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Solution calorimetry as a tool for investigating drug interaction with intestinal fluid

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Abstract

Solution calorimetry offers a reproducible technique for measuring the enthalpy of solution ($\Delta_{sol}H$) of a solute dissolving into a solvent. The $\Delta_{sol}H$ of two solutes, propranolol HCl and mannitol were determined in simulated intestinal fluid (SIF) solutions designed to model the fed and fasted states within the gut, and in Hanks' balanced salt solution (HBSS) of varying pH. The bile salt and lipid within the SIF solutions formed mixed micelles. Both solutes exhibited endothermic reactions in all solvents. The $\Delta_{sol}H$ for propranolol HCl in the SIF solutions differed from those in the HBSS and was lower in the fed state than the fasted state SIF solution, revealing an interaction between propranolol and the micellar phase in both SIF solutions. In contrast, for mannitol the $\Delta_{sol}H$ was constant in all solutions indicating minimal interaction between mannitol and the micellar phases of the SIF solutions. In this study, solution calorimetry proved to be a simple method for measuring the enthalpy associated with the dissolution of model drugs in complex biological media such as SIF solutions. In addition, the derived power–time curves allowed the time taken for the powdered solutes to form solutions to be estimated.

Keywords: Solution calorimetry; Simulated intestinal fluids; Dissolution

1. Introduction

Solution calorimetry is used primarily to determine the enthalpy change due to the formation of a solution [1]. The enthalpy of solution, $\Delta_{sol}H$, depends on the morphology of the solute, the structure of the liquid and the molecular interactions between the dissolved solid and the liquid. Therefore, a common industrial application of solution calorimetry is the detection and characterisation of the potential polymorphs of a new drug [2,3]. In such experiments, the enthalpies of solution for potential new polymorphic forms, prepared from different crystallisation media, are measured in a common solvent. For example, the difference in $\Delta_{sol}H$ between forms I and II of terfenadine is approximately $14\,kJ\,mol^{-1}$ using ethanol as the solvent [2].

However, an interesting but as yet unexplored application of solution calorimetry is to reverse this pattern, whereby the enthalpy of solution for a stable form of a drug is measured in a number of different solvents. These solvents can be biological fluids, model biological fluids or complex dispersions, and by measuring $\Delta_{sol}H$ in both the whole solvent system and its individual components valuable information may be obtained. A simple example is to compare $\Delta_{sol}H$ for a solute in both aqueous buffer and a buffered solution of micelles. The apparent change in enthalpy associated with the transfer of the solute from buffer to the micellar phase may be determined using a simple application of Hess's law. It is also possible to convert the temperature offset data from a semi-adiabatic solution calorimeter into a power–time plot [4,5]. When using gastrointestinal fluid as the solvent such measurements are extremely pertinent to the dissolution and absorption of orally administered drugs.

The objective of this study is to investigate the potential of solution calorimetry to characterise drug interaction with simulated intestinal fluids. In effect, the heat absorbed during the formation of a solution (the enthalpy of solution), will be used to identify the interaction of compounds with simulated intestinal fluids. If the enthalpies of solution in buffer and in a SIF are different, then the solute must

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be interacting in some way with the SIF. Furthermore, as the heat absorbed or liberated is measured as a function of time, solution calorimetry has the potential to rank the rate of formation of solution between different solute/solvent systems.

Conventional dissolution experiments use simple aqueous solvents such as distilled water, salt solutions or 0.1N HCl. However, these media lack many components of the fluids found within the GI tract [6]. To improve the accuracy of in-vivo dissolution prediction using in-vitro dissolution tests, simulated intestinal fluid (SIF) solutions have been developed for use as dissolution media, which reflect the fluids found within the GI tract [7–9]. Using SIF solutions rather than simple aqueous solvents or salt solutions in conventional dissolution apparatus allows the measurement of drug dissolution under conditions that mimic different physiological states, such as fasted and fed intestinal conditions. SIF solutions contain mixtures of bile salts and lipids [7–9] that form mixed micelles within the buffered solution [10]. The presence of bile salts with surface-active properties and the ability to form mixed micelles contributes to improving the solubility of many pharmaceutically important substances [11]. This paper seeks to illustrate the potential of solution calorimetry to provide a rapid means to identify interactions of solutes with SIF solutions and provide supplementary information to that provided by conventional dissolution testing.

As the free fraction of drug available for absorption at the intestinal mucosal surface is determined by interaction between drug and intestinal fluid, for example solubilisation of drug by bile salt:lecithin mixed micelles, the development of methods to study such interactions is of great interest to the pharmaceutical industry. However, if SIF solutions and biological fluids are used to investigate solubility and dissolution under conditions that mimic those found in the gut, the heterogeneous and opaque nature of such fluids cause difficulties in solute quantification using conventional assays based on UV detection. Solution calorimetry, as a consequence of measuring small changes in temperature, can monitor processes in-situ with the added benefit that the solute is not required to posses a chromophore in its molecular structure.

