Characterisation of the Ion Exchange Reaction Between Propranolol-H^+ or K^+ with Amberlite™ IRP 69 Resin by Both, Isothermal Titration Calorimetry and (Flame) Photometric Equilibrium Analysis

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Abstract: The model system propranolol hydrochloride (PROP-HCl)/Amberlite™ was studied in terms of equilibrium concentrations and amount drug bound to the ion exchanger, and compared to the system potassium chloride (KCl)/Amberlite™. It was found that both the affinity and exchange capacity of Amberlite™ for PROP-H^+ ions is higher than for K^+. Specific heat effects of the exchange reaction measured by isothermal calorimetry and spectroscopy revealed that even at the lowest degree of loading with propranolol, the heat effects surprisingly change continuously with the degree of loading, while they are constant for potassium. Involvement of non-specific forces in the binding of propranolol-H^+ to Amberlite™ is discussed as a possible reason for this behaviour.

Keywords: Adsorption, Langmuir equation, isothermal titration calorimetry (ITC), ion exchanger, binding enthalpy, polymeric drug delivery systems, thermodynamics, Amberlite™ IRP 69, propranolol hydrochloride.

1. INTRODUCTION

Ion exchangers (IE) are frequently used not only for preparative and analytical chromatography, but also in pharmaceutical products to modify the release of drugs (for a recent review see [1]). Many drugs as weak acids or weak bases are dissociated at physiological pH, and as such possible candidates for ion exchange formulations. For rational drug design, a detailed understanding of the exchange reaction for both loading and release is essential.

Material properties of strong cation exchange resins of the styrene type have been a matter of studies since their introduction in 1945 [2-4], and [5] after [6]. It has been generally acknowledged that particle size affects the kinetics of the exchange reaction. The degree of cross linking, which itself affects the degree of swelling, alters the diffusion coefficient inside the ion exchanger. Other factors like temperature, nature (size) of the exchanging ions as well as their diffusion behaviour in the exterior phase (which can be altered by flow schemes and stirring) also strongly affect the rate of the ion exchange reaction, whereas the degree of loading is affected to a much lesser extent [6, 7].

The purpose of the present study is to look into the alteration of the mechanism of the ion exchange reaction when small organic dissociated molecules are used instead of inorganic ions. Amberlite™ IRP 69 was chosen as the ion exchanger because it is a pharmaceutical quality of sodium polystyrene sulfonate which complies with monographs both in the US Pharmacopeia (USP) [8] and the European Pharmacopeia (Ph. Eur) [9]. This ion exchange material is being used for therapeutic goals in dialysis patients in order to replace sodium ions with potassium ions. This exchange reaction is studied here as a reference. Propranolol-HCl is used as a (model) drug, because this system has been studied before as to yield reproducible equilibrium of loading within reasonable time [7, 10-12]. Moreover, more complex drug delivery systems have been developed [13, 14] based on the same ion-exchanger-drug system.

The basic theory of ion exchange reactions of this type of resins dates back to Baumann [2] who used sodium polystyrene sulfonate (Dowex™ 50), and revealed a number of useful mathematical expressions for the description of the systems. Although numerous studies have been carried out since, the mechanism of the ion exchange reaction is still widely unknown.

In a recent study, isothermal titration calorimetry has been introduced as a novel tool to characterise the exchange reaction of small molecular weight ionic drug compounds with polystryene sulfonate in terms of exchange enthalpies and mass equilibrium constants [12]. The aim of the current study was to relate the heat effects of step-wise analysis of the exchange reaction (isothermal calorimetry) with the binding equilibrium, both for potassium and propranolol HCl.

2. MATERIALS AND METHODS

Materials

The cation-exchange resin Amberlite™ IRP 69 (Sodium polystyrene sulfonate USP; Lot 6210TD12) was obtained as

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a generous gift from Rohm and Haas France S.A.S., Chauny, France. (±)-Propranolol hydrochloride was purchased from NMD AS, Oslo, Norway (batch 1H106/1 and 5E045/1) and from Synopharm GmbH, Barsbüttel, Germany (batch 0112A044). Potassium chloride was from Merck, Darmstadt, Germany. The substances were used as received. Distilled water was used as a solvent and dispersion medium.

Methods

Isothermal Titration Calorimetry (ITC) Measurement

ITC measurements were carried out as described in Zeiss *et al.* [12], in brief:

Propranolol Hydrochloride

A 0.1mol/L propranolol hydrochloride solution was added in ten consecutive injections, each of 15µL, to a dispersion of approximately 5mg (accurately weighed on balance Sartorius M2P microbalance; ± 0.001mg) ion exchange material Amberlite™ IRP 69 in 3.2mL distilled water. Heat effects were measured and recorded, and specific binding enthalpy (ΔH), as well as a binding constant (β) were calculated using Digitam software (Thermometric, Järfälla, Sweden). 8 replicates were measured for each data point.

Potassium Chloride

The experiment was carried out in the same way as mentioned above using a dispersion of approximately 10mg ion exchange material in 3.2ml distilled water. To this dispersion, ten injections of a 0.8 mol/L potassium chloride solution, each of 15µL, were added, and heat effects measured. Each experiment was carried out four times.

