Experimental and Model Studies on Continuous Separation of 2-Phenylpropionic Acid Enantiomers by Enantioselective Liquid–Liquid Extraction in Centrifugal Contactor Separators

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ABSTRACT Multistage enantioselective liquid–liquid extraction (ELLE) of 2-phenylpropionic acid (2-PPA) enantiomers using hydroxypropyl-β-cyclodextrin (HP-β-CD) as extractant was studied experimentally in a counter-current cascade of centrifugal contactor separators (CCSs). Performance of the process was evaluated by purity (enantiomeric excess, *ee*) and yield (Y). A multistage equilibrium model was established on the basis of single-stage model for chiral extraction of 2-PPA enantiomers and the law of mass conservation. A series of experiments on the extract phase/washing phase ratio (W/O ratio), extractant concentration, the pH value of aqueous phase, and the number of stages was conducted to verify the multistage equilibrium model. It was found that model predictions were in good agreement with the experimental results. The model was applied to predict and optimize the symmetrical separation of 2-PPA enantiomers. The optimal conditions for symmetric separation involves a W/O ratio of 0.6, pH of 2.5, and HP-β-CD concentration of 0.1 mol L^{-1} at a temperature of 278 K, where ee_{eq} (equal enantiomeric excess) can reach up to 37% and Y_{eq} (equal yield) to 69%. By simulation and optimization, the minimum number of stages was evaluated at 98 and 106 for $ee_{eq} > 95\%$ and $ee_{eq} > 97\%$. *Chirality 28:235–244, 2016.*

Research highlights are as follows:

(1) Multistage enantioselective liquid-liquid extraction is suitable for the separation of 2-phenylpropionic acid enantiomers with HP-β-CD as hydrophilic chiral selector.
(2) Model predictions of multistage countercurrent centrifugal extraction of 2-phenylpropionic acid enantiomers are in good agreement with the experimental results.
(3) Purity for 2-phenylpropionic acid enantiomers could be remarkably improved by changing W/O ratio or extractant concentration, and or adding the number of centrifugal contact separators.
(4) Multistage enantioselective liquid-liquid extraction in centrifugal contactor separators can be hopeful for separations of various enantiomers at a large-scale.

KEY WORDS: enantioselective liquid-liquid extraction; multistage equilibrium model; symmetrical separation; simulation and optimization; 2-phenylpropionic acid; hydroxypropyl-β-cyclodextrin

There is a growing demand for enantiopure compounds in the pharmaceutical and chemical industry because different enantiomers often show a large difference in pharmacological activity and toxicity in living organisms.[1,2] (R)-thalidomide, for example, has the desired sedative effects, while (S)-thalidomide causes severe birth defects and deformities.[3,4] Therefore, it is very important and necessary to develop technologies for obtaining optically pure products. Recently, a variety of methods have become available for separating optically active compounds. The most used technology on a commercial scale is the crystallization technique,[5] but this method is not always applicable and the search for an appropriate resolving agent is rather time-consuming. Many other impressive technologies such as liquid membrane,[6] chromatographic techniques,[7,8] kinetic resolution, and capillary electrophoresis,[9–11] and so on, are being developed rapidly and provide very promising approaches for enantiomeric separation. However, these technologies have either low versatility or high cost, and they are difficult to achieve for industrialization. Compared with the technologies mentioned above, enantioselective liquid–liquid extraction (ELLE) exhibits several advantages, including relatively mature theoretical guidance, lower cost in energy consumption, easier to scale up to commercial scale, and has a wide range of application.[12]

ELLE combines the concepts of solvent extraction and chiral recognition in a single technology, which is considered a promising technology for chiral separation. Although more

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than half a century has elapsed since the first report of ELLE and many researchers have attempted to obtain enantiopure compounds by ELLE, the number of literature studies has only significantly increased in the past two decades.[13–23] Studies cited in the literature focus mainly on the single-stage extraction equilibrium and the synthesis of new chiral selectors. Only a few studies report the fundamental insights about the reaction engineering mechanism by combining experimental investigation and mathematical modeling to predict the extraction performance and optimize the separation process.[21–23] Recently, studies providing the approaches for application of ELLE in multistage processes have drawn more and more attention of researchers.

The centrifugal contactor separator (CCS) is an example of compact continuous flow equipment that possesses the beneficial properties of large centrifugal forces and excellent mass transfer. In the CCS device, reaction and separation are combined in a single device, and the two immiscible liquids are intensely mixed and subsequently separated by centrifugal force. Because of these advantages, CCS is very suitable for continuous separation of enantiomers by ELLE. CCS has been successfully used for the synthesis and refining of biodiesel,[24] for separation of ionic liquid dispersions,[25] for oil-water separation,[26] and for several other extraction processes.[27,28] Although the separation of enantiomers by multistage ELLE in CCS has attracted increasing attention in recent years, studies on experimental and modeling of the multistage ELLE have been rarely reported.[22,29–32]

2-Phenylpropionic acid (Figure 1) is an important 2-arylpropionic acid class which is widely used to synthesize chiral drugs such as loxoprfen. It has been revealed that 2-arylpropionic acid enantiomers have their main pharmacological activity on the (S)-enantiomer, while the (R)-enantiomer is inactive. Several studies attempting to separate 2-phenylpropionic acid (2-PPA) enantiomers have been reported, which are regularly achieved by using capillary electrochromatography,[33] synthesis,[34] high-performance liquid chromatography (HPLC) techniques, and high-speed counter-current chromatography.[35] A limitation of these technologies is their difficulty in large-scale production. Thus, it is important to explore a high-efficiency technology for large-scale production of a single 2-PPA enantiomer.

In this work, we report the process optimization of continuous separation of 2-PPA enantiomers using ELLE in CCS devices. HP-β-CD (Figure 2) was used as the chiral selector. It has been regarded as a very promising extractant and has been widely investigated because of the unique physical properties and nontoxic side effects. A multistage counter-current ELLE equilibrium model for separation of 2-PPA enantiomers was built. Important process parameters such as the extract phase/washing phase ratio (W/O), the concentration of chiral selector, the pH value of aqueous phase, and the number of stages were investigated. Additionally, the model was further used to predict and optimize the process.

MATERIALS AND METHODS

Materials

Racemic 2-phenylpropionic acid was purchased from J&K (Beijing, China), with a purity ≥98%. The hydrophilic extractant,

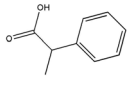

Fig. 1. Chemical structure of 2-phenylpropionic acid.

