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ScienceDirect
Chemical Engineering and Processing 47 (2008) 1–8
Chemical Engineering and Processing Process Intensification
www.elsevier.com/locate/cep

Study on the reactive extraction and stripping kinetics of certain β-lactam antibiotics

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Received 9 April 2007; received in revised form 9 August 2007; accepted 9 August 2007
Available online 25 August 2007

Abstract

The extraction equilibrium and stripping of certain β-lactam antibiotics such as 7-aminocephalosporanic acid (7-ACA), 7-aminodeacetoxy cephalosporanic acid (7-ADCA), 6-aminopenicillanic acid (6-APA), cephalosporin-C (CPC) and cephalexin from aqueous solution of phosphate and carbonate buffers were studied with Aliquat-336 (tricaprylylmethylammonium chloride) dissolved in *n*-butylacetate as the solvent over an aqueous phase pH range of 5–10. The extraction equilibrium constant K_p was found to increase with aqueous phase pH, which is attributed to the increase in ionisation of the β-lactam. A systematic study on kinetic of stripping or re-extraction of 7-ADCA and cephalexin from the extracted phase was carried out using an aqueous solution of citrate buffer at different pH values and was found to be pH dependent which is also attributable to ionisation behaviour of the β-lactams. Such observation is considered important, as re-extraction at an appropriate pH value is possible. The rate of stripping was found to be weakly dependent on Cl^- concentration of the aqueous phase and the same was analysed with a simple mass transfer model based on film theory.

Keywords: Stripping kinetics; Reactive extraction; β-Lactam antibiotics; Liquid–liquid ion exchange; Aliquat-336

1. Introduction

Reactive extraction in liquid membrane can provide an attractive method for separation and purification of cephalosporin antibiotics from dilute solution and the principle can be effectively exploited to develop liquid membrane system, which can provide enhanced separation potential [3,8,9,16]. We had earlier reported studies on reactive extraction of 6-APA and 7-ACA with secondary, tertiary and quaternary amines and found that Aliquat-336, a quaternary amine salt is the best choice of carrier for cephalosporin antibiotics [3,4,11].

For design of extractors using the principle of reactive extraction, the knowledge on kinetics and mechanism of stripping of the β-lactam from the loaded organic phase is as important as that of extraction equilibrium and kinetics. Reschke and Schugerl [15] were perhaps the first workers who reported stripping kinetics of penicillin-G, which was extracted to an organic phase with a secondary amine. Subsequently, Lee et al. reported [14] useful data on optimisation of the various parameters on extraction and re-extraction process using the same extractant.

There is practically no report in stripping kinetics of cephalosporin antibiotics except [11] who, however, demonstrated that cephalosporin-C extracted from an aqueous carbonate buffer solution to an organic phase of butyl acetate containing Aliquat-336 as the extractant could be stripped or 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 paper, the extraction equilibrium of certain β-lactams and a comprehensive study on stripping of 7-ADCA and cephalexin including the kinetics have been reported.

1.1. Theoretical considerations

7-ADCA and cephalexin are zwitterionic molecules and the pK_{a1} and pK_{a2} values are 2.95 and 4.78 for 7-ADCA and 2.56 and 5.88 for cephalexin. In the pH range between 2.95 and 4.78 for 7-ADCA, the zwitterion as a whole is predominant as is evident from the dissociation behaviour.

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0255-2701/$ – see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.cep.2007.08.008

The pH at which the amine group ionises keeps the carboxyl group in the COO^- form. The anionic forms of 7-ADCA and cephalexin at pH > pK_{a2} are amenable for ion-exchange with an anionic exchanger such as Aliquat-336 (a carrier hereafter termed as QCl). β-Lactam anion (P^-) complexes with carrier, QCl, dissolved in the organic solvent according to the following reaction:

$$P^- + QCl \rightleftharpoons QP + Cl^- \quad (1)$$

The extraction efficiency depends on the type of β-lactam molecule (dissociation constant) and the solvent used. For the ion-exchange extraction to be efficient, it is necessary that the β-lactam molecule to be present in the anionic form, i.e. at pH above the pK_a value.