Equilibrium Studies

a) In a Wide Concentration Range

Upon dispersing 1 g of ion exchange material Amberlite™ IRP 69 in distilled water, different volumes (20mL-150mL) of a 0.1 mol/L propranolol hydrochloride aqueous solution were added and made up to the same total volume (dispersion medium + drug solution) of 1120ml. The dispersions were kept at 37ºC and stirred in a Sotax™-dissolution-tester at 150rpm (Sotax AT 7 smart, Sotax AG, Basel, Switzerland). 48 hours after adding the respective drug solution to the dispersions, samples were taken with a syringe, filtered through a 0.22µm membrane filter (cellulose acetate), and the propranolol hydrochloride concentration measured by UV-spectroscopy (λ = 290nm; SPECTRAmax™ 190, Molecular Devices Corp., Sunnyvale, USA). Amount drug bound on the ion exchanger was calculated from a calibration curve. Each experiment was carried out once.

b) At Low Concentration According to ITC Set Up

These experiments were carried out analogous to the time schedule of the ITC-experiments on a larger scale to enable photometric quantification of equilibrium concentrations. These experiments will in the further text be referred to as "calorimeter-simulation".

Propranolol Hydrochloride

Upon dispersing 1.9 g of the ion exchange material Amberlite™ IRP 69 in 1070mL of distilled water at a temperature of 37ºC and stirring with 150 rpm in a Sotax™-dissolution-tester for 4h to allow for swelling, 50.0mL of a 0.1 mol/L propranolol hydrochloride solution were added in ten consecutive injections of 5.0mL each with 1 hour break in-between each injection. Samples of approximately 5mL were taken 58 minutes after each injection through a 0.22µm membrane filter. To avoid ion exchange material being stuck on the membrane filter, samples of more than 5mL volume were first taken and the excess solution flushed back to adjust a sample size of 5mL, whereby ion exchange material possibly attached to the filter was redispersed.

The samples were measured by UV-spectroscopy (λ = 290nm) as described above. Amount of drug bound was calculated. 4 replicates were carried out for each experiment.

Potassium Chloride

3.4 g of the ion exchange material Amberlite™ IRP 69 was dispersed in 1070mL of distilled water in a Sotax™-dissolution-tester using the same conditions as mentioned above. 50.0mL of a 0.8 mol/L potassium chloride solution were added in ten consecutive injections of 5.0mL each with 1 hour break in-between each injection. Sample collection and handling was done as mentioned above.

Samples were assayed by flame photometer (PFP 7, Jenway, Dunmow, England) using a set of standard-solutions with defined concentration. 3 replicates were carried out.

3. THEORETICAL BACKGROUND

The ion exchange reaction itself may be described by the following equilibrium equation:

$$IE - Na_{aq} + PropH - Cl_{aq} \leftrightarrow IE - PropH_{aq} + Na\,Cl_{(aq)} \quad (1)$$

This equation can be used under the prerequisite that propranolol hydrochloride is sufficiently soluble and dissociated. As the chloride concentration is constant, Equation 1 can be simplified for the current case:

$$IE\text{-}Na + PropH^{+} \leftrightarrow IE\text{-}PropH + Na^{+} \quad (2)$$

For this reaction, the equilibrium constant K_a can be defined as:

$$K_a = \frac{[IE - \mathrm{Pr\,opH}]\cdot[Na^{+}]}{[IE - Na]\cdot[\mathrm{Pr\,opH}^{+}]} \quad (3)$$

Apparent K_a values calculated from experimentally derived concentrations disregarding thermodynamic activities are used in the current case.

The ion exchange process can also be described as the interaction between the ions and limited number of reactive sites in the matrix. This approach is formally analogous to what has been proposed by Langmuir for the adsorption of gas molecules on plane surfaces of glass, mica, and platinum [15], which in its original form describes the adsorption of the gas molecules onto surfaces with a limited number of (empty) reaction sites. The difference to the present case is the involvement of bulk material, and the previous occupation of the respective reaction sites with sodium ions (exchange reaction).

Under equilibrium conditions, where adsorption and desorption rates are equal, we can write:

$$k_{des} * \Theta = k_{ads} * (1 - \Theta) * c \quad (4)$$

where Θ is the degree of coverage of reaction sites, and 1- Θ is the fraction of unoccupied sites. Rearrangement reveals a linear function:

$$\frac{c}{y} = \frac{1 + b * c}{y_{max} * b} \quad (5)$$

with c= equilibrium concentration of the molecules to adsorb, $y/y_{max} = \Theta$; $b = k_{ads}/k_{des}$. By plotting c/y *vs* c. a linear function is revealed with $1/y_{max}$ as the slope and $1/y_{max}*b$ as the intercept.

The Langmuir approach has first been applied to ion exchange reactions by Boyd *et al*. [4]. It has later been applied in many more works on ion exchange, mainly in the field of inorganic chemistry including other types of adsorbents [4, 16, 17], as well as for drug substances [18]. It has been discussed that in principle, the Langmuir approach as being based on the mass action law can only be applied under certain conditions [4, 15]. Firstly, the approach has been developed for "empty" reaction sites, and thus for our case, it is a prerequisite that binding and release of Na^+ is non-rate determining, and that these ions are highly diffusive in the resin. Secondly, the rate of desorption of the sorbens in Langmuir´s approach is set independent of the concentration in the surrounding phase (equation 4). In our case, it is thus a prerequisite that the $PropH^+$-desorption is independent of the propranolol-concentration in the solution. This can be assured by a constant $PropH^+$ -concentration, or by keeping this concentration very low. If higher concentrations should be used, dependency of desorption kinetics on concentration is to be taken into consideration in the respective calculations. In the present study, very low equilibrium concentrations were used throughout as well as the solutions stirred thoroughly, and therefore the rate of desorption of the $PropH^+$-ions for the calculations is supposed to depend only on the degree of loading.

