CHAPTER 4

STUDIES ON STRIPPING KINETICS
4.1 Introduction

In order to develop a total process for reactive extraction of beta-lactam antibiotics from aqueous solution and for design of extractors, the knowledge on kinetics and mechanism of re-extraction / stripping of the beta-lactam from the loaded organic phase is an important as that of extraction equilibrium and kinetics. However, as evident from current literature (Schugerl, 1994) very limited studies have been reported on re-extraction of beta-lactams from systems involving amines and quaternary amine salts as the extractants. Reschke and Schugerl, (1984) are perhaps the first workers who reported re-extraction kinetics of Penicillin-G which was extracted to an organic phase with a secondary amine. Subsequently Lee and Lee (1994) reported useful data on optimisation of the various parameters on extraction /re-extraction process of Penicillin-G in a similar system and analysed stripping kinetics using buffer solution of carbonate as the stripping phase.

As regards reactive extraction of cephalosporin antibiotics, there is practically no report in re-extraction kinetics at all. Hano et al., (1992) are perhaps the only workers who demonstrated that cephalosporin-c extracted from an aqueous carbonated buffer solution to an organic phase of butyl acetate containing Aliquat-336 as the extractant could be re-extracted by around 70% to another aqueous solution of acetate buffer. However, a systematic kinetic investigation was not reported by these authors.

In this chapter, a comprehensive study has been presented on kinetics of stripping of a certain beta-lactams like cephalosporin-c, 7-ACA, 7-ADCA, cephalaxin and 6-APA from an organic phase of Aliquat-336-butyl acetate system only as the same was found to be the most effective from equilibrium consideration (chapter 2).

4.2. Theoretical considerations and Kinetics models

Reactive extraction of zwitterionic beta-lactams under study with Aliquat-336 conforms to liquid-liquid ion exchange mechanism involving dissociated beta-lactam anion. The nature of the ion-exchange reaction (equation 2.25, page no. 41) and observed pH dependence of the distribution coefficient as discussed in chapter 2.
indicates possibility of re-extraction into an aqueous phase of lower pH and substantial chloride ion concentration. Study made by Hano et al., (1992) revealed that stripping of cephalosporin-c from butyl acetate solution of cephalosporin-c-Aliquat-336 complex into a NaCl containing aqueous solution of acetate buffer (pH 4 by using 100 mol/m³ buffer) was about 60–70%.

According to the extractive reaction, the extent of stripping should increase by an increase in Cl⁻ concentration in the stripping phase, but Hano et al., (1992) found that the stripping was almost independent of Cl⁻ concentration. Though it is difficult to explain this observation, the same may be attributed to the effect of another anion exchange reaction between Aliquat-336 (carrier) and acetate of the buffer i.e.

\[ QC_1 + Ac^- \rightleftharpoons QAc + Cl^- \] (4.1)

This is more likely to be the case particularly when the loaded organic phase contains the carrier in sufficient excess of that present as complex. Such an additional reaction would also further cause increased Cl⁻ concentration in the stripping phase thereby providing driving force for the stripping of cephalosporin anion.

Considering the two anion exchange reactions of beta-lactam anion (feed phase) and acetate (stripping phase) and QC1, the overall distribution ratio (D) for the beta-lactam may be deduced from a mass balance of acetate as

\[
D = \frac{K_F \left[ C_{Ac^-1} - \left\{(1+K_d) C_{H^+} / K_a + 1\right\} C_{Ac^-} \right]}{K_A C_{Ac^-1}}
\] (4.2)

where \(K_A\) and \(K_F\) are the extraction equilibrium constants of the reaction of acetate and beta-lactam, respectively, \(K_d\) and \(K_a\) are the distribution equilibrium constant and dissociation constant, respectively of acetic acid. The reported values of \(K_d\) and \(K_A\) are 0.3 and 0.045, respectively. The above equation indicates a decrease of D value with an increase acetate ion concentration but in a range below that required for a constant pH acetate buffer solution as the stripping phase. Accordingly, the stripping may be
enhanced by using a stripping solution of acetate buffer as was demonstrated at least for
the extraction-stripping of cephalosporin-c (Hano et al., 1992). Thus, from the above
considerations and the results on pH dependence of distribution coefficient presented in
chapter 2, it is apparent that acetate buffer solution (pH 4) would be an ideal choice of
the stripping phase. Accordingly, all experimentals on stripping kinetics will be carried
out with this aqueous solution of acetate buffer.