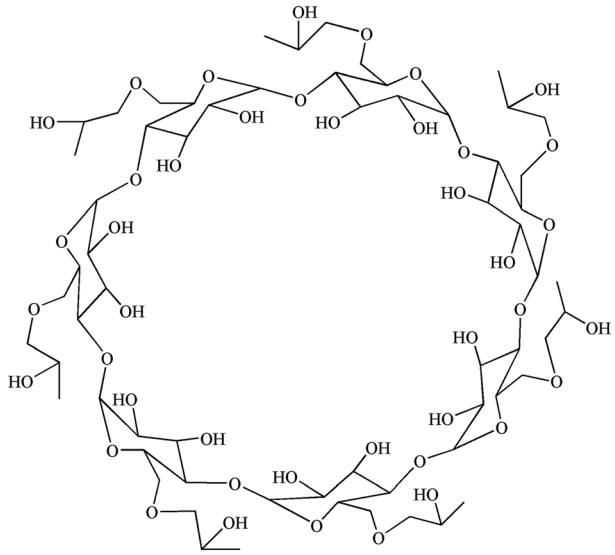

Fig. 2. Chemical structure of HP-β-CD.

hydroxypropyl-β-cyclodextrin (HP-β-CD), was bought from Zhiyuan Biotechnology (Binzhou, China), and 1,2-dichloroethane with a purity of 99.0 % was obtained from Kermel (Tianjin, China). Sodium dihydrogen phosphate and phosphoric acid were supplied by Huihong Reagent (Hunan, China). Solvent for chromatography was of HPLC grade. All other chemicals used in this work were of analytical reagent grade.

Experiment Setup

Multistage extraction experiments were performed in a cascade of centrifugal contactor separators, which were connected in line by tubes. The CINC V02 separators were applied, in which the rotor diameter was 5.1 cm and the height of the annulus was 7 cm. The CCSs were settled in a thermostatic water bath containing circulated cooling water to maintain a stable temperature of 278 K. The rotational speed of the CCSs was set at a stirring rate of 3000 rpm. Both aqueous phase and organic phase were transferred to the CCSs by constant flow pumps. Flow rate of the extract phase (water phase, W) was set at 6 mL min^{-1} unless otherwise specified. The effluent was collected in glass containers.

Multistage Extraction Experiments

The chiral extraction system was established by adding HP-β-CD in aqueous phase as chiral selector, which preferentially recognizes the (R)-enantiomer. The extract phase (aqueous phase) was prepared by dissolving HP-β-CD in 0.1 mol L^{-1} NaH_2PO_4/ H_3PO_4 buffer solution, racemic 2-PPA was dissolved in 1,2-dichloroethane to obtain the feeding phase, and the raffinate phase (organic phase) was pure 1,2-dichloroethane. Multistage extraction experiments were performed by starting the engines of all CCSs, opening the tap of the cooling water flow, and starting the heavy phase (organic phase) pump. After starting the heavy pump, the CCSs were filled up in the order from Stage 1 to Stage N. After the organic phase ran from heavy phase outlet (Stage N), the pump of the light phase (aqueous phase) was started. Only when the aqueous phase ran from light phase outlet could the feed pump be started. As soon as the feed pump started running, samples from the aqueous phase outlet were taken every 25 min. The concentrations of (S)-2-PPA and (R)-2-PPA in the aqueous phase outlet were analyzed by HPLC, while that in organic phase outlet were calculated by the law of the conservation of mass. When the concentrations of (S)-2-PPA and (R)-2-PPA in the aqueous phase outlet were no longer changed, the experiment was stopped and each CCS acted as a single equilibrium stage at that moment.

Analytical Method

The quantification of 2-PPA enantiomers in the aqueous outlet was determined by HPLC (Waters e2695 Separation Module), and a UV detector

(Waters 2998 Photodiode Array Detector) with a UV wavelength of 254 nm. The column was Inertsil ODS-3 C18, 5 μm particle size of the packing material, 250 mm × 4.6 mm I.D. (GL Sciences, Tokyo, Japan). The mobile phase was glacial acetic acid: methanol: 0.025 mol L^{-1} HP-β-CD aqueous buffer solution (pH = 4.0, adjusted with triethylamine) (0.5:15:85, v/v/v).[35,36] The operating conditions were as follows: flow rate, 0.8 mL min^{-1}; column temperature, 45 °C; injection volume, 10 μL. The retention time of (R)-2-PAA was less than that of (S)-2-PPA.

THEORY AND MODEL

Theory of Enantioselective Extraction Mechanism

ELLE is based on the selective recognition of one of the enantiomers by a chiral selector. The mechanism of ELLE by HP-β-CD is schematically shown in Figure 3. In the system for enantioselective extraction of 2-PPA enantiomers with HP-β-CD as selective extractor, HP-β-CD was dissolved in the aqueous phase, which preferentially recognized the (R)-enantiomer rather than the (S)-enantiomer, indicated by a series of experiments. Depending on the solubility of 2-PPA enantiomers in the organic phase and the aqueous phase, the location of complexation reaction will either be in the organic phase, in the aqueous phase, or at the interface. Due to the fact that HP-β-CD is highly hydrophilic and insoluble in the organic phase, the possibility of that the reaction will take place in the organic phase is excluded. Therefore, the complexation reactions will take place either in the aqueous phase or at the interface. The solutes of 2-PPA enantiomers can distribute over the organic and aqueous phases. Thus, the homogeneous aqueous phase reaction mechanism was applied here and is depicted it in Figure 3.

The physical distribution of two enantiomers between the two phases is unselective and equal. It is described by the ratio of the two enantiomer concentrations within the aqueous and organic phase. The physical partition coefficient of molecular (R)-2-PPA and (S)-2-PPA is defined as:

$$P_0 = \frac{[A_R]_{aq,j}}{[A_R]_{org,j}} = \frac{[A_S]_{aq,j}}{[A_S]_{org,j}} \tag{1}$$

where $[A_R]_{aq}$ and $[A_S]_{aq}$ are the concentrations of the free (R)- and (S)-2-PPA in aqueous phase at equilibrium, respectively; $[A_R]_{org}$ and $[A_S]_{org}$ are the concentrations of the free (R)- and (S)-2-PPA in organic phase at equilibrium, respectively. The subscript j indicates the sequence number of the stages.

The physical partition coefficient of ionic (R)-2-PPA and (S)-2-PPA is defined as:

$$P_i = \frac{[A_R^-]_{aq,j}}{[A_R^-]_{org,j}} = \frac{[A_S^-]_{aq,j}}{[A_S^-]_{org,j}} \tag{2}$$

where $[A_R^-]_{aq}$ and $[A_S^-]_{aq}$ are the concentrations of the ionic (R)- and (S)-2-PPA in aqueous phase at equilibrium, respectively; $[A_R^-]_{org}$ and $[A_S^-]_{org}$ are the concentrations of the ionic (R)- and (S)-2-PPA in organic phase at equilibrium, respectively.