Parameter b in the Langmuir equation (equation 5) is a constant related to the free enthalpy of sorption, and as such related to the mass equilibrium constant, in the Langmuir sense, of sorption of a single component. Therefore, another prerequisite to apply the Langmuir equation is - in the case of single-site surface adsorption, that selectivity of the binding site remains unchanged over the range of compositions involved throughout the exchange experiment. The Langmuir equation leaves the equilibrium constant K_L to be formally defined through:

$$K_L = \frac{\Theta}{(1-\Theta)\cdot c} \quad (6)$$

In the present case, the equilibrium constant K_{LX} derived under the conditions of the Langmuir experiments at low concentrations of sodium ions can consequently be defined as to be:

$$K_{LX} = \frac{[IE - \mathrm{Pr\,opH}]}{[IE - Na]\cdot[\mathrm{Pr\,opH}^+]} \quad (7)$$

which formally is equal to K_L derived from the Langmuir approach.

In the present study, adsorption of drug molecules was studied rather than their release. The commercially available material is by default loaded with inorganic ions (sodium ions). Under the assumption that the ion exchange reaction is a chemical equilibrium for the competition between two ions, the mechanism of drug release is expected similar to the adsorption mechanism: the release rate can be derived from adsorption rate and equilibrium constant.

4. RESULTS AND DISCUSSION

Concentrations of Solutions

Literature values for the aqueous solubility for propranolol hydrochloride differ widely between 3g/L and 100g/L, corresponding to 0.01 to 0.3 mol/L [19-21]. Moreover, propranolol hydrochloride is reported to aggregate in aqueous solutions above a critical concentration of 150 mmol/L at 35ºC and 163 mmol/L at 40°C respectively [22]. All the concentrations in the present study were therefore chosen to be much lower than this value. PropHCl was added to aqueous dispersions of the pre-swollen resin in the form of a (concentrated) solution (100 mmol/L) to dilute immediately by a factor of approximately 10. The maximum concentration of a solution used in the experiments is therefore almost a factor of 10 lower when added to the ion exchanger, and during the exchange reactions, the equilibrium concentration of the free drug becomes even lower (by approx. a factor of 100). Therefore, it is assumed that perfect sink conditions are maintained throughout the experiments (i.e. < 1% of solubility of propranolol), and that therefore desorption rates of the molecules are independent of this concentration.

Furthermore, the ion exchanger was used in its Na^+- form as to maintain practically constant pH-conditions throughout the experiments. The pK_A value of $PropH^+$ is 9.45 [23], and all the solutions handled during experiments were in the pH range of between 5.9 and 6.3, which accounts for more than 99.9% of the molecules being dissociated. Moreover, chloride-ions are not considered to take part in the exchange process due to repulsive forces between chloride ions and the electric potential difference barrier (Donnan potential) which repel the co-ions from the ion exchanger.

In the case of potassium chloride, despite of use of higher concentrations as compared to the experiments with propranolol hydrochloride, the requirement of diluted solution was fulfilled as well.

Calorimetric Approach

Heat effects of the binding reaction between potassium chloride and Amberlite™ IRP 69 were measured by ITC and compared to those of propranololHCl which has been previously described elsewhere [12]. A typical ITC-curve for propranolol hydrochloride and potassium hydrochloride is shown in Figs. (**1**) and (**2**) respectively.

The curves have similar patterns, but also distinct differences: While both experiments show a decrease in heat effects, the curve for potassium chloride shows a logarithmic decay while for propranolol, the curve decreases linearly. For potassium ions, there is a more pronounced occupation of available binding sites for the first step followed by fewer binding in subsequent steps. The individual peaks of potassium are also less wide than those of propranolol, which indicates that the overall reaction between the ion exchanger

and small inorganic ions is faster than with larger organic ions.

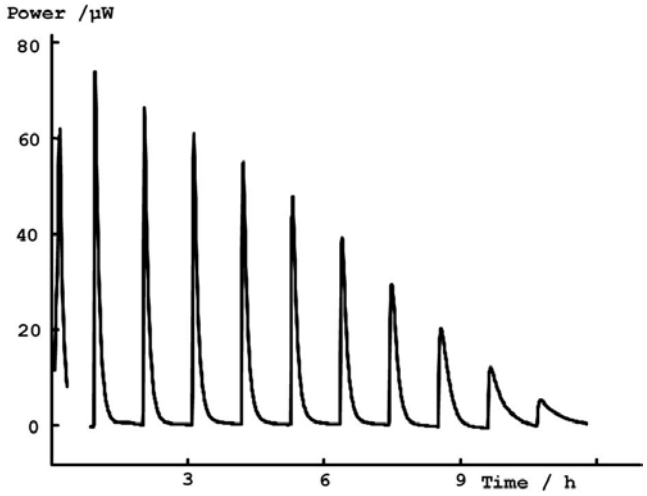

Fig. (1). Typical ITC (isothermal titration calorimetry) plot for Amberlite™® IRP 69/Propranolol; experimental conditions: 5.6 mg Amberlite™TM IRP 69 in 3.2 ml water; addition of 10 x 15µl of propranolol-solution 0.1 mol/L; equilibrium concentration after 10 injections 0.140 mmol/L.

