r_o}\frac{1}{k_s} \tag{3.9}$$

where r_{lm} is the log-mean radius of the hollow fiber, r_o is the external radius of the hollow fiber (cm), k_f is the aqueous mass transfer coefficient in tube side, k_s is the stripping mass transfer coefficient in shell side and P_m is the membrane permeability coefficient.

The relation between P_m and the distribution ratio (D) are as follows:

$$P_m = Dk_m \tag{3.10}$$

Combining Eq. (3.5) and Eq. (3.10), thus

$$P_m = K_{ex}\, k_m[(S)\text{-amlodipine}]_f\,[(+)\text{-DBTA}]_m \tag{3.11}$$

where k_m is the mass transfer coefficient of membrane, a value of liquid membrane permeability coefficient (P_m) from Eq. (3.11) is substituted into Eq. (3.9). Assuming that the stripping reaction is instantaneous and the contribution of the stripping phase is neglected, Eq. (3.9) becomes:

$$\frac{1}{P} = \frac{1}{k_f} + \frac{r_i}{r_{lm}} \frac{1}{K_{ex}\, k_m[(S)\text{-amlodipine}]_f\,[(+)\text{-DBTA}]_m} \tag{3.12}$$

where k_f is the mass transfer coefficient of the feed solution

In this research, the extractability of (*S*)-amlodipine was determined by the percentage of extraction:

$$\%\text{Extraction} = \frac{C_{f,in} - C_{f,out}}{C_{f,in}} \times 100 \tag{3.13}$$

The percentage of recovery was calculated by:

$$\%\text{Stripping} = \frac{C_{s,out}}{C_{f,in}} \times 100 \tag{3.14}$$

where $C_{f,in}$, $C_{f,out}$ are the inlet and outlet feed concentrations of component i (mmol/L) and $C_{s,out}$ is the outlet stripping concentrations of component i (mmol/L).

The selectivity is defined as enantioselectivity. The enantioselectivity of the membrane process is given in terms of enantiomeric excess. The enantiomeric excess is defined by the ratio of the difference between the concentrations of both enantiomers in the feed or stripping phase to the total amount of both enantiomers present at any time, and was calculated according to Eq. (3.15):

$$\%\text{Enantiomeric excess} = \frac{C_{(S)} - C_{(R)}}{C_{(S)} + C_{(R)}} \times 100 \qquad (3.15)$$

3.3.3 Enantiomeric flux modeling of (*S*)-amlodipine

The facilitated transport and concentration profile of (*S*)-amlodipine through HFSLM is shown in Figure 3.3.

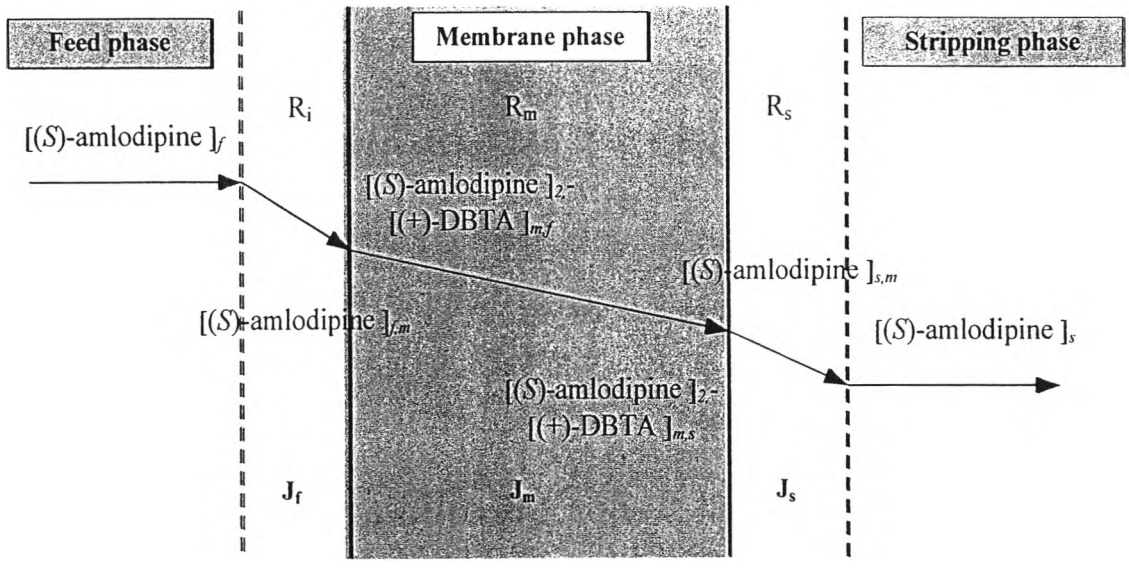


Figure 3.3 Mass transfer of amlodipine with (+)-DBTA and concentration profile in HFSLM

Modeling of the diffusive mass transport flux is performed under the following assumptions:

1) The system is considered to be at pseudo-steady state.

2) The extraction reaction takes place at the interface between the aqueous solution and the liquid membrane. The influence of the interface curvature in the mass transfer rate can be considered negligible.

3) No solute transport occurs through the non-porous parts of the membrane.

4) The solubility of both fluids in each other is negligible.

5) Mass transfer is described by simple film-type mass-transport coefficients.

The objective of the mathematical model to prediction the overall mass transport flux (J) of the solute from the feed solution to the organic phase, as defined as follows:

$$J = J_f = J_m = J_s \tag{3.16}$$

$$J_f R_f = [(S)\text{-amlodipine}]_{f,0} - [(S)\text{-amlodipine}]_{f,m} \tag{3.17}$$

$$J_m R_m = [(S)\text{-amlodipine}]_{m,f} - [(S)\text{-amlodipine}]_{m,s} \tag{3.18}$$

$$J_s R_s = [(S)\text{-amlodipine}]_{s,m} - [(S)\text{-amlodipine}]_{s,0} \tag{3.19}$$

where $R_m = 1/k_m$ and $R_f = 1/k_f$ are the membrane and aqueous mass transfer resistance, respectively, and $[(S)\text{-amlodipine}]_{f,0}$, $[(S)\text{-amlodipine}]_{f,m}$ are the concentrations of the (S)-amlodipine complexes in the feed solution and at the interface between aqueous feed solution and membrane phase at subsequent time (t).

