A novel continuous re-extraction procedure of penicillin G by a micro-extractor based on ceramic membrane

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ABSTRACT

A ceramic membrane micro-extractor (CME), employed for continuous re-extraction of penicillin G (PEN G), was studied systematically. The droplet size was investigated in the re-extraction process. Re-extraction efficiency (RE) and degradation rate of PEN G were extensively examined by superficial Reynolds number (Re s), phase ratio (R), initial PEN G concentration and membrane pore size. To further understand and quantitatively analyze the re-extraction behavior, resistance-in-series (RIS) model was developed to predict the re-extraction efficiency at steady-state conditions. First of all, a three-parameter correlation was defined for quantitative description of droplet size. The main factors affecting the re-extraction efficiency of PEN G were superficial Reynolds number and phase ratio. The re-extraction efficiency of PEN G reached 99% or above at Re s > 934 and R > 0.08. Meanwhile, the degradation rate of PEN G (D) decreased to 0.5% when Re s was 934. Compared with the re-extraction performance of the batch extractor, less residence time was needed and the degradation rate decreased 50%. The theoretical re-extraction efficiency (RE T ) was in good agreement with the experimental data.

1. Introduction

Penicillin G (PEN G), belongs to the β-lactam class of antibiotics, is the first antibiotic for curing human bacterial disease, which can inhibit bacterial cell wall synthesis [1–2]. It is widely applied in clinical treatment because of its high anti-bactericidal activity, broad spectrum, low toxicity, and excellent distribution. In addition, PEN G is the raw material of the semi-synthetic penicillins [3]. Therefore, the commercial demand of PEN G increased drastically in the past two decades.

Conventional process of PEN G usually involves five distinct steps: filtration, solvent extraction, re-extraction, crystallization, and drying. The re-extraction process is one of the most important steps. The process is that undissociated PEN G, which is extracted from the fermentation broth by physical extraction with n-butyl acetate, return aqueous phase to react with carbonate anions. Due to the weakness of β-lactam ring, PEN G is unstable, and decomposes irreversibly at alkaline conditions [4], and the main degradation product of PEN G was penicilloic acid [2,5]. In addition, it is reported that these degradation products are related to 3–5% of patients of penicillin allergic reactions [5,6]. Some processes are developed to increase mass-transfer rate and reduce side products. First of all, reactive extraction of PEN G was applied at pH 5.0, but the solubility of the extractant is too high to be utilized in industry [6–8]. For this reason, emulsion liquid membrane (ELM) is adopted and provided large interfacial area. Meanwhile, one step recovery of PEN G is carried out efficiently by eliminating equilibrium limitation, whereas de-emulsification step of re-extraction is difficult to be operated [9–10]. In addition, some extractors are used for the process such as centrifugal extractors [11] and Karr column [12–14]. Nevertheless, centrifugal extractor and Karr column are expensive and difficult to maintain. Although hollow fiber membrane contactor has many advantages such as continuous operation free dispersion, small equipment volume, which is used for the extraction and re-extraction of PEN G, the resistance of membrane film results in a slower mass-transfer rate in the free dispersion process, and membrane materials are easy to be corroded by organic solvent in comparison with other processes [15–16]. As a result, up to now, large stirred tank extractor has been used in the pharmaceutical industry, and the part of PEN G is decomposed in the re-extraction process.

Based on the above analysis, a fundamental factor of PEN G re-extraction is mass-transfer rate. Micro-dispersion droplets have many advantages, such as larger specific interfacial area,
shorter diffusion distance, narrow distribution of residence time and smaller mass-transfer resistance [17]. It is reported that the specific interfacial area can be achieved in the range of 5000–30,000 m² m⁻³ in the micro-extractor, and the mass-transfer rate is much higher in comparison to the conventional device [18]. Some side products can be reduced by enhancing mass-transfer rate [19–21]. Furthermore, the increase in yield is only related to the quantity of micro-device. The other important advantage is easy scale-up because the mean droplet size and size distribution are accurately controlled [22–23]. Nowadays, the micro-devices are mainly manufactured by costly modern micro-fabrication techniques. As a common micro-dispersion method, ceramic membrane dispersion has been widely applied a variety of fields such as emulsification [24], solvent distillation [25], fast reaction [26], etc. In addition, it has better chemical stability and favorable mechanical strength in comparison to organic membranes. Therefore, ceramic membrane can be used as a basic element of micro-dispersion.