The equilibrium constant, K_p, of this reaction is given by

$$K_p = \frac{C_{QP} C_{Cl^-}}{C_P - C_{QCl}} \quad (2)$$

The following material balance equations hold for Aliquat-336/Cl^- and for the β-lactam:

$$V_{org} C_{QCl_{org,e}} = V_{org} C_{QCl_{org,i}} - V_{aq} C_{Cl^-} \quad (3)$$

and for 7-ADCA and cephalexin (β-lactam anion):

$$V_{org} C_{QP_{org,e}} = V_{aq}(C_{HP_i} - C_{HP_e})$$

where i and e stand for the initial and equilibrium values, respectively, and the V_{aq} and V_{org} represent the volumes of the aqueous and organic phases, respectively.

The extraction equilibrium constant can be arranged as

$$K_p = \frac{V_{aq}(C_{HP_{aq,i}} - C_{HP_e}) C_{Cl_q}}{(V_{org} C_{QCl_{org,i}} - V_{aq} C_{Cl_{aq}}) C_P} \quad (4)$$

Eq. (4) follows from Eq. (2) and thus by plotting $C_{QP}C_{Cl}$ versus $C_{QCl}C_P$, the equilibrium constant K_p can be determined. In absence of the measurement of Cl^- concentration in the aqueous phase, C_{Cl^-} may be determined from $V_{aq}C_{Cl} = V_{org}C_{QP}$. Thus C_{Cl^-} can be eliminated from the K_p expression, which can be simplified to the following forms:

$$K_p = \frac{C_{QP}^2 V_{org}/V_{aq}}{C_{QCl} C_P} \quad (5)$$

The co-extraction of buffer anion, A^- by QCl at the interface may take place according to

$$A_{aq}^- + QCl_{org} \rightleftharpoons QA_{org} + Cl_{aq}^- \quad (6)$$

The equilibrium constant, K_A, of co-extraction is given by

$$K_A = \frac{C_{QA_{org}} C_{Cl_{aq}^-}}{C_{QCl_{org}} C_{A_{aq}^-}} \quad (7)$$

The co-extraction effect can be considered implicitly by the excess chloride moles present in the aqueous phase after equilibrium:

$$V_{org} C_{QA_{org}} = V_{aq} C_{A_{aq,i}} - V_{aq} C_{Cl_{aq}^-} \quad (8)$$

1.2. Stripping kinetics

The reactive extraction system conforms to liquid–liquid ion exchange mechanism involving dissociated form of the β-lactam anion. The nature of the ion-exchange reaction and observed high extraction at high pH and re-extraction into an aqueous phase of lower pH at substantial chloride ion concentration determines the re-extraction efficiency of the system.

According to the extractive reaction, the extent of stripping should increase by an increase in Cl^- concentration in the stripping phase, but it was found [11] 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 as represented by

$$QCl + Ac^- \rightleftharpoons QAc + Cl^- \quad (9)$$

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

1.3. Kinetic model

The reaction diffusion phenomena involved in stripping are essentially the same with those encountered in the forward extraction process. Stripping rate may be controlled either by the reaction rate or by diffusion. Accordingly, either the simple mass transfer model based on two film theory 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 [14,13] and carboxylic acid [13] using Amberlite LA-2 as the carrier, while interfacial reaction model has been applied for analyzing the stripping kinetics of metal ions such as copper ion involving acidic extractants [20].

In the present work, only the mass transfer model proposed for extraction of DL-phenylanine with Aliquat-336 as the carrier [10] has been considered to analyse stripping kinetics of cephalosporin antibiotics. 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 stripping phase. The kinetic model can be represented as

$$-J_S = \frac{V_a dC_{P_S}}{S dt} = K_P(C_{P_S} + 0.5B \pm \sqrt{0.25B^2} - R \quad (10)$$

swhere

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

and

$$R = \frac{-k_{QCl}(k_{QP}C_{QP} + k_{P_s}C_{P_s})^2}{k_{P_s}k_{QP}^2K_P - k_{P_s}^2k_{QCl}}$$

2. Experimental

2.1. Chemicals and reagents

7-ADCA, cephalexin, 6-APA, cephalosporin-C (CPC) and 7-ACA β-lactams were procured from Sigma Chemical Co. (St. Louis, Missouri, USA) and are of 99.9% purity. Aliquat-336 (Aldrich, Milwakee, USA) were used as received, butyl acetate and other analytical grade buffer reagents were procured from BDH (Mumbai, India) and were used as received.