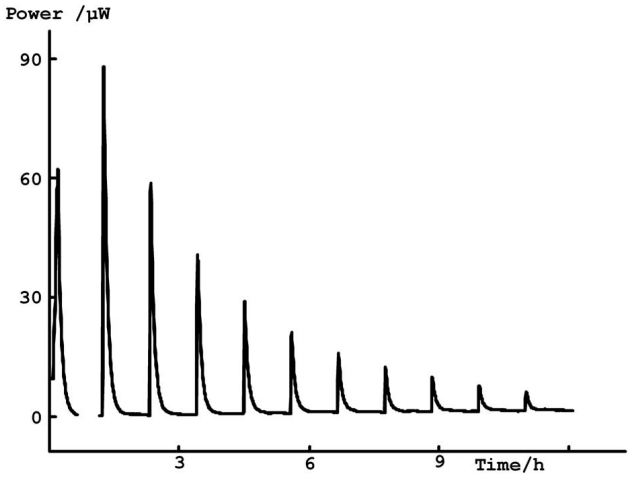

Fig. (2). Typical ITC (isothermal titration calorimetry) plot for Amberlite™® IRP 69/Potassium chloride; experimental conditions: 10 mg Amberlite™ IRP 69 in 3.2 ml water; addition of 10 x 15µl of propranolol-solution 0.8 mol/L.

A typical evaluation of the data would include fitting of heat of effects measured for the individual steps (area under the peaks) for a two-component reaction using Digitam™ software (Thermometric, Järfälla, Sweden). In the case of potassium, the exponential decay yields a good fit (Fig. **3**), revealing values for an equilibrium constant equal to K_L=4.5*10^1 L/mol and a reaction enthalpy of approximately ΔH^0_{310} = -2.4 kJ/mol (Table **1**).

For propranolol, the values decrease according to a different pattern (Fig. **4**). However, the fit is considered satisfying for a calorimetric method, and the value found for the equilibrium constant is formally equal to K_L=1.9 *10^2 L/mol, and the reaction enthalpy of approximately ΔH^0_{310} = -16 kJ/mol (Table **1**).

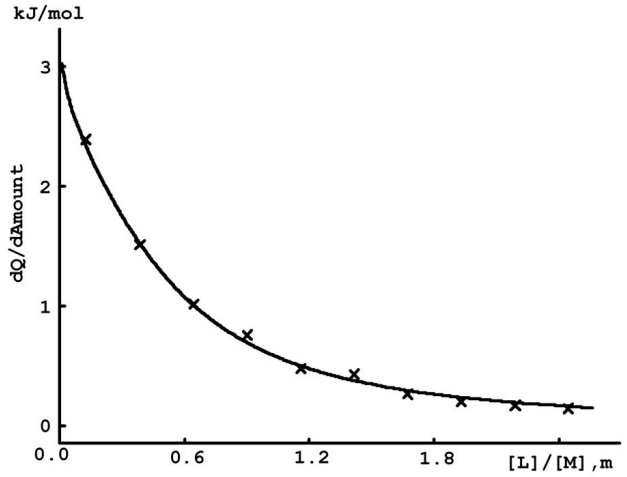

Fig. (3). Evaluation for the system potassium chloride/Amberlite™IRP 69 (Digitam software): M + xL → MLx; x= 0.7281.

Table 1. Results of ITC Experiments for Propranolol Hydrochloride and Potassium Chloride Exchange Reaction with Sodium-Loaded Amberlite™IRP 69

	Potassium Chloride	Propranolol Hydrochloride
ΔH/kJ mol^{-1}	- 2.44 ± 0.09	- 15.67 ± 0.85
β/L mol^{-1}	44.6 ± 2.5	189.1 ± 11.04
M + x L → MLx x =	0.7281	0.7347
Number of replicates	4	8

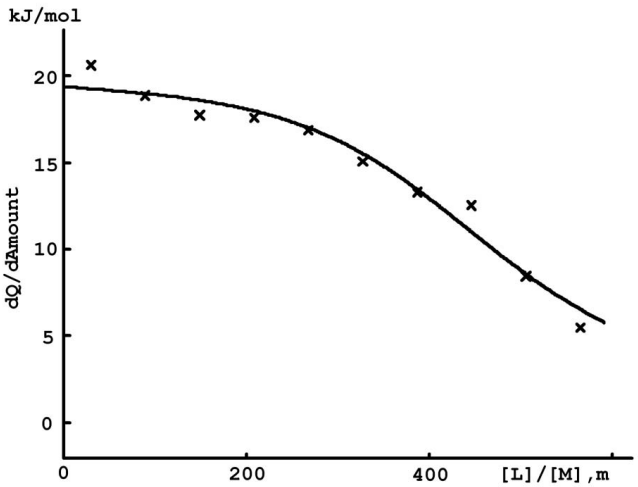

Fig. (4). Evaluation for the system propranolol hydrochloride/Amberlite™IRP 69 (Digitam software): M + xL → MLx; x= 0.7347.

These results reveal two surprising conclusions: 1) The equilibrium constant for the binding of propranolol to Amberlite is more than 4 times larger than for potassium, which means that the affinity of propranolol-H$^+$ ions to Amberlite™ is larger than for potassium ions. 2) The exchange enthalpy for potassium is much smaller than for propranolol.

The different shapes of the ITC evaluation plots (Figs. **3**, **4**) were not expected and are indicative for differences in the binding mechanism. Additional experiments were therefore carried out in order to study the nature of the binding.