Kinetic model The reaction—diffusion phenomena involved in stripping are essentially
the same with those encountered in the forward extraction process as discussed in the
preceding section. Stripping rate with reaction may be controlled either by the kinetics or
by diffusion. Accordingly, either the simple mass transfer model based on two film
theories or the interfacial reaction model considering reaction of the adsorbed carrier and
solute at the interface may describe the stripping kinetics. Simple mass transfer model
was found applicable to analyse stripping kinetics for penicillin-G (Reschke and
Schugerl, 1984; Lee and Lee, 1994) and carboxylic acid (Juang and Huang, 1995) using
Amberlite LA-2 as the carrier, while interfacial reaction model has been applied for
analysing the stripping kinetics of mostly metal ions such as copper involving acidic
extractants i.e. Bis-(2-ethyl hexyl) phosphoric acid, 2-ethyl hexyl-phosphoric acid,
mono-2-ethyl hexyl ester, N-8-Quinolysulformide etc. (Komasawa and Otake, 1983;
Sato et al., 1989; Yoshizuka et al., 1986). The essential aspects and physico-chemical
parameters of both the models have been highlight in the previous chapter.

In the present work, only the mass transfer model proposed for extraction of dl-
phenylalanine with Aliquat-336 as carrier (Haensel et al., 1986) has been examined for
stripping kinetics of certain cephalosporin-antibiotics. The concentration profile during
stripping may be depicted as shown in Figure 4.1. The concentration of Cl⁻ at the
interface may be considered to be equal to that in the bulk due to stabilizing effect of the
buffer present in the aqueous the stripping phase. The kinetic model can thus be
represented in a final form as

\[
V_a \frac{dC_{Ps}}{dt} = J_s = \frac{K_p (C_{Ps} + 0.5B \pm \sqrt{0.25B^2 - R})}{S dt}
\]
Figure 4.1: Concentration profile for the mass transfer model during stripping of beta-lactams.
where,

$$B = \frac{k_{QCI} k_{QP}^2 K_P C_{QCI} + 2 k_{Ps}^2 k_{QCI} C_{Ps}}{k_{Ps} k_{QP}^2 K_P - k_{Ps}^2 k_{QCI}} + \frac{2 k_{Ps} k_{QCI} k_{QP} C_{QP} - k_{Ps} k_{QP}^2 K_P C_{Ps}}{k_{Ps} k_{QP}^2 K_P - K_P^2 K_{QCI}}$$

and

$$R = \frac{-k_{QCI} (k_{QP} C_{QP} + k_{Ps} C_{Ps})^2}{k_P k_{QP}^2 K_P - k_P^2 k_{QCI}}$$

### 4.3 Experimental study

#### 4.3.1 Chemicals and reagents

The chemicals and reagents as well as the analytical procedure used were the same as described in sections 2.3.1 to 2.3.4. (page no. 43 to 46)

#### 4.3.2 Procedure of kinetic experiments and data reduction

The experiments on stripping kinetics were carried out in a Lewis type all glass stirred cell described in the previous chapter for extraction kinetics (section 3.3.2 page no. 168). For stripping, the aqueous solution was acetate buffer of pH 4 made by using 100 mol/l acetate ion. In the organic phase, the initial concentration of solute-carrier complex (QP) and free carrier (QC1) was varied from 0.7 to 0.9 mM and 0.52 to 9.8 mM, respectively. The organic phase was loaded with beta-lactam ion by equilibrating equal volumes of the aqueous beta-lactam solution at appropriate pH and n-butyl acetate solution of Aliquat-336 (organic phase) under intense stirring in a glass vessel for one hour. The concentration of the complex (QP) and free carrier (QC1) was varied by taking different concentration of QC1 during loading experimentals.

The stripping aqueous solution and loaded organic solutions in equal volumes were then poured carefully into the stirred glass cell. Thereafter, stirring of the phases was started immediately. The stirring speed was maintained at 120 rpm however, without
causing phase dispersion at the interface. Samples of the aqueous phase were collected at equal interval of time and the concentration of the solute was determined by a UV-Visible spectrophotometer (chapter 2 section 2.3.3, Page no 46 for details of analysis). The stripping phase pH was varied between 3 to 5 in order to assess the pH effect on stripping rate.