The two solutes, mannitol and propranolol HCl (propranolol), were chosen for this study because they represent small readily soluble compounds with hydrophilic ($\log D_{\text{oct/water}}$ −2.65 [12]) and hydrophobic properties ($\log D_{\text{oct/water}}$ 1.55 [12]), respectively. In addition, propranolol and mannitol have been used previously to evaluate the drug delivery potential of mixed surfactant:lipid micelles [13]. In these studies the micellar systems retarded the transepithelial transport of propranolol but not mannitol; a finding that was attributed to an interaction of propranolol, but not mannitol, with the micellar phase. The use of mannitol also illustrates the utility of the technique to monitor a compound that possesses no chromophore.

2. Experimental

2.1. Materials

The two solutes used in this study were D(+) mannitol (Acros Organics, Belgium, purity = 98%) and propranolol HCl (Sigma, UK, purity > 99%), and both compounds were used as received. Taurocholic acid and Hanks' balanced salt solution (H8264) used in the preparation of the SIF solutions were purchased from Sigma (UK). The lecithin (Epikuron 200, 97% phospatidylcholine) was a gift from Lucas Meyer (Germany) and was stored at −20 °C as recommended by the manufacturer.

The purity of mannitol and propranolol was evaluated using differential scanning calorimetry (DSC) (Mettler DSC 20, Mettler Instumente, Switzerland). The instrument was calibrated using the melting points of indium and zinc at the experimental scan rate of 10 °C/min. DSC gave a single melting point peak for each compound, thus confirming these samples contained a single polymorph.

Particle sizing was performed on samples of both model compounds used in this study. A thin layer of each powder was spread onto a microscope slide and a total of 700 particles were randomly chosen and sized. The particles were sized by digital image analysis using a Panasonic wv-CL310 camera mounted on a Nikon microscope linked to a basic-based particle sizing programme developed by King's College London. This programme takes the digital image of a selected particle and, from the contrast between the particle and the background, determines the perimeter of the particle. From this data the equivalent spherical geometric diameter is determined. The mean particle size for propranolol was 26.92 μm ± 3.06, with the mannitol mean size being 25.01 μm ± 2.48.

2.2. Simulated intestinal fluids

Three solvent systems were used in this study [14]: (i) fasted state SIF (FaSIF); (ii) fed state SIF (FeSIF); (iii) Hanks' balanced salt solution (HBSS); in which the pH was adjusted by the addition of morpholinoethansulfonic acid. The compositions of the SIF solutions are presented in Table 1. The amounts of bile salt and lipid were varied within the FeSIF and FaSIF in order to model the environment within the gut in the fed (post-prandial) and fasted state. The SIF solutions were prepared daily, by dissolving the relevant quantities of taurocholic acid and lecithin in HBSS. These solutions were stirred using a magnetic flea on an electric stirrer for 1 h before the pH was adjusted to the required level. Both SIF solutions were opaque in appearance, with the FeSIF being clearer than the FaSIF. The osmolality of the SIF solutions was measured using a Micro-Osmometer (Vitech Scientific Ltd.) using freezing point osmometry.

The sizes of the micelles present within the SIF solutions were analysed using a ZetaPlus Zeta Potential Analyser (Brookhaven Instruments Corporation, USA). The zeta

Table 1
Composition and properties of the simulated intestinal fluids used in this study [14]

	HBSS	Fasted state SIF	Fed state SIF
Sodium taurocholate	0.00 g	1.62 g	8.06 g
Lecithin	0.00 g	0.58 g	3.06 g
HBSS	N/A	Make up to 1000 mL	Make up to 1000 mL
pH	6.0, 6.5, 7.4[a]	6.5	6.0
Osmolarity	260 mOsmol (pH 7.4)	336 mOsmol	356 mOsmol
Micelle diameter, polydispersity	N/A	270.1 nm, 0.26	10.6 nm, 0.25
Viscosity	0.9123 cP (pH 7.4)	0.9298 cP	0.9511 cP

[a] HBSS used at pH 7.4, except when comparing with fasted state SIF (pH 6.5) and fed state SIF (pH 6.0).

potential analyser utilises photon correlation spectroscopy to measure the sizes of the micelles by determining the diffusion coefficient. Before measurement, the SIF solutions were filtered by passing the solution through a 0.45 μm filter (Schleicher & Schuell, Germany) to remove dust particles. Size analysis was conducted on two samples each run seven times for each solution, and the effective size and the polydispersity were recorded for each SIF solution.

