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Thermochimica Acta 450 (2006) 56–60
thermochimica acta
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Solution calorimetry to monitor swelling and dissolution of polymers and polymer blends

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Available online 31 July 2006

Abstract

The observed rate of drug release from a polymeric drug delivery system is governed by a combination of diffusion, swelling and erosion. It is thus not a simple task to determine the effects of the polymer on the observed drug release rate, because the swelling characteristics of the polymer are inferred from the drug release profile. Here we propose to use solution calorimetry to monitor swelling. Powdered polymer samples (HPMC E4M, K4M, K15M and NaCMC, both alone and in a blend) were dispersed into water or buffer (pH 2.2 and 6.8 McIlvaine citrate buffers) in a calorimeter and the heat associated with the swelling phenomena (hydration, swelling, gelation and dissolution) was recorded. Plots of normalised cumulative heat (i.e. q_t/Q, where q_t is the heat released up to time t and Q the total amount of heat released) versus time were analysed by the power law model, in which a fitting parameter, n, imparts information on the mechanism of swelling.

For all systems the values of n were greater than 1, which indicated that dissolution occurred immediately following hydration of the polymer. However, while not suitable for determining reaction mechanism, the values of n for each polymer were significantly different and, moreover, were observed to vary both as a function of particle size and dissolution medium pH. Thus, the values of n may serve as comparative parameters. Properties of the polymer blends were observed to be different from those of either constituent and correlated with the behaviour seen for polymer tablets during dissolution experiments. The data imply that solution calorimetry could be used to construct quantitative structure–activity relationships (QSARs) and hence to optimise selection of polymer blends for specific applications.

Keywords: Solution calorimetry; HPMC; Swelling; Hydration; Polymer blends

1. Introduction

Many drug delivery systems (DDS) are polymeric, the polymer network forming a matrix for the encapsulation, and subsequent controlled or sustained release, of a drug. A number of processes govern the rate of release of a drug from a hydrophilic matrix following addition to a dissolution medium; diffusion (both of water into the matrix and of drug out of the matrix), swelling (which includes various steps, including but not limited to hydration, gelling and swelling [1,2]) and dissolution (erosion of the polymer) [3]. Clearly knowledge of, and control over, these characteristics is essential to tailor drug release to a specific pharmacological profile [4].

To note a couple of points regarding these definitions; firstly, the rates of diffusion (of water ingress and drug egress) are usually assumed to be constant. Secondly, to avoid unnecessary complication, the term swelling will be used to describe the process that a polymer system undergoes following addition to solvent; this is a composite, and not simple, term that encompasses all of the processes described above, including dissolution.

The measurement of swelling is not straightforward. Two common approaches are (i) to remove the DDS from the dissolution medium periodically and assess the extent of swelling visually (by light microscopy for instance) or (ii) to measure the rate of drug release from the DDS (dissolution testing). Neither approach is ideal. In the former the polymer system must (usually) be removed from the dissolution medium and excess liquid must be blotted off prior to measurement. This can be hampered both by the shape of the system and by any erosion that has occurred. It is also invasive and not practicable for microparticulate systems. In the latter it must be assumed that drug release from the polymer matrix occurs instantaneously following swelling and is not a rate-limiting step. The method is not a direct measurement of swelling, so all conclusions drawn about the behaviour of the polymer are inferred.

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doi:10.1016/j.tca.2006.07.017

The fact that swelling is accompanied by heat means that the event is amenable to study by calorimetric methods. Few examples exist in the literature, although flow calorimetry has been used to study the dissolution of tablets [5,6] in the presence of foodstuffs.

The demonstration of the utility of solution calorimetry for the study of polymer swelling and an exploration of its sensitivity to changes in polymer composition and experimental variables are thus the main aims of this paper using, as a model, a number of cellulose ethers. Cellulose ethers represent a broad class of polymers, which satisfy the key criteria for the development of controlled release oral solid dosage forms. One of the most widely employed for the development of swellable matrices is hydroxypropylmethylcellulose (HPMC [7,8]).

