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Kinetic and thermodynamic evaluation of phosphate ions binding onto sevelamer hydrochloride

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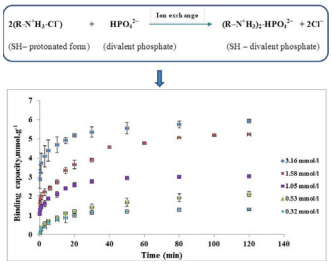

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ABSTRACT

Sevelamer hydrochloride is the first non-aluminium, non-calcium-based phosphate binder developed for the management of hyperphosphatemia in end stage renal diseases. It is a synthetic ion-exchange polymer which binds and removes phosphate ions due to the high content of cationic charge associated with protonated amine groups on the polymer matrix. This is the first in-depth study investigating phosphate removal *in vitro* from aqueous solutions using commercially available sevelamer hydrochloride at physiological conditions of phosphate level, pH and temperature. The kinetic and thermodynamic parameters of phosphate binding onto the sevelamer hydrochloride particles were evaluated in order to define the binding process. A series of kinetic studies were carried out in order to delineate the effect of initial phosphate concentration, absorbent dose and temperature on the rate of binding. The results were analysed using three kinetic models with the best-fit of the experimental data obtained using a pseudo-second order model. Thermodynamic parameters provide in-depth information on inherent energetic changes that are associated with binding. Free energy ΔG°, enthalpy ΔH°, and entropy ΔS° changes were calculated in this study in order to assess the relationship of these parameters to polymer morphology. The binding reaction was found to be a spontaneous endothermic process with increasing entropy at the solid–liquid interface.

1. Introduction

Polymers as drugs present interesting and novel functionalities and properties not inherent in traditional small molecule pharmaceuticals. Sevelamer HCl or Renagel® is an example of the remarkable success of a polymer synthesised with high content of cationic amine groups in a structure that is insoluble and non-absorbable in the body. It is a cross-linked polyallylamine hydrochloride (PAA-HCl) hydrogel formulated as an oral dose to prevent the absorption of dietary phosphate for patients with end-stage renal failure (Dhal et al., 2009; Holmes-Farley et al., 1999; Rosenbaum et al., 1997). Sevelamer hydrochloride binds to trivalent anions such as phosphate, citrate and sulphate. It will also bind excretion bile acids and other intestinal anions especially chloride, bicarbonate, and short-chain fatty acid anions (SCFAA) which would compete with phosphate for uptake by the resin. This competition is considered as critical factor in determining the resin 's ability to remove phosphate during transit through the gut (Bellasi et al., 2006; Ferramosca et al., 2005). It is also a cause of the major drawback of sevelamer hydrochloride which is the large pill burden. However, the phosphate binding capacity depends on the protonation of the polymer as well as the extent to which this insoluble polymer hydrates or swells in aqueous solution.

Sevelamer hydrochloride (SH) is a weakly basic anion-exchange resin in the chloride form. It contains amine groups which are protonated fully at low pH, and exists as the free form in a strongly alkaline media. These groups can be involved in chemical bonding and are responsible for the cation exchange capacity of SH. The reaction of SH and phosphate ions may be represented as (Wrong and Harland, 2007):

$$\underset{\text{(SH–protonated form)}}{2(R\text{—}N^{+}H_3\text{—}Cl^{-}} + \underset{\text{(divalent phosphate)}}{HPO_4^{2-}} \rightarrow \underset{\text{(SH–divalent phosphate)}}{(R\text{—}N^{+}H_3)_2 - HPO_4^{2-}} + 2Cl^{-} \quad (1)$$

The rate at which phosphate ions binding takes place is very important. It describes how fast the drug removes phosphate ion