The selective recognition takes place in the aqueous phase depending on the complexation reaction. The complexation constant K_R and K_S can be calculated according to Eqs. 3 and 4:

$$K_R = \frac{[A_R - HP - \beta - CD]_{aq}}{[A_R]_{aq}[HP - \beta - CD]_{aq}} \tag{3}$$

$$K_S = \frac{[A_S - HP - \beta - CD]_{aq}}{[A_S]_{aq}[HP - \beta - CD]_{aq}} \tag{4}$$

where $[A_R\text{-HP-}\beta\text{-CD}]_{aq}$ and $[A_S\text{-HP-}\beta\text{-CD}]_{aq}$ represent the concentrations of the complexes between (R)-2-PPA and HP-β-CD and between (S)-2-PPA and HP-β-CD at equilibrium, respectively.

The dissociation constant of (R)-2-PPA and (S)-2-PPA in the aqueous phase can be calculated according to Eq. 5:

$$K_a = \frac{[H^+]_{aq,j}[A_R^-]_{aq,j}}{[A_R]_{aq,j}} = \frac{[H^+]_{aq,j}[A_S^-]_{aq,j}}{[A_S]_{aq,j}} \tag{5}$$

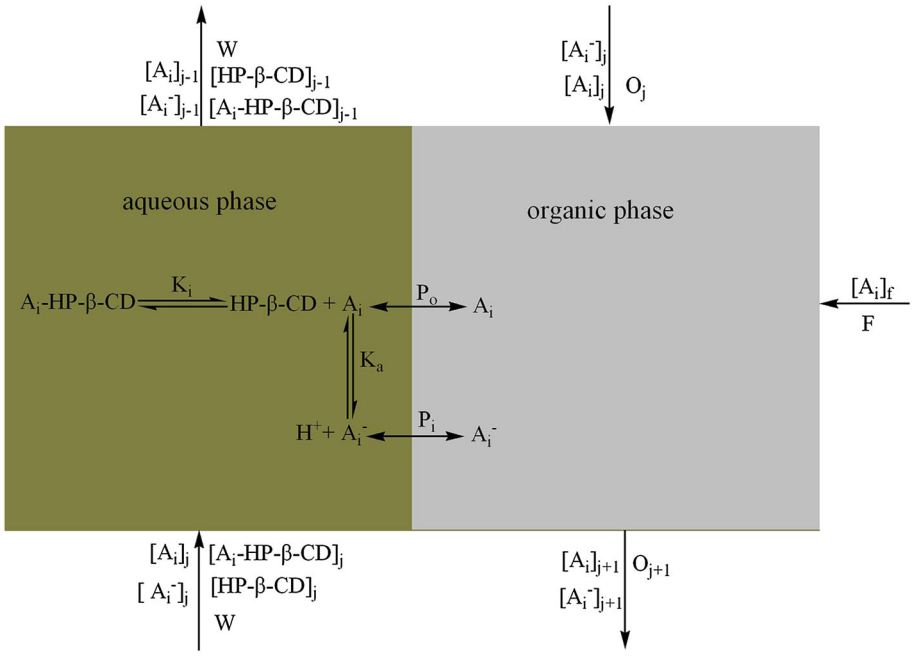

Fig. 3. Diagram of the mechanism of reactive extraction of 2-PPA enantiomers by HP-β-CD (i = R or S).

Multistage Countercurrent Equilibrium ELLE Model

A flow diagram of a cascade for the separation of racemic 2-PPA enantiomers into a single enantiomer, (R)-2-PPA and (S)-2-PPA, is depicted in Figure 4. The racemic 2-PPA in 1,2-dichloroethane is fed to the CCSs at the feed stage, indicated with f. The 1,2-dichloroethane (organic phase) was pumped into the CCSs at the first stage. Dissolving HP-β-CD in 0.1 mol L^{-1} NaH_2PO_4/H_3PO_4 buffer solution, the aqueous phase is pumped into the CCSs at the last stage, indicated with N. The stages f to N form the stripping section, where (R)-2-PPA (A_R) is preferentially extracted to the extract phase (aqueous phase). The co-extracted (S)-2-PPA (A_S) is washed out of the extract stream in stages 1 to f-1 (wash section). After multistage extraction, the A_R is primarily left in the aqueous phase and, consequently the A_S is predominantly enriched in the organic phase.

The component balances for A_R or A_S in wash section (j = 1…f-1), can be written as follows (the subscript, i, represents R or S):

$$\begin{aligned} &O\left([A_i]_{org,j-1} + \left[A_i^-\right]_{org,j-1}\right) + W([A_i]_{aq,j+1} + \left[A_i^-\right]_{aq,j+1} \\ &\quad +[A_i - HP\text{-}\beta\text{-}CD]_{aq,j+1}) = O\left([A_i]_{org,j} + \left[A_i^-\right]_{org,j}\right) \\ &\quad +W\left([A_i]_{aq,j} + \left[A_i^-\right]_{aq,j} + [A_i - HP - \beta - CD]_{aq,j}\right) \end{aligned} \tag{6}$$

For the feed stage, the component balances for A_i is defined as:

$$\begin{aligned} &W\left([A_i]_{aq,f+1} + \left[A_i^-\right]_{aq,f+1} + [A_i - HP - \beta - CD]_{aq,f+1}\right) \\ &\quad +O\left([A_i]_{org,f-1} + \left[A_i^-\right]_{org,f-1}\right) \\ &\quad +F[A_i]_0 = W\left([A_i]_{aq,f} + \left[A_i^-\right]_{aq,f} + [A_i - HP - \beta - CD]_{aq,f}\right) \\ &\quad +(O+F)\left([A_i]_{org,f} + \left[A_i^-\right]_{org,f}\right) \end{aligned} \tag{7}$$

where $[A_i]_0$ is the initial concentration of (R)- and (S)-2-PPA in the feed stream.

The component balances for A_i in the stripping section (j = f+1, f+2…N) can be written as follows:

$$\begin{aligned} &(O+F)\left([A_i]_{org,j-1} + \left[A_i^-\right]_{org,j-1}\right) + W([A_i]_{aq,j+1} + \left[A_i^-\right]_{aq,j+1} \\ &\quad +[A_i - HP - \beta - CD]_{aq,j+1}) = (O+F)\left([A_i]_{org,j} + \left[A_i^-\right]_{org,j}\right) \\ &\quad +W\left([A_i]_{aq,j} + \left[A_i^-\right]_{aq,j} + [A_i - HP - \beta - CD]_{aq,j}\right) \end{aligned} \tag{8}$$

The overall component mass balances for the enantiomers A_i is defined as:

$$\begin{aligned} F[A_i]_0 &= W\left([A_i]_{aq,N} + \left[A_i^-\right]_{aq,N} + [A_i - HP - \beta - CD]_{aq,N}\right) \\ &\quad +(O+F)\left([A_i]_{org,1} + \left[A_i^-\right]_{org,1}\right) \end{aligned} \tag{9}$$

The component mass balance for HP-β-CD in aqueous phase is given by Eq. 10.

$$\begin{aligned} &[HP - \beta - CD]_0 = [HP - \beta - CD]_{aq,j} + [A_R - HP - \beta - CD]_{aq,j} \\ &\quad +[A_S - HP - \beta - CD]_{aq,j} = [HP - \beta - CD]_{aq,j+1} \\ &\quad +[A_R - HP - \beta - CD]_{aq,j+1} + [A_S - HP - \beta - CD]_{aq,j+1} \end{aligned} \tag{10}$$

where $[HP\text{-}\beta\text{-}CD]_0$ is the initial concentration of HP-β-CD in the aqueous phase.