In this paper, a novel ceramic membrane micro-extractor (CME) was developed for a continuous re-extraction of PEN G, which will replace batch re-extraction step. Meanwhile, it has a cylinder in the center of the ceramic membrane tube for enhancing turbulence and reducing the diffusion distance. The effects of two-phase flow on the droplet size and distribution were investigated. The effects of operating conditions, including phase ratio, superficial Reynolds number, initial concentration of PEN G and membrane pore size on re-extraction efficiency of PEN G, together with the degradation rate, were studied experimentally. In comparison to the batch extractor, the performance of the CME was evaluated. The re-extraction efficiency of PEN G in the micro-extractor was predicted by the combination of resistance-in-series (RIS) model and semi-empirical droplet size model.

2. Experimental

2.1. Chemicals and analytical methods

Materials for this study were of analytical grade and used without further purification. PEN G potassium with a purity of 99.5% was kindly provided by North China Pharmaceutical Co., Ltd., China. n-Butyl acetate with a purity of more than 99.0% (Beijing Chemical Corporation, China) was used as a loading phase for PEN G. Potassium carbonate of 99.0% purity (Beijing Chemical Corporation, China) was used as a re-extraction solution. Sodium citrate of 99.0% purity (Jingqiu Chemical Corporation, China) was used as dilute solution for the dispersed phase. Potassium phosphate monobasic of 99.5% purity (Jinguu Chemical Corporation, China) was used as a buffer solution for mobile phase of HPLC. Methanol of 99.8% purity (Caledon laboratories Ltd., Canada) was used as mobile phase of HPLC.

PEN G and penicilloic acid were analyzed by means of HPLC (HP1100 Agilent Technologies, USA) equipped with a VWD detector. A C18 column (250 mm × 4.6 mm × 5 μm, Agilent Technologies, USA) was used at room temperature. A mixture containing 40% (v/v) methanol and 60% (v/v) of 0.01 mol L⁻¹ phosphate buffer solution was used as mobile phase with a flow rate of 1 mL min⁻¹, operated at a wavelength of 220 nm.

2.2. Membranes and membrane module

Fig. 1 shows the schematic diagram of the module for PEN G re-extraction with a micro-porous ceramic membrane. Ceramic membrane (20 mm length × 9.7 mm outer diameter × 1 mm wall thickness) was kindly provided by Membrane Science and Technology Research Center, Nanjing University of Technology, PRC. The mean membrane pore sizes, \( d_{pore} \) were 0.2 μm, 0.8 μm and 5 μm, respectively. The porosity of the ceramic membrane was 35%. The micro-device based on the membrane dispersion was an external-pressure type micro-kit with an effective membrane area of 290.2 mm². The detail was listed in Table 1.

2.3. Experimental setup and re-extraction procedure of PEN G in the CME

PEN G loading in n-butyl acetate was used as the continuous phase. Potassium carbonate solution was used as the dispersed phase. The direction of mass transfer was from the continuous phase to the dispersed phase. Potassium carbonate concentration in the dispersed phase was high enough for PEN G re-extraction in the continuous phase. Fig. 2 shows the experimental setup of PEN G re-extraction. The continuous phase was pumped into the lumen side of the tube membrane by the peristaltic pump (Lead 2, Baoding Longer Precision Pump Co., Ltd., China). The CME module was initially filled with the continuous phase in the lumen side. The dispersed phase was pressurized from the shell side into the lumen side and formed micro-scale droplets under the action of shear force by the three-piston pump with damper (3JX-60/1, Zhejiang Ailipu Pump Co., Ltd., China). Two phases contacted each other in the lumen side. The effective residence volume was 100 cm³. In addition, fast phase separation was in favor of precisely measuring the re-extraction performance of the CME, so a double-layer fiber bundle was designed and placed at the outlet of the module. The

Table 1 The parameters of CME for re-extraction of PEN G.