The relative viscosity of the three solvents used in this study was measured by comparison with that of pure water, which has a viscosity of 0.8904 cP at 298.15 K. Viscosities were determined using a ViscoDoser AVS 20 viscometer (Schott Gerate GmbH, Germany). These experiments were repeated three times for single samples of each solvent system.

2.3. Solution calorimetry

The $\Delta_{sol}H$ were measured using a Thermometric 2225 Precision Solution Calorimeter (Thermometric AB, Sweden), in conjunction with a Heto–Holten precision water bath (Denmark). Between 30 and 40 mg of drug was weighed accurately and placed within a 1 mL glass crushing ampoule. The ampoules were sealed with a silicone bung, and a double layer of melted beeswax. All experiments were performed in triplicate and the mean and S.D. (standard devation) are reported.

Exactly 100 mL of solvent was placed in the glass reaction vessel of the calorimeter, and the sealed glass ampoule containing the drug sample was inserted into the gold stirrer. The stirrer containing the ampoule was placed within the reaction vessel, and the stirrer speed was set at 500 rpm. The temperature of the reaction vessel was brought to within 200 mK below 298.15 K, as the calorimeter operates under semi-adiabatic conditions. The calorimeter was calibrated electrically, by supplying a known amount of heat to the solution via an electrical heater, before the ampoule was broken [5] (marked calibration one on Fig. 1). The breaking of the ampoule released the sample into the solvent, and the temperature change associated with the formation of the solution was measured by the thermistor located within the reaction vessel (marked break on Fig. 1). Calibration was repeated after the break (marked calibration two on Fig. 1). The enthalpy of solution of the solute in the solvent was

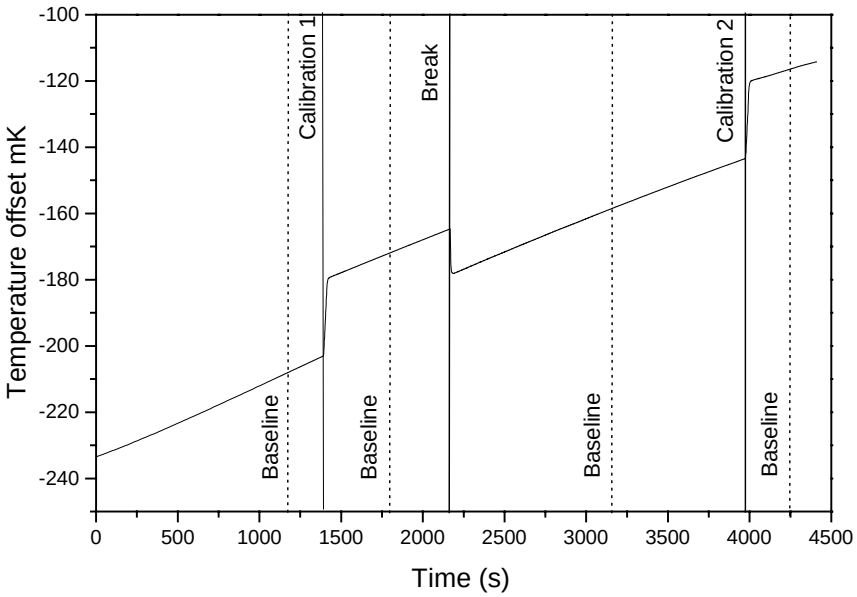

Fig. 1. Temperature offset against time for a typical experiment, mannitol dissolving in HBSS at pH 7.4.

determined from the change in the temperature within the reaction vessel (refer to Section 2.4).

2.4. Data analysis

An example of the raw data recorded by the solution calorimeter are given in Fig. 1, and it shows the fluctuation of temperature measured by the thermistor as a function of time during the formation of the solution. The solution calorimeter was operated under semi-adiabatic conditions, whereby the initial temperature was offset by 200 mK from the temperature of surrounding air bath of 298.15 K (controlled by the Heto–Holten water bath). Thus during baseline sections of the experiment, the temperature slowly decayed towards the air bath temperature. In addition to the baseline sections, the temperature offset data contains two calibration sections, and the break section, as indicated in Fig. 1. In the calibration sections, the abrupt changes in temperature are caused by the heater supplying 10 J of heat. Whereas, in the break section the change in the offset temperature is associated with the rapid exposure of the solute to the solvent, and subsequent formation of a dilute solution.