The enantiomeric excess (*ee*) is used as a measure of the optical purity of the raffinate and the extract. The *ee* of 2-PPA in the extract and raffinate can be calculated by:

$$ee_{R,extract} = \frac{[A_R]_{aq}^{all\ forms} - [A_S]_{aq}^{all\ forms}}{[A_R]_{aq}^{all\ forms} + [A_S]_{aq}^{all\ forms}} \tag{11}$$

$$ee_{S,raffinate} = \frac{[A_S]_{org}^{all\ forms} - [A_R]_{org}^{all\ forms}}{[A_S]_{org}^{all\ forms} + [A_R]_{org}^{all\ forms}} \tag{12}$$

Besides the *ee*, another important parameter is the yield, Y. The yield of (R)-2-PPA and (S)-2-PPA are, respectively, defined as:

$$Y_{R,extract} = \frac{totalA_R extract[mol]}{totalA_R feed\quad [mol]} \tag{13}$$

$$Y_{S,raffinate} = \frac{totalA_S raffinate[mol]}{tatalA_S feed\quad [mol]} \tag{14}$$

The multistage counter-current ELLE equilibrium model was programmed in MatLab (MathWorks, Natick, MA). The influence of several factors, including phase ratio, extractant concentration, the pH value of aqueous phase, and the number of stages were modeled.

RESULTS AND DISCUSSION

An experimental study of the multistage ELLE of 2-PPA enantiomers in CCSs was performed. The racemic feed was pumped to the cascade at the middle stage. The CCS cascade was run successfully for 300 min at a temperature of 278 K.

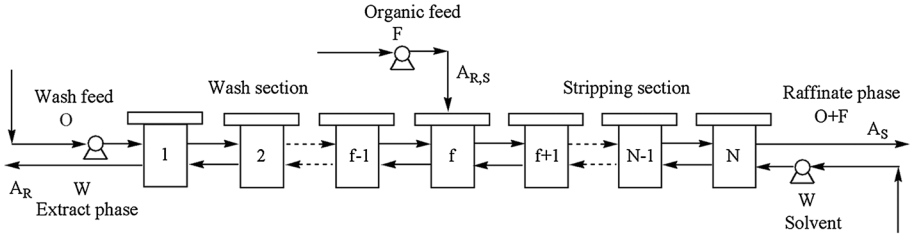

Fig. 4. Flow diagram of the multistage centrifugal counter-current extraction of 2-PPA enantiomers.

The concentrations of (R)- and (S)-2-PPA enantiomers in the aqueous outlet were detected every 25 min. For exploration of the equilibrium time, the development of the concentrations of the enantiomers in a particular experiment versus runtime is depicted in Figure 5. As shown in Figure 5, the concentrations of enantiomers in aqueous outlet increase gradually in the first 125 min, and then fluctuated within a narrow range. Furthermore, the concentration of the (R)-enantiomer remains higher than the (S)-enantiomer. The results indicate that the time needed for the aqueous concentration to achieve a steady state is about 125 min. Thus, it can be suggested that the time needed for chemical and physical equilibrium is relatively short.

In order to verify the multistage ELLE equilibrium model and better understand the relationship between process parameters and extraction performance, the influence of several parameters on the multistage separation process, including phase ratio (W/O), extractant concentration, pH value of aqueous phase, and the number of stages were investigated by experiment and modeling.

Influence of W/O Ratio

In the multistage extraction system, the W/O ratio has a significant influence on purity and yield. In order to investigate the influence of the W/O ratio on extraction performance, a series of extraction experiments were performed with a W/O ratio in the range from 0.2 to 1.2 at W/F = 6 (F represents flow of feeding phase), pH = 2.5, [HP-β-CD] = 0.1 mol L^{-1}, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, and N = 10 (N represents number of stages). A comparison of the experimental data with the model predictions of *ee* and yield is shown in Figure 6. It is observed from Figure 6 that the experimental data of *ee* and yield are in good agreement with the model predictions. The mean relative deviations between model and experiment were 7.69% for *ee* and 3.43% for Y. As shown in Figure 6a, the *ee* decreases gradually in the extract phase (aqueous phase) with the increase of W/O ratio, while an opposite tendency is observed for the *ee* in the raffinate phase (organic phase). From Figure 6b, with the increase of W/O ratio, the yield of (R)-enantiomer in the extract phase increases while the yield of (S)-enantiomer in the raffinate phase decreases. The possible reasons for this may be that with the increase of W/O, more complexes form between

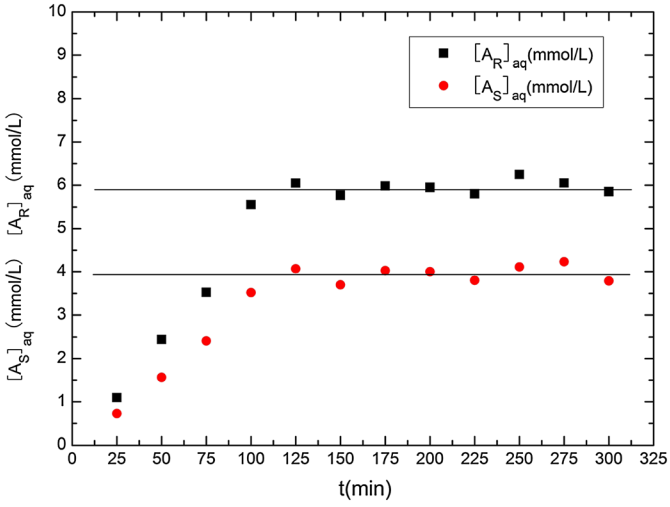

Fig. 5. Concentration of 2-PPA enantiomers in aqueous outlet.