Considering the extraction reaction in Eq. (3.1), $[(S)\text{-amlodipine}]_{f,m}$ is the concentration of the amlodipine in the interface between aqueous feed phase and membrane phase and $[(S)\text{-amlodipine}]_{m,f}$ is the concentration of the amlodipine complex in the membrane phase, respectively, as follows:

$$[(S)\text{-amlodipine}]_{m,f} = [[(S)\text{-amlodipine}]_2\text{-}(+)-\text{DBTA}]_m \tag{3.20}$$

From Eq. (3.3), $[(S)\text{-amlodipine}]_{m,f}$ is defined in term of equilibrium constant K_{ex},

$$[(S)\text{-amlodipine}]_{m,f} = K_{ex}\,[(S)\text{-amlodipine}]^2_{f,m}[(+)-\text{DBTA}] \tag{3.21}$$

The flux equation of the diffusion of the (S)-amlodipine$_2$-(+)-DBTA complex through the membrane phase can be written as per Eq. (3.18). The concentration of the strip solution can be neglected [50]. Therefore:

$$J_m R_m = [(S)\text{-amlodipine}]_{m,f} \tag{3.22}$$

$[(S)\text{-amlodipine}]_{m,f}$ from Eq. (3.21) was substituted into Eq. (3.22) to obtain the following expression:

$$[(S)\text{-amlodipine}]^2_{f,m} = \frac{J_m R_m}{K_{ex}[(+)-\text{DBTA}]} \tag{3.23}$$

By substituting $[(S)\text{-amlodipine}]^2_{f,m}$ from this expression into Eq. (3.17) and under the pseudo-steady-state condition assumption that $J_m = J_f = J$, the equation flux can be expressed as follows:

$$[(S)\text{-amlodipine}]^2_{f,m} = ([(S)\text{-amlodipine}]_{f,0} - J_f R_f)^2 \tag{3.24}$$

Hence, rearranging Eq. (3.24) in the form of a quadratic equation gives:

$$\frac{J_m R_m}{K_{ex}[(+)-\text{DBTA}]} = (J_f R_f)^2 - 2J_f R_f[(S)\text{-amlodipine}]_{f,0} + [(S)\text{-amlodipine}]^2_{f,0} \tag{3.25}$$

$$J^2 R_f^{\,2} - J(2R_f[(S)\text{-amlodipine}]_f + \frac{R_m}{K_{ex}[(+)-DBTA]}) + [(S)\text{-amlodipine}]^2_f = 0 \tag{3.26}$$

$$J = \frac{-\mathrm{b} \pm \sqrt{\mathrm{b}^2 - 4\mathrm{ac}}}{2\mathrm{a}} \tag{3.27}$$

where $\mathrm{a} = R_f^{\,2}$

$$\mathrm{b} = [-(2R_f[(S)\text{-amlodipine}]_f + \frac{R_m}{K_{ex}[(+)-\mathrm{DBTA}]})]$$

$$\mathrm{c} = [(S)\text{-amlodipine}]_f^2$$

The term $\sqrt{b^2 - 4ac}$ can be neglected because:

$$(2R_f[(S)\text{-amlodipine}]_f + \frac{R_m}{K_{ex}[(+)-\mathrm{DBTA}]}) >>$$

$$\sqrt{[-(2R_f[(S)\text{-amlodipine}]_f + \frac{R_m}{K_{ex}[(+)-\mathrm{DBTA}]})]^2 - 4R_f^{\,2}[(S)\text{-amlodipine}]_f^2}$$

Eventually, the enantiomeric flux is derived thus:

$$J = \frac{R_m}{2K_{ex}R_f^{\,2}[(+)-\mathrm{DBTA}]} + \frac{[(S)\text{-amlodipine}]_f}{R_f} \tag{3.28}$$

From the definition of flux given in Reference [51], the equation flux of (*S*)-amlodipine can be presented as:

$$J = -\frac{d[(S)-\mathrm{amlodipine}]_f}{dt}\frac{V}{A} \tag{3.29}$$

where V is volume of the feed solution (cm^3) and A is membrane area (cm^2). In accordance with the relationship between the fluxes equation in Eq. (3.28), Eq. (3.29) and Eq. (3.30) thus becomes:

$$-\frac{d[(S)-\mathrm{amlodipine}]_f}{dt}\frac{V}{A} = \frac{R_m}{2K_{ex}R_f^{\,2}[(+)-\mathrm{DBTA}]} + \frac{[(S)\text{-amlodipine}]_f}{R_f} \tag{3.30}$$

Finally, by integrating with initial conditions $t = 0$ and $[(S)\text{-amlodipine}]_f = [(S)\text{-amlodipine}]_{f,0}$, the equation for amlodipine concentration can be expressed as:

$$[(S)-\text{amlodipine}]_f = -\frac{R_m}{2K_{ex}R_f[(+)-\text{DBTA}]} + \left(\frac{R_m}{2K_{ex}R_f[(+)-\text{DBTA}]}\right)\exp\left(-\frac{A}{VR_f}t\right) \quad (3.31)$$

3.4 EXPERIMENT

3.4.1 Chemicals and reagents

(*R*)-amlodipine, (*S*)-amlodipine and racemic amlodipine, all of pharmaceutical grade, were provided from the Government Pharmaceutical Organization (GPO) of Thailand. *O,O'*-Dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) was obtained from Acros, USA. The solvents *N,N*-dimethylformamide, cyclohexane, 1-decanol and 1-propanol were all of analytical reagent grade and obtained from Merck, Germany. All reagents used in this experiment were of GR grade and also purchased from Merck, Germany. Aqueous solutions were prepared using Milli-Q® deionized water (Millipore®, USA). Doubly deionized water was used throughout the experiments.

3.4.2 Apparatus

The hollow fiber supported liquid membrane (HFSLM) system (Liqui-Cel® Extra-flow 2.5 in. × 8 in. membrane contactor) was manufactured by Hoechst Celanese, USA. The module uses celgard microporous polypropylene fibers that are woven into fabric and wrapped around a central tube feeder that supplies the shell side fluid. The woven fabrics provided more uniform fiber spacing, which in turn leads to higher mass transfer coefficients than those obtained with individual fibers [52]. The properties of the hollow fiber module are specified in Table 3.3. The fibers were put into a solvent-resistant polyethylene tube sheet and shell casing in polypropylene.