2.2. Procedure

2.2.1. Procedure of equilibrium experiments

The equilibrium experiments were carried out at 25 °C by mixing 10 ml each of buffered aqueous β-lactam solution and the organic solution of Aliquat-336 dissolved in butyl acetate in a stopper glass flask of 50 ml capacity round-bottom flask placed over a magnetic plate with magnetic capsule. The aqueous phase pH was maintained at a value of 8–10 by using phosphate and carbonate buffer. In case of extraction with the quaternary amine salt, the aqueous phase pH values were maintained at 8–10, i.e. above the upper pK_a value at which the β-lactam exists in the anionic form. In case of CPC, the pH was maintained at 10.0 (above the pK_{a2} value of 9.3) by using carbonate–bicarbonate buffer. The method for preparation of the buffer solution is the same as reported in our previous papers [3–5]. A set of preliminary experiments were carried out to ensure that equilibrium was attained. The data collection was concentration of solute in aqueous phase versus time and upon attainment of equilibrium the concentration remained constant, the time of equilibration for the extraction was 2–3 h. After attainment of equilibrium, the aqueous and organic phases were separated and the aqueous phase concentrations were determined by UV–vis spectrophotometer (Shimadzu, Model 160 A) calibrated at the wave lengths of 264, 265, 262, 260, 240, 204 nm for 7-ACA, 7-ADCA, cephalexin, cephalosporin-C, cephaloridine and 6-APA, respectively. The Cl^- concentration was estimated by the well-known Volhardt method involving precipitation with silver nitrite and those of the buffer ions, that is, phosphate and carbonate, were estimated by a standard gravimetric method using molybdate blue and $BaCl_2$, respectively [17]. The extraction equilibrium experiments were carried out in triplicate and the reproducibility was found to be ±5%.

2.2.2. Procedure of kinetic experiments

The experiments on stripping kinetics were carried out in a Lewis type all glass stirred cell of standard design reported in literature [6,21] and used in our previous paper [2]. The schematic diagram of the cell is shown in Fig. 1. The cell was a glass cylinder with inside diameter of 5 cm and a height of 10 cm which

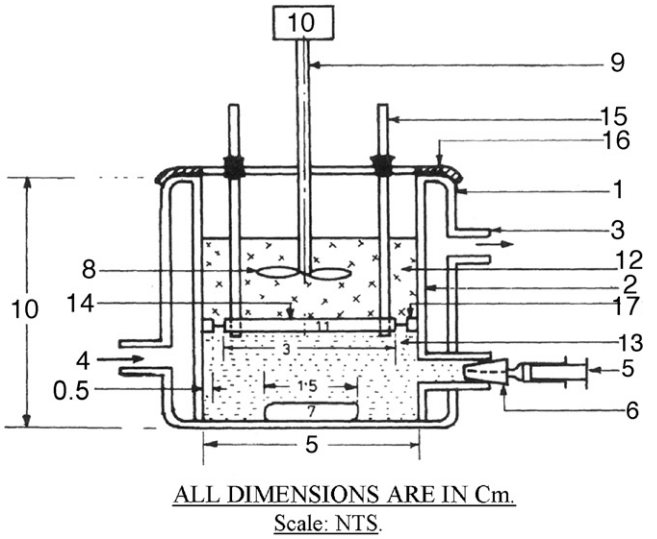

Fig. 1. Schematic diagram of all glass stirred cell: (1) glass cell; (2) water jacket; (3) water outlet; (4) water inlet; (5) sample collector; (6) rubber septum for sample collector; (7) magnetic stirrer; (8) teflon stirrer; (9) glass rod; (10) motor with speed regulator; (11) Circular disc; (12) aqueous phase; (13) organic phase; (14) interface of two liquid; (15) stainless steel rod; (16) glass lid; (17) O' baffle.

was divided by acrylic circular disc placed right at the interface in order to reduce the disturbance of the interface.