<table>
<thead>
<tr>
<th>Ceramic membrane characteristics</th>
<th>Ceramic membrane type</th>
<th>ZrO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceramic membrane internal diameter (mm)</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Ceramic membrane wall thickness (mm)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Effective pore size (μm)</td>
<td>0.2, 0.8, 5</td>
<td></td>
</tr>
<tr>
<td>Ceramic membrane porous support</td>
<td>α-Al₂O₃</td>
<td></td>
</tr>
<tr>
<td>Operating parameters</td>
<td>Maximum trans-membrane differential pressure (MPa)</td>
<td>0.25</td>
</tr>
<tr>
<td>Operating temperature (°C)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Maximum operating pressure (kPa)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Cartridge options</td>
<td>Cartridge length (mm)</td>
<td>28</td>
</tr>
<tr>
<td>Effective membrane length (mm)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Ceramic membrane effective area (mm²)</td>
<td>298.2</td>
<td></td>
</tr>
<tr>
<td>Effective residence volume (cm³)</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
phase separator consisted of the top and bottom layers, which were made of polytetrafluoroethylene and glass fibers, respectively. The mixed phases were quickly separated into two phases. This bundle with high specific surface and special wetting ability improved effectively phase separation. The samples of the bottom phase were quickly poured into the volumetric flask, and then were diluted with 0.068 mol L$^{-1}$ buffer solution of sodium citrate to graduation, which avoided the further degradation of samples [27]. The samples of the top phase were diluted by $n$-butyl acetate. PEN G and penicilloic acid of the top and the bottom phases were analyzed by HPLC. $R$ is a volume ratio of the dispersed phase to the continuous phase. The re-extraction process of PEN G is operated at the high phase ratio. In other words, the continuous phase flow rate is much higher than the dispersed phase flow rate. Therefore, the dispersed phase flux has little influence on the drop size. The mean linear velocity is defined as total fluid velocity of the middle position in the CME. Superficial Reynolds number ($Re_h$) is defined as follows.

$$Re_h = \frac{d_h u_c \rho_c}{\mu_c}$$

where $d_h$ is hydrodynamics diameter (m), $u_c$ is total fluid velocity of the middle position in the CME, $\rho_c$ is continuous phase density (kg m$^{-3}$), $\mu_c$ is continuous phase viscosity (Pa s), $A_c$ is effective flow cross-sectional area ($m^2$) and $L$ is wetted perimeter ($m$).

The re-extraction efficiency of PEN G can be defined as follows:

$$RE = \frac{(c_0 - c_1)}{c_0} \times 100\%$$

where $c_0$ is PEN G concentration of the inlet in the continuous phase (mol L$^{-1}$), $c_1$ is PEN G concentration of the outlet in the continuous phase (mol L$^{-1}$). The degradation rate of PEN G is defined as follow:

$$D = \frac{c_{loss}}{c_d + c_{loss}} \times 100\%$$

where $c_d$ and $c_{loss}$ are PEN G concentration (mol L$^{-1}$) and penicilloic acid concentration of the dispersed phase (mol L$^{-1}$), respectively.

### 2.4. Measurement of droplet size

Droplets were observed through the glass plate using a microscope. The images were captured by Digital camera (A720IS, Canon Co. Ltd., Japan), which was attached to the microscope (B204, Chongqing Optec Instrument Co. Ltd., China) to observe the droplet size. The imaging rate was 2 frames s$^{-1}$. The exposure time was 0.001 s. The rectangular cell size is 3 mm × 8 mm × 80 mm. The mean droplet size of the prepared droplets was determined by counting over 500 droplets at $c_0$ = 0.098 mol L$^{-1}$. The uniformity of droplets is evaluated by transforming into coefficient of variation ($CV$), which is defined as:

$$CV = \frac{S_d}{d_{avg}}$$

$$S_d = \left( \frac{1}{N} \sum_{i=1}^{n} (d_i - d_{avg})^2 \right)^{1/2}$$

$$d_{avg} = \frac{\sum_{i=1}^{n} d_i}{N}$$

where $S_d$ represents the standard deviation of the droplet diameter (m), $d_i$ is the diameter of the ith droplets (m), $d_{avg}$ is the number mean diameter (m), and $N$ is the measured number of droplets.