HPMC is a non-ionic polymer, which has a cellulose backbone, a natural carbohydrate containing a basic repeat unit of anhydroglucose. There are three established 'chemistries' or substitution classes for HPMC, according to the percentage of methoxyl or hydroxypropyl groups on the main cellulose chain. The USP defines, among others, HPMC 2901 (Methocel E), HPMC 2906 (Methocel F) and HPMC 2208 (Methocel K). The ratios and degree of substitution vary between grades. Variations in the molecular weights of various HPMC grades are reflected in the viscosities of aqueous solutions prepared at a standard concentration. In discussions regarding controlled release, the terms 'viscosity' or 'viscosity grade' and the associated value for a 2% (w/w) aqueous solution are frequently used to refer to the molecular weight of the HPMC grade being used. In this work HPMC E4M (4000 mPa), HPMC (K4M) (4000 mPa) and HPMC K15M (15,000 mPa) grades are used.

Here, we discuss the calorimetric data obtained, focussing in particular on the recovery of quantitative parameters, for these HPMC grades and sodium carboxymethylcellulose (NaCMC) both individually and in a formulated mixture; the results are correlated with parameters obtained from dissolution experiments.

2. Materials and methods

HPMC (grades E4M, K4M and K15M) were supplied by Colorcon Ltd. NaCMC was purchased from Hercules Inc. All polymers were used as received. Samples were sieved to obtain two particle size fractions (90–125 and 45–53 μm). McIlvaine buffer solutions (pH 2.2 and 6.8) were prepared in accordance with the pharmaceutical codex using citric acid (>99%) and disodium hydrogen phosphate dodecahydrate (>99%), both from Sigma. Polymer blends were prepared by mixing 1:1 mass ratios using a blend-sieve-blend method (Turbula mix, 10 min, sieve (either 125 or 53 μm depending upon the sample), Turbula mix, 10 min).

Data were recorded with a 2265 20 mL micro solution ampoule (Thermometric AB, Järfälla, Sweden), the design and operating principles of which have been discussed previously [9]. Briefly, the unit is designed to operate within a TAM (Thermal Activity Monitor, Thermometric AB) and operates on heat-conduction principles. It contains three metal cartridges (each comprising three pieces) that can be charged with solid sample (typically up to ∼20 mg); the cartridges are loaded into the underside of the lid of the sample vessel. The lower part of the vessel (stainless steel) holds a reservoir of solvent (15 mL) into which the cartridges are introduced once thermal equilibrium has been attained.

In this work we elected to load sample only into cartridge 1. The cartridges were coated with Repelcote (Sigma) prior to use to prevent adherence of the polymer to the inner cartridge surfaces. The power associated with the introduction of cartridge 1 (empty) into the solution was determined in a separate control experiment and was used to correct the experimental data. Polymer samples were weighed on a Sartorious microbalance (HPMC, 3 mg, NaCMC, 15 mg, both accurate to ±0.05 mg). The vessel was charged with either distilled, deionised water or buffer (15 mL). The instrument was maintained at 298 K and left to reach thermal equilibrium (indicated by a zero baseline signal). Cartridge 1 was then broken into the solvent, dispersing the polymer sample. The vessel's contents were stirred at 120 rpm (the maximum attainable) with a turbine stirrer. Power was recorded (every second) with the software package Digitam 4.1; the amplifier was set to its maximum range (3000 μW) and a 20 mL stainless steel ampoule containing water or buffer as appropriate (15 mL) was used as a reference. The instrument was calibrated weekly by the electrical substitution method. Data analysis was performed with Origin (Microcal Software Inc., USA). Experiments were repeated a minimum of three times and data are quoted throughout with a standard deviation (S.D.). Upon removal of the ampoules after each experiment, complete polymer dissolution was noted.