Equilibrium Experiments at Low Concentration

For this purpose, "calorimeter simulation experiments" were carried out with similar time schedules as for the steps in the titration calorimeter experiments, and concentrations in the solutions were measured spectroscopically. The amount of propranolol and potassium bound to the ion exchanger is shown in Figs. (**5**, **6**), respectively.

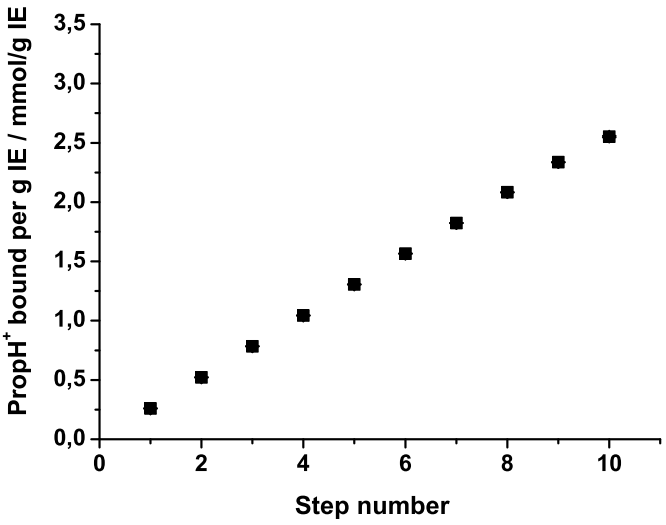

Fig. (5). Cumulative loading of $PropH^+$ onto Amberlite™; experimental details as in Table **3**. Mean and std.dev., n=4.

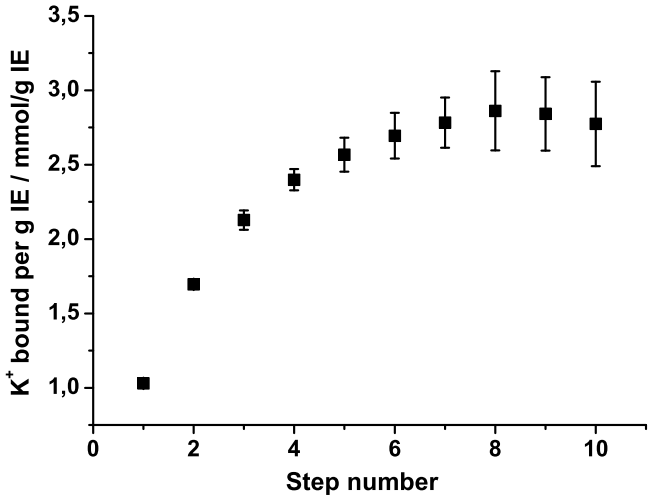

Fig. (6). Cumulative plot of potassium bound; experimental details as in Table **2** (mean and std.dev.; n=3).

As can be seen from these figures, the amount bound in each consecutive step decreases for potassium as is expected, whereas for propranolol, the amount bound additionally in each step is almost constant. This is surprising, since the heat effects of the consecutive steps decrease (Fig. **1**) as is expected for equilibrium reactions.

Specific Heat of Binding

Comparison of the amount bound at each step and the respective heat effect measured for the same step in the calorimeter allows us to directly calculate specific reaction enthalpies without the need of mathematical fitting procedures. Fig. (**7**) shows the specific heat effect plotted *vs* the step number in the titration calorimeter:

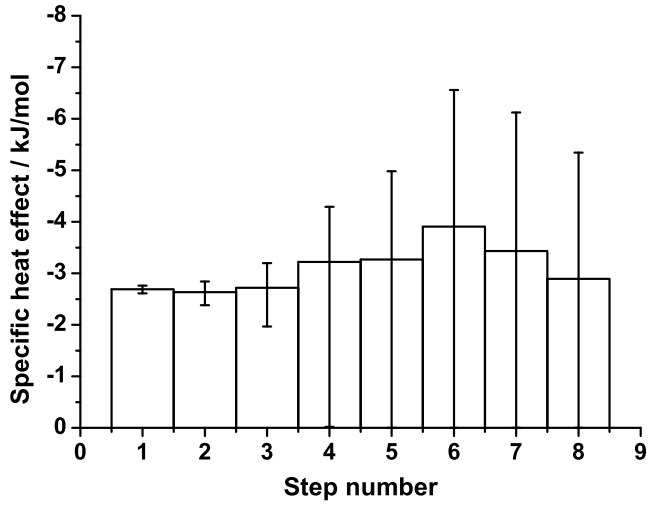

Fig. (7). Specific heat effect of exchange reaction Amberlite™ IRP 69/potassium chloride; mean and std.dev., n=3.

As can be seen from the figure, the specific heat effect of exchange for K^+ is approx. -3 kJ/mol, and widely independent of the composition in a wide concentration range within experimental error. Furthermore, the specific heat effect measured directly is in reasonable agreement with the value yielded by the ITC method (-2.44 kJ/mol). ITC may therefore be regarded as a valid tool to estimate enthalpies of exchange reactions for small inorganic ions.

For propanolol, an analogous plot is shown in Fig. (**8**), where the specific heat effect, i.e. heat effect per mole adsorbed propranolol-H^+, is not constant, but surprisingly changes continuously throughout the experiment. In other words, the reaction enthalpy is not constant, but depends on composition of the solution and/or on the degree of occupation of the binding sites of the ion exchanger with propranolol, although all experiments take place in much diluted solutions. It must be concluded that in the case of propranolol, in contrast to potassium, binding sites and/or binding types of different quality are involved when the degree of occupation increases. The value of reaction enthalpy for propranolol calculated from calorimeter data is a measure for an average value over the concentration range covered. This fact also explains different fit of heat effects of the experimental steps to the expected decay model (Fig. **4**).