Table 3.3 Physical characteristics of the hollow fiber module

Properties	Descriptions
Material	Polypropylene
Inside diameter of hollow fiber	240 μm
Outside diameter of hollow fiber	300 μm
Effective length of hollow fiber	15 cm
Number of hollow fibers	10,000
Average pore size	0.03 μm
Porosity	30 %
Effective surface area	1.4×10^4 cm^2
Area per unit volume	29.3 cm^2/cm^3
Module diameter	6.3 cm
Module length	20.3 cm
Contact area	30 %
Tortuosity factor	2.6

3.4.3 Procedures

The single module operation is shown in Figure 3.4. The selected organic carrier (+)-DBTA was dissolved in 1-decanol (500 mL) and was simultaneously pumped into the tube and shell sides of the hollow fiber module for 40 min to ensure the extractant was entirely embedded in micro pores of the hollow fibers. Subsequently, 5 L of feed solution and stripping solution were fed counter-currently into the tube side and the shell side of the single module operation, respectively.

The concentration of feed solution was deliberately varied to find the optimum value for (*S*)-amlodipine extraction. The concentration of chiral selector ((+)-DBTA)) in the liquid membrane, volumetric flow rates of feed and stripping solutions, the number of separation cycles, and stability of HFSLM were each investigated in turn. The operating time for each run was 50 min. The concentrations of (*S*)-amlodipine in samples from feed and stripping solutions were determined by high performance liquid chromatography (HPLC) in accordance with United States

Patent No US 6646131 B2 [53] to estimate the percentages of extraction and stripping. To achieve higher enantioseparation and to study membrane stability, the number of separation cycles was varied. The feed of the second cycle was obtained from the first outlet feed solution and so on, whereas the inlet stripping solution was fresh.

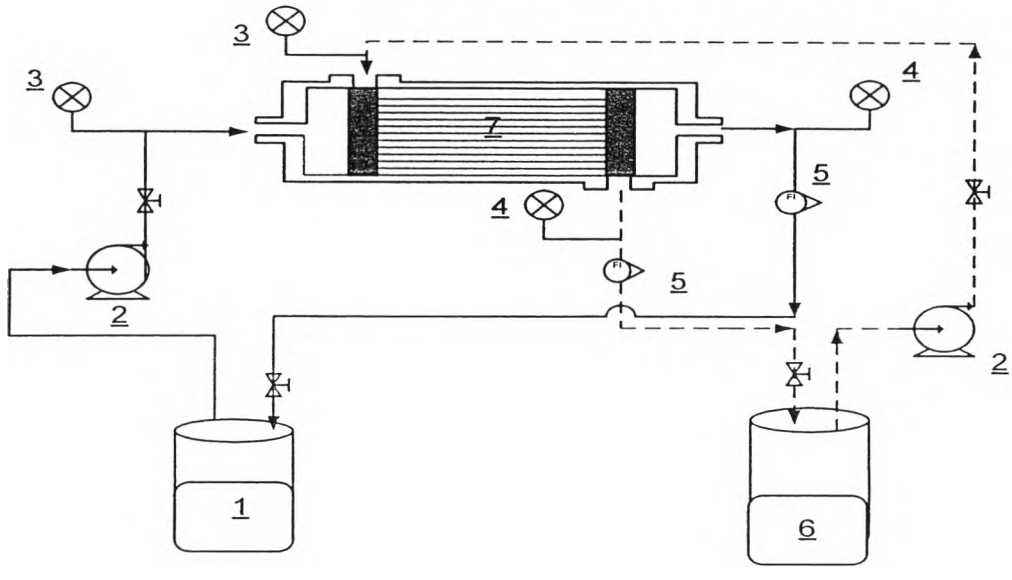


Figure 3.4 Schematic representation of the counter-current flow diagram for recirculation mode operation in HFSLM 1) feed reservoir, 2) gear pumps, 3) inlet pressure gauges, 4) outlet pressure gauges, 5) outer flow meter, 6) strip reservoir, 7) hollow fiber module.

3.4.4 Analytical instruments and chromatographic conditions

The chromatographic system consisted of Agilent® 1100 Compact LC system series (Agilent Technologies, Palo Alto, CA, USA). The chromatographic system used was equipped with an in built solvent degasser, quaternary pump, column compartment, photodiode array detector with variable injector and an auto sampler. Data analysis was carried out using Chemstation® Version B.04.01 software.

The chromatographic procedure was carried out by using chiral column ultron ES-OVM, Ovomucoid column (5 μm, 4.6 x150 mm) [53]. The column was thermo stated at 25 °C by using a column heater. Mobile phase is a mixture of

disodium hydrogen phosphate buffer (20 mmol/L) and acetonitrile (80:20 %v/v). A flow rate of mobile phase was 0.3 ml/min. Injection volume was 20 μL. The relative retention times of (*R*)-amlodipine was about 1.0 and (*S*)-amlodipine was about 1.2 as detector a spectrophotometer set at UV 237 nm. The analysis time was set at 20 min per sample to eliminate potential interference from late eluting peaks. The pH of the aqueous phase was measured with a pH meter model: SevenMulti™ Modular expansion (Mettler-Toledo, Greifensee, Switzerland).

3.5 RESULTS AND DISCUSSION

3.5.1 The influence of the (initial) pH of the feed phase

The pH is an important factor for consideration in the separation of enantiomers as pH impacts the ionized form of amlodipine enantiomers. The influence of the feed phase pH were studied 4 mmol/L (+)-DBTA in 1-decanol solvent and 4 mmol/L racemic amlodipine in NaH_2PO_4/H_3PO_4 buffer at different pH values. Amlodipine has one distinct group which can be protonated to give an increase and decrease of pH, which is the amine group as shown in Figure 3.1 (a)-(b). The pKa of amlodipine is about 8.6 at 25 °C [22]. In aqueous solution, amlodipine exists in two states of neutral molecule and anion. Therefore, there exists influence of pH on the distribution behavior of amlodipine enantiomers in enantioselective extraction. From the Figure 3.5, the enantiomeric excess (% *e.e.*) increases with the increase of pH until it reaches at pH 5.0 and then it starts to decrease. The possible reasons may be that the ratio between protonated and unprotonated amlodipine decreases with the rise of pH value. Ionic amlodipine only exists in aqueous phase. At pH 5.0, the enantiomers of amlodipine are expected to be unprotonated because the pKa of amlodipine is about 8.6 at 25 °C [22]. So, pH 5.0 was an appropriate choice in view of the bigger enantioselectivity of the enantioselective extraction.