3. Results and discussion

Typical data sets for the dispersion of the individual polymers are shown in Fig. 1. One concern with this type of experiment is the effect of stirring on the baseline, because the solution at the start (water or buffer) can be considerably less viscous than that at the end (polymer solution). Here, small sample sizes were used (3 mg for HPMC, giving a final concentration of 0.02% (w/v)). In all cases the baseline value returned to zero (indicating no causal effect of a change in viscosity; note that for

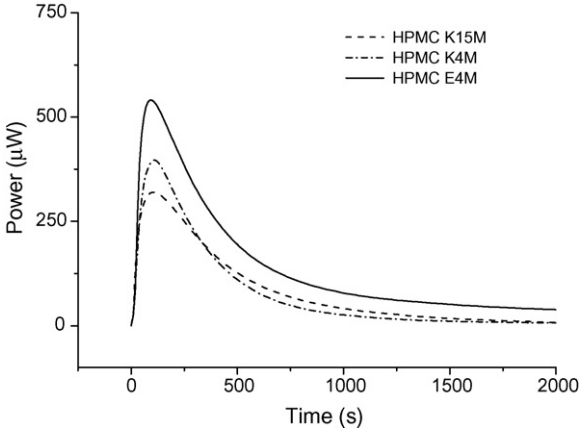

Fig. 1. Power-time data for the dissolution of various grades of HPMC into water.

clarity some of the subsequent data are truncated) and no significant noise was noted over that of an unstirred experiment. As a consequence, the effect of stirring can be considered negligible. The data represent the sum of all the events that are occurring in the vessel during the measurement period; since, as noted earlier, polymer powder dissolution is much more complicated than that of low molecular weight solids, these events include hydration, swelling and gelation as well as dissolution [1,2] and the fact that the signal represents multiple processes should be borne in mind during the subsequent discussion.

The responses of the three HPMC grades are different, which immediately indicates that solution calorimetry offers a level of sensitivity to swelling sufficient to discriminate between polymer grades. However, to compare the calorimetric data between polymers, and with other more conventional approaches, it is convenient to convert them to a ratio. This is most easily achieved by assuming that the total heat output during the experiment (Q, obtained by integration of the power–time data) corresponds to complete swelling while the heat output to any time t (q_t) corresponds to the fraction of swelling that has occurred to that point. Hence, a plot of q_t/Q versus time gives a set of data that represents the swelling response; typical plots of this type are shown in Fig. 2.

Many models have been derived in the literature for analysing drug release profiles [3] and it is important to note that there is not one universal model applicable to all samples. A very commonly used model is the power law, first discussed by Ritger and Peppas [10], Eq. (1);

$$\frac{q_t}{Q} = kt^n \tag{1}$$

where k is a constant and n is a parameter, the value of which indicates the mechanism of swelling. Hence, a plot of $\log q_t/Q$ versus $\log t$ should result in a straight line, the slope of which gives the value of n. These plots are given in Fig. 3; derived values of n for each polymer are given in Table 1.

This model is empirical and does not attempt to describe drug dissolution. Rather, it can be used to infer a mechanism and

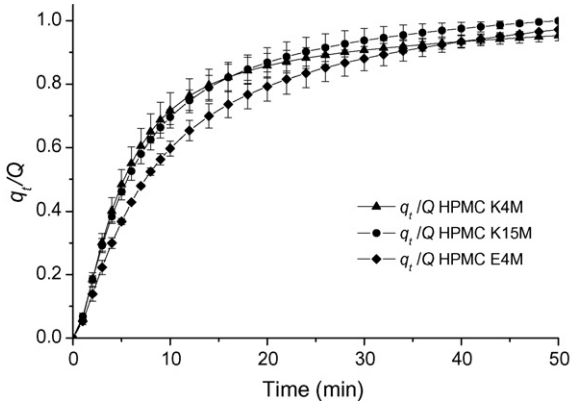

Fig. 2. The swelling profiles of various grades of HPMC calculated from the power–time data shown in Fig. 1.