It is interesting to discuss possible reasons for the fact that the specific reaction enthalpy changes with the degree of loading of Amberlite™ with Propranolol-H^+.

Firstly, inhomogeneities of the degree of cross-linking in the matrix of the ion exchanger have been discussed, which are expected to reveal fractions of different degree of swelling. This has been shown through measurements of

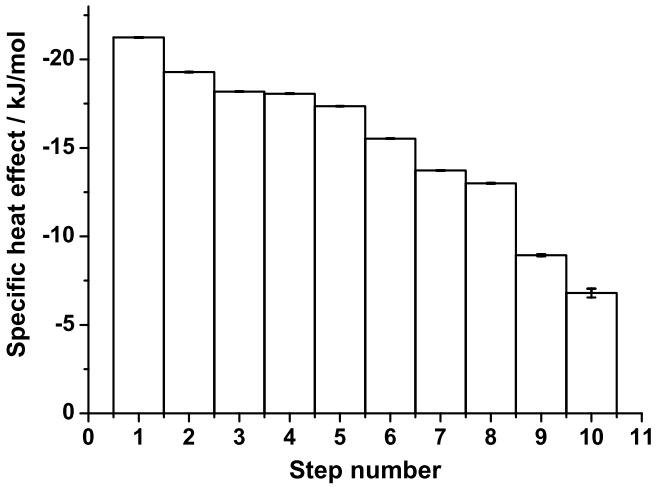

Fig. (8). Specific heat effect of exchange reaction Amberlite™ IRP 69/propranolol hydrochloride; mean and std. dev., n=4.

diffusion coefficients within resins [24]. It would result in different degrees of loading, and in conclusion, the resin cannot be treated as a single phase. The present data suggest this to be unlikely, since there is no significant effect in the case of potassium. Secondly, let us take a closer look at the molecular structure of the resin (Fig. **9**), and recall that the sulfonation of the matrix is the last step in the synthesis of the styrene polymer. There is one sulfonic acid group on almost every benzene ring. Para-positions are probably the most preferred positions [6], but ortho- and meta-positions may also be substituted. Furthermore, the rings derived from the divinylbenzene (DVB) are also sulfonated and give rise to additional 6 isomers. If ethylstyrene as a common impurity in the DVB is also considered, a total of 19 position isomers of sulfonate groups exist. Each of these 19 isomers probably exerts slightly different attractions for a given pair of exchanging cations. This fact may be the reason for reaction sites of different reaction enthalpies and binding strengths: first, the most preferred sites with highest (absolute) enthalpies will be occupied, and with increasing degree of loading, the less preferred sites will also be occupied. In other words: the selectivity coefficient would not be a constant but vary with molar ratio of the respective cations. This structural difference may only be of importance in the case of propranolol, because the same effect was not observed with potassium ions, and it is possibly connected with steric hindrance.

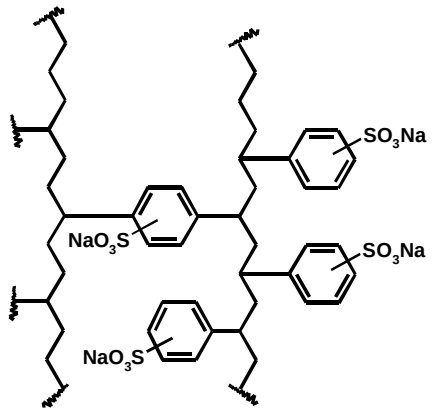

Fig. (9). Schematic molecular structure of Amberlite™® IRP 69.

Thirdly, in contrast to small inorganic ions that exclusively interact by ion-ion-attraction forces, many drug molecules are amphiphilic. For propranolol it is known that the molecules in aqueous solution tend to self-association above 150mmol/L [22]. Similar effects may take place in the bulk of the ion exchanger material, where the concentration of the drug is high, even though the surrounding solution is much more diluted (approx. factor 100). Furthermore, amphiphilic molecules may interact with the polymer not only by ionic interaction, but also by non-specific interactions, probably to an increasing extent as the degree of occupation increases. It is a common rule that ion- ion- interactions are stronger than non-specific forces, and this fact results in non-constant and decreasing molar reaction enthalpies with increased propranolol content, as was measured in the present study. It has been hypothesised for substituted salicylic acid derivatives of different lipohilicity [25, 26] that non-specific interactions between ion exchanger polymers and drug-like molecules may exist. However, in the present study, for the first time evidence for such type of interaction has been experimentally found.

Furthermore, it has been described elsewhere [7] that the kinetics of the ion exchange reaction between Amberlite™ and propranolol cannot be explained with models based on diffusion only, but it would be composed of at least 2 independent reactions of different kinetics that take place simultaneously. It has further been suggested [7] that the mechanism may be connected to the matrix of the resin that becomes “tighter” and “tighter” during the course of the loading. The explanation for such behaviour may possibly also be steric hindrance, together with the balance between specific and non-specific interaction and changing binding forces as found in the present study. Furthermore, it has been found in even another previous study [24], using anion exchanger membranes consisting of polymerized styrene-divinylbenzene mixtures, that kinetics of the exchange reaction shows abnormally high dependence on the co-ion concentration. From this, it has been concluded that ion exchange polymers, at least cross linked ones, cannot be treated as a single phase. This is in line with an earlier hypothesis of Baumann [2] that it may be possible to describe the ion exchange reaction by the difference in thermodynamic activities of the respective solutions inside the resin and in the outside solution without involving any specific affinity of $-SO3^-$ groups for one ion over another. In other words: there may not be a simple correlation between the rate and the extent of the ion exchange reaction on the one hand and the bonding strength on the other.