### 2.5. Procedure for conventional re-extraction

An ordinary re-extraction experiment was carried out by a conventional method in the stirred cell extractor for comparing membrane dispersion re-extraction to the conventional re-extraction. The stirred cell is 40 mm diameter × 100 mm height. A 50 mL portion of the continuous phase loading PEN G was mixed well with 5 mL of K$_2$CO$_3$ solution at different residence time, and the re-extraction of PEN G was also carried out at the different phase ratio. Then, the cell was allowed to stand until the liquid sample separated completely into two phases. Finally, the re-extraction efficiency and degradation rate of PEN G were measured by HPLC.

### 3. Results and discussion

#### 3.1. Droplet size and droplet size distribution of PEN G re-extraction

**3.1.1. Effect of $Re_h$ on droplet size and droplet size distribution**

In the re-extraction process of PEN G, both the mean droplet size and size distribution are very important properties, since they determine mass-transfer rate and the re-extraction efficiency for the intended uses. Furthermore, the interfacial area and the diffusion distance are related to the droplet size and droplet size distribution [28]. Fig. 3a is the photomicrographs showing variations of droplet size as a function of $Re_h$. It was obvious that the droplet size decreased as $Re_h$ increased. Moreover, some large droplets occurred at times. The possible reason is that the low $Re_h$ resulted in low flow resistance force. Occasionally, the droplets growing on neighboring pores...
touch each other. Coalescence takes place easily on the inner membrane surface. Consequently, the formed droplets at low $Re_h$ are much larger than those at high $Re_h$. In addition, the range of the droplet diameter was from 100 $\mu$m to 300 $\mu$m in Fig. 3b.

The variation of droplet size distribution is shown in Fig. 4 when $Re_h$ is 467. Mean droplet size is inversely proportional to the wall shear stress. The droplet size decreased due to increasing $Re_h$. However, the droplet diameter changed little when $Re_h$ was more than 900. The reason is that the droplet size is controlled by flow resistance force ($F_R$). The polydispersity of the droplets can be interpreted as non-uniformity of membrane pore and flow turbulence. It was surprising to note that coefficient of variation keeps at 21% using the same trans-membrane flux when $Re_h$ was more than 900. The results indicated that the collision and coalescence of the droplets reached balance. The fluid turbulence does not affect the polydispersity of the droplets at $Re_h > 900$.

### 3.1.2. Effect of dispersed phase flux on droplet size and droplet size distribution

The dispersed phase flux plays an important role in preparing uniform-sized droplet, and the high dispersed phase flux is preferred in order to reduce the preparation time. However, the high flux results in higher energy consumption due to higher trans-membrane pressure drop. Thus, appropriate dispersed phase flux is crucial for uniform-sized droplets and reducing the preparation time. The dispersed phase flux, $J$ ($dm^3 dm^{-2} h^{-1}$) through the membrane is defined as follows

$$J = \frac{Q_v}{A \varepsilon}$$

where $Q_v$ is the volumetric flow rate of the dispersed phase ($dm^3 h^{-1}$), $A$ is inner surface area of ceramic membrane ($dm^2$) and $\varepsilon$ is the membrane porosity (%). Fig. 5 shows that the droplet size decreased with the increase of the dispersed phase flux. Static pres-
3.2. Effect of Reh on re-extraction efficiency and degradation rate

The local pH value was much higher. Therefore, the degradation products were small and PEN G had the surfactant properties.