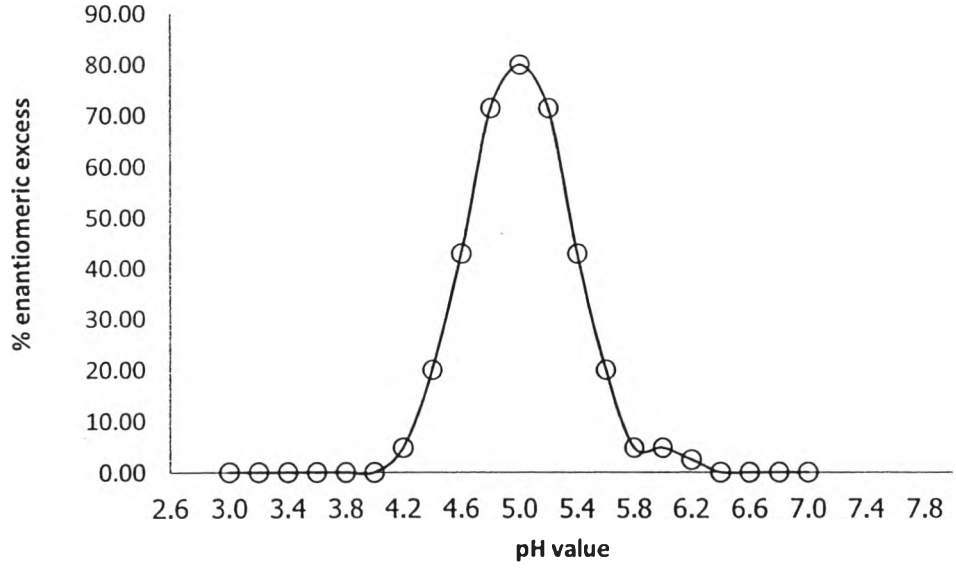


Figure 3.5 Influence of pH on enantiomeric excess (%)

3.5.2 The influence of amlodipine concentration in the feed phase

The concentration of initial feed concentration was studied at 2, 4, 6, 8 and 10 mmol/L to investigate the influence of amlodipine concentration in the feed phase on percentage of extraction, stripping and enantiomeric excess as shown in Figure 3.6. It was observed that higher extraction of (*S*)-amlodipine can be achieved by increasing the concentration of the initial feed concentration. The optimum concentration was found about concentration 4 mmol/L. That acquired the extraction of (*S*)-amlodipine about 77.50%. The extraction was likely decreased in higher concentration above concentration 6 mmol/L. The increase in initial concentration in feed phase results in higher fluxes. But, the flux decreases apparently in higher concentration above concentration 6 mmol/L. The flux decreases because the increase in film viscosity becomes dominant and obstructs mass transfer. This reason was published with the earlier report by Wannachod *et al.* [52]. This result is in agreement with this study as demonstrated. However, for the all subsequent experiments the concentration of (*S*)-amlodipine was fixed at concentration 4 mmol/L.

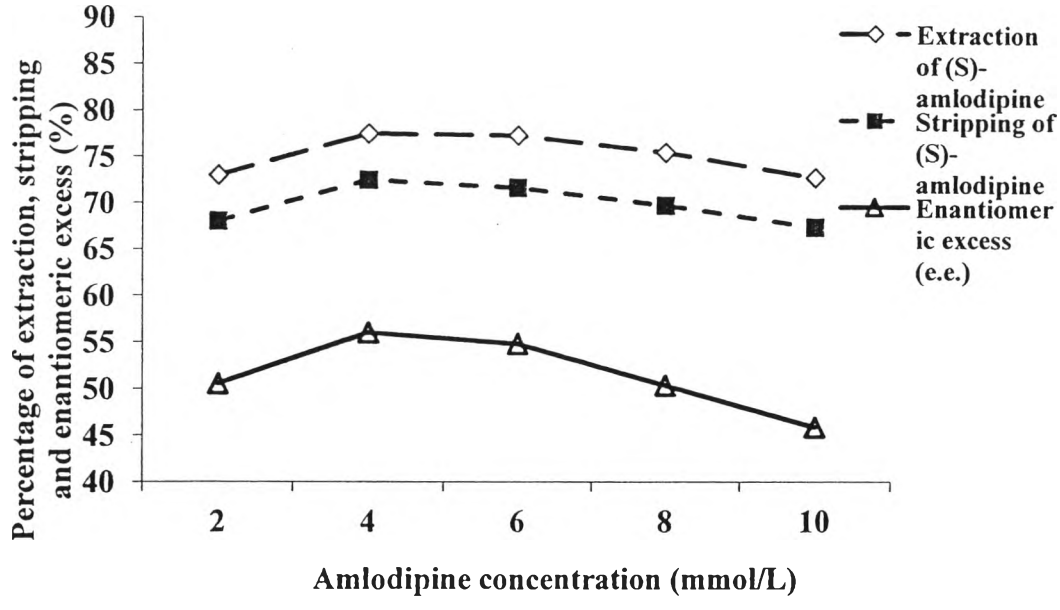


Figure 3.6 Influence of amlodipine concentration in the feed phase on percentages of extraction and recovery of (*S*)-amlodipine and the enantiomeric excess (% *e.e.*)

3.5.3 The influence of chiral selector concentration in the membrane phase

Figure 3.7 shows influence of chiral selector concentration in in the membrane phase on percentages of extraction, stripping and enantiomeric excess. The concentrations of (+)-DBTA were studied at 2, 4, 6, 8 and 10 mmol/L. (*S*)-amlodipine extraction increased with an increase in the extractant concentration. The highest percentage of (*S*)-amlodipine extraction about 77.50% was obtained at the concentration around 4 mmol/L and it was recorded as the optimized concentration to use in further run. However, in this work, the (*S*)-amlodipine extraction decreases apparently in higher concentration above 4 mmol/L. It was noted that the results agreed with the earlier report by Wannachod *et al.* [52]. The fluxes decreased at higher extractant concentrations because the viscosity of the film between the feed solution and the liquid membrane increased and obstructed the mass transfer.