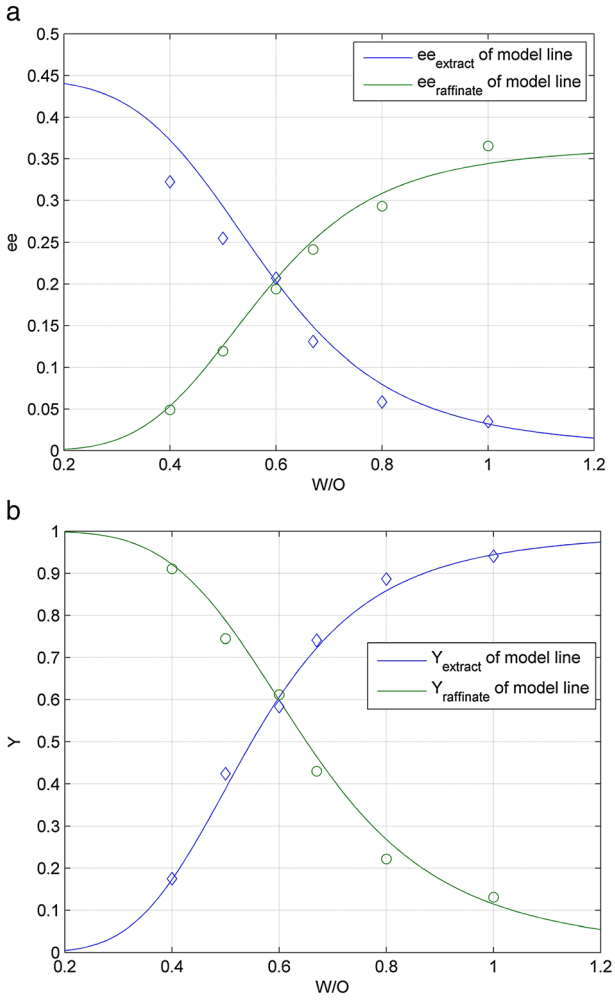

Fig. 6. Influence of W/O ratio on *ee* and yield for separation of 2-PPA enantiomers. (**a**) Influence on *ee*, (**b**) Influence on yield. Condition: W/F = 6, pH = 8.5, [HP-β-CD] = 0.1 mol L^{-1}, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, N = 10, feed in the middle stage.

HP-β-CD and enantiomers in the extract phase, and the co-extraction of the nonpreferential enantiomer is enhanced, so the *ee* in the extract phase and the yield of (S)-enantiomer in the raffinate phase are decreased. While in the raffinate phase, with the increase of W/O, fewer enantiomers are left in the raffinate, and the extracted (R)-enantiomer is always more than the (S)-enantiomer, so the yield of (R)-enantiomer in the extract phase and the *ee* in the raffinate phase are increased. Furthermore, it is found that the *ee* and yield in the extract phase are equal to those in the raffinate phase at W/O = 0.6. The crosspoint with ee_{eq} (equal enantiomeric excess) and Y_{eq} (equal yield) is the operating point for symmetric separation.[29]

Influence of Extractant Concentration

The extractant concentration is an important parameter in the multistage extraction process, and it is directly related to the economic efficiency of enterprises. Therefore, it is vital to work at a suitable extractant concentration in an industrial production process. The influence of HP-β-CD concentration on the purity and yield in both streams was investigated by varying the concentration from 0 to 0.16 mol L^{-1} at W/O = 0.6, W/F = 6, pH = 2.5, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, and

N = 10. A comparison of the experimental data with the model predictions of purity and yield is shown in Figure 7. The mean relative deviations between model and experiment were 8.98% for *ee* and 10.38% for Y. It is clear from Figure 7a that the *ee* in the extract phase increases rapidly when the HP-β-CD concentration increases from 0 to 0.05 mol L^{-1}, and then decreases with a further increase in HP-β-CD concentration. The *ee* in the raffinate phase maintains a rising trend with the increase of the HP-β-CD concentration. This phenomenon can be explained as follows: At first, the extractant concentration in the aqueous phase is very small and the solubility of 2-PPA in the aqueous phase is poor, which results in that most of the enantiomers are in the raffinate phase (Figure 7b), thus the *ee* values in the extract and raffinate phase are very small. With the concentration of HP-β-CD increasing to 0.05 mol L^{-1}, more and more 2-PPA enantiomers are extracted to the aqueous phase (Figure 7b), and the *ee* in the extract phase increases rapidly. This is due to the increase of enantioselectivity with the increase of HP-β-CD concentration. With the further increase of HP-β-CD concentration, the extractant is present in excess with respect to the desired enantiomer and a considerable amount of undesired enantiomers are also extracted to the extract phase, which leads to the decrease of *ee* in the extract phase and yield in raffinate.

Influence of pH

The pH value is one of the most important factors for consideration in the separation of enantiomers, since it has a significant influence on the existing forms of 2-PPA enantiomers. The *ee* and yield of multistage ELLE of 2-PPA enantiomers were performed with the pH value ranging from 2 to 6.5. A comparison between the experimental results and the model predictions of the *ee* and yield in both streams is shown in Figure 8. The mean relative deviations between model and experiment were 7.79% for *ee* and 4.63% for Y.

It can be seen from Figure 8a that the *ee* in the extract phase fluctuates within a narrow range at pH value lower than 3.5, and then decreases with a further increase in pH value. A similar tendency is observed for the *ee* in the raffinate phase. It can also be seen from Figure 8b that the yields in both streams fluctuate within a narrow range with the pH value increasing from 2 to 3.5. With the further increase of the pH value, the yield in the extract phase increases gradually, while an opposite tendency is observed for the yield in the raffinate phase.

The possible reasons for this may be that HP-β-CD mainly has a chiral recognition ability and affinity for molecular 2-PPA, but not for ionic 2-PPA. When the pH value is lower

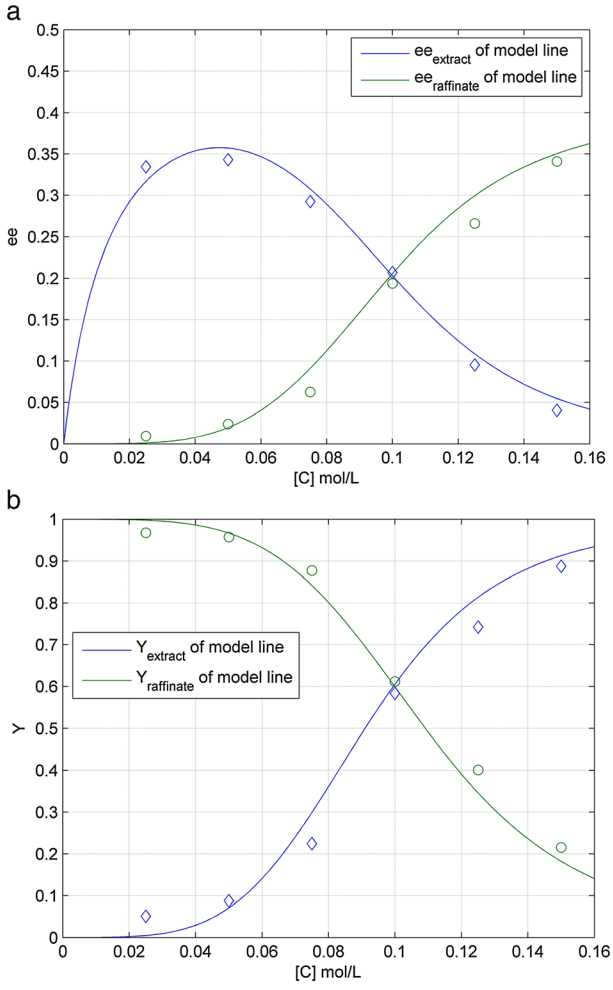

Fig. 7. Influence of HP-β-CD concentration on *ee* and yield for separation of 2-PPA enantiomers. (**a**) Influence on *ee*. (**b**) Influence on yield. Condition: W/O = 0.6, W/F = 6, pH = 2.5, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, N = 10, feed in the middle stage.