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and what conditions affect the rate. Consequently, it is important to establish the time dependence of such systems under various binding conditions. The published body of work in the literature focuses on the equilibrium capacity of sevelamer hydrochloride (Swearingen et al., 2002, 2004), which is fundamental for evaluation of the binding affinity and capacity of sevelamer hydrochloride. However, it is important to identify the rate determining step and evaluate how the reaction rate is affected by the conditions involved in the binding reaction. Many attempts have been made in the literature to formulate a general expression describing the kinetics of sorption onto solids for liquid–solid phase sorption systems. Liquid–solid sorption kinetic data are mostly interpreted by a limited number of rate equations, some of which are pseudo first order, second order, pseudo-second order and Elovich (Stavropoulos, 2011). Shek et al. (2009) studied the equilibrium exchange capacity and kinetics of zinc ion removal from effluents using ion exchange resin. The results were analysed using three kinetic models, pseudo-first order, pseudo-second order and the Elovich model and the best-fit correlation of the experimental data was obtained using the Elovich model. Rengaraj et al. (2007) studied the adsorption of copper(II) onto Amberjet 1500H and Ambersep 252H synthetic ion exchange resins by a batch method to determine the equilibrium and kinetic parameters. Sorption kinetic data were tested using pseudo-first-order, pseudo-second-order and intraparticle diffusion models. For the systems studied, pseudo-second-order kinetics provided the best correlation of the experimental data for both the 1500H and 252H resins. Similar results were also observed when copper(II) sorbed onto chitin, chitosan and Rhizopus arrhizus with the pseudo-second order rate expression providing the best fitting kinetic model (Sag and Aktay, 2002). According to Sun et al. (2011) the sorption of mercury ions onto silica gel functionalised with polyamidoamine polymers was found to occur via chemisorption. The kinetic data fitted well with the second-order model and the calculated thermodynamic parameters indicated a spontaneous and endothermic process with increased randomness at the solid-solution interface of Hg^{2+} adsorption onto the resins. Many authors explained the removal or sorption of other ions onto ion exchange resins or polymeric material via pseudo second order kinetics. Some examples in which the sorption process in resins or polymeric material was described as a spontaneous and endothermic reaction are available in these references (Cam et al., 2014; Rahman and Haseen, 2014).

However, little is known about the rate of phosphate ion binding by sevelamer hydrochloride and the energies involved in the binding process. The only published data on the kinetic of the phosphate binding reaction was by Holmes-Farley et al. (1999). The authors found that the kinetics of phosphate binding was far faster than the transit times through the gastrointestinal tract (hours). But there were no kinetic or thermodynamic data describing the effect of the parameters involved in the binding reaction. Therefore, this study was focused on a detailed kinetic investigation of phosphate absorption using an agitation batch reactor to study the effects of the initial phosphate concentration, polymer dose and temperature on the binding properties of Renagel and its implications for renal patients.

2. Materials and methods

2.1. Materials

Sevelamer hydrochloride, SH, was synthesised using a method based on a USA patent no. 5,496,545 (Holmes Farley et al., 1996). The following materials were used: phosphate reagent (vanadium molybdate), potassium phosphate monobasic (KH_2PO_4), *N,N*-bis (hydroxyethyl)-2-aminoethanesulfonic acid (BES) (100 mM), NaOH (0.1 M) and NaCl (0.1 M). All chemicals were of ACS grade or higher and were used without further purification.

2.2. Equipment and instrumentation

A Stuart scientific orbital incubator (SI500) was used for all equilibrium studies. A HACH UV–vis spectrophotometer was used for determining phosphate concentrations.

2.3. Kinetic studies

2.3.1. Effect of initial phosphate ion concentration on the phosphate binding process

Binding isotherms were generated by placing a constant mass of SH (0.006 g ± 0.001) of known particle size (150–325 nm) in 12 centrifuge tubes. 50 ml of phosphate solution was added to each bottle. The mixture was agitated at a speed of 230 rpm at the physiological conditions of 310 K and a pH of 7.0 ± 0.2. The initial concentration of phosphate ion solution was varied, (0.32, 0.53, 1.05, 1.58 and 3.16 mmol/l). The phosphate concentrations were chosen to be above and below the plasma phosphate level in a healthy human which is 1.6 mmol/l (Friedman, 2005; Spasovski et al., 2009), in order to understand the impact of varying the initial phosphate concentration on the rate of ion binding onto SH *in vitro*. Each bottle was removed from the shaker and filtered at specified times of 0.25, 05, 1, 3, 5, 10, 15, 20, 30, 50, 80 and 120 min. The final concentration of free phosphate ions in solutions was determined using the UV–vis spectrophotometer.

2.3.2. The effect of polymer mass on the phosphate binding process

The reaction rate was studied using the same conditions as in Section 2.3.1, except that the initial phosphate concentration was set at 1.58 mmol/l, as the plasma phosphate level in human should be maintained between 0.8 to 1.6 mmol/l (Friedman, 2005; Spasovski et al., 2009). SH masses of 0.005 and 0.012 g ± 0.001 were used. Sampling, analysis and treatment of results, as previously described in Section 2.3.1.

2.3.3. Effect of temperature on the phosphate binding process

The reaction rate was studied using the same conditions as in Section 2.3.1 with an initial phosphate ion concentration of 1.58 mmol/l equal to the highest limit of normal range of plasma phosphate levels in humans (Friedman, 2005; Spasovski et al., 2009). The experiment was carried out at 278, 292, 298, 310 and 323 K. These temperatures covered a wide range to get sufficient data points to apply the Eyring relationship to obtain the thermodynamic parameters. Analysis and treatment of results were as previously described in Section 2.3.1.