3.1.3. Development of a droplet size correlation

From the above experimental results, the droplet formation mainly depends on the continuous phase flow rate and the dispersed phase flux. According to force analysis of the droplet [29–30], the droplet size is related to capillary number \( Ca \) [31], \( Re_h \) and membrane pore size [32].

\[
Ca = \frac{\sigma}{\mu d^3} \quad \text{(9)}
\]

where \( Ca \) is the capillary number and \( \sigma \) is the interfacial tension between the continuous phase and the dispersed phase (N m\(^{-1}\)). Therefore, mean droplet diameter can be calculated with the following semi-empirical model:

\[
\frac{d_{\text{ave}}}{d_{\text{pore}}} = \alpha Ca^\beta Re_h^\gamma (1000 < Ca < 13, 000, 400 < Re_h < 1500) \quad \text{(10)}
\]

where \( d_{\text{pore}} \) is the mean diameter of the membrane pores (m), \( \alpha \), \( \beta \) and \( \gamma \) are dimensionless. The comparison of experimental data with the predicted data is shown in Fig. 6, which shows the predicted data fit well with the experimental data. The parameter values were \( \alpha = 21,684 \), \( \beta = 0.15135 \) and \( \gamma = -1.15493 \). The relative deviation of these data was 5.269%.

3.2. Effect of Reh on re-extraction efficiency and degradation rate of PEN G

Previous studies about droplet formation found that the mean droplet diameter is related to \( Re_h \) at the experimental range, since an increase in \( Re_h \) increases the tangential force [33]. Fluid turbulence can also be enhanced by increasing \( Re_h \). In addition, the re-extraction efficiency in a traditional process rises with the decrease of phase ratio and increase of residence time when the two phases fully contacts. Fig. 7 shows the effect of \( Re_h \) on the re-extraction efficiency under the different phase ratio when the initial concentration of PEN G is 0.098 mol L\(^{-1}\). As mentioned above, at high \( Re_h \), the droplet size approaches a minimum value with the increase of \( Re_h \) from 467 to 1426, and hence, the droplet size is not further decreased. The re-extraction efficiency reached a maximum value at high \( Re_h \). The increase in specific interfacial area is dominant in the experimental range.

At low \( Re_h \), the residence time is inversely related to \( Re_h \). The re-extraction efficiency increases due to the prolonged residence time. The experimental results are in accordance with our assumption. At \( R = 0.0901 \) and \( Re_h = 467 \), the maximum re-extraction efficiency reached 99.90%, but there was no obvious change in the re-extraction efficiency with the decrease of the phase ratio under the same \( Re_h \). The main reason was the local equilibrium limitation of K\(_2\)CO\(_3\) solution due to high mass-transfer rate of PEN G.

The re-extraction efficiency at high \( Re_h \) was slightly higher than that at low \( Re_h \) under the same phase ratio. The reason can be that diffusion coefficient of PEN G in the continuous phase can be improved by the turbulence intensity, but the droplet size decreases slightly with the further increase of \( Re_h \), and the mass-transfer distance is not further shortened [34]. Therefore, the variation of the re-extraction efficiency is small. In addition, it was found that the phase separation was finished fast in the re-extraction process of PEN G, although the formed droplets were small and PEN G had the surfactant properties.

The degradation product can be reduced by enhancing the mass transfer [35]. The CME enable re-extraction process to facilitate highly selective reactions, which are difficult to achieve by the conventional extractors. Meanwhile, high dispersed phase flux has an advantage over the eddy formation on the droplet surface, which can enhance mass transfer of PEN G in the continuous phase. As a result, appropriate \( Re_h \) and residence time are favorable to reduce the degradation products in the re-extraction process. As shown in Fig. 8, when \( Re_h \) was 934, the degradation rate of PEN G ranged from 0.373% to 0.462%. The degradation rate of PEN G at \( Re_h = 934 \) was obviously lower than those at \( Re_h = 467 \) and 1426. Low \( Re_h \) resulted in high degradation rate. The obvious reason was longer residence time in the CME. However, high \( Re_h \) also led to high degradation rate. The possible reason is that the local concentration of PEN G is too high due to high mass-transfer rate. K\(_2\)CO\(_3\) solution was also buffer solution. The local pH value was much higher. Therefore, the degradation rates of PEN G at \( Re_h = 467 \) and 1426 were higher than those at \( Re_h = 946 \).
3.3. Effect of membrane pore size on re-extraction efficiency and degradation rate of PEN G