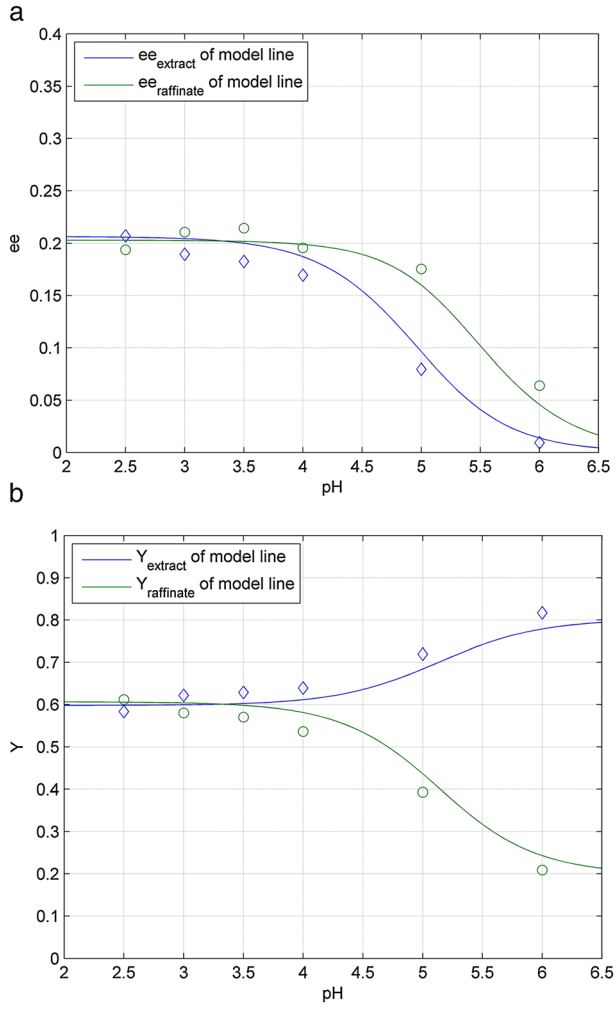

Fig. 8. Influence of pH value on *ee* and yield for separation of 2-PPA enantiomers. (**a**) Influence on *ee*. (**b**) Influence on yield. Conditions: W/O = 0.6, W/F = 6, [HP-β-CD] = 0.1 mol L^{-1}, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, N = 10, feed in the middle stage.

than 3.5, the rising of the pH value has little influence on the existence state of 2-PPA and the amount of molecular species remain nearly unchanged, which leads to the *ee* and the yield in both streams to fluctuate within a narrow range at pH values lower than 3.5. With the increase of pH value from 3.5 to 6.5, more and more molecular 2-PPA turned into ionic 2-PPA and entered the extract phase, and the amount of complexes formed by extractant and enantiomers decreases. As a result, the *ee* in both streams and the yield in the raffinate phase decrease, while the yield in the extract phase increase. Thus, it should be kept at a low pH value to carry out the extraction process.

Influence of Number of Stages

In the CCS cascade, the number of stages has a great effect on *ee* and yield. High enantiomeric purity and yield are demanded for the production of a chiral drug. The influence of the number of stages on *ee* and yield was modeled at 10 and 20 stages. Experiments were performed by changing the W/O ratio of 0.4, 0.6, and 0.8 at 10 and 20 stages, respectively. Experimental results and model predictions are shown in Figure 9. It can be observed from Figure 9 that the ee_{eq} and Y_{eq} are obviously increased after the number of stages changed from 10 stages to 20 stages. According to the experimental results, the ee_{eq} can reach 37% and the Y_{eq} can reach 69% at a W/O ratio of 0.6 and N = 20, which are basically in conformity with the simulation. The mean relative deviations between model and experiment were 8.19% for *ee* and 7.55% for Y. Therefore, higher ee_{eq} and Y_{eq} can be obtained with more extraction stages.

Modeling and Optimization of the Mutilstage Extraction System

The results of the above studies show that CCS device is suitable for multistage counter-current ELLE. Comparison of the model predictions with the experimental results indicates that the established multistage equilibrium model is a good way of predicting the extract efficiency for separation of 2-PPA enantiomers in CCSs over a range of experimental conditions. Thus, we used the model to explore the influence of various operating parameters on extraction performance in the multistage extraction system to predict and optimize the separation process.

Location of Feed Stage

The location of the feed stage is an important parameter in a multistage extraction system. The change of the location of feed stage could cause a change of the number of stages in the stripping section and wash section, which could generate a different extraction efficiency of the symmetric separation. The ee_{eq} and Y_{eq} in extract phase and raffinate phase with location of the feed at different stages is shown in Figure 10. It can be seen from Figure 10 that both the ee_{eq} and the Y_{eq} reach a maximum when the feed stage is located exactly at the middle stage. Therefore, higher ee_{eq} and Y_{eq} can be obtained by using an equal amount of stages in the stripping section and wash section.

Extractant Concentration and pH Value

The influence of HP-β-CD concentration and pH value on ee_{eq} for separation of 2-PPA enantiomers has been modeled. Figures 11 and 12 show the ee_{eq} for separation of 2-PPA enantiomers as a function of HP-β-CD concentration and pH value.