2.4. Kinetic models applied to the phosphate binding process by sevelamer hydrochloride

The batch kinetic experimental data was substituted into an Excel spread sheet to identify the most suitable kinetic model. Three types of kinetic models were utilised to investigate the binding of phosphate ions onto SH; a pseudo-first order model Eq. (2), a second order model Eq. (3) and a pseudo-second order model Eq. (4).

- The pseudo-first order model equation (Ho and McKay, 1998b):

$$\frac{dq}{dt} = k_1(q_e - q_t) \quad (2)$$

where q_e and q_t are the amount of ion sorbed per gram of sorbent at

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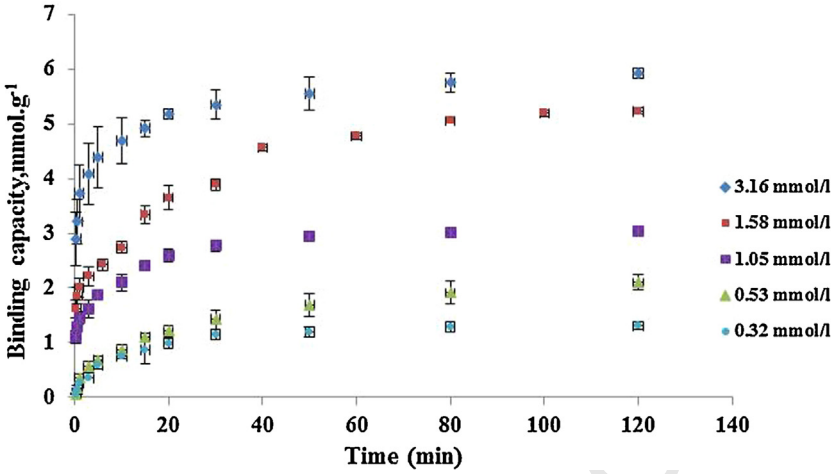

Fig. 1. Experimental isotherms generated for SH by loading 0.32–3.16 mM phosphate solutions (310 K, pH 7.0 ± 0.1 and a polymer mass of 0.006 g). Data is based on the average values from triplicate analyses and ±1 standard deviation.

equilibrium and at any time t, respectively (mmol g^{-1}) and k_1 the rate constant of the pseudo-first order sorption (min^{-1}).

- The second order model equation (Atkins, 1996):

$$\frac{1}{q_e - q_t} = \frac{1}{q_e} + k_2 \times t \quad (3)$$

- The pseudo-second order model equation (Benaissa and Benguella, 2004; Ho and McKay, 1999).

$$\frac{t}{q_t} = \frac{1}{k'_2 q_e^2} + \frac{1}{q_e} t \quad (4)$$

If : $h = k'_2 q_e^2$ (5)

Substituting Eq. (5) into Eq. (4) yields:

$$\frac{t}{q_t} = \frac{1}{h} + \frac{1}{q_e} t \quad (6)$$

where k'_2 is the equilibrium rate constant of a pseudo-second order reaction (mmol^{-1} g min^{-1}) and h is the initial rate (mmol g^{-1} min^{-1}). The rate constant can be determined by plotting t/q_t versus t. If pseudo-second order kinetics is applicable, the plot of t/q_t against t should give a straight line from which q_e, and h can be determined from the inverse of the slope and intercept of the plot respectively. k'_2 can be obtained by applying the q_e and h values in Eq. (5).