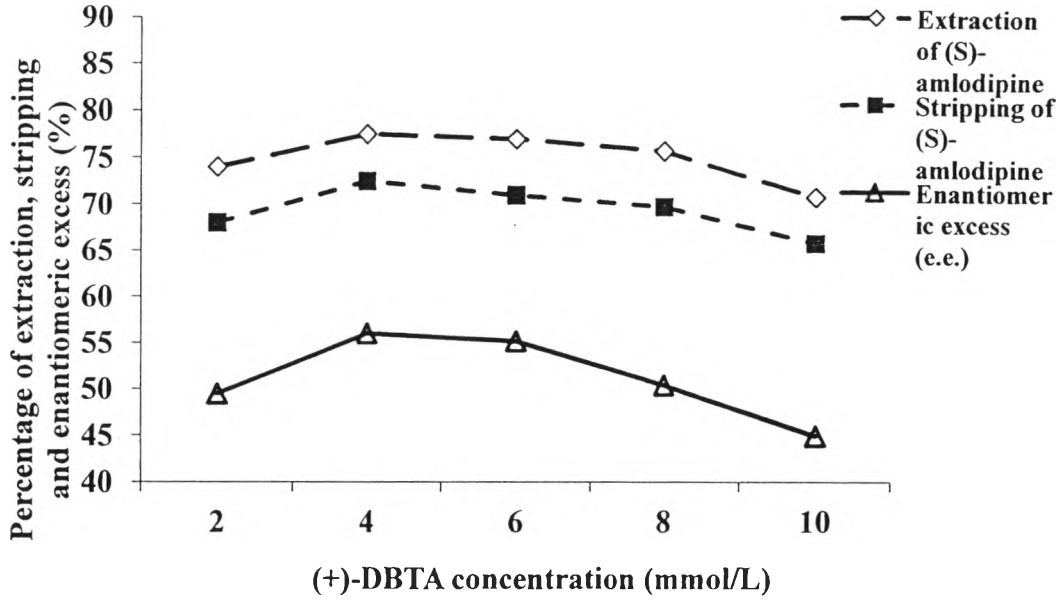


Figure 3.7 Influence of chiral selector ((+)-DBTA) concentration in the membrane phase on percentages of extraction and recovery of (*S*)-amlodipine and the enantiomeric excess (% *e.e.*)

3.5.4 The influence of stripping phase concentration

The influence of concentrations of benzenesulfonic acid, a stripping solution, was studied at 2, 4, 6, 8 and 10 mmol/L on the percentage of extraction, stripping and enantiomeric excess in the stripping process of (*S*)-amlodipine is shown in Figure 3.8. The chiral selector used 4 mmol/L (+)-DBTA. From Figure 3.5 is evident very strong influence of pH of the feed phase on the enantiomeric excess (% *e.e.*). The maximum % *e.e.* at pH 5.0 is explained by the formation of unprotonated enantiomers of amlodipine. However, the pH of stripping phase can be influenced by the concentration of benzenesulfonic acid in a stripping solution. From Figure 3.8, benzenesulfonic acid accelerated the stripping process, but similarly as in Figure 3.5, at higher concentrations in the stripping solution, stripping process of (*S*)-amlodipine decreases. This reason is same in section 3.5.1. From Figure 3.8, for single-module operation, the highest stripping of (*S*)-amlodipine about 72.50% was achieved at the benzenesulfonic acid concentration of 4 mmol/L. This concentration (4 mmol/L) will

be referred for the next study run in an attempt to establish the highest possible (*S*)-amlodipine recovery.

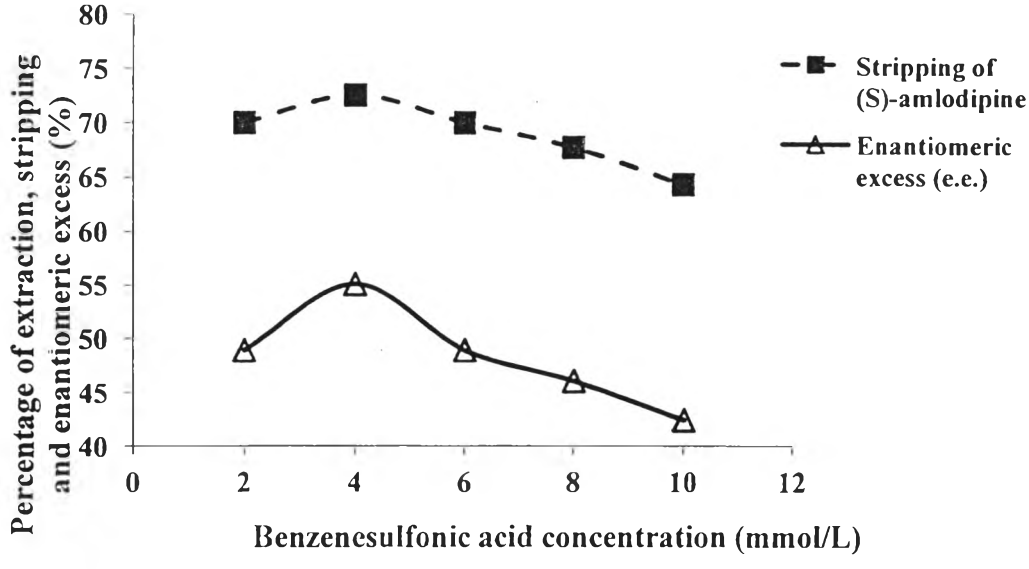


Figure 3.8 Influence of stripping phase (benzenesulfonic acid) concentration on percentages of extraction and recovery of (*S*)-amlodipine and the enantiomeric excess (% *e.e.*)

3.5.5 The influence of the flow rates of feed solution

Figure 3.9 shown the relationship between the percentage of extraction and stripping of (*S*)-amlodipine and the enantiomeric excess at equal flow rates of feed and stripping solutions having a counter flow pattern were studied at 50, 100, 150 and 200 mL/min. The extractant used 4 mmol/L (+)-DBTA and the concentration of stripping solution was 4 mmol/L. The results indicate that by using the flow rates of feed solutions of 100 ml/min obtain the highest percentage of the extraction of (*S*)-amlodipine about 77.50%. The flow rates of feed solutions tremendously play an important role on the percentages of extraction and stripping of (*S*)-amlodipine. Too high flow rates results in less resident time of the solutions or less contact time of the relevant molecule in the reaction in the HFSLM process. In other words at too high flow rates, especially at 200 mL/min may deteriorate the membrane system which can be seen from poor liquid membrane stability and lower percentage of extraction [54, 55].

