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ISOTHERMAL TITRATION CALORIMETRY (ITC) METHOD TO STUDY DRUG/ION EXCHANGER INTERACTION

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An isothermal titration calorimetry (ITC) method to measure the heat effects evolving from the binding between cation exchanger Amberlite® IRP 69 and the cationic drug substances propranolol hydrochloride (PROP), metoprolol tartarate (METO), acebutolol hydrochloride (ACEB) and chlorpheniramine maleate (CPR) has been developed. The method gives repeatable results with an error about 5% for the beta-blockers PROP, METO and ACEB, and about 10% for the antihistamine CPR.

The calculation of the thermodynamic parameters enthalpy change (ΔH_{bind}) and Gibbs free energy change (ΔG_{bind}) show significant differences between the different drug substances.

Keywords: *Amberlite® IRP 69, β-blockers, ion exchange, isothermal titration calorimetry, thermodynamics*

Introduction

The development of synthetic ion-exchange materials has increased their range of application dramatically [1], and ion exchange materials are today, amongst others, used in the food-industry, analytical chemistry, biochemistry, biotechnology and pharmaceutics [2]. In the field of pharmaceutics, ion exchangers are, according to a recent review, in most cases used as drug-delivery vehicles [3].

Such systems comprising of drug and ion-exchanger have in more detail been described in a number of research papers, of which only few works deal with the pharmaceutically used ion exchanger Amberlite® IRP 69, e.g. [4–6].

Isothermal titration calorimetry (ITC) as a method to investigate binding reactions in biochemical systems is well established and frequently used for protein ligand binding studies [7]. In the field of pharmaceutics, ITC-studies of interaction between macromolecules, polymers and oligomers and drug substances, e.g. complexation reactions between ibuprofen and cyclodextrin [8, 9], have also been described. Furthermore, ITC has been used to study the interaction between ion-exchanger and protein molecules [10]; however, drug – ion exchanger interaction has to our knowledge not been studied from a thermodynamic point of view so far.

The objective of the present study is to investigate whether ITC can be used to characterize the interaction between drug substances and the ion exchange material Amberlite® IRP 69.

As model substances, three β-blockers (PROP, METO, ACEB) have been used in this study, because of their similar structures, and the antihistamine chlorpheniramine maleate as another ionic drug substance (Table 1).

Experimental

Materials and methods

The cation-exchange resin Amberlite® IRP 69 (Sodium polystyrene sulfonate USP; Lot 6210TD12) was obtained as a generous gift from Rohm and Haas France S.A.S, Chauny, France. (±)-Propranolol hydrochloride (batch 1H106/1) was purchased from NMD AS, Oslo, Norway, while (±)-metoprolol- (+)- tartarate (Lot 064K1197/101K1517), (±)-acebutolol hydrochloride (Lot 023K0752/17F04511) and (±)-chlorpheniramine maleate (Lot 116H0612) were purchased from Sigma-Aldrich Norway AS, Oslo, Norway. All the substances were used as received. Distilled water was used as solvent and dispersion medium.

The experiments were carried out using the Thermal Activity Monitor (TAM 2277; Thermometric, Järfälla Sweden) which is a multichannel microcalorimetric system based on the (thermopile) heat conduction principle with a measuring range of 100 μW. The micro reaction system consists of titration insertion vessels with two 4 mL glass ampoules (sample and reference). In the sample ampoule, a certain amount of the ion-exchange material (Table 2) was weighed accurately (Sartorius M2P

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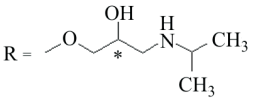
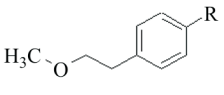
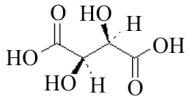
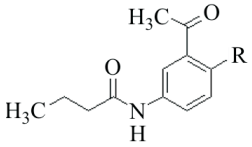
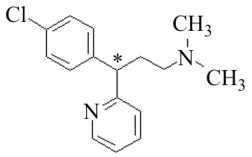
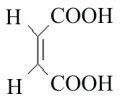
Table 1 Chemical structure of drug substances studied

Name	Structure	Salt
Propranolol hydrochloride		HCl
Metoprolol tartarate		
Acebutolol hydrochloride		HCl
Chlorpheniramine maleate		

microbalance) in and filled up with a certain volume of distilled water (3.2 mL), while the reference ampoule was filled with distilled water only (3.25 mL). A homogenous suspension of the ion-exchange material in the sample ampoule was assured with a propeller stirrer and a special stirrer motor (Thermometric) at 300 rpm. All experiments were performed at a temperature of 310 K. After thermal equilibration the drug solution was injected into the ion-exchange suspension through a Hamilton syringe fitted with a stainless steel needle clamped in a motor driven syringe pump (Thermometric). Ten injections of the drug solution (0.1 mol L^{-1}), 15 μL each for propranolol hydrochloride and metoprolol tartarate, 20 μL each for acebutolol hydrochloride and 10 μL each for chlorpheniramine maleate respectively, were added to the ion exchanger at time intervals of 1 h. The heat effect was measured and recorded as power, *p*, *vs*. time, *t*. The molar mass of the ion-exchange material was defined as 222 g per 'mol of active sites', based on specifications from the producer (Rohm and Haas). The heat effects measured were corrected for heat of dilution of the respective drug solutions. For this purpose experiments were carried out under the same conditions without ion-exchange material present in the sample cell. The binding enthalpy change (ΔH_{bind}) and a binding constant (β_{bind}) were calculated by the software DIGITAM 4.1 for Windows® (Thermometric). Experiments were replicated until the standard deviation of the heat effects assessed for each peak was below 5% (in the case of chlorpheniramine maleate 10%).