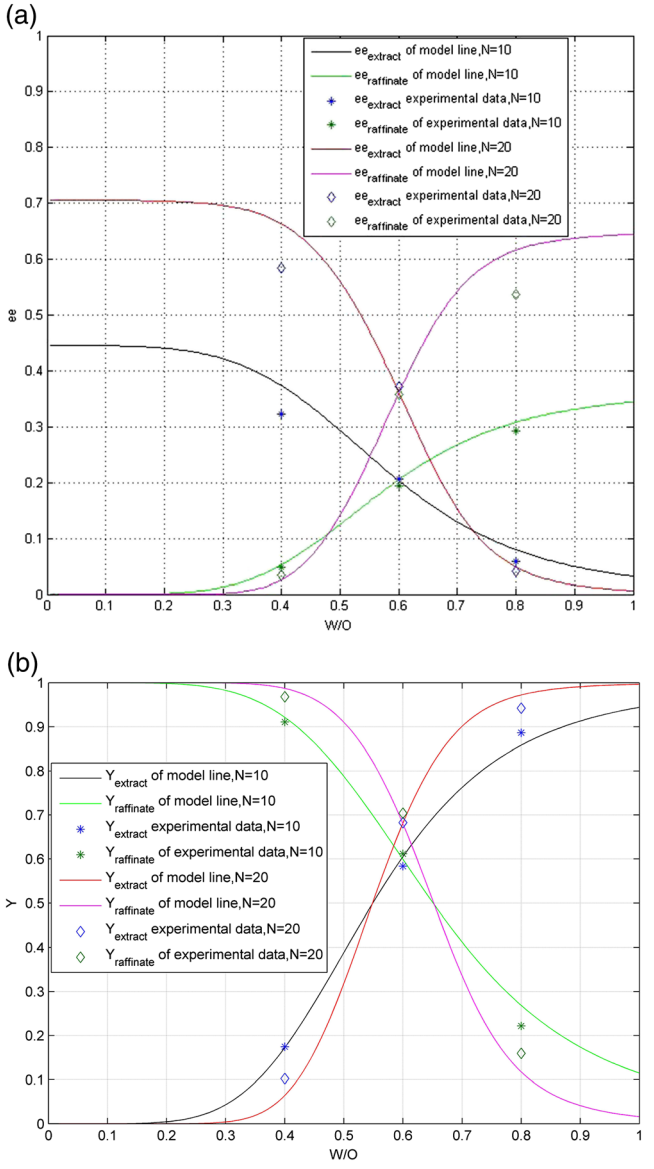

Fig. 9. Influence of number of stages on *ee* and yield for separation of 2-PPA enantiomers. (**a**) Influence on *ee*. (**b**) Influence on yield. Condition: W/F = 6, pH = 2.5,[HP-β-CD] = 0.1 mol L^{-1}, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, feed in the middle stage.

It can be observed from Figure 11 that the ee_{eq} increases rapidly with HP-β-CD concentration increasing from 0.02 mol L^{-1} to 0.1 mol L^{-1}, and then it increases slightly. When the pH value is less than 3.0 and the HP-β-CD concentration is greater than 0.1 mol L^{-1}, a plateau appears. From Figure 12, it is obvious that the ee_{eq} at different HP-β-CD concentrations follows a similar tendency with the increase of the pH value. The ee_{eq} rises rapidly with the HP-β-CD concentration increasing from 0.025 mol L^{-1} to 0.10 mol L^{-1}, and then it increases slowly from 0.10 mol L^{-1} to 0.15 mol L^{-1}. Within the HP-β-CD concentration range, the ee_{eq} keeps nearly invariable at a pH value less than 3.0. When the pH value is greater than 3.0, the ee_{eq} gradually decreases. Therefore, a pH value between 2.0 and 3.0 is suitable for separation of 2-PPA enantiomers. In this work, the pH value of 2.5 is the optimal pH value during our actual operation. In view of the economic efficiency and the solution viscosity, the HP-β-CD

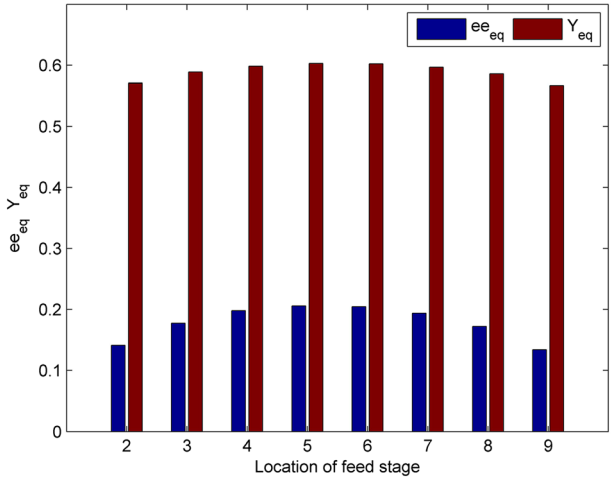

Fig. 10. Influence of the location of feed stage on ee_{eq} and Y_{eq} for Separation of 2-PPA enantiomers. Condition: W/F = 6, pH = 2.5, [HP-β-CD] = 0.1 mol L^{-1}, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, N = 10.

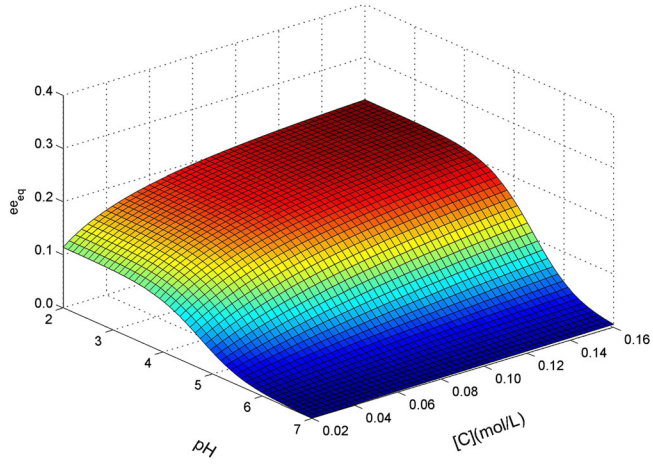

Fig. 11. Influence of pH and HP-β-CD concentration on ee_{eq} for separation of 2-PPA enantiomers. Condition: W/O = (0.01, 5), W/F = 6.0, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, feed in the middle stage, N = 10.

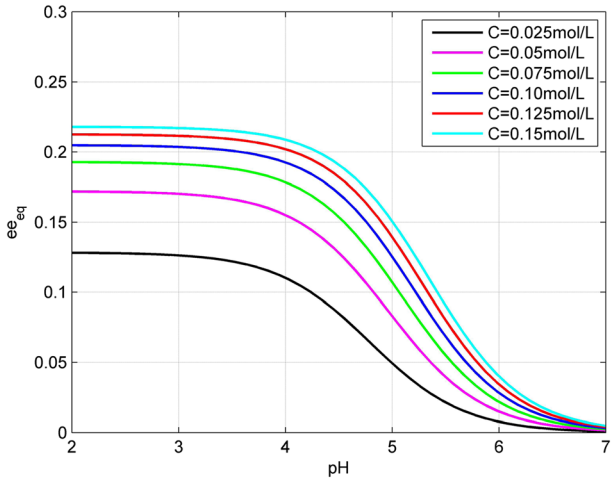

Fig. 12. Influence of pH on ee_{eq} for separation of 2-PPA enantiomers at different HP-β-CD concentration. Condition: W/O = (0.01, 5), W/F = 6.0, pH = (2, 7), $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, feed in the middle stage, N = 10.

concentration is recommended to be set at about 0.1 mol L^{-1}, where the separation efficiency is near its optimum.