For stripping, the aqueous solution taken was an acetate buffer of pH 4 made by using 100 mM acetate ion. In the organic phase, the initial concentration of solute–carrier complex (QP) and free carrier (QCl) was varied from 0.7 to 0.9 mM and 0.52 to 9.8 mM, respectively. The organic phase was loaded with β-lactam ion by equilibrating equal volumes of the aqueous β-lactam solution at appropriate pH and *n*-butyl acetate solution of Aliquat-336 (organic phase) under intense stirring in a glass vessel for 1 h. The concentration, of the complex (QP) was varied by taking different concentrations of QCl during loading experiment and determine from a material balance.

The stripping aqueous solution of the lower part as well as the upper phase loaded organic solutions in equal volumes (25 ml each solution) was 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. It may be noted that this stirring speed was fixed on the basis of the observation of separately conducted experiment that above this stirring speed the mass transfer effect was negligible. The temperature was maintained at 25 ± 0.5 °C by circulating water from a constant temperature bath through a jacket provided in the cell. Samples of the aqueous phase were collected at equal interval of time and the concentration of the solute was determined by a UV–vis spectrophotometer calibrated at appropriate wave length [5]. The stripping phase pH was varied between 3 and 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:

$$J_s = -\frac{V_a}{S}\left(\frac{dC_{P_s^-}}{dt}\right)_{t=0} \quad (11)$$

where S is the interfacial contact area taken as the geometric cross-sectional area of the stirred cell (12.56 cm^2) and $(dC_{P_s}-/dt)_{t=0}$ is the initial slope of the curve representing concentration in the aqueous stripping phase (C_{P_s}) 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.

3. Results and discussion

3.1. Extraction equilibrium

The equilibrium experiments were conducted at different Aliquat-336 and β-lactam concentration and at a pH above the pK_{a2} such that only the anionic from of the β-lactam exists in the aqueous medium. Determination of the value of K_p for various β-lactams when *n*-butyl acetate was used as the solvent and also assessing the co-extraction effect through of K_A values [4] was the primary emphasis.

The K_p values determined from linear regression of the data have been listed in Table 1. The agreement between experimental and predicted K_p values seems to be fairly well and the correlation coefficient for linear regression of data for determination of experimental K_p value is appreciable. However, the observed deviation over the range pH value which may be attributed to the co-extraction of the buffer anion used to maintain the pH. It is apparent that the K_p obtained without considering co-extraction are higher than those obtained by considering co-extraction. The difference in the values is assigned to the co-extraction constant K_A, which is also shown in Table 1. At high pH, co-extraction becomes significant whereas at lower pH, co-extraction is negligible an observation identical to that reported for extraction of 6-APA [4] and DL-phenylanine [10] with Aliquat-336. Indeed, analysis of the Cl^- concentration in the aqueous phase indicated appreciable degree of co-extraction particularly at a high pH. It is also apparent that the K_P values for Aliquat-336 increase with an increase of pH for both 7-ADCA and cephalexin. As expected, K_P increases with an increase of pH within the range of pH studied apparently due to larger fraction 7-ADCA and cephalexin anion that exist at high pH conditions.

This may be considered reasonable as the anionic form of the β-lactam that exists predominantly at pH higher than pK_{a2} value is amenable for liquid anion exchange extraction with the carrier. Such an observation is akin to that reported in our previous work [5].

It appears that the equilibrium is weakly dependent on the concentration of the species in the two liquid phases and therefore, the equilibrium behaviour can be explained by considering the ideality of both the phases [7]. Any probability of the non-identity of the organic phase can be ruled out because of the negligibly small aggregation of the lipophilic carrier in polar butyl acetate as the solvent [1].