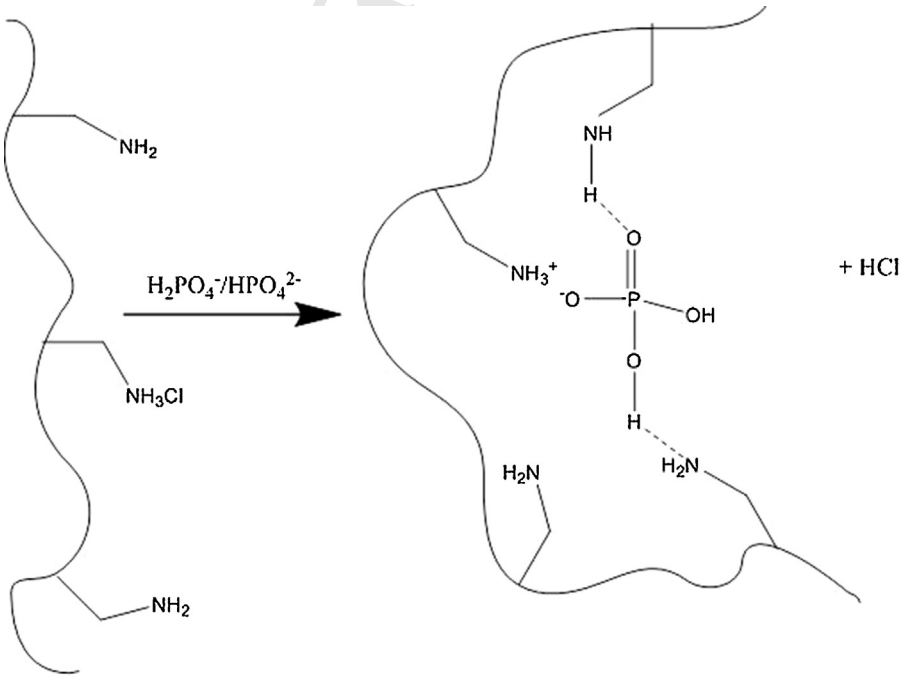

Fig. 2. Schematic illustration of binding interactions between poly ally amine hydrochloride and phosphate anions.

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2.5. Thermodynamic evaluation of the phosphate binding process

The thermodynamic parameters ΔG°, ΔH° and ΔS° were evaluated using the equilibrium constant equation, which depends on temperature (Bektas et al., 2004; Cruz et al., 2004):

$$K_d = \frac{q_e}{C_e} \quad (7)$$

where K_d is the binding distribution coefficient, C_e is the equilibrium phosphate concentration in solution (mmol/L) and q_e is the equilibrium capacity of phosphate ions in the hydrogel (mmol/g). K_d values were used in Eq. (8) to determine the ΔG° (kJ/mol), of the binding process at different temperatures.

$$\Delta G^\circ = RT \ln K_d \quad (8)$$

where T is the temperature (Kelvin) and R is the universal gas constant (8.314 J K^{-1} mol^{-1}).

Eyring demonstrated that the binding distribution coefficient may be expressed in terms of enthalpy changes (ΔH°) as a function of temperature, Eq. (9) (Ho, 2003; Lawrence and Atherton, 1970):

$$\ln K_d = -\frac{\Delta H^\circ}{RT} + Y \quad (9)$$

where ΔH° is the heat of the reaction (kJ/mol) and Y is a constant. Eq. (9) can be rearranged to obtain Eq. (10):

$$\Delta S = RY \quad (10)$$

where ΔS° is the standard entropy change (J K^{-1} mol^{-1}).

The Gibbs free energy change, ΔG°, can be represented as follows:

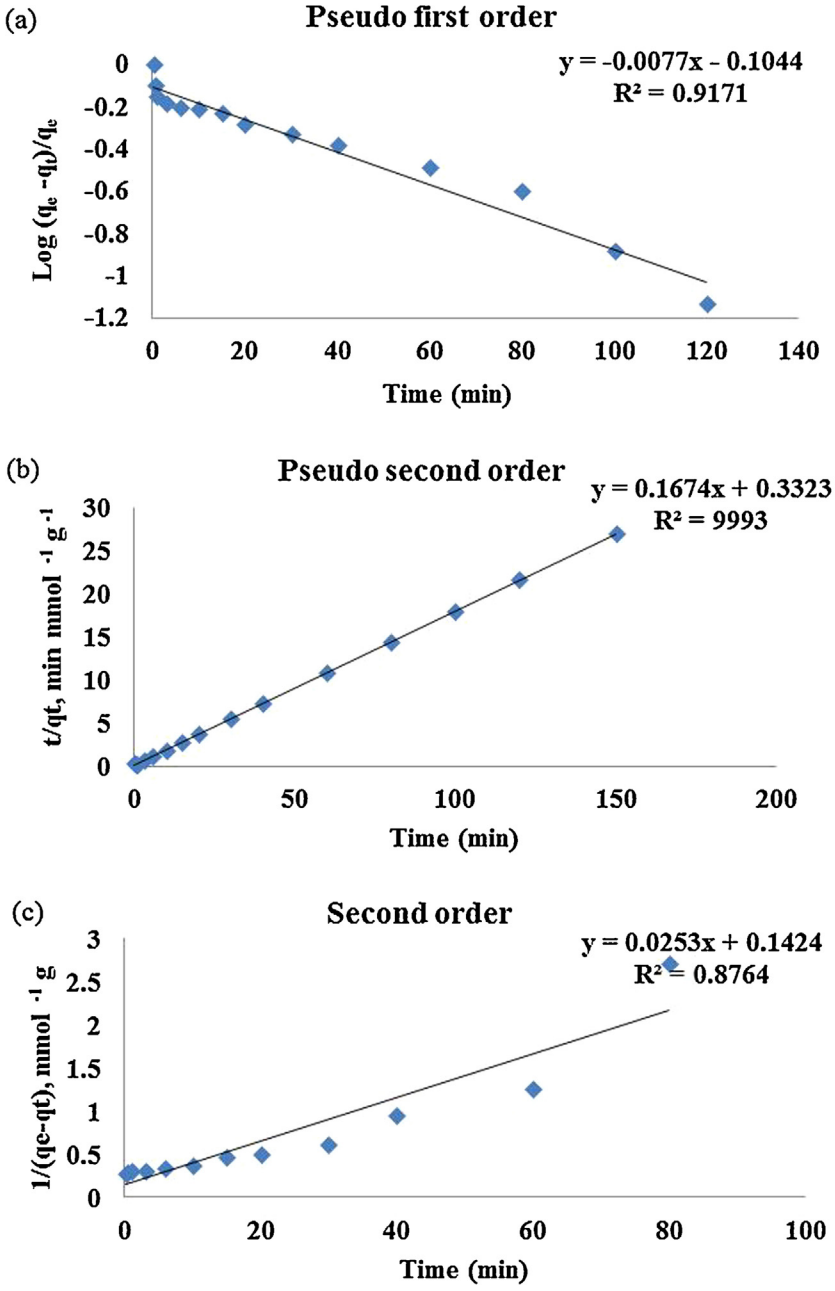

Fig. 3. Pseudo-first order (a), pseudo-second order (b) and second order (c) kinetic plots. An initial phosphate ion concentration of 3.16 mmol/L at 310 K and pH 7.0 ± 0.2 was used.

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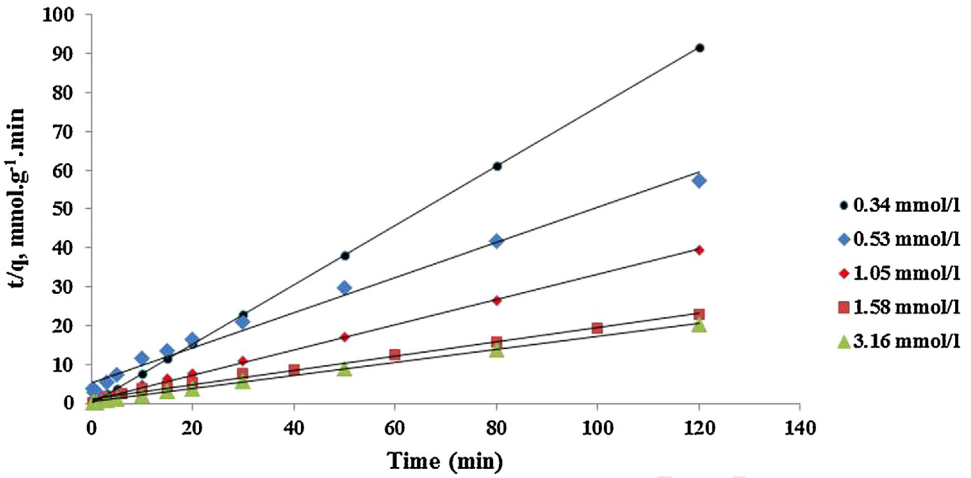

Fig. 4. Overlay of the pseudo second-order rate kinetic plots for phosphate removal by SH (0.005 g) at 310 K and pH 7.0 ± 0.1. Data is based on the average values from triplicate analyses.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (11)$$

The values of ΔH° and ΔS° can be obtained from the slope and intercept of a plot of ln K_d versus $1/T$.

3. Results and discussion

3.1. Effect of initial phosphate ion concentration

The Kinetic curves generated for SH are shown in Fig 1. The binding capacity increased noticeably in the first 5–10 min. At the beginning of the binding process, the polymer particles are not fully swollen, as a result, only the surface amino groups were able to interact with the sorbate molecule. This step is very fast, followed by a slow increase in sorption until equilibrium was reached. This second phase of binding is a slow diffusion process and rearrangement of polymer chains may be considered as the rate limiting step. At this stage, the enhanced availability of the amine groups allows solvent molecules to diffuse into the polymer matrix. Accordingly, the phosphate ions (HPO_3^{2-} and H_2PO^{3-} at pH 7) were able to diffuse into the resin and have contact with the inner binding sites, Fig 2.

The binding dynamics can be described by the following three consecutive steps which are as follows:

(a) Diffusion of ions through the liquid film surrounding the particle (film diffusion).
(b) Diffusion of ions through the polymeric matrix of the resin. This step involves greater resistance therefore, it can be considered as the rate-limiting step of the process.
(c) Ion exchange.

The necessary time to reach equilibrium was dependant upon the initial phosphate concentration. It was found to be approximately 120 min when the initial phosphate concentration was 0.32 mM and decreased to 40 min when the phosphate concentration was 3.16 mM. Also the binding capacity of the hydrogel at equilibrium increased with increasing initial phosphate concentration.