There are three methods available for the determination of the enthalpy of solution from the temperature offset data [5,15,16]. In all three methods the temperature decay during the baseline sections is fitted to an exponential equation in order to determine the calorimeter time constant, τ, and the extrapolated temperature at $t = \infty$, T_∞. The calorimeter approaches this temperature as the experimental time nears infinity. In the present study, the Regnault–Pfaundlers method was applied. This method is based on the reaction dynamics of the break [5,15], and uses baseline sections from before and after the break to determine τ and T_∞. These two parameters allow a correction to be made on the temperature changes observed at both the calibrations and break sections. The corrected values, $\Delta T_{\text{corr, calibration}}$ and $\Delta T_{\text{corr, reaction}}$ are the change in temperature that would be observed during a calibration or break section, respectively, if the experiment was carried out in an ideal adiabatic calorimeter. For an adiabatic calorimeter, no heat is exchanged with the surroundings and so an observed temperature change within the calorimeter is directly proportional to the heat absorbed or evolved associated with the process being studied. The constant of proportionality, ε, or the effective heat capacity of the system is given by

$$\varepsilon = \frac{Q_{\text{calibration}}}{\Delta T_{\text{corr, calibration}}} \quad (1)$$

Eq. (1) defines ε in terms of a calibration. Therefore ε can be easily determined, as $Q_{\text{calibration}}$ is the known amount of heat evolved by the heater and $\Delta T_{\text{corr, calibration}}$ is the corrected temperature change determined from the deflection in the temperature offset response. For the break section, where the amount of heat absorbed or evolved, Q_{reaction}, is unknown, ε is used as a calibration constant to determine Q_{reaction} using the known value of $\Delta T_{\text{corr, reaction}}$. This calculation is described by Eq. (2)

$$Q_{\text{reaction}} = \varepsilon \Delta T_{\text{corr, reaction}} \quad (2)$$

Dividing Q_{reaction} by the moles or grams of solute gives the enthalpy of solution. This is a simplified description of how the temperature offset data was used to determine the enthalpy of solution. The theoretical basis of solution calorimetry is well established and the specific equations used in the calculations have been reported previously [5,15,16]. The calculation summarised above was carried out using the Thermometric software to produce the enthalpies of solution (Table 2).

The heat flow was also calculated by conversion from recorded temperature offsets using the Thermometric software. This calculation is based on a modified version of the Tian equation [17], which is given below:

$$-\frac{\mathrm{d}Q}{\mathrm{d}t} = \varepsilon \left(\frac{\mathrm{d}T}{\mathrm{d}t} + \frac{1}{\tau}(T - T_\infty) \right) \quad (3)$$

where $\mathrm{d}Q/\mathrm{d}t$ is the heat flow, and is defined as negative for exothermic reactions. The values for τ, T_∞ and ε were determined in the same ways as described above. T is the temperature of the calorimetric vessel at time t, recorded by the thermistor. However during the conversion in the software this temperature is dynamically corrected to account for the dullness or inertia of the thermistor at the beginning of a re-

Table 2
Enthalpies of solution of solutes in simulated intestinal fluids (SIF) solutions and Hanks' balanced salt solutions (HBSS) and the time for 50 and 90% of the solute to dissolve into SIF solutions and HBSS of varying pH ($n = 3$, mean ± S.D.)

Solvent	$\Delta_{\text{sol}}H$		Times for 50 and 90% to dissolve			
	Propranolol (kJ mol^{-1})	Mannitol (kJ mol^{-1})	Propranolol (s)		Mannitol (s)	
			t_{50}	t_{90}	t_{50}	t_{90}
Fed state SIF	15.4 ± 0.12	22.0 ± 0.19	24 ± 1.0	81 ± 7.0	17 ± 1.5	23 ± 1.5
Fasted state SIF	23.6 ± 0.25	21.9 ± 0.40	36 ± 1.7	127 ± 7.0	14 ± 0.6	23 ± 1.5
HBSS pH 6.0	25.0 ± 0.21	21.9 ± 0.21	35 ± 0.0	161 ± 7.9	16 ± 1.7	25 ± 1.2
HBSS pH 6.5	25.7 ± 0.19	21.5 ± 0.34	31 ± 2.6	171 ± 8.5	15 ± 2.1	23 ± 1.0
HBSS pH 7.4	26.4 ± 0.21	21.5 ± 0.00	32 ± 2.5	184 ± 7.6	16 ± 1.5	24 ± 2.6

Significant differences ($P < 0.001$) between: $\Delta_{\text{sol}}H$ propranolol; fed state SIF vs. fasted state SIF all HBSS solvents; $\Delta_{\text{sol}}H$ propranolol; fasted state SIF vs. HBBS solvents of pH 6.0, 6.5 and 7.4. No significant differences ($P > 0.05$) between: $\Delta_{\text{sol}}H$ propranolol; HBSS solvents of pH 6.0, 6.5 and 7.4; $\Delta_{\text{sol}}H$ mannitol; fed state SIF, fasted state SIF; HBBS solvents of pH 6.0, 6.5 and 7.4.