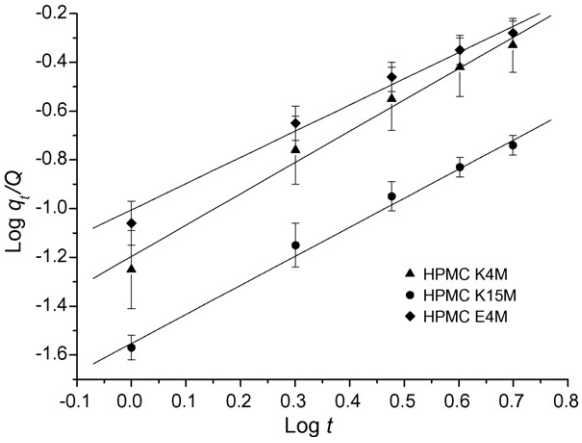

Fig. 3. Plots of log q_t/Q vs. log t for the three grades of HPMC swelling in water.

usually reduces to two special cases; $n = 0.5$ (Fickian diffusion) and $n = 1$ (case II, or zero-order, release). Siepmann and Peppas [3] note that although widely used, these special cases hold only when applied to slab geometry. When other geometries are used, the log plots obtained can be nonlinear. The correlation coefficients obtained for the data in Fig. 3 were 0.993,

Table 1
The values of n and k derived from $\log q_t/Q$ vs. t plots for polymer swelling

	n	$\log k$	R^2
HPMC K4M H_2O	1.28 ± 0.08	−1.20 ± 0.12	0.9926
HPMC K15M H_2O	1.19 ± 0.07	−1.55 ± 0.02	0.9975
HPMC E4M H_2O	1.08 ± 0.08	−1.01 ± 0.19	0.9915
HPMC E4M H_2O (90–125 μm)	1.20 ± 0.05	−1.03 ± 0.10	0.9801
HPMC E4M H_2O (45–53 μm)	1.36 ± 0.06	−1.28 ± 0.14	0.9922
NaCMC pH 2.2 (90–125 μm)	1.05 ± 0.04	−0.82 ± 0.02	0.9788
NaCMC pH 2.2 (45–53 μm)	1.31 ± 0.05	−1.17 ± 0.06	0.9896
NaCMC pH 6.8 (90–125 μm)	1.13 ± 0.03	−0.91 ± 0.03	0.9808
NaCMC pH 6.8 (45–53 μm)	1.61 ± 0.08	−1.55 ± 0.21	0.9934
HPMC E4M pH 2.2 (90–125 μm)	1.03 ± 0.11	−0.96 ± 0.02	0.9886
HPMC E4M pH 6.8 (90–125 μm)	1.01 ± 0.05	−0.79 ± 0.04	0.9871
HPMC E4M pH 6.8 (45–53 μm)	1.09 ± 0.04	−1.07 ± 0.06	0.9888
HMPC E4M:NaCMC pH 6.8 (45–53 μm)	1.32 ± 0.10	−1.31 ± 0.18	0.9892
HPMC E4M pH 2.2 (45–53 μm)	1.20 ± 0.06	−1.21 ± 0.03	0.9875
HMPC E4M:NaCMC pH 2.2 (45–53 μm)	1.23 ± 0.07	−1.22 ± 0.09	0.9892

The linear regression R^2 values are also shown.

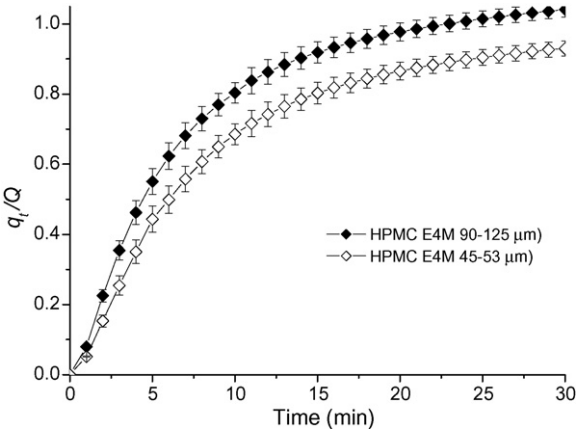

Fig. 4. The swelling response for different particle size fractions of HPMC E4M in water.

