CHAPTER VIII

CONCLUSION AND RECOMMENDATIONS

8.1 CONCLUSION

Hollow fiber supported liquid membrane (HFSLM) has been used as a separation process for the removal of dilute heavy metals from waste waters. The HFSLM system has specific characteristics of simultaneous extraction and stripping processes of low concentration of target species in single stage. The advantages of the hollow fiber contactor over traditional separation techniques include lower capital and operating costs, lower energy consumption, less solvent used and high selectivity. These advantages of HFSLM are suitable to apply for enantioseparation and treatment of chemical synthesis-based pharmaceutical wastewater.

As stated in the introduction, the aim of the research presented in this thesis was to develop the potential process for the enantioseparation and treatment of chemical synthesis-based pharmaceutical wastewater. The chiral selective extractant, *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) was investigated in the first experiment. A two-phase chiral extraction system containing (+)-DBTA in 1-decanol organic phase and aqueous phase was demonstrated for the chiral resolution of amlodipine as presented in CHAPTER II. The second experiment was presented in CHAPTER III. The HFSLM system was applied for the recovery of (*S*)-amlodipine from racemic amlodipine. Several experimental parameters affecting the enantioselective separation of (*S*)-amlodipine by using HFSLM technology based on *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) as chiral extractant were investigated. In the third experiment (CHAPTER IV), the novel synergistic effects by using mixture of chiral selective extractant, *O,O'*-dibenzoyl-(2*S*,3*S*)-tartaric acid ((+)-DBTA) and achiral extractant, di(2-ethylhexyl) phosphoric acid (D2EHPA) on enantioseparation of (*S*)-amlodipine were investigated. The new concept of synergistic enantioseparation was found. The novel derivative complex structure, namely (*S*)-amlodipine-(+)-DBTA-D2EHPA was shown in Figure 8.1.

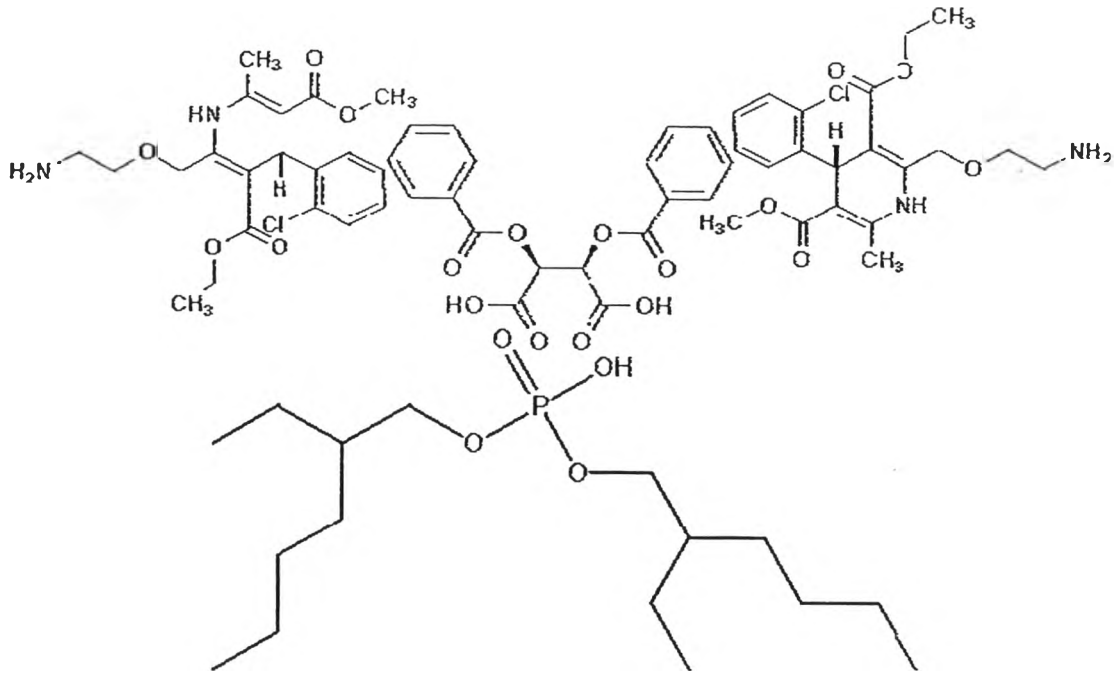

Figure 8.1 (*S*)-amlodipine-(+)-DBTA-D2EHPA complex

The measurement and the correlation of solubility data of (*S*)-amlodipine in aqueous and different organic solvents were presented in CHAPTER V. The influence of temperature on molar solubility was investigated.

This dissertation evaluates the effect of temperature on mass transfer in a single HFSLM process as presented in CHAPTER VI. In CHAPTER VII, the novel recovery process by the specific stripping phase was demonstrated. The effects of polarity indexes of diluents and stability of the liquid membrane were investigated. Several experimental parameters were experimented for the recovery of (*S*)-amlodipine from chemical synthesis-based pharmaceutical wastewater.