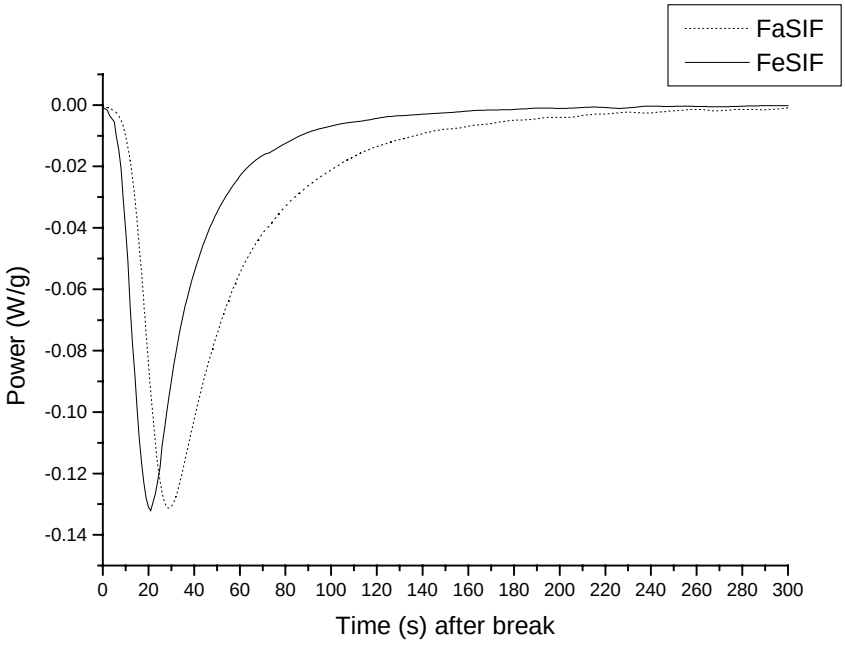

Fig. 2. Power–time curves for propranolol HCl dissolution in the fasted state simulated intestinal fluid (FaSIF) and fed state simulated intestinal fluid (FeSIF), showing that the drug went into solution quicker within the FeSIF than within the FaSIF ($n = 3$). Each line represents the mean of three solution calorimetry experiments, with $t = 0$ s being the point at which the propranolol HCL containing ampoule was broken.

action or calibration. The software requires a value for the thermistor time constant to perform this correction. It should be noted that the thermistor time constant is different from the calorimeter time constant τ, which is associated with the thermal leakage from the calorimeter vessel and reflects the rate at which the temperature of the solution within the vessel approaches T_∞. The thermistor time constant is a measure of the lag between temperature change in the solution and its detection by the thermistor [5].

The selection of the thermistor time constant used in the present study was based on analysis of the calibration sections before and after the break [5]. Various time constants were evaluated for each solvent system. This analysis took the form of integrating the calibration peaks that were produced when the calibration sections were converted to heat flow using the selected thermistor time constant. A thermistor time constant of 1 s gave calibration peak areas that matched the number of joules supplied by the heater. Therefore, this value was used to determine the dynamically corrected heat flow signals for all the experiments. Typical results of the conversion to dynamically corrected heat flow over the break section are shown in Figs. 2 and 3. As heat flow is measured in units of power (W), these figures are described as power–time curves.

The power–time curves were integrated using a mathematical software package (Origin^{TM}) to estimate the time for 50% (t_{50}) and 90% (t_{90}) of the drug to dissolve in the various solvents. This integration was performed over many narrow time intervals to produce cumulative area as a function of time, allowing the change in cumulative heat with time to be plotted (Fig. 4). These curves show that the cumulative heat approaches a constant value towards the end of the time range plotted, and this is equal to the total heat absorbed during the solution process, or $Q_{reaction}$. This value represents the heat associated with the total amount of solute held in the ampoule going into solution. Points along this curve may be calculated as a percentage of the total heat. Therefore, the time in seconds where the cumulative heat is 50% of the total heat, was taken as the time for 50% of the solute to dissolve, or t_{50}. This calculation was performed for both propranol HCl and mannitol (Table 2).

All statistical analyses were performed using one-way ANOVA in Minitab Version 13.1.

3. Results

The physical properties of the fasted and fed state SIFs are shown in Table 1. The osmolarity and viscosity of the two dispersions were similar. These values were slightly higher than those of the pure HBSS. The most dramatic difference in between the SIF solutions was observed in the micelle size. It appears that adjustment in the ratio of bile salt to lecithin, and changes in the total amount of bile salt and pH has a large influence on micelle size. The composition of SIF solutions used here have been reported before [14] and are similar to the composition of SIF solutions reported in the literature [7–9]. However, the size of the micelles are rarely described in these reports.