The initial stripping rate \( J_s \) (mol/cm\(^2\)s) was calculated from experimental data by using the following equation

\[
J_s = \frac{V_a \cdot \frac{dC_p^-}{dt}}{S} \left. \right|_{t=0}
\]

(4.4)

where, \( S \) is the interfacial contact area taken as the geometric cross-section area of the stirred cell (12.56 cm\(^2\)) and \( \left. \left( \frac{dC_p^-}{dt} \right) \right|_{t=0} \) is the initial slope of the curve representing concentration in the aqueous stripping phase \( (C_{pa}) \) versus time \( (t) \). The values of \( J_s \) were determined under various experimental conditions so as to assess the probable effect of the pertinent variables and draw inference on the appropriate kinetic model.

4.4 Results and Discussion

Considering the nature of the extractive reaction, the pertinent variables affecting the stripping rate may be expected to be the aqueous phase pH and chloride ion concentration as well as the solute-carrier complex and free carrier concentration in the organic phase. Accordingly, the discussion of results is restricted to these factors only in this complimentary study on stripping kinetics.

4.4.1 Effect of stripping phase pH and chloride ion concentration

Due to zwitterionic character of the beta-lactams studied in this work, the pH dependence of stripping rate may be considered as cursory as that of extraction equilibria and kinetics. However, the extent of stripping and pH dependence seem to be different for different beta-lactams as shown in Table 4.1 and Figure 4.2. The data presented in
Table 4.1 Maximum percentage stripping of various beta-lactams and the corresponding pH values. $Ct^- = 0$

<table>
<thead>
<tr>
<th>Beta-lactam</th>
<th>pH</th>
<th>% of Stripping</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-APA</td>
<td>4</td>
<td>67.4</td>
</tr>
<tr>
<td>Cephalosporin -c</td>
<td>4</td>
<td>72.9</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>4</td>
<td>74.1</td>
</tr>
<tr>
<td>7-ACA</td>
<td>4</td>
<td>75.5</td>
</tr>
<tr>
<td>7-ADCA</td>
<td>3</td>
<td>83.3</td>
</tr>
</tbody>
</table>
Figure 4.2: Effect of aqueous phase pH on initial stripping rate of beta-lactams. $C_{Cl^-} = 0$ (aqueous phase).
Table 4.1 and Figure 4.2 pertain to stripping from an organic phase of n-butyl acetate containing 10 mM QCl which was equilibrated with 1mM aqueous beta-lactam solution whose pH was maintained at 8 in all cases (pH 9.8 for cephalosporin-c). Thus, although the equilibrium complex concentrations ($C_{QP}$) for various beta-lactams are essentially but marginally different, the amount of free QCl present in the organic phase is almost equal. Thus, a comparison of the extent of stripping and pH dependence of the stripping rate ($J_s$) based on Table 4.1 and Figure 4.2 may be considered reasonable. The pH values at which maximum extents of stripping are obtained also correspond to maximum initial rate of stripping of various beta-lactams as shown in Figure 4.2. This observation perhaps indicates the role of the molecular structure of the beta-lactam whose dissociation (pKₐ values) constants are different from each other. However, the observed decrease of $J_s$ with an increase of pH of the stripping phase appears to be consistent with the zwitterionic character of the beta-lactams studied in this work.

The effect of chloride (NaCl) ion concentration ($C_{Cl}^-$) in the stripping phase is shown in Figure 4.3 which is a semi-log plot of $J_s$ versus $C_{Cl}^-$ obtained under otherwise identical experimental conditions of Figure 4.2. It may be noted that the data in Figure 4.2 and Table 4.1 pertain to $C_{Cl}^- = 0$, but still finite stripping takes place implying that the chloride ion driving force for stripping is provided by an additional anion exchange reaction between free QCl in organic phase and buffer anion of the stripping phase. Therefore, it may be believed that additional chloride ion in the stripping phase may have insignificant effect on the initial stripping rate.