According to membrane emulsification process, droplet size can be adjusted by the membrane pore besides the continuous phase flow rate, the dispersed phase flux and physiochemical properties of solvent [29]. The mean droplet diameter decreases with the decrease of the membrane pore size, but energy consumption is proportional to the square of membrane pore diameter. As a result, the high dispersed phase flux needs much more energy in comparison to the low dispersed phase flux. It can be seen in Table 2 that the effect of membrane pore size on the re-extraction efficiency and the degradation rate of PEN G is investigated at low dispersed phase flux. By decreasing membrane pore size, the same dispersed phase flux produces the smaller droplets, thereby, provided larger specific interfacial area. Nevertheless, the re-extraction efficiency and the degradation rate slightly changed when the membrane pore size was 0.2 μm, 0.8 μm and 5 μm, respectively. The reason can be that the dispersed phase easily spread on the hydrophilic surface. Due to the occurrence of coalescence between the adjacent droplets, the large droplets are formed. There is no obvious change in the droplet size. As a result, there was a slight difference in the re-extraction efficiency using the different membrane pore size, although the membrane pore size changed drastically.

3.4. Effect of initial concentration on re-extraction efficiency and degradation rate of PEN G

Nowadays, PEN G concentration in the fermentation broth is about 60000 PEN G units mL⁻¹ in China. The molar initial concentration of PEN G is 0.098 mol L⁻¹. The effect of the initial concentration of PEN G on the re-extraction efficiency is shown in Fig. 9. The re-extraction efficiency improved with the increase of the initial concentration at \( Re_h = 934 \). When \( Re_h = 0.0837 \), the final re-extraction efficiency was more than 99.4%. However, the re-extraction efficiency was not proportional to the initial concentration. Meanwhile, an interesting result was also obtained that the re-extraction efficiency was not affected by the initial concentration at high phase ratio. The reason is that larger specific surface area was provided due to high phase ratio. Mass-transfer rate is high enough to complete the re-extraction of PEN G in the CME.

Fig. 10 shows the effect of PEN G concentration on the degradation rate. Unexpected result was obtained that the degradation rate of PEN G at \( c_0 = 0.098 \text{ mol L}^{-1} \) were lower than those at \( c_0 = 0.049 \text{ mol L}^{-1} \). The pH values of K₂CO₃ solution varied slightly under the experimental concentrations. Due to the same residence time and the similar pH value, the absolute degradation amount of PEN G was lower compared with the concentration variation of PEN G. Consequently, the degradation rate of PEN G was lower at high concentration value. In addition, two-phase concentration affects the droplet formation. Higher concentration of PEN G in the continuous phase is, higher K₂CO₃ concentration in the dispersed phase is. The interfacial tension between the two phases decreases with the increase of K₂CO₃ concentration. An increase in PEN G concentration also results in an increase of mass-transfer rate, which decreases the interfacial tension [29]. Furthermore, smaller droplets are formed. Therefore, the mass-transfer rate of PEN G can be enhanced, and the degradation rate of PEN G is decreased [21].

3.5. Comparison of the micro-extractor with the batch extractor

The comparison between conventional batch extractor and the micro-extractor is necessary. The CME \((Re_h = 934)\) and the batch extractor \((600 \text{ rev min}^{-1} \text{ stirring speed, } 3 \text{ min residence time})\) were investigated for PEN G re-extraction. The volume ratio of 1:10

<table>
<thead>
<tr>
<th>( Re_h )</th>
<th>Pore size (μm)</th>
<th>( R ) (W/O)</th>
<th>RE (%)</th>
<th>D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>234</td>
<td>0.2</td>
<td>0.0333</td>
<td>81.9</td>
<td>0.436</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.0333</td>
<td>70.1</td>
<td>0.382</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.0333</td>
<td>71.6</td>
<td>0.936</td>
</tr>
<tr>
<td>467</td>
<td>0.2</td>
<td>0.0250</td>
<td>75.4</td>
<td>0.500</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.0250</td>
<td>64.0</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.0250</td>
<td>67.1</td>
<td>0.929</td>
</tr>
</tbody>
</table>

Fig. 10. Effect of initial concentration on degradation rate of PEN G.
was selected in order to make a strict comparison. As shown in Fig. 11, the results indicated that the re-extraction efficiency was highly dependent on the two-phase contact conditions. Well mixing and fast mass-transfer rate of PEN G was achieved in the CME with a short residence time. The residence time for PEN G re-extraction in the micro-extractor, 0.2 min, was about fifteen-fold shorter than that in the conventional batch extractor using mechanical shaker. Meanwhile, the re-extraction efficiency of PEN G in the CME reached almost 100% if a multi-stage series re-extraction process was adopted. According to equipment production intensity, the volume of CME was much less than the volume of the conventional extractor. Moreover, the phase separation in the CME was prompt. The result was similar to the previous study [34].