Both solutes exhibited endothermic reactions in all solvents, indicated by their positive enthalpies (Table 2). Endothermic enthalpies of solution are common for crystalline

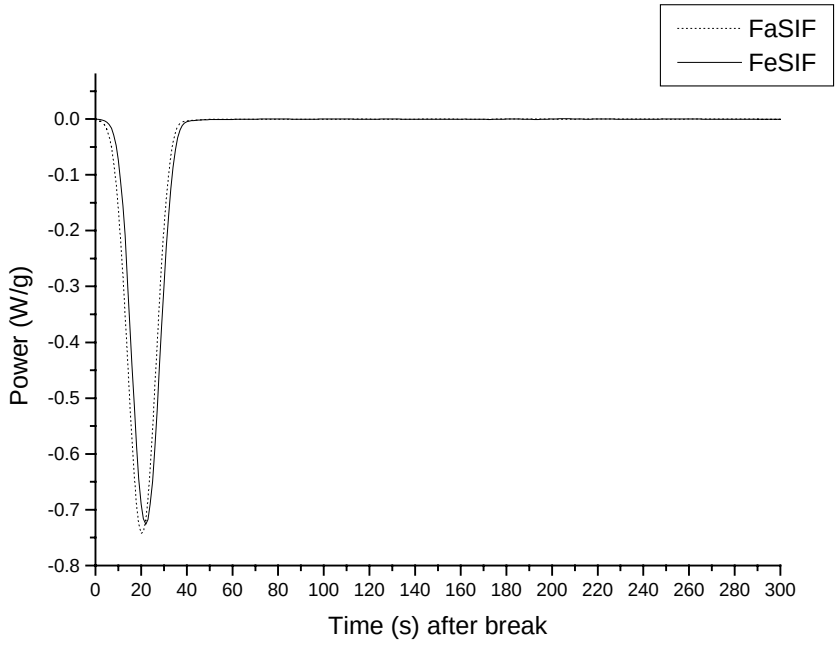

Fig. 3. Power–time curves for mannitol dissolution in the fasted state simulated intestinal fluid (FaSIF) and fed state simulated intestinal fluid (FeSIF), showing that there was no difference in the dissolution time of mannitol in the two SIF solutions used ($n = 3$). Each line represents the mean of three solution calorimetry experiments, with $t = 0$ s being the point at which the mannitol containing ampoule was broken.

materials [1]. The enthalpies of solution were not pH dependant as there was no significant difference ($P > 0.05$, one-way ANOVA) in the $\Delta_{sol}H$ values recorded for either drug in HBSS of varying pH (Table 2). The $\Delta_{sol}H$ for propranolol in the SIF solutions differed from those values determined in the HBSS, however, for mannitol there were no significant differences. The $\Delta_{sol}H$ for propranolol in the FeSIF was significantly less ($P < 0.05$, one-way ANOVA) than in either the FaSIF or the HBSS solvents (Table 2).

The change in enthalpy for the transfer ($\Delta_{trans}H$) of propranolol from HBSS to the mixed micelles within the SIF solutions was calculated. The $\Delta_{sol}H_{(HBSS)}$ was subtracted from the $\Delta_{sol}H$ value determined in the fed and fasted state SIF solutions. The $\Delta_{trans}H$ for FeSIF was calculated to be