However, as shown in Figure 4.3, $J_s$ increase of $C_{Cl}$ from 0 to 5 mM beyond, which $J_s$ appears to be independent of $C_{Cl}^-$. Quantitatively, the relationship of $J_s$ with $C_{Cl}^-$ (below 5 mM) for various beta-lactams may be deduced as

$$J_s \propto C_{Cl}^n$$ (4.5)

The values of $n$ estimated by a linear regression of experimental data are 0.032, 0.02, 0.036, 0.026, 0.03 for 6-APA, 7-ACA, 7-ADCA, cephalixin and cephalosporin-c, respectively and the standard deviation was found to be within 10%. The observed weak dependence of $J_s$ on $C_{Cl}$ appears to substantiate the inference of Hano et al., (1992) that
Figure 4.3: Effect of chloride ion concentration on initial stripping rate of beta-lactams.
an additional anion exchange reaction of QCl with buffer anion augments the stripping process.

4.4.2 Effect of solute-carrier complex / carrier concentration in organic phase

The relative concentrations of solute-carrier complex (QP) and free carrier (QCl) in the organic phase is a measure of the loading of the solute which is expected to be a dominant factor in determining the initial stripping rate (Js). The effect of both CQP and loading can be assessed simultaneously from a relation of CQP and Js. It may be noted that CQP was varied by varying CQCl at constant Cp in equilibration experiments and therefore, free CQCl in loading organic solution would also vary.

The effect of concentration of the complex is shown in Figure 4.4 which is a log-log plot of Js versus CQP at various loading. The effect of free QCl (not bound to beta-lactams) on Js seems to be appreciable since the rate obtained at low loading (high free QCl concentration) is much higher than that obtained at high loading (low free QCl concentration) Figure 4.5 show the relationship of Js with free CQCl in the organic phase. This is reasonable in as-much as the higher free CQCl may be considered to enhance the rate of the additional ion-exchange reaction with buffer ion thereby providing the CCl during force for the stripping process.

Inspite of this limiting factor of the stripping process, a quantitative estimate of the data of Figure 4.4 revealed that Js is directly proportional to CQP implying that the rate first order with respect to the complex concentration for all the beta-lactams studied in this work. This relationship of Js versus CQP was deduced from a linear regression of the experimental data with an estimated standard deviation within 8 %.

4.4.3 Validation of kinetic model

The mass transfer model given by equation 4.3 was used to generate theoretical profile of CPs versus time (t). The theoretical curves were fitted to the experimentally measures CPs values by identification of the three mass transfer coefficients kPs, kQP and kQCl where the ratio of kQCl / kQP was kept constant at 1.18/1. The computation
Figure 4.4: Effect of the complex concentration in organic phase on initial stripping rate of beta-lactams. $C_{Cl^-} = 0$ (aqueous phase).

<table>
<thead>
<tr>
<th>Symbol</th>
<th>7-ADCA</th>
<th>CPC</th>
<th>7-ACA</th>
<th>Cephalexin</th>
<th>6-APA</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>1.5:1</td>
<td>1.13:1</td>
<td>1.85:1</td>
<td>1.08:1</td>
<td>1.5:1</td>
</tr>
<tr>
<td>△</td>
<td>2.4:1</td>
<td>2.28:1</td>
<td>3.54:1</td>
<td>2.2:1</td>
<td>3.08:1</td>
</tr>
<tr>
<td>□</td>
<td>6.3:1</td>
<td>5.9:1</td>
<td>7.3:1</td>
<td>5.85:1</td>
<td>7.0:1</td>
</tr>
<tr>
<td>⊙</td>
<td>11.8:1</td>
<td>10.2:1</td>
<td>12.3:1</td>
<td>10.9:1</td>
<td>12.1:1</td>
</tr>
</tbody>
</table>
Figure 4.5: Effect of free QCl concentration on initial stripping rate.
procedure is given Appendix 3. This ratio was evaluated from the diffusion coefficient calculated from Wilke-Chang (1995) equation. The equilibrium constant values were taken from chapter 2 (page no. 78). The estimated values of the mass transfer coefficient for various beta-lactam are shown in Table 4.2. The experimental and theoretical $C_{Ps}$ versus time (t) profiles (calculated with $k_{Ps}$ values of Table 4.2) for various beta-lactams are shown in Figure 4.6. It appears that the agreement between theoretical and experimental $C_{Ps}$ versus time (t) profile is fairly well for 7-ACA and cephalaxin. The estimated deviation of the experimental data from theoretical profiles lies between 10-20% which may be considered reasonable. However, substantial deviation occurs in case of 7-ADCA, CPC and 6-APA which is however, difficult to explain from the molecular properties of the beta-lactam under study. The observed deviation perhaps implies that the stripping rate may be controlled by the other probable mechanism. The loaded organic phase contains appreciable proportion of free QC1 which has already been shown to have surface active properties and to have surface active properties and is likely to take part in another anion exchange reaction with buffer anion of the stripping aqueous solution. It may therefore, be expected that model based on interfacial reaction may provide better representation of the stripping kinetics. However, due to the probable additional ion-exchange reaction occurring in the stripping process the model may be quite complicated and extensive theoretical and experimental exercise will be required to provide a better model for the stripping kinetics. This is kept beyond the purview of the present study.