According to the results in this dissertation, it can be said that the HFSLM is a challenging method for the enantioseparation of (*S*)-amlodipine. Furthermore, it is possible to recover the chiral drugs of very low concentrations in the aqueous solutions. By using the synergistic extraction of chiral-to-achiral mixture (4 mM (+)-DBTA and 4 mM D2EHPA) at equal volume of 1:1 dissolved in 1-decanol, the feed solution of pH 5.0, *β*-cyclodextrin as the stripping solution, equal flow rates of the feed and the stripping solutions of 100 ml/min, experimental time of 300 min, the highest percentages of extraction and stripping of 84 and 80% were achieved, respectively. The enantiomeric excess (% *e.e.*) of (*S*)-amlodipine was 70%. The mass-

transfer coefficients of the aqueous phase (k_f) and organic phase (k_m) were 4.87×10^{-2} and 2.89×10^{-2} cm/s, respectively. Therefore, the mass transfer-controlling step is the diffusion of (*S*)-amlodipine complex through liquid membrane. Moreover, the parameters have an effect on the mass transfer such as distribution ratio. Fluxes were determined at different temperatures ranging from 278.15 K to 313.15 K. The thermodynamic parameters, ΔH and ΔG, were determined. An interesting relationship with stoichiometric value was found: higher temperatures lead to an increase in distribution ratio but a decrease in enantioselectivity. The temperature strongly affects D_S, D_R, and α, as well as $K_{ex(S)}$ and $K_{cx(R)}$ values.

In this dissertation, the activation energy (E_a) of (*S*)-amlodipine extraction is 71.10 kJ/mol. It indicates that the extraction and the recovery of (*S*)-amlodipine through the HFSLM is controlled by the chemical reaction. The $K_{ex(S)}$ was 1.32 $(L/mmol)^3$ and ΔG was -684.89 J/mol. From the Gibbs–Helmholtz equation, the molar enthalpy and the molar entropy changes (ΔH and ΔS) for (*S*)-amlodipine extraction were 6.77 kJ/mol and 24.60 J/(mol·K), respectively. The positive value of ΔH indicates that the (*S*)-amlodipine extraction is an endothermic reaction. The negative value of ΔG and the positive value of ΔS indicate that the (*S*)-amlodipine extraction is a spontaneous reaction. The thermodynamic parameters are important for the design of the enantioseparation system and for controlling the separation temperature.

The potential application of HFSLM for separation of (*S*)-amlodipine from pharmaceutical wastewaters has also been discussed. The use of a HFSLM is an effective technique. It is here firstly to implement for enantiomeric drug compounds separation from pharmaceutical wastewater when the amount of enantiomeric drug compounds in the solution is traced. The results showed that HFSLM can be applied for scale-up to production scale of the pure enantiomer.

Furthermore, the mathematical model was found to be a very useful design equation. The mathematical model was presented in order to predict the concentration of (*S*)-amlodipine at different times. The predicted results showed good agreements with the experimental data. The experimental results show that the proposed model is validated to calculate the concentration of the enantiomers in the enantioselective process satisfactorily. The model could be easily applied to the enantioseparation of chiral drugs by changing a few parameters such as the equilibrium rate constant, the

mass-transfer coefficient, the reaction order and the reaction rate constant, depending on the chiral carrier and the enantiomers of interest.

8.2 LIMITATIONS OF THE RESEARCH

HFSLM has applications in both industrial and analytical fields for separation, pre-concentration, and treatment of wastewater. Major drawbacks of HFSLM are fouling, mechanical stability of the support and instability of supported liquid membrane. In spite of its positive potentials such as high selectivity and effective separation of desired organic compound, the limited number of uses of HFSLM as well as scaling up to industrial scale are found. The major concern of the rare applications of HFSLM in industrial scale is attributed to the membrane instability in terms of long time performance which leads to the reduction of solute flux and membrane selectivity. At present, the major drawbacks of HFSLM mean that this technique is not often used in large-scale industry. Some of these limitations were addressed in this work and some possible solutions were provided. Moreover, the suggestions for future research to improve the HFSLM system are provided in the next paragraph.

8.3 RECOMMENDATIONS FOR FUTURE RESEARCH

According to the results in this dissertation, HFSLM has demonstrated the successful extract and recover of (*S*)-amlodipine from chemical synthesis-based pharmaceutical wastewater. Other enantiomeric drugs can also be studied. There are groups of drugs which are more advanced with regards to pure enantiomeric compound in the same pharmacological activity like (*S*)-amlodipine in cardiovascular drug such as propranolol and atenolol. Many therapeutic drug groups such as the central nervous system, antibiotic, antiviral and anticancer drugs have been described to separate the chiral compounds to single enantiomeric compound. The groups of enantiomeric drugs are of interest to study such as L-dopa, levofloxacin, lamivudine and levocetirizine. The new approaches developed in this dissertation could be used as a separation process for enantioseparation and pharmaceutical wastewater treatment. As this work has shown, this novel process worked well in many respects

and showed several beneficial features in the pharmaceutical industry. However, further researches should be done to improve the process performance to be more efficient and useful, such as:

1. The major drawbacks of HFSLM such as fouling and mechanical stability of the support should be solved.

2. Increasing the number of running times should result in the higher extraction and selectivity.

3. The reuse of the organic membrane solution should be investigated.

4. The experimental period should be 30 – 60 days to test the stability of the process for industrial scale.

5. The performance of this HFSLM system should be tested with the other industrial wastewater which contains more or other pharmaceutical or organic ingredients.