3.2. Extraction efficiency

The extraction efficiency (E) obtained for the β-lactam studied at different pH and at constant concentrations of Aliquat-336 and β-lactam are shown in Fig. 2. It is observed that the degree of extraction increases with an increase in pH due to dissociation behaviours at high pH values and increase in ionisation ability of the β-lactams. In order to support this observation, additional data were also generated for extraction of cephaloridine in the same carrier–solvent system. For instance, Aliquat-336 provides finite extraction at both low and high pH values unlike the behaviour exhibited by any of the secondary and tertiary amine carriers. Using any of the amines, longer pH shift will be required for extraction and re-extraction of the β-lactams [4]. Furthermore, Aliquat-336 may be considered to extract both dissociated and undissociated forms of the β-lactam while the amine carrier better extracts the undissociated molecule as reported for carboxylic acid extraction by similar carriers [18]. Aliquat-336 was however found to extract olivanic and clavulanic acids solely by liquid–liquid ion exchange mechanism [12] and provides higher extraction efficiency than Amberlite LA-2.

The degree of extraction of the β-lactams with any of these carriers is found to be considerably lower than that reported

Table 1
Equilibrium constant for extraction (K_p) and co-extraction (K_A) for various β-lactams Aliquat-336-butylacetate system C_{QCl} = 1–10 mM, C_P = 0.5–1.5 mM

β-Lactam	pH	K_P (×10²)		K_A (×10²)	R^{2a}
		Experimental	Predicated		
6-APA	8	23.0	21.84	11.8	0.89
7-ACA	8	20.0	21.7	9.0	0.91
Cephalosporin-C	9.8	89.0	94.0	38.2	0.99
7-ADCA	8	30.0	29.0	12.5	0.98
	7	16.11	15.8		0.92
	6	3.41	2.7		0.89
	5	0.88	0.8		0.92
Cephalexin	8	75.0	73.0	38.2	0.94
	7	15.0	13.8		0.85
	6	3.07	3.0		0.94
	5	0.937	0.88		0.90

[a] Correlation coefficient.

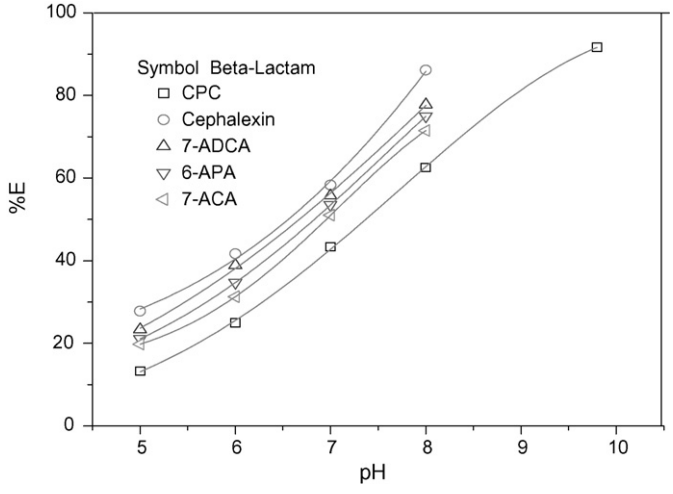

Fig. 2. Effect of degree of extraction on pH for extraction of different solutes with Aliquat-336, C_P = 1.0 mM; C_{QCl} = 1–10.0 mM.

Table 2
Maximum percentage stripping of various β-lactams and the corresponding pH values

β-Lactam	pH	% of stripping	J_s (mol/(cm^2 s))
6-APA	4	67.4	3.74×10^{-10}
Cephalosporin -C	4	72.9	4.0×10^{-10}
Cephalexin	4	74.1	3.4×10^{-10}
7-ACA	4	75.5	3.22×10^{-10}
7-ADCA	3	83.3	5.15×10^{-10}

$C_{Cl^-} = 0$.

for penicillin-G ($\%E = 30$ at pH 8) [15,14] and phenyl acetic acid ($\%E = 13$ at pH 8) and phenoxy acetic acid ($\%E = 10$ at pH 8) [15] under comparable experimental conditions probably as a result of lower pK_{a1} (dissociation constant) values of 6-APA and 7-ACA [3,4]. It may however be expected that higher extraction (E) value can be obtained using large excess of carrier.

3.3. Stripping kinetics

Considering the nature of the extractive reaction, the pertinent variables affecting the stripping could 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 followed by an analysis of the kinetics model.