The binding data obtained was fitted to pseudo first order, pseudo second-order and second order equations. Fig 3(a–c), illustrates an example of the kinetic plots of SH using 3.16 mM phosphate concentration. Plots were drawn, with the highest R^2 values obtained when fitting the binding data to a pseudo second-order equation indicating that the process follows pseudo second-order kinetics. The same trend was obtained for all phosphate concentrations, Fig 4. Equilibrium binding capacities, q_e, and the initial rate of reaction, h, were obtained from the inverse of the slopes and intercepts of the lines respectively. Rate constants, k'_2, were calculated by applying the values of q_e and h to Eq. (6). Data obtained from these rate experiments are given in Table 1.

Data presented in Table 1, demonstrated that the rate constant, binding capacity and the initial rate increased as the initial phosphate concentration increased. This could be attributed to the increase in concentration gradient during diffusion. Diffusion is a term used to describe the mixing of two different substances that are placed in contact. Substances can be solids, gases or liquids which consist of particles. These particles are migrating by random motion and move in every direction, however, there is a net flow from the more concentrated solution to the less concentrated solution until the system reaches equilibrium (Helfferich, 1962).

The results in Table 1 also shows good agreement with pseudo-second-order kinetics. The regression coefficients for the linear plots were greater than 0.997 for all the systems studied. No kinetic data describing sevelamer hydrochloride or PAA-HCl hydrogel as an adsorption system is available in the literature to date to compare the sorption kinetic data obtained in this study. However, the system here showed similarities with some works in which polymers and ion exchange resins were used in sorption systems.

Table 1
Influence of initial phosphate concentration on binding capacity and rate constants.

Conc, mM	k'_2, mmol^{-1} g^{-1} min^{-1}	q_e, mmol g^{-1}	h, mmol g^{-1} min^{-1}	R^2
0.32	0.006×10^{-2}	1.3	0.001	0.998
0.53	2.6×10^{-2}	2.1	0.16	0.999
1.05	10.0×10^{-2}	3.1	1.18	0.999
1.58	11.3×10^{-2}	5.4	1.22	0.998
3.16	11.6×10^{-2}	5.8	3.01	0.997

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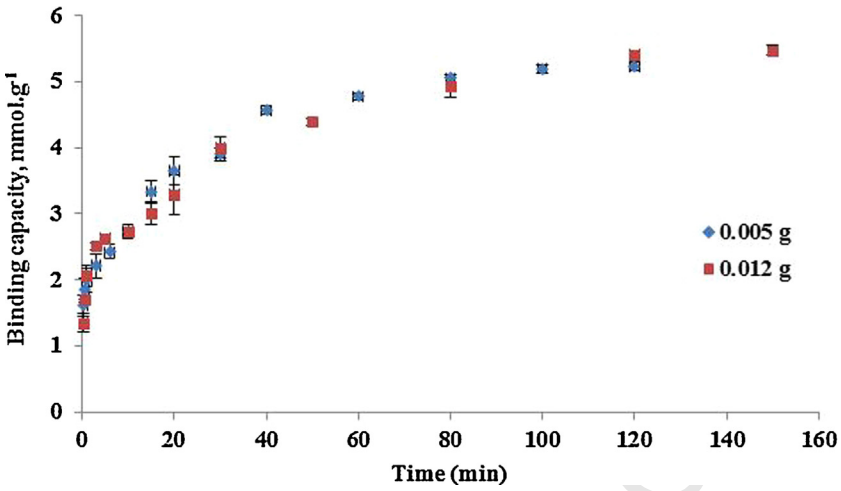

Fig. 5. Effect of polymer mass on phosphate binding capacity. Phosphate ion concentration was 1.58 mmol/l loaded at a temperature of 298 K and pH of 7.2 ± 0.2. Data is based on average values from triplicate analyses.

The pseudo-second order equation has been adequately employed to describe sorption reactions of liquids onto solid surfaces for different systems. Ho and McKay (1998b), investigated the sorption of basic dyes onto wood. The authors studied the sorption process by pseudo-second order, intra-particle diffusion and pseudo-first order equations. Ho and Mckay (Ho and McKay, 1999) have also tested 11 sorption systems that have been previously reported in the literature as first order reactions and one system reported as second order using the pseudo second order model. According to the authors, in all 12 systems, the highest correlation coefficients were obtained for the pseudo-second order kinetic model. The advantages of using the pseudo second order equation is that it covers the whole experimental time required by the system to reach equilibrium, unlike the second order model and pseudo first order model which covers only the first 15–20 min of the sorption process (Ho and McKay, 1998a).