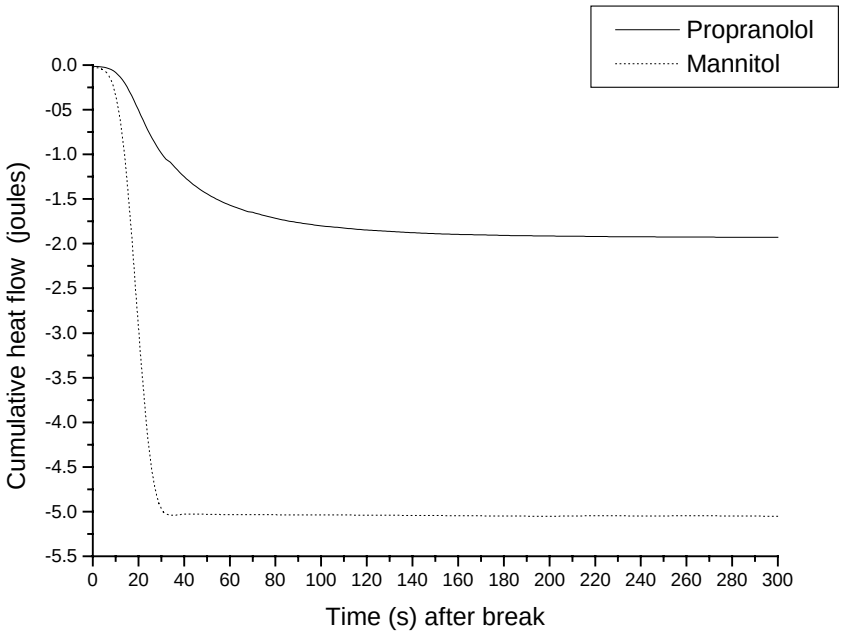

Fig. 4. Cumulative heat against time of propranolol and mannitol in fed state simulated intestinal fluid.

$-10.3\,kJ\,mol^{-1}$, and that for FaSIF to be $-2.1\,kJ\,mol^{-1}$. A similar calculation using the results from the mannitol experiments was not attempted, because the $\Delta_{sol}H$ values were not significantly different ($P > 0.05$), indicating no interaction of mannitol with the bile salt:lipid mixed micelles.

The power–time curves (Figs. 2 and 3) reflect the differences in the enthalpies of solution and allow t_{50} and t_{90} values to be calculated (Table 2). The cumulative heat flow versus time plot illustrates the temporal profile of solute dissolution into the solvent (Fig. 4). These curves indicate that the dissolution process is faster for propranolol in FeSIF than in the FaSIF, as shown by the reduced t_{50} and t_{90} for propranolol in the FeSIF, compared to the FaSIF and HBSS solvents (Fig. 2, Table 2). The similar dissolution profiles of mannitol in both the fed and fasted state SIF solutions (Fig. 3) are reflected by the similar enthalpies of solution and t_{50} and t_{90}. It took significantly less time for propranolol to dissolve in the FeSIF ($P < 0.05$ for the t_{50} and t_{90}, one-way ANOVA) than in the other solvents. It took 24 s for half the drug to dissolve, and 81 s for 90% of the drug to dissolve into the FeSIF. In all other solvents, it took over 30 s for half the propranolol to dissolve, and over 120 s for 90% of the drug to go into solution. For mannitol, there were no significant differences in t_{50} and t_{90} for the different solvents. It should be noted that these values for t_{50} and t_{90} are only estimates, as a consequence of the lag time associated with the solution calorimeter. The t_{50} and t_{90} values only give a qualitative description of the difference in response between solute/solvent systems and are not necessarily equivalent to the t_{50} and t_{90} values determined in conventional dissolution apparatus. However, in the present case this estimation did illustrate the difference in the rates of solution formation between propranolol HCl and mannitol in the presence of SIF.

4. Discussion

The hydrochloride salt of propranolol is fully ionised in the aqueous solvents. The p*K*a of propranolol at 298.15 K is 9.45 [18], thus the protonated form of propranolol can be considered as a weak acid and tends to reduce pH, although over the pH range used in this study, this would have little effect on the ionisation equilibrium of propranolol. The pK_a of mannitol at 291.15 K is 13.5 [19], so over the pH range used here mannitol would be unionised. Thus the enthalpies of solution obtained in this study are expected to be constant through the pH range of 6–7.4 and the results support this prediction.

The $\Delta_{trans}H$ values for both FeSIF and FaSIF indicate that the transfer of propranolol into the mixed micelles present within the SIF solutions is an exothermic process. This implies an enthalpically favourable interaction between the propranolol and the bile salt containing micelles. A large contribution will be made by the interaction between the ionised propranolol and the polar regions of the micelles, with also a small but significant contribution from hydrophobic interactions.

Beezer et al. [20] have suggested that $\Delta_{trans}H$ is an important and easy-to-measure parameter that could be used to assess a model solvent's ability to mimic the properties of a biological membrane. Their study involved the use of microcalorimetric measurements to determine the $\Delta_{trans}H$ from water to *Escherichia coli* cells for a group of alkoxyphenols. It would therefore appear that solution calorimetry has the potential to measure the $\Delta_{trans}H$ associated with drug partitioning into biological membranes. A combination of Caco-2 cells and SIF solutions has recently been proposed as a model for studying intestinal drug permeability [14]. Solution calorimetry may have utility as an analytical tool to investigate the transfer equilibrium between SIF solutions, Caco-2 cells and buffer. This approach would require solutes to show a change in enthalpy upon transfer, but results in this study indicate that certain beta-receptor antagonists may be compounds that fulfil this criterion.