3.3.1. Effect of stripping phase pH and chloride ion concentration

Due to zwitterionic character of the β-lactams studied in this work, the pH dependence of stripping rate may be considered reasonable. However, the extent of stripping and pH dependence seem to be different for different β-lactams as shown in Table 2 and Fig. 3. The data presented in Table 2 and Fig. 3 pertain to stripping from an organic phase of *n*-butyl acetate containing 10 mM QCl which was equilibrated with 1 mM aqueous β-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 β-lactams are essentially the same with but marginal difference, 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 2 and Fig. 3 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 β-lactams as shown in Fig. 3. This observation perhaps indicates the role of the molecular structure of the β-lactam whose pK_a values 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 β-lactams studied in this work.

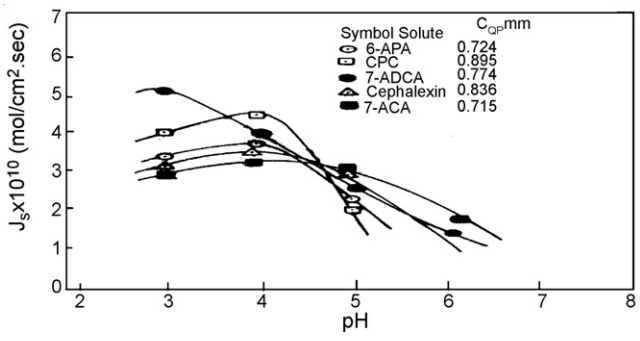

Fig. 3. Effect of aqueous phase pH on initial stripping rate of β-lactams. $C_{Cl^-} = 0$ (aqueous phase).

The effect of chloride (NaCl) ion concentration (C_{Cl^-}) in the stripping phase is shown identical experimental conditions of Fig. 3. It may be noted that the data in Fig. 3, the 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 which is further substantiated by rather weak dependence of J_s on C_{Cl} as given by the following relation:

$$J_s \alpha C_{Cl}^n, \qquad J_s = k_e C_{Cl}^n \tag{12}$$

where k_e and n are empirical constants, the values of 'k_e' and 'n' estimated by linear regression of experimental data. The values of k_e are 0.6557, 0.8757, 0.7107, 0.7119, 0.7727 for 6-APA, 7-ACA, 7-ADCA, cephalexin and cephalosporin-C, respectively, and the standard deviation was found to be within ±10%. The values of n are 0.032, 0.02, 0.036, 0.026, 0.03 for 6-APA, 7-ACA, 7-ADCA, cephalexin 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. [11] that an additional anion exchange reaction of QCl with buffer anion which augments the stripping process.

3.3.2. Effect of carrier/solute–carrier complex 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 (J_s). The effect of both C_{QP} and loading can be assessed simultaneously from a relation of C_{QP} and J_s. It may be noted that C_{QP} was varied by varying C_{QCl} at constant C_P in equilibration experiments and therefore, free C_{QCl} in loading organic solution would also vary.

The effect of concentration of the complex is shown in Fig. 4 which is a log–log plot of J_s versus C_{QP} at various loading. The effect of free QCl (not bound to β-lactams) on J_s 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). Fig. 5 shows the relationship of J_s with free C_{QCl} in the organic phase which seems to be reasonable in as-much as the higher free C_{QCl} may be considered to enhance the rate of the additional ion exchange reaction with buffer ion thereby providing the C_{Cl} driving force for the stripping process.

In spite of this limiting factor of the stripping process, a quantitative estimate of the data of Fig. 4 revealed that J_s is directly proportional to C_{QP} implying that the rate is first order

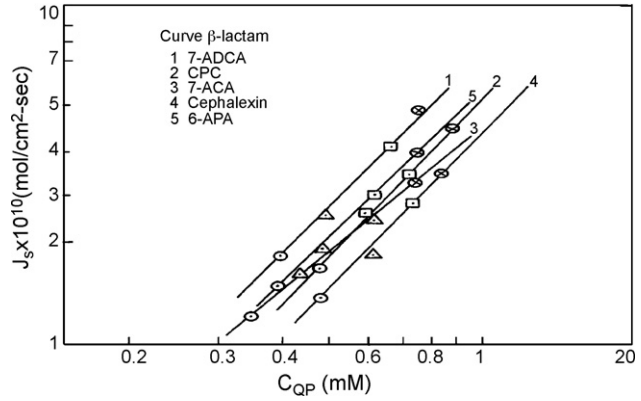

Fig. 4. Effect of the complex concentration in organic phase on initial stripping rate of β-lactams, $C_{Cl^-} = 0$ (aqueous phase):