Fig. 12 shows that degradation rate of PEN G in the micro-extractor and the batch extractor at different phase ratios. Due to high mass transfer of micro-dispersion and the short residence time, the amount of degradation product was reduced. The degradation rate of PEN G in the micro-extractor was lower than 0.5% at R ranging from 0.0204 to 0.0706. In addition, due to high mass-transfer rate, the phase ratio in the micro-extractor had less influence on the degradation rate of PEN G compared with the batch extractor.

3.6. PEN G re-extraction efficiency modeling in the micro-extractor

The re-extraction process of PEN G is described as follows. Firstly, PEN G diffuses into the organic phase film, and then PEN G diffuses from the organic phase film into the aqueous reaction zone. At the same time, OH\(^{-}\), CO\(_3\)\(^{2-}\) and HCO\(_3^{-}\) in the bulk aqueous solution diffuse into the aqueous reaction zone. Instantaneous chemical reaction occurs in the zone. Thus, the overall mass-transfer coefficient \(K_w\) is:

\[
\frac{1}{K_w} = \frac{1}{k_c} + \frac{1}{m_{id}} + \frac{1}{k_i}\tag{11}
\]

The concentration of the free penicillin acid in aqueous phase can be neglected in re-extraction process of PEN G. The partition coefficient \(m\) is much greater than 1. The third item in Eq. (11) can be neglected. \(1/k_i\) presents the interfacial resistance of PEN G re-extraction process. Due to instantaneous neutralization of the interfacial zone, the intrinsic kinetics is extremely fast. It is assumed that the interfacial resistance is not important in the re-extraction process. The interfacial resistance term in Eq. (11) is neglected. Therefore, the simplified equation of the overall mass-transfer coefficient can be changed as:

\[
K_w = k_c\tag{12}
\]

where \(k_c\) refers to individual mass-transfer coefficient of the continuous phase (m/s). \(k_c\) is obtained by empirical correlation for the prediction of mass-transfer coefficient [15,36].

\[
Sc_c = 1 + 0.724Re^{0.48}Sc_c^{1/3}\quad (100 < Re < 2000, Sc_c > 200)\tag{13}
\]

\[
Sh_c = \frac{\mu_c}{\rho_cD_c}, \quad Re = \frac{d_{avg}u_c\rho_c}{\mu_c}, \quad Sh_c = \frac{k_c d_{avg}}{D_c}\;
\]

where \(Sc_c\) represents Schmidt number, \(Re\) represents Reynolds number of the droplet, \(Sh_c\) represents Sherwood number, \(D_c\) represents diffusion coefficient of PEN G in the organic phase, PEN G has a diffusion coefficient of \(4.26 \times 10^{-10}\) m\(^2\) s\(^{-1}\) in the organic phase [37]. The droplet size is predicted by Eq. (10). The mass-transfer performance of the droplet may be obtained through a prediction of the mass-transfer coefficient. Therefore, the mass-transfer rate of PEN G can be written as follows:

\[
\frac{dc}{dt} = K_w a_V \Delta c\tag{14}
\]

\[
a_V = \frac{6R}{(1+R)d_{avg}}\tag{15}
\]

where \(\Delta c\) is PEN G concentration differential between the continuous phase and the dispersed phase (mol m\(^{-3}\)). \(a_V\) are the total interfacial area of dispersed phase per unit volume (m\(^2\) m\(^{-3}\)). As mentioned above, PEN G re-extraction was extremely fast. The concentration differential between the phases was assumed to be

\[
\Delta c = c_{oc} - c_{id} \approx c_{oc}\tag{16}
\]
Combining the approximation given in Eq. (16) with Eq. (14), the theoretical re-extraction rate of PEN G can be calculated by Eq. (17) [28].

$$RE_T = (1 - e^{-(K_w d^2)}) \times 100\%$$  

(17)

where $t_R$ is the mean residence time in the micro-extractor. The theoretical results and the experimental data of the re-extraction efficiency are shown in Fig. 13. The simulated data fit well with the experimental results. The results also indicated that the main mass-transfer resistance was controlled by the bulk continuous phase.