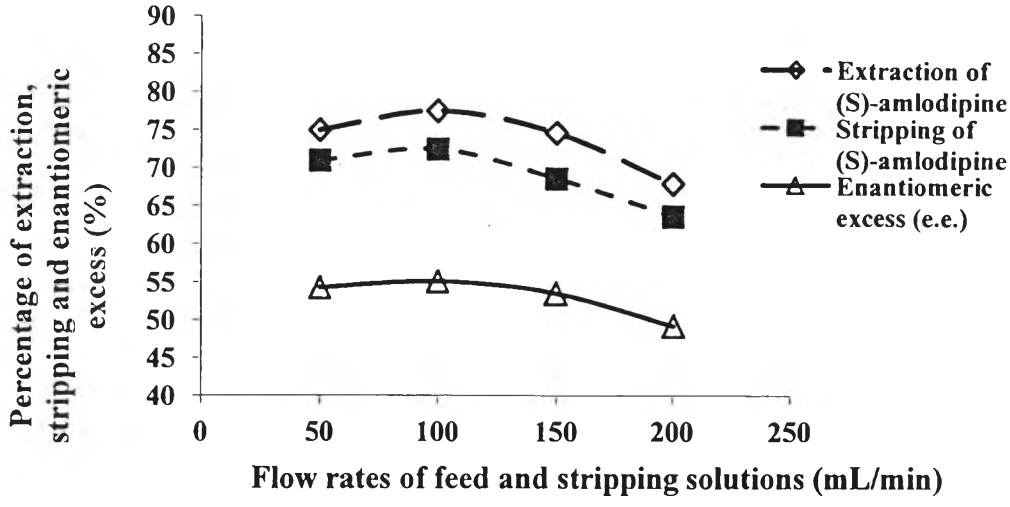


Figure 3.9 Influence of the flow rate of feed and stripping solution on percentages of extraction and recovery of (*S*)-amlodipine and the enantiomeric excess (% *e.e.*)

3.5.6 The influence of the flow rates of stripping solution

The results indicated that by using a single module operation for 50 min at the flow rates of stripping solutions of 100 ml/min, the highest percentages of (*S*)-amlodipine extraction and stripping of 77.50% and 72.50%, respectively, were obtained. However, the percentage of (*S*)-amlodipine extraction and stripping decreased with an increase of the flow rates of feed and stripping solutions due to resident time of solution in the hollow fiber module.

3.5.7 The influence of number of separation cycle through the hollow fiber module

The numbers of separation cycle were studied using the optimum conditions in a single-module operation to expect the highest possible separation. Besides, this study was indicated the least possible (*S*)-amlodipine concentration in the feed as well as to inspect the membrane stability. Figure 3.10 shows that the percentages of (*S*)-amlodipine cumulative extraction and cumulative stripping were obtained at 6-cycle operation for 300 min. The cumulative extraction and stripping reached 77.50% and 72.50%, respectively.

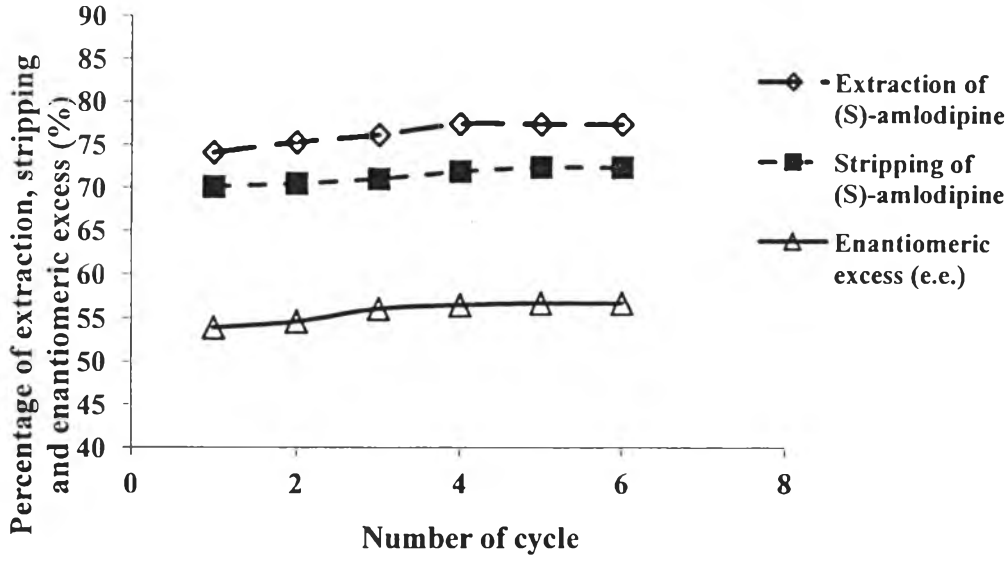
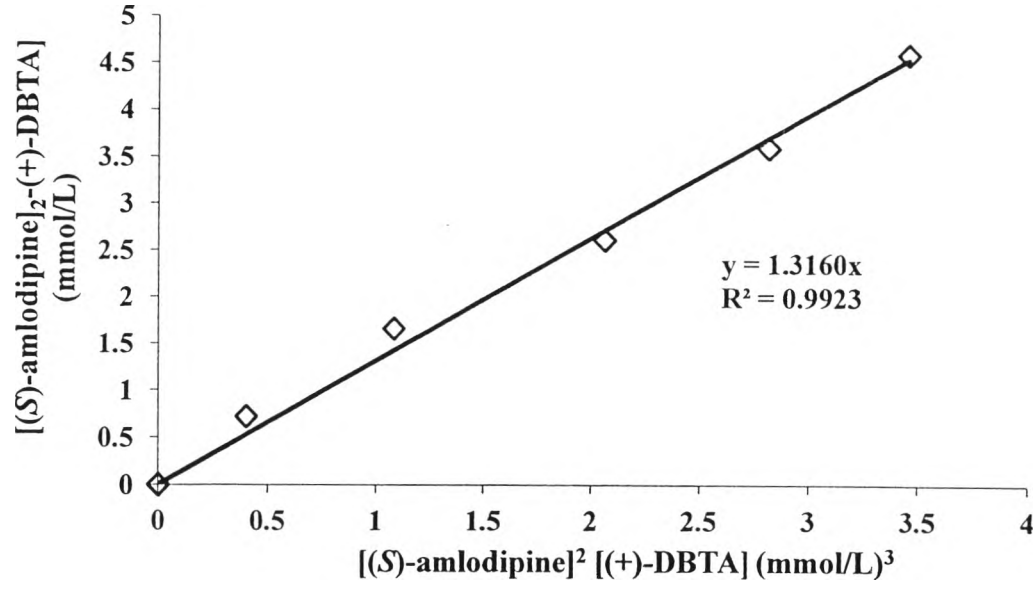