The $\Delta_{trans}H$ for propranolol in the FeSIF was observed to be lower than the $\Delta_{trans}H$ in the FaSIF ($-10.3\,kJ\,mol^{-1}$ versus $-2.1\,kJ\,mol^{-1}$). The size and thus the encapsulated volume of the micelles differ by orders of magnitude between the two SIF solutions, however the difference between the enthalpies is only approximately five times (see Tables 1 and 2). The concentrations of bile salt and lecithin in the fed state SIF are approximately fives times the values found in the fasted state SIF. Therefore, the difference in $\Delta_{trans}H$ would seem to originate from a specific interaction of propranolol with the components of the micelle, as their concentration changes by five times, rather than a mechanism associated with the volume of the micelle. If the size and volume of the micelle were contributing factors to the differences in $\Delta_{trans}H$, then the magnitude of this difference would be expected to be much greater than five times. It should be noted that the enthalpy values were calculated per mole of propranolol added to the calorimeter vessel. Thus, the micellar partition coefficients of propranolol between HBSS and the micelles present in both fasted and fed SIF, would be required to confirm that micellar size does not contribute to the observed differences in $\Delta_{trans}H$.

The power–time plots generated by SolCal software from the raw data should be treated qualitatively because of the assumptions made in the calculation and the time constants associated with the calorimeter [5,15,16]. However, the heat capacity of the calorimeter vessel was determined to be approximately constant pre- and post-break, and was similar in value for each of the different solvent systems. This suggests that the differences in the profiles in Fig. 2 are real and not a result of differences in the heat transfer within the vessel due to differences in the heat capacities of the solvents.

The cumulative heat versus time plots as described in Section 2.4 can be used to estimate the amount of solute dissolved as a function of time. Thus, a number of dissolution rate models were fitted to this data, but none proved satisfactory. For example, the cube root of the remaining

weight of solute was plotted against time for both propranolol and mannitol in HBSS (data not shown). Anderberg and Nyström [21] have shown that for fine particulate material, a linear relation is observed for this plot. However, a nonlinear relationship was obtained for both propranolol and mannitol, indicating that the present case of the cube root law does not describe the solution kinetics observed by the solution calorimeter. The major assumption of this law, is that the dissolving material is monodisperse and predominantly spheroidal. The sizing results indicate that this was not case with the propranolol and mannitol used. In addition, the solutes usually investigated by this approach are sparingly soluble. Both solutes investigated in this study dissolved rapidly and so the lag time of the instrument at the start of the reaction would have effected the early data. Such an explanation would be consistent with the tendency of the cube root plots for propranolol and mannitol to approach a straight line towards completion of the solution process. Thus, for the two solutes investigated in the present study, the rank order of the time to form a solution could be compared, but specific kinetic analysis was not applicable. However, future studies by the authors are planned using less soluble materials, that are more spheroidal and monodisperse in nature, for example microspheres or granules.

The power–time curves, t_{50} and t_{90}, indicate that propranolol dissolved faster in the fed SIF than in fasted SIF. A similar result has been observed by Ashby et al. [22], who report that the presence of food can remove drug from solution and thus increase the dissolution rate. In the present study, the fasted state SIF with a lower amount of bile salt and lipid has a lower capacity for the drug, and thus the power–time curve indicates a slower dissolution rate compared to the response for the fed state. It is well recognised that dissolution and interaction with intestinal fluids effect drug absorption, therefore if power–time curves derived from solution calorimetry can characterise drug dissolution qualitatively in complex media, this may predict effects on drug absorption.

Clearly, this technique will not replace the standard dissolution tests as set out by the British Pharmacopoeia (Appendix XII D, 2002), or provide comparable data. The necessity of enclosing the solute within a 1 mL ampoule, accessed through the small opening of the ampoule, limits the use of this technique for monolithic dosage forms such as tablets. In addition, the technique can only be applied to drugs with adequate aqueous solubility, i.e. those that conform to classes I and III of the biopharmaceutics classification system (BCS) [23]. Thus, classes II and IV compounds for which dissolution has the most importance cannot be studied readily, although poorly soluble drugs incorporated into solubilising formulations might be studied. This study shows the ability of solution calorimetry to identify and quantify solute interaction with SIF solutions. Extending this work to incorporate drug delivery systems such as self emulsifying drug delivery systems, lipid formulations or microspheres will determine the potential of the technique to study drug/formulation/intestinal fluid interactions.

5. Conclusions

This study has shown the potential of solution calorimetry for the characterisation of solute dissolution into simulated intestinal fluids and biological media in general. The t_{50} and t_{90} values were estimated from the power–time plots for crystalline powders of propranolol and mannitol. Thus, the derived power–time curves can be used to give a ranked comparison of the time required to form a solution. In addition, if a dispersion of micelles is used as the solvent system the enthalpy of transfer for a solute partitioning into these micelles can be determined.

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