3.2. Effect of hydrogel mass on the phosphate binding process

The effect of hydrogel mass on phosphate binding kinetics was studied and shown in Fig 5. Masses of 0.005 and 0.012 g were used to study the effect of higher hydrogel dose on binding equilibrium and kinetic data. It must be noted that if a larger amount of SH hydrogel was added to the batch reactor; nearly complete anion removal would be achieved. However, the aim of these experiments was to calculate the binding capacities per gram of the gel and not to achieve maximum removal of phosphate anions. Hence, SH gel amounts used were small enough for the gel to reach its saturation point before complete removal of phosphate anions from the standard solutions.

Table 2
Kinetic data obtained applying the pseudo second order rate equation and using different SH masses.

Mass, g	k'_2, mmol^{-1} g min^{-1}	q_e, mmol/g	h, mmol g^{-1} min^{-1}	R^2
0.005	3.1×10^{-2}	5.30	0.91	0.993
0.012	3.2×10^{-2}	5.37	0.93	0.989

The experimental data shown in Fig 5 was fitted to a pseudo-second order rate equation. The rate did not change when using 0.005 and 0.012 g of SH hydrogel. The results of rate constants, equilibrium binding capacities and initial rates were obtained from the slopes and intercepts and are listed in Table 2. The pseudo second order model was deemed to provide the best fit to the results compared with two other models based on R^2 values. The results, in Table 2, demonstrated no significant increase in the rate constant k'_2, initial rate, h and equilibrium capacity, q_e. This indicated that the reaction rate was independent of hydrogel mass. The dependency of the rate constants on one reactant, the

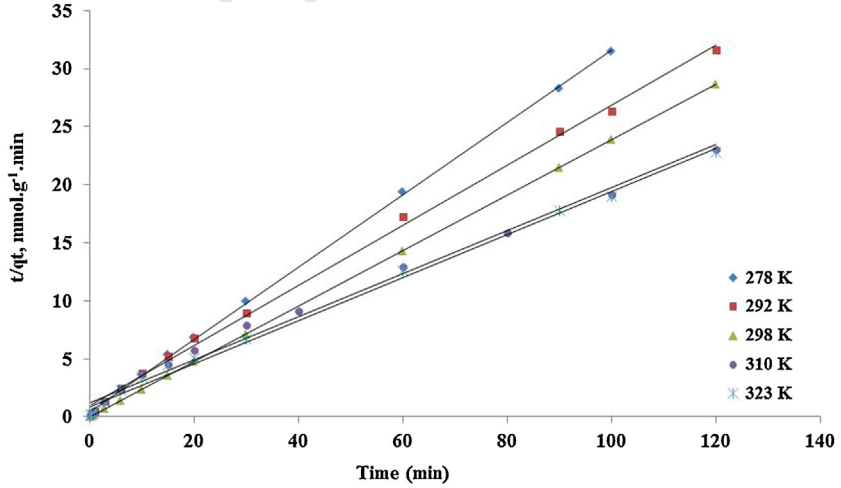

Fig. 6. Overlay of pseudo-second order rate kinetic plots for phosphate removal by SH at different temperatures using an initial phosphate concentration of 1.58 mmol/l.

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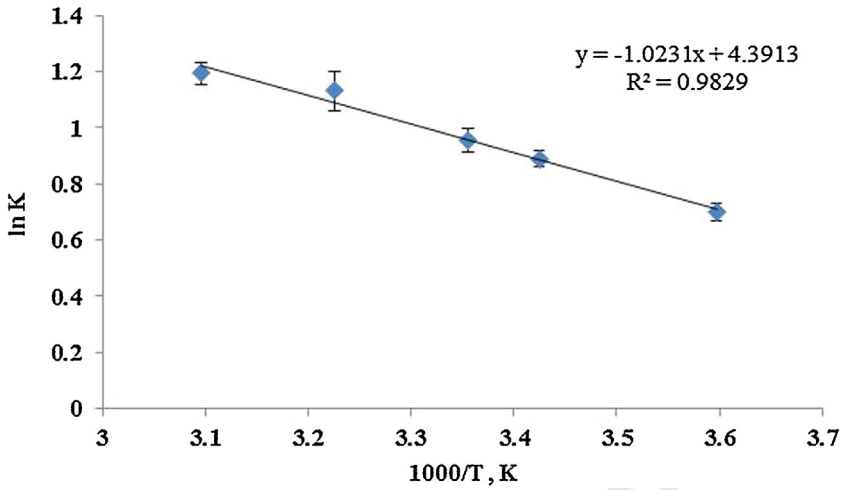

Fig. 7. Linear form of the Eyring equation for the assessment of the thermodynamic parameters of phosphate binding by SH.

initial phosphate concentration, rather than the hydrogel mass further indicates that the reaction is pseudo second order with respect to the phosphate ion concentration. As the concentration of phosphate is so much larger than the number of binding sites on the polymer, changes in the concentration of phosphate ions during the reaction are negligible when compared with changes in the number of binding sites on the hydrogel. The rate equation may be expressed as below (Lawrence and Atherton, 1970):

$$-\frac{d[A]}{d_t} = k'_2[A]^2 \quad (12)$$

where A is the concentration of phosphate solution (mmol L^{-1}), and k'_2 is the pseudo second order rate constant (mmol^{-1} g min^{-1}).