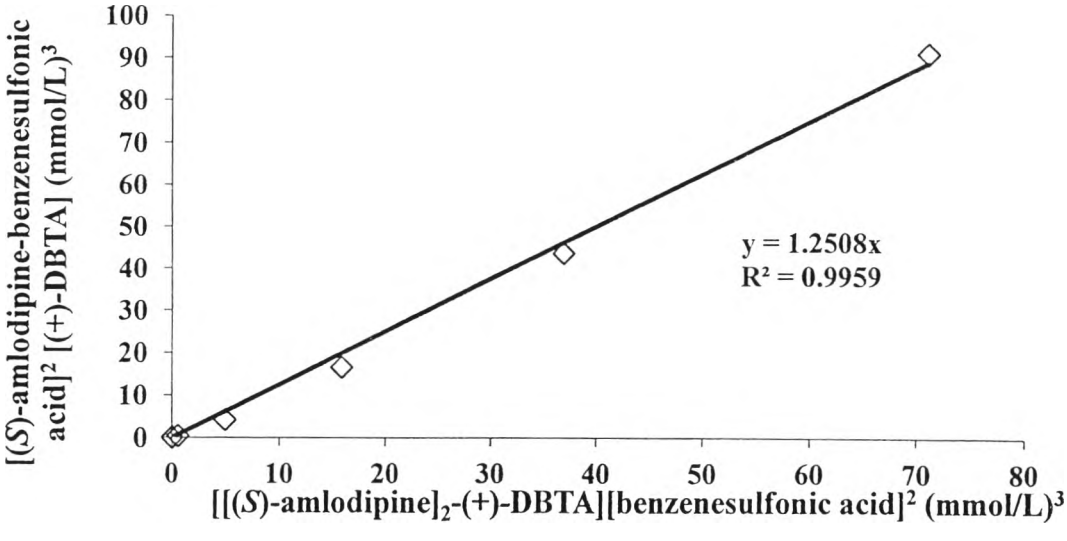
Figure 3.10 Influence of number of separation cycle through the hollow fiber module on percentages of extraction and recovery of (*S*)-amlodipine and the enantiomeric excess (% *e.e.*)

3.5.8 Extraction equilibrium constant, stripping equilibrium constant and distribution ratio

The extraction equilibrium constant (K_{ex}) was calculated by the slope of the graph in Figure 3.11(a) and found to be 1.3160 $(L/mmol)^2$. The stripping equilibrium constant (K_{st}) was calculated by the slope of the graph in Figure 3.11(b) and found to be 1.2508. The distribution ratio (D) at the (+)-DBTA concentration of 4 mmol/L were calculated by Eq. (3.3) and Eq. (3.4) as shown in Table 3.4. It was noted that the distribution ratio increased with the extractant concentration, agreed with the earlier report by Wannachod *et al.* [52].



(a)



(b)

Figure 3.11 (a) (*S*)-amlodipine extraction with (+)-DBTA as a function of equilibrium $[(S)\text{-amlodipine}]^2[(+)\text{-DBTA}]$.

(b) (*S*)-amlodipine-(+)-DBTA stripping with benzenesulfonic acid as a function of equilibrium $[[(S)\text{-amlodipine}]_2\text{-}(+)\text{-DBTA}][\text{benzenesulfonic acid}]^2$.

Table 3.4 The distribution ration (D) at the (+)-DBTA concentrations in the range 2, 4, 6, 8 and 10 mmol/L

[(+)-DBTA] (mmol/L)	2	4	6	8	10
The distribution ration	1.29	2.44	3.35	4.50	5.75

3.5.9 Permeability and mass transfer coefficients

The permeability coefficients of (*S*)-amlodipine as function of concentration of (+)-DBTA from 2 to 8 mmol/L, were calculated by the slope obtained in Figure 3.12 as shown in Table 3.5. The results showed that the permeability coefficient increased with the extractant concentration agreed with the earlier report by Pancharoen *et al.* [55].

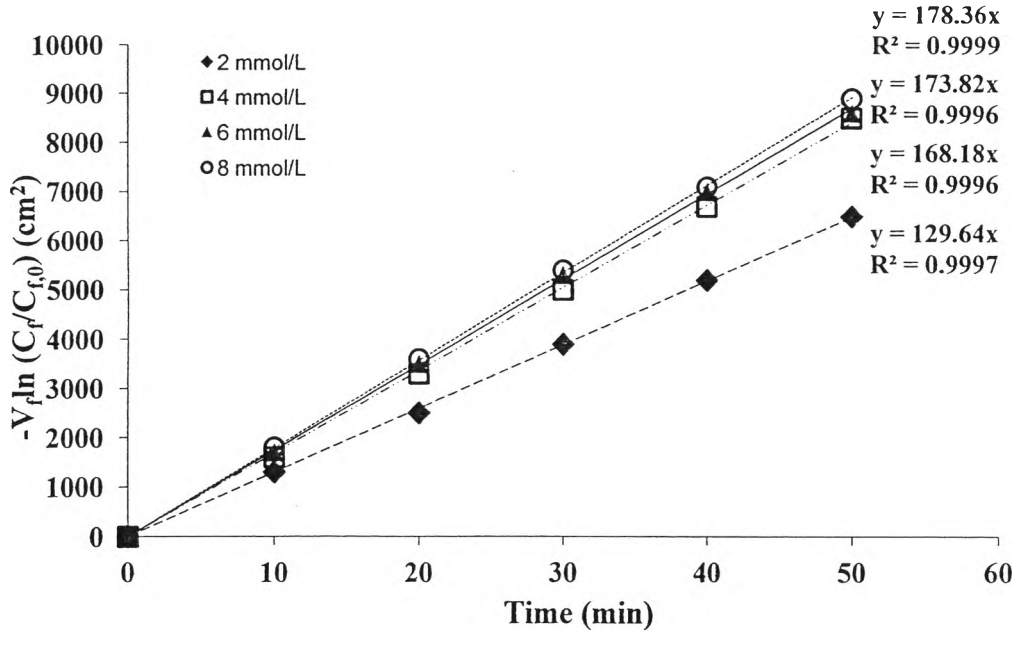


Figure 3.12 Plot of $-V_f \ln(C_f/C_{f,0})$ of (*S*)-amlodipine in feed solution against time with different (+)-DBTA concentrations

Table 3.5 Permeability coefficients (P) at (+)-DBTA concentrations in the range 2, 4, 6 and 8 mmol/L

[(+)-DBTA] (mmol/L)	Permeability coefficients (×100 cm/s)
2	1.33
4	1.99
6	2.10
8	2.20

Eq. (3.12) was attained by substituting the membrane permeability coefficient (P_m) in Eq. (3.11) into Eq. (3.9); assuming that the stripping reaction of (*S*)-amlodipine was instantaneous and no contribution of the stripping phase. Eq. (3.12) was used to calculate the aqueous mass transfer coefficient (k_f) and the membrane mass transfer coefficient (k_m). By plotting $1/P$ as a function of $1/[(S)\text{-amlodipine}]_f$ $[(+)\text{-DBTA}]_m$ for different carrier concentrations of (+)-DBTA, a straight line with slope $r_i/(r_{lm} \cdot K_{ex} \cdot k_m)$ and ordinate $1/k_f$ for calculation is obtained (Figure 3.13). Thus, the values of k_f and k_m were found to be 2.74×10^{-2} and 2.52×10^{-2} cm/s, respectively. Since the membrane mass transfer coefficient (k_m) is less than the aqueous feed mass transfer coefficient (k_f) we conclude that the mass transfer across the membrane phase is the rate-controlling step.