4. Conclusions

Continuous re-extraction of PEN G was carried out in the CME. The increase of $R_{E_T}$ had a significant influence on the droplet size when $R_{E_T}$ was less than 934. The semi-empirical equation of the droplet diameter was established. The re-extraction efficiency and the degradation rate of PEN G in the micro-extractor were improved by increasing $R_{E_T}$, initial concentration of PEN G and decreasing membrane pore size and phase ratio. Particularly, $R_{E_T}$ and phase ratio were the controlling factors for PEN G re-extraction in the micro-extractor. The re-extraction efficiency of PEN G was 99% and the degradation rate was 0.5% when $R_{E_T}$ was 934 and $R$ was less than 0.075. Compared with the batch extractor, the degradation rate of PEN G was reduced more than 50%. In addition, the re-extraction efficiency can predict well by the combination of the RIS model and the semi-empirical equation of droplet size in the CME, and theoretical analysis also indicated that the bulk continuous phase was the main mass-transfer resistance.

Nomenclature

- $A$: inner surface area of ceramic membrane (dm$^2$)
- $A_e$: effective flow cross-sectional area (m$^2$)
- $a_V$: interfacial area per volume (m$^2$ m$^{-3}$)
- $C_a$: capillary number
- $C_V$: coefficient of variation (%)
- $c$: molar concentration of PEN G (mol L$^{-1}$)
- $c_d$: PEN G concentration of the dispersed phase (mol L$^{-1}$)
- $c_{id}$: PEN G concentration inside the droplet (mol m$^{-3}$)
- $c_{oc}$: PEN G concentration outside the droplet (mol m$^{-3}$)
- $c_{loss}$: concentration of penicilloic acid in the dispersed phase (mol L$^{-1}$)
- $D$: degradation rate in the re-extraction of PEN G (%)
- $d_{avg}$: mean droplet diameter (m)
- $d_h$: hydrodynamics diameter (m)
- $d_i$: diameter of the ith droplets (m)
- $d_{pore}$: mean membrane pore diameter (m)
- $J$: dispersed phase flux through the membrane (dm$^3$ dm$^{-2}$ h$^{-1}$)
- $K_w$: overall mass-transfer coefficient (m s$^{-1}$)
- $k_c$: individual mass-transfer coefficient of the continuous phase (m s$^{-1}$)
- $L$: wetted perimeter (m)
- $m$: partition coefficient
- $N$: measured number of droplets
- $Q_V$: volumetric flow rate of the continuous phase (dm$^3$ h$^{-1}$)
- $R$: volume ratio of the dispersed phase to the continuous phase
- $R_{E_T}$: re-extraction efficiency of PEN G (%)
- $S_C$: Schmidt number of the continuous phase
- $S_d$: standard deviation of droplet diameter
- $S_{h}$: Sherwood number of the continuous phase
- $t_R$: mean residence time (s)
- $u_c$: superficial continuous phase velocity (m s$^{-1}$)

Greek letters

- $\alpha, \beta, \gamma$: dimensionless number
- $\Delta c$: PEN G concentration differential between the continuous phase and the dispersed phase (mol m$^{-3}$)
- $\Delta \rho$: density differential between the continuous phase and the dispersed phase (kg m$^{-3}$)
- $\varepsilon$: membrane porosity (%)
- $\mu_c$: dynamic viscosity of the continuous phase (Pa s)
- $\rho_c$: density of the continuous phase (kg m$^{-3}$)
- $\sigma$: dynamic interfacial tension (mN m$^{-1}$)

Subscripts

- $c$: the continuous phase
- $d$: the dispersed phase
- $0$: initial state of the continuous phase
- $1$: final state of the continuous phase

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