Table 2 Experimental details

	PROP	METO	ACEB	CPR
Amount ion-exchanger/mg	~5.6	~17.8	~18.4	~5.4
Conc. drug solution/mol L^{-1}	0.100	0.100	0.100	0.0994
Volume drug solution per injection/μL	15	15	20	10
Estimated error ΔH_{bind}/kJ mol^{-1}	2.02±1.04	1.16±0.10	0.73±0.17	1.23±0.53
Estimated error β_{bind} mol L^{-1}	25.30±6.89	0.16±0.02	0.40±0.08	2.87±0.77
Number replicates	8	8	8	8

Table 3 Thermodynamic parameters normalised per mol ion-exchanger (mean±*s.d.*, *n*=8)

	PROP	METO	ACEB	CPR
ΔH^{IE}_{bind}/kJ mol^{-1}	–15.67 ± 0.85	–6.21±0.33	–10.15±0.58	–21.95±2.52
β^{IE}_{bind}/L mol^{-1}	189.07±11.04	1.33±0.04	7.96±0.37	47.99±5.88
ΔG^{IE}_{bind}/kJ mol^{-1}	–13.51±0.15	–0.74±0.08	–5.35±0.12	–9.96±0.29

Finally, the Gibbs free energy change (ΔG_{bind}) for the system drug/ion exchanger can be derived from the noted values by Eq. (1):

$$\Delta G_{bind} = -RT \ln \beta_{bind} \quad (1)$$

Results and discussion

Figure 1 shows a typical power *vs*. time-plot for the system drug/ion-exchanger obtained from the calorimeter, exemplified by acebutolol hydrochloride.

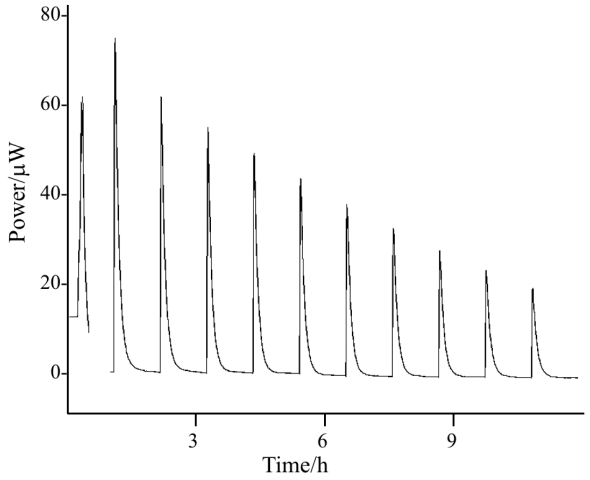


Fig. 1 Calorimeter plot for the system acebutolol hydrochloride/Amberlite® IRP 69

ΔH_{bind} is calculated by integration the area under the peaks and quantified by the amount of ion exchange material. The continuous decrease of heat effects within the 10 injections is important in order to get the optimum ratio between the drug substance and the ion-exchange material.

The amount of ion-exchange material and the volume of drug solution injected, were varied to assess the ideal ratio drug/ion-exchange material with respect to the model fitting (estimated errors in ΔH_{bind} and β_{bind} see Table 2).

In Table 2 the number of necessary replicates and the experimental conditions in order to yield good results for the calculation of ΔH_{bind} and β_{bind} by Digitam® are presented. Table 3 shows the results of the thermodynamic parameters, given in units of kJ mol^{-1} ion-exchange material. The values of the Gibbs free energy (ΔG^{IE}_{bind}) and the enthalpy (ΔH_{bind}) between the different drug substances are clearly different from each other. However, since it is the drug substance and not the ion exchanger that is of main interest in this investigation and the stoichiometry of the drug/ion-exchange complex is different from 1:1 according to the model (Table 4), the results were recalculated with reference to 1 mol of drug substance. These results are shown in Table 4. The enthalpies of binding per mol of drug substance are all in the same range of approximately –20 kJ mol^{-1} for the three beta-blockers, but for chlorpheniramine maleate, the value is approximately twice as large. However, the

Table 4 Enthalpy of drug/ion exchange interaction normalised per mol drug substance (mean ± *s.d.*, *n*=8)

	PROP	METO	ACEB	CPR
$M+x\ L \rightarrow MLx \quad x =$	0.7347±0.0221	0.2749±0.0069	0.5285±0.0131	0.5757±0.0167
ΔH^{D}_{bind} /kJ mol^{-1}	– 21.32±0.60	– 22.58±0.76	–19.20±0.69	–38.06±3.40

M: ion exchanger, *L*: drug substance

small differences between propranolol hydrochloride, metoprolol tartarate and acebutolol hydrochloride are significant (α=5%). The similar values of the enthalpy of the three β-blockers might be explained by their similar chemical structure, whereas the antihistamine chlorpheniramine maleate is different in the chemical structure and enthalpy (Table 1).

Conclusions

Isothermal titration calorimetry is suitable to measure drug/ion exchanger interaction. The uncertainty of the method for ΔH_{bind} is approximately 1–2 kJ mol^{-1}, and the repeatability is approximately 5–10%. From the present results it may be assumed that the differences in the thermodynamic parameters of drug substances can be studied.

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