Number of Stages and Flow Ratios

According to the experiments above, the phase ratio of W/O and W/F have great influence on the extraction performance. Figures 13 and 14 show the ee_{eq} as a function of the number of stages at different flow ratios. It can be seen from Figure 13 that there is a significant effect of the number of stages and flow ratios on ee_{eq}. The ee_{eq} increases with the increase of W/F at first, and then remains nearly unchanged. However, the ee_{eq} decreases with the increase of the W/O ratio. When the W/O ratio is lower than 0.58, the ee_{eq} increases slowly. It can also be seen that the ee_{eq} rises rapidly when the number of stages is less than 60, and then the change is slight with a further increase of the number of stages. In order to further optimize the W/F ratio, the relationship between the number of stages and ee_{eq} at a different W/F ratio has been modeled. As shown in Figure 14, the ee_{eq} at a different W/F ratio follows a similar tendency with the increase of number

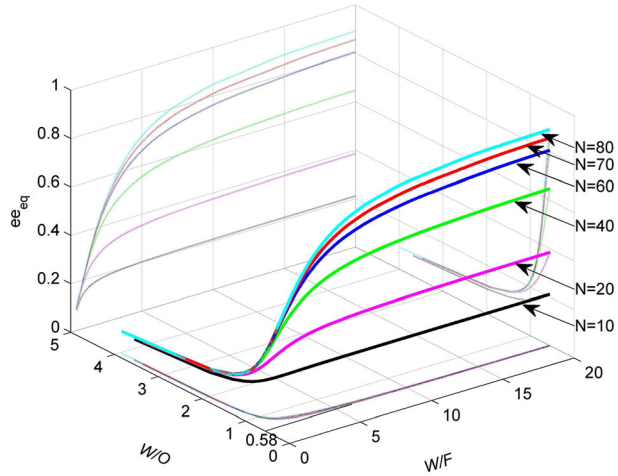

Fig. 13. Influence of W/O ratio and W/F ratio on ee_{eq} for separation of 2-PPA enantiomers at different number of stages. Condition: W/O = (0, 5), W/F = (0, 20), [HP-β-CD] = 0.1 mol L^{-1}, pH = 2.5, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, feed in middle stage.

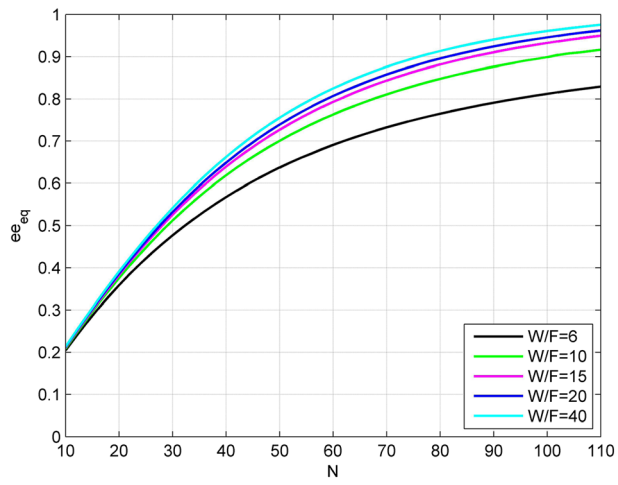

Fig. 14. Influence of number of stages on ee_{eq} for separation of 2-PPA enantiomers at different W/F ratio. Condition: pH = 2.5, [HP-β-CD] = 0.1 mol L^{-1}, $[A_{R,S}]$ = 0.02 mol L^{-1}, T = 278 K, feed in the middle stage.

TABLE 1. Optimized settings for symmetrical separations with $[A_{R,S}] = 0.02\,mol\,L^{-1}$, pH = 2.5, T = 278 K

Variable	$ee_{extract}$ and $ee_{raffinate}$ > 95% settings	$ee_{extract}$ and $ee_{raffinate}$ >97% setings
N	98	106
f	50	54
[HP-β-CD] ($mol\,L^{-1}$,)	0.10	0.10
W/F	40	40
W/O	0.54	0.55

of stages. The ee_{eq} increases greatly when the W/F ratio is less than 10, and then the ee_{eq} increases slowly with a further increase of the W/F ratio. Therefore, a higher W/F ratio, a lower W/F ratio, and a greater number of stages are required to achieve higher ee_{eq}.

For a symmetrical separation, the minimum number of stages needed for ee_{eq} >95% and ee_{eq} >97% was calculated by modeling and optimization at a W/F ratio of 40, pH = 2.5, $[A_{R,S}] = 0.02\,mol\,L^{-1}$, [HP-β-CD] = $0.10\,mol\,L^{-1}$, T = 278 K. The optimized settings for the two cases are shown in Table 1. When the ee_{eq} is higher than 95%, a cascade of 98 stages is needed, whereas for ee_{eq} higher than 97% a minimum of 106 stages is required. Since the enantioselectivity for 2-PPA enantiomers with HP-β-CD as chiral selector is moderate, a very large number of stages are required to obtain higher ee_{eq}. With the optimal process parameters, the ee_{eq} can be up to 99% with the number of stages of 130. Considering the economical exploitation of the principle, the symmetrical separation of 2-PPA can be replaced by asymmetrical separation, in which the flow ratios are adjusted to obtain the desired enantiomer with high purity while the undesired enantiomer with low purity. The asymmetrical separation can make the number of stages considerably reduced even though the enantioselectivity is moderate.

CONCLUSION

Multistage enantioselective liquid–liquid extraction in a centrifugal contactor was performed for the separation of 2-PPA enantiomers with HP-β-CD as chiral extractant. The experimental results show that the performance of extraction is significantly influenced by the process parameters such as the extract phase/washing phase ratio, extractant concentration, the pH value of the aqueous phase, and the number of stages. A multistage equilibrium model of ELLE was built on the basis of a single-stage model for chiral extraction of the 2-PPA enantiomers and the law of mass conservation. The model has been verified experimentally and provides a good means for fast optimization of the operational conditions.

The performance of the multistage separation process was evaluated by *ee* and yield. Higher ee_{eq} can be achieved at a higher W/F ratio, lower W/O ratio, and greater number of stages. The best process conditions were obtained by modeling and optimization at a W/O ratio of 0.6, pH of 2.5, and HP-β-CD concentration of $0.1\,mol\,L^{-1}$ at 278 K. The optimal operational ee_{eq} of 37% and Y_{eq} of 69% was close to the model predictions. By modeling and optimization, the minimum number of stages for full separation was calculated as 98 and 106 for ee_{eq} > 95% and ee_{eq} > 97% at both stream exits, respectively.

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