Equilibrium Constant

Another question arises from the fact that the specific reaction enthalpy is not constant during the binding reaction: what impact does this have on the equilibrium constant? For the ITC-experiments, equilibrium constants were calculated and compared to directly derived ones by quantitative analysis of equilibrium concentrations for each step. The values derived for mass equilibrium constant K_{LX} for potassium were calculated for individual experiments, using equation (7), the results of which are given in Table **2**.

The values decrease continuously with increasing equilibrium concentration of unbound potassium; the overall range covers approximately a factor of 10. The trend is obvi-

Table 2. "Calorimeter Simulation" Experiments of the System Potassiumchloride/Amberlite™ IRP 69 in the Dissolution Tester; Flame-Photometric Detection at Equilibrium

Experimental Step	Equilibrium Concentration KCl [mmol/L]	Amount KCl Bound per g IE [mmol/g IE]	Equilibrium Constant K_{LX} [L/mol]	Specific Heat of Reaction [kJ/mol]
1	0.412	1.031	$7.2 * 10^2$	- 2.69
2	1.998	1.695	$3.0 * 10^2$	- 2.63
3	4.320	2.127	$2.1 * 10^2$	- 2.72
4	7.149	2.399	$1.6 * 10^2$	- 3.22
5	10.297	2.567	$1.3 * 10^2$	- 3.27
6	13.561	2.694	$1.1 * 10^2$	- 3.91
7	16.934	2.783	$0.95*10^2$	- 3.43
8	20.318	2.863	$0.86*10^2$	- 2.89
9	24.014	2.842	$0.71*10^2$	----[a]
10	27.840	2.774	$0.58*10^2$	----[a]

[a] Experimental error larger than the measured value due to very small heat effect.

ous, while the factor may be affected by the large experimental errors in potassium assay for the last steps (Fig. **6**). The trend may reflect the change in thermodynamic activities for Na^+ and K^+ in the bulk of the resin. It is difficult to estimate ion activities within the matrix of the ion exchanger, because the activities in the resin cannot be measured independently [2, 4]. A comprehensive review about the historical development of the thermodynamic theory of cation exchange reactions is found in [27]. This work may be regarded as a summary of various approaches to find activity coefficients in ion exchange materials. It may be even possible to use the decay function of K_{LX} as a measure of the otherwise not accessible activities, as was suggested by Argersinger *et al*. [28].

Values for mass equilibrium constant K_{LX} for propranolol were also calculated for individual experimentally derived values, using equation (7), the results of which are given in Table **3**.

The values for the equilibrium constant K_{LX} for propranolol vary by a factor of 2.5 between experiments, and there is no clear tendency. Even though the variation for propranolol is comparably small, it shows clearly a larger value compared to the values of potassium. However, it is widely different from the value found by ITC (Table **1**).

Wide Concentration Range Equilibrium Studies for Propranolol ("Langmuir Approach")

A different approach for the description of equilibrium phenomena is the commonly used method of Langmuir. The advantage compared to the ITC method is that a wider concentration range can be covered. Fig. (**10**) shows the Langmuir plot for the Amberlite™ IRP69 ion exchanger/propranolol concentration ratios given in Table **4**. The Langmuir model appears to describe the present adsorption process with excellent linearity (r = 0.99999) for concentration range up to 4 mmol/L in equilibrium concentration.

Table 3. "Calorimeter Simulation" Experiments of the System Propranolol Hydrochloride/Amberlite™ IRP 69 in the Dissolution Tester; UV-Spectrophotometric Detection at Equilibrium

Step Number	Concentration PropHCl at t_0 [mmol/L]	Equilibrium Concentration PropHCl [mmol/L]	Amount PropHCl Bound per g IE [mmol/g IE]	Equilibrium Constant K_{LX} [L/mol]
1	0.465	0.005	0.260	$1.2*10^4$
2	0.470	0.007	0.522	$1.8*10^4$
3	0.472	0.010	0.784	$2.0*10^4$
4	0.475	0.014	1.045	$2.1*10^4$
5	0.478	0.019	1.305	$2.2*10^4$
6	0.483	0.024	1.565	$2.2*10^4$
7	0.488	0.031	1.824	$2.2*10^4$
8	0.494	0.039	2.083	$2.2*10^4$
9	0.501	0.056	2.336	$1.9*10^4$
10	0.517	0.140	2.552	$9.4*10^3$

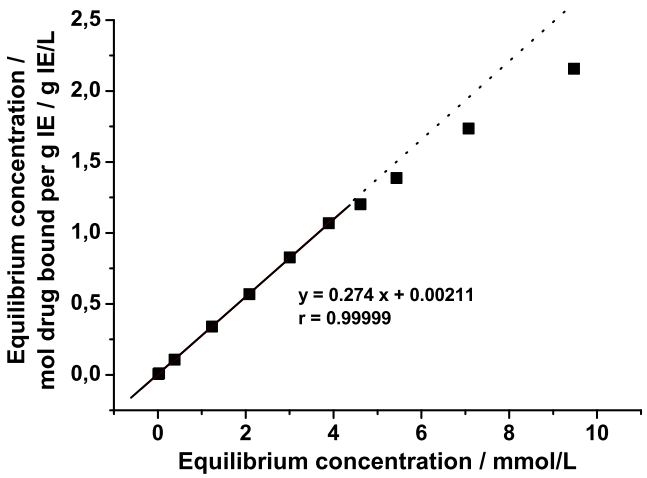

Fig. (10). Langmuir Plot of Propranolol hydrochloride/Amberlite™® IRP 69.