Symbol	Ratio of C_{QCl}/C_{QP}				
	7-ADCA	CPC	7-ACA	Cephalexin	6-APA
○	1.5:1	1.13:1	1.85:1	1.08:1	1.5:1
△	2.4:1	2.28:1	3.54:1	2.2:1	3.08:1
□	6.3:1	5.9:1	7.3:1	5.85:1	7.0:1
⊗	11.8:1	10.2:1	12.3:1	10.9:1	12.1:1

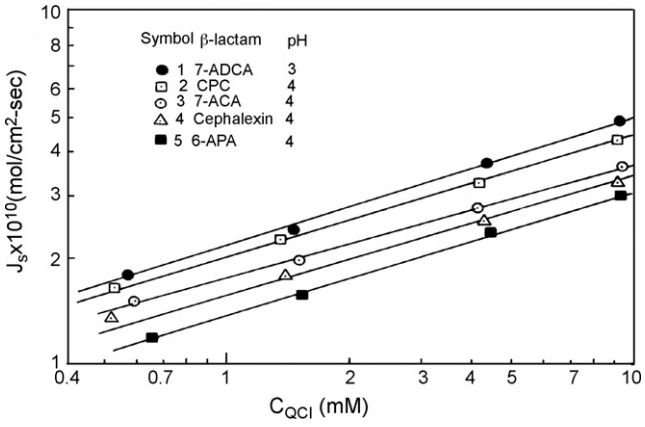

Fig. 5. Effect of free QCl concentration on initial stripping rate.

with respect to the complex concentration for all the β-lactams studied in this work. This relationship of J_s versus C_{QP} was deduced from a linear regression of the experimental data with an estimated standard deviation of ±8%.

Table 3
Estimated mass transfer coefficient of the stripping kinetic model

β-Lactam	k_{P_s} (cm/s)	k_{QCl} (cm/s)	k_{QP} (cm/s)
6-APA	1.29×10^{-4}	1.215×10^{-4}	1.02×10^{-4}
CPC	1.91×10^{-4}	1.386×10^{-4}	1.189×10^{-4}
7-ACA	2.24×10^{-4}	1.216×10^{-4}	1.04×10^{-4}
Cephalexin	1.59×10^{-4}	1.15×10^{-4}	0.98×10^{-4}
7-ADCA	2.18×10^{-4}	1.127×10^{-4}	0.951×10^{-4}

3.3.3. Validation of kinetic model

The mass transfer model given by Eq. (10) was used to generate theoretical profile of C_{P_s} versus time (t). The theoretical curves were fitted to the experimentally measured C_{P_s} values by identification of the three mass transfer coefficients k_{P_s}, k_{QP} and k_{QCl} where the ratio of k_{QCl}/k_{QP} was kept constant at 1.18/1. This ratio was evaluated from the diffusion coefficient calculated following the procedure reported elsewhere [19,20]. The estimated values of the mass transfer coefficient for various β-lactam are shown in Table 3 The experimental and theoretical C_{P_s} versus time (t) profiles (calculated with k_{P_s} values of Table 3) for various β-lactams are shown in Fig. 6(a) and (b). It appears that the agreement between theoretical and experimental C_{P_s} versus time (t) profile is fairly well for 7-ADCA and cephalexin. The estimated deviation of the experimental data from theoretical profiles lies between 10 and 12% 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 β-lactam under study. The observed deviation perhaps implies that the stripping rate may be controlled by another probable mechanism. The loaded organic phase contains appreciable proportion of free QCl which has certain surface active properties and is likely to take part in another anion exchange reaction with buffer anion of the stripping aqueous solution [13]. It may, therefore, be expected that the 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 beyond the purview of the present study.