However altering the interior concentration of the polymer binding sites by modifying the crosslinker concentration may change the swelling rate of the polymer and increase the concentration of binding sites and hence may impact the kinetics. This factor was investigated by the authors and preliminary results showed that, reducing the crosslinker concentration produced polymers with higher swelling ratios and faster rates of binding but the polymer was very sensitive to moisture and difficult to store dry. Further investigation of methods to improve the degree of swelling and optimising the manufacturing process is required.

3.3. Effect of temperature on phosphate binding process

The temperature dependence of sorption was studied with a constant initial phosphate ion concentration of 1.58 mM (typical plasma phosphate level in humans) with various temperatures in the range of 278–323 K at pH 7.0 ± 0.2. Fig 6, illustrates the experimental kinetic data obtained which shows good compliance with pseudo-second-order kinetics. Rate constants k'_2 were found to increase, from 0.5×10^{-2} to 4.0 mmol^{-1} g min^{-1} $\times 10^{-2}$ mmol^{-1} g min^{-1}, as the temperature increased from 278 to 323 K respectively. Also q_e increased from 3.2 to 5.4 mmol g^{-1} when the temperature increased from 278 to 323 K (data not shown here).

Table 3
Thermodynamic parameters for the reaction of phosphate ions with SH.

$\Delta H°$, (kJ/mol)	$\Delta S°$, (J/mol K)	$\Delta G°$, (kJ/mol) 278 K	292 K	298 K	310 K	323 K
8.5	36.5	−1.6	−2.2	−2.4	−2.8	−3.3

The increase in q_e of sevelamer hydrochloride with increased temperature suggests that the binding reaction is an entropically favoured process (see Section 3.4).

3.4. Thermodynamic evaluation of the phosphate binding process

Thermodynamic parameters such as free energy of binding ($\Delta G°$), the heat of binding ($\Delta H°$) and standard entropy change ($\Delta S°$) were evaluated using Eqs. (7)–(11). The temperature range used was from 278 to 323 K. An Eyring plot was obtained by plotting ln K versus $1/T$, Fig 7. From the straight line obtained Fig. 7, the parameters $\Delta S°$ and $\Delta H°$ were calculated, and are given in Table 3.

Analysing the data in Table 3, the negative values of $\Delta G°$ indicates the spontaneous nature of the binding process. The positive value of enthalpy of 8.5 kJ/mol, is related to an adsorption that is endothermic. The positive value of $\Delta S°$ is probably due to a number of factors. Firstly the binding of one divalent HPO_3^{-2} ion releases two Cl^- ions into solution thereby increasing entropy. Secondly in order to bind to the polymer, the phosphate ions must lose their water solvation shell and the subsequent solvent reorganisation is entropically favourable (although this may be offset somewhat by solvation of any released chloride ions). These factors appear to overcome the reduction in entropy of the polymer which may occur where a divalent HPO_3^{-2} ion acts as an additional crosslink (Fig. 2). Therefore, the adsorption was spontaneous, entropically favoured and proportional to the temperature. However, the Eyring plot showed a low steep slope which gave an indication of the low sensitivity of the reaction rate towards temperature changes (Lawrence and Atherton, 1970).

4. Conclusion

This novel and first in-depth kinetic and thermodynamic investigation of phosphate ions bound by sevelamer hydrochloride, suggests that the sorption of the phosphate ion is a two-step process. The first step, which is rate determining, involves the diffusion of the phosphate ions through the polymer matrix. The second step is ion exchange which is relatively fast. The rate of the first step may be tailored by changing the swelling ability of the particles by reducing the crosslinker concentration in the synthesis reaction of sevelamer hydrochloride. Based on the present study, the following conclusions can be drawn:

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- The mechanism of phosphate ion binding by sevelamer hydrochloride has been investigated and assessed via a pseudo second order kinetic model, as a combination of diffusion and ion exchange processes.
- The process of phosphate binding by SH was found to be a spontaneous endothermic reaction. The process is entropically driven with ΔG° decreasing with increasing temperature. However, limited sensitivity to temperature changes was observed. The positive values of ΔS° showed the increased randomness at the solid/solution interface during the adsorption process.
- The time needed for SH to bind phosphate ions and reach equilibrium was found to be faster than normal gastric emptying of solid and liquid food which is 3 h approximately thus having no effect on the efficacy of the drug.

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