The ion exchange capacity y_{max} can be calculated from the inverse slope of the Langmuir plot (Fig. **10**), and is found to be 3.65 meq/g wet IE in the present study, corresponding to 4.00 meq per g of dry ion exchange material.

Above a certain degree of loading (i.e. above equilibrium concentrations of unbound drug of 4 mmol/L), for increasing concentration of free propranolol in the equilibrium, deviation from the fitted line of the linear Langmuir isotherm is observed (Fig. **10**). The Langmuir value for higher equilibrium concentrations of unbound propranolol is smaller than expected. This means that at higher concentrations, more PropranololH^+ is bound than the predicted maximum loading capacity (as obtained from the extrapolation of the Langmuir fit). This is surprising, and to our knowledge for the first time reported for drug/ion exchange systems. The absolute maximum of loading appears not to be reached with the concentrations of propranolol used here as can be seen in a continuously increase of drug bound to the ion exchanger within the experimental range, but higher amounts of drug were not used in the present study due to expected solubility (aggregation) problems. The maximum value for drug bound in the present study is 4.4 mmol/g Amberlite™ (Table **4**), corresponding to 4.8 mmol per g dry Amberlite™. This is by far larger than the manufacturer´s specification for the exchange of sodium by potassium (max. 3.45 meq. /g). Moreover, the above discussed involvement of non-specific interaction would explain why propranolol can be bound to the polymer in larger fractions even exceeding the ion exchange capacity.

The Langmuir approach has been reported to yield reasonable results with respect to maximum loading for other ion exchange systems, for example, the adsorption of inorganic ions to soils, as has been described by Elprince and Sposito [29], in a narrow range of low concentrations where no secondary precipitation takes place. For another drug /ion exchanger system (verapamil/ Sephadex™) [18], the experimentally found loading has also been reported in good agreement with theoretical, Langmuir-based expectations.

However, for propranolol, there is a clear and increasing deviation from the fitted line for higher concentrations. This may indicate that the Langmuir model does not describe the exchange reaction between Amberlite™ and propranolol sufficiently for the entire range of observed concentrations.

The maximum loading yielded in the current experiments corresponds to approximately 1170mg propranolol per g ion exchanger. This is regarded a large proportion, and such highly-loaded ion exchange-drug-complex appears thus favourable for the development of drug delivery systems, where the maximum mass of single doses is limited for practical reasons.

Again, a mass equilibrium constant K_L was derived from

Table 4. Propranolol Hydrochloride/Amberlite™®IRP 69 System; Equilibrium Studies in the Dissolution Tester, Spectrophotometric Detection

Experiment Number	Concentration PropHCl at t_0 [mmol/L]	Equilibrium Concentration PropHCl [mmol/L]	Amount of Substance PropHCl Bound [mmol]	Equilibrium Constant K_{LX}† [L/mol]
1	1.786	0.01288	1.986	$6.1*10^4$
2	2.679	0.0305	2.966	$6.3*10^4$
3	3.571	0.3814	3.573	$1.0*10^4$
4	4.464	1.233	3.619	$3.3*10^3$
5	5.357	2.083	3.667	$2.1*10^3$
6	6.250	3.005	3.634	$1.4*10^3$
7	7.143	3.891	3.642	$1.1*10^3$
8	8.036	4.612	3.834	$1.2*10^3$
9	8.929	5.431	3.917	$1.2*10^3$
10	10.71	7.075	4.076	$1.3*10^3$
11	13.39	9.472	4.391	$4.1*10^3$

†: Calculated by equation (7).

Amount of ion exchange-material 1.000g; Amberlite ™®IRP 69 pre-swollen in water; concentration propranolol hydrochloride solution to add:0.1 mol/L; volume propranolol hydrochloride solution added 20mL; 30mL; 40mL; 50mL; 60mL; 70mL; 80mL; 90mL; 100mL; 120mL;150mL. Total volume 1120mL.

the linear part of the Langmuir plot (equation 6). This value is found to be 1.3 * 10^5 L/mol, which is by far the largest value compared to the calculated K_{LX}-values for the single data points.

5. CONCLUSION

ITC experiments combined with photometric quantification reveal that the specific heat effect of adsorption of propranolol-HCl is in general high and – in contrast to potassium ions - changes continuously for increasing degree of drug loading for low concentrations. This surprising fact is probably due to involvement of non-specific interactions between the ion exchange polymer and the drug molecules. It hampers prediction of loading properties by models based on mass equililbrium theory for the system propranolol/ Amberlite™, as well as using calorimetric methods to estimate the binding energies. Nevertheless, in a certain range of concentrations, the Langmuir approach yields data of high reproducibility and excellent goodness of fit. It may be discussed, how far its loading prediction abilities are reasonable. However, in agreement with Barrow´s suggestion [30], the Langmuir approach should not be used to estimate the mass equilibrium constant: a constant value of the selectivity coefficient is a theoretically derived prerequisite to apply a simple Langmuir equation [17].

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