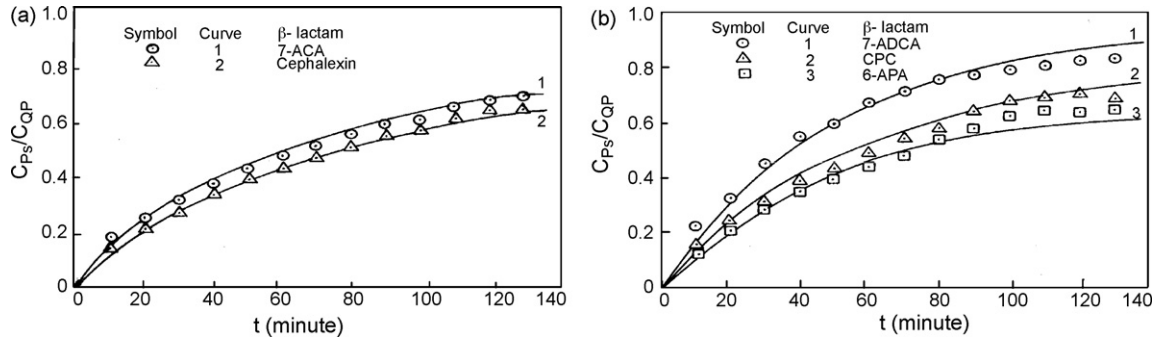

Fig. 6. Comparison of experimental results on stripping kinetics with model calculation: (a) $C_{QP} = 0.715$ and 0.836 mM for 7-ACA and cephalexin, respectively; (b) $C_{QP} = 0.77$, 0.895 and 0.742 mM for 7-ADCA, CPC, and 6-APA, respectively.

4. Conclusion

A systematic investigation on equilibrium of reactive extraction of certain β-lactam antibiotics such as 6-APA, 7-ACA, 7-ADCA, cephalexin, cephalosporin-C has been made using quaternary ammonium salt (Aliquat-336) as the carriers and butyl acetate as organic solvent, with an emphasis on a complimentary stripping kinetic study.

The extraction efficiency increases with increase of pH for liquid ion exchange extraction with Aliquat-336. The pH dependence is important as re-extraction at appropriate pH (3–4) value is possible. Increase of solute concentration in aqueous phase decreases the equilibrium extraction while increase of carrier concentration exhibits positive effect. Furthermore, increase in ionisation ability of the β-lactams appears to increase the extraction efficiency of Aliquat-336 in butyl acetate as the solvent.

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

The initial rate of stripping is dependent on Cl^- concentration of the aqueous phase but is the first order with respect to the complex concentration in the organic 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 an interfacial reaction controlled mechanism will be necessary to provide a more accurate description of the stripping kinetics.

Appendix A. Nomenclature

Ac	acetate ion
7-ACA	7-aminocephalosporinc acid
7-ADCA	7-aminodeacetoxy cephalosporinic acid
6-APA	6-aminopenicillanic acid
B	constant (Eq. 10)
C	molar concentration species (mM)
Cl^-	chloride ion (counter-ion of anion carrier)
CPC	cephalosporin-C
E	degree of extraction
H^+	proton
HP	β-lactam molecule
J_s	stripping rate (mol/(cm^2 s))
k_P	mass transfer coefficient of β-lactam ion (cm s^{-1})
k_{QCl}	mass transfer coefficient of carrier (cm s^{-1})
k_{QP}	mass transfer coefficient of loaded β-lactam-carrier complex (mol cm^{-1})
K_a	dissociation constant
K_A	equilibrium co-extraction constant
K_d	distribution equilibrium constant
K_P	equilibrium constant
P	β-lactam
P^-	β-lactam anion (at equilibrium)
QAc	Aliquat-336-acetate complex
QCl	Aliquat-336
QP	Aliquat-336-β-lactam complex
QA	Aliquat-336-buffer anion complex
R	constant (Eq. (10))
S	specific interfacial area (cm^2)
t	time of stripping (s)
V	volume of organic/aqueous phase (l)

Subscripts/superscripts

aq	aqueous phase
i	initial
org	organic phase
s	aqueous strip phase
*	interface

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