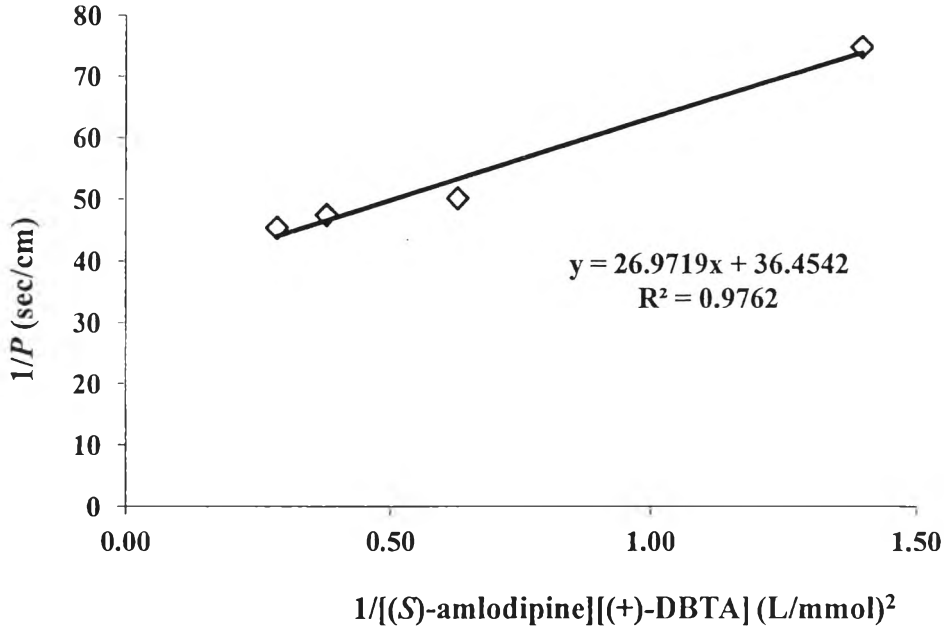


Figure 3.13 Plot of $1/P$ as a function of $1/[(S)\text{-amlodipine}]_f\,[(+)\text{-DBTA}]_m$

3.5.10 Enantiomeric flux modeling of (*S*)-amlodipine

The mass transfer reaction of (*S*)-amlodipine through hollow fiber supported liquid membrane was assessed by enantiomeric flux modeling, as represented in Figure 3.14. Eq. (3.31) was used to calculate the percentage of (*S*)-amlodipine extraction as a function of time for feed concentrations at 2, 4, 6, 8 and 10 mmol/L. The computational results were shown by the solid line which was in good agreement and fit well with the experimental data. The diffusion process is explained by Fick's law of diffusion. Mass transfer flux was presented in this model. Therefore, it could be concluded that the enantiomeric flux model was satisfactory for extraction of (*S*)-amlodipine through hollow fiber supported liquid membrane.

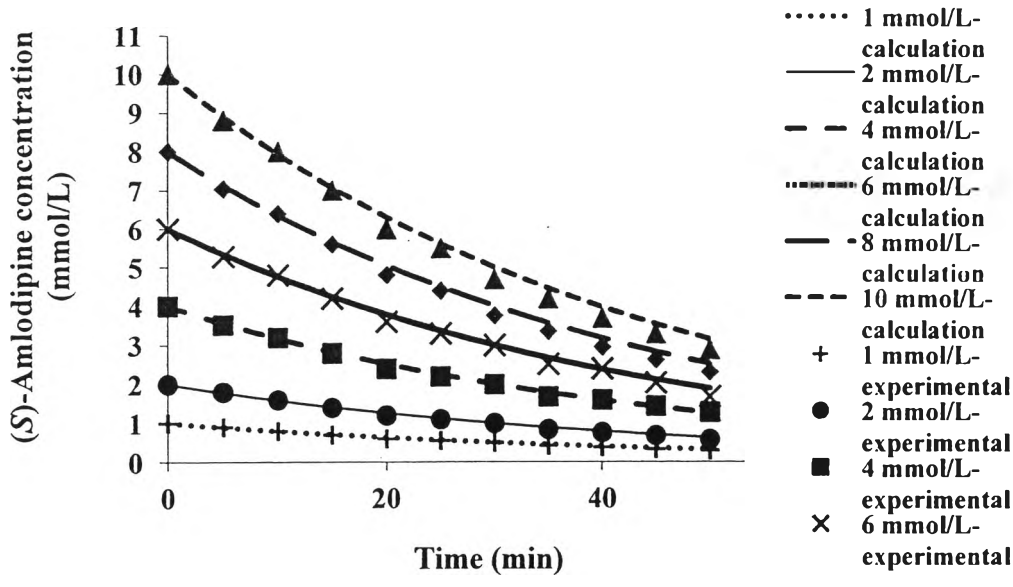


Figure 3.14 Concentration of (*S*)-amlodipine in feed phase plotted as a function of time at different (*S*)-amlodipine concentrations (using stripping solution containing benzenesulfonic acid at 4 mmol/L)

3.6 CONCLUSIONS

Progressive previous research in the pharmaceutical industry has spawned steady refinements in the enantioseparation of racemic amlodipine. Optimised parameters were applied to the racemic mixture separation to attain high yields of (*S*)-amlodipine. Extraction and stripping with those used by (+)-DBTA, which is a acid extractant. In this work, for 300 min at 6-cycle operation via HFSLM system, the (*S*)-amlodipine percentages of cumulative extraction and cumulative stripping were 77.50% and 72.50%, respectively, from initial concentration of feed solution of 4 mmol/L, 4 mmol/L (+)-DBTA, 4 mmol/L benzenesulfonic acid, and 100 ml/min of feed and stripping solutions. The mass transfer coefficients of the aqueous phase (k_f) and organic phase (k_m) were 2.74×10^{-2} and 2.52×10^{-2} cm/s, respectively.

Our study demonstrates that (*S*)-amlodipine could be selectively extracted from racemic amlodipine by solvent extraction in HFSLM at room temperature. The results demonstrate the energy-economic benefits offered by HFLSM extraction and the technique's potential to improve other industrially-relevant chiral separations.

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