4.5 Conclusion

Beta-lactams extracted from an aqueous carbonate and phosphate buffer solution into an organic phase of Aliquat-336-n-butyl acetate was stripped to an aqueous phase of acetate buffer. An additional ion-exchange reaction between free QC1 and buffer anion is expected to facilitate the stripping process. The role of additional $Cl^-$ concentration seems to be insignificant.

The initial rate of stripping is weekly dependent an $Cl^-$ concentration of the aqueous phase but is first order with respect to the complex concentration in the organic
<table>
<thead>
<tr>
<th>Beta-lactam</th>
<th>$k_{Pb}$ (cm/s)</th>
<th>$k_{QCl}$ (cm/s)</th>
<th>$k_{QP}$ (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-APA</td>
<td>$1.29 \times 10^{-4}$</td>
<td>$1.215 \times 10^{-4}$</td>
<td>$1.02 \times 10^{-4}$</td>
</tr>
<tr>
<td>CPC</td>
<td>$1.91 \times 10^{-4}$</td>
<td>$1.386 \times 10^{-4}$</td>
<td>$1.189 \times 10^{-4}$</td>
</tr>
<tr>
<td>7-ACA</td>
<td>$2.24 \times 10^{-4}$</td>
<td>$1.216 \times 10^{-4}$</td>
<td>$1.04 \times 10^{-4}$</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>$1.59 \times 10^{-4}$</td>
<td>$1.15 \times 10^{-4}$</td>
<td>$0.98 \times 10^{-4}$</td>
</tr>
<tr>
<td>7-ADCA</td>
<td>$2.18 \times 10^{-4}$</td>
<td>$1.127 \times 10^{-4}$</td>
<td>$0.951 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
Figure 4.6: Comparison of experimental results on stripping kinetics with model calculation.

a: $C_{QP} = 0.715$ and $0.836$ mM for 7-ACA and cephalexin respectively and b: $C_{QP} = 0.774$, $0.895$ and $0.742$ mM for 7-ADCA, CPC and 6-APA respectively.
phase. The rate is also affected by free QCl present in the organic phase. A simple mass transfer model based on two-film theory provides an approximate description of the stripping kinetics. However, a model based on an interfacial reaction controlled mechanism will be necessary to provide a more accurate description of the stripping kinetics.
4.6 Nomenclature

Ac  Acetate ion
7ACA  7-Aminocephalosporanic acid
7-ADCA  7-Aminodecocephalosporanic acid
6-APA  6- Aminopenicillanic Acid
B  constant (equation 4.3)
C  concentration (mM)
Cl\(^-\)  chloride ion (counter-ion of anion exchange carrier)
CPC  cephalosporin-c
H\(^+\)  proton.
HP  7-ACA
J_s  stripping rate, (mol/cm\(^2\)-Sec)
K_a  dissociation constant.
K_d  distribution equilibrium constant
K_p  extraction equilibrium constant, [-]
k_p  mass transfer coefficient of beta-lactam ion, (cm sec\(^{-1}\))
k_QCl  mass transfer coefficient of carrier, (cm sec\(^{-1}\))
k_QP  mass transfer coefficient of loaded beta-lactam-carrier complex, (mol/cm\(^{-1}\))
P  beta-lactam ion.
QAc  Aliquat-336-acetate complex.
QCl  Aliquat-336.
QP  Aliquat-336-beta-lactam complex.
R  constant (equation 4.3)
S_A  specific interfacial area (cm\(^2\))
t  time of stripping, (sec.)
V  volume of solution, (lt)

Subscript/superscript
i  initial
s  aqueous strip phase
*  interface
4.7 References