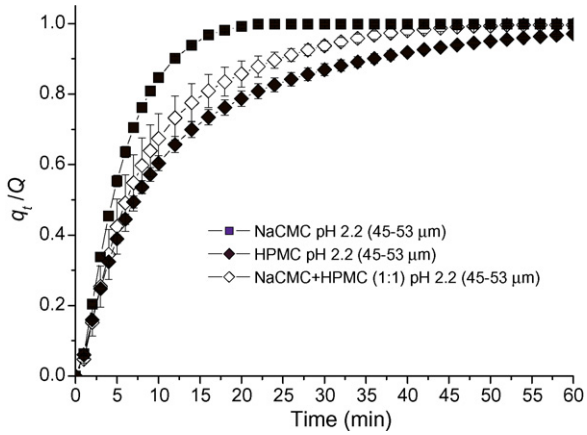

Fig. 5. The swelling response for HPMC E4M and NaCMC, both alone and in combination at pH 2.2.

0.998 and 0.992. These compare favourably with other cases in the literature where this model has been applied (for instance 0.942–0.982 for release of 4-aminopyridine from HPMC matrices [11]; 0.995–0.983 for the swelling of HEC and HPC matrices [12]; values ranging from 0.967 to 0.990 for the drug release profile of HPMC/ECA matrices [13]). The slight nonlinearity in the data reflects the fact that the model is empirical and does not strictly apply to powdered systems; however, we selected it for study because it provided a parameter (n) with which to contrast systems, because it is widely used in the literature and thus allows data comparison and because the focus of this work was to demonstrate the utility of the calorimetric technique rather than to understand the nature of the polymer swelling.

The values of n were significantly different between some polymers and were all greater than 1, which indicates that dissolution occurs immediately following hydration. This is not surprising as powdered samples with very high surface areas were used. Values of n less than 1 would be expected for tablets.

To determine the sensitivity of the technique to changes in swelling caused by differences in experimental parameters, two principal factors were selected; the particle size distribution of the polymer and the pH of the dissolution medium. In the former case, two particle size fractions were obtained by sieving the samples (90–125 and 45–53 μm). The calorimetric responses for both particle size fractions of E4M are represented in Fig. 4 where it can be seen that the responses are significantly different (the values of n were 1.2 ± 0.05 and 1.36 ± 0.06 for the 90–125 and 45–53 μm fractions, respectively). As the particle size distribution decreases, the value of n increases; this suggests that there is a concomitant increase in the dissolution rate of the polymer with a decrease in particle size.

To examine the effect of pH, swelling experiments were conducted in two buffered systems (pH 2.2 and 6.8 McIlvaine citrate buffers). HMPC polymers have no ionisable functional groups and, hence, should give the same swelling responses regardless of pH. This was indeed observed to be the case, being 1.03 ± 0.11 and 1.01 ± 0.05 at pH 2.2 and 6.8, respectively. NaCMC, on the other hand, has carboxyl functional groups and is affected by pH; accordingly, its swelling response was observed to alter as a function of pH, the values of n for the 90–125 μm fraction being 1.05 ± 0.04 and 1.13 ± 0.03 and for the 45–53 μm fraction being 1.31 ± 0.05 and 1.61 ± 0.08 at pH 2.2 and 6.8, respectively.

It was then decided to study the swelling response of a binary mixture of two polymers, HPMC E4M and NaCMC, since previous dissolution studies using matrix tablets of the two polymers showed some synergistic effects as a function of pH [14].

The calorimetric swelling responses of HPMC, NaCMC and their 1:1 mixture at pH 2.2 are represented in Fig. 5. NaCMC showed the fastest swelling, completion being reached in about 20 min. Conversely, the swelling of HPMC was slower, total heat release occurring in about 60 min. The mixture of the two polymers behaved in an intermediate way, the thermal profile lying between those of the individual polymers. The values of n did not show a significant difference (1.31 ± 0.05, 1.20 ± 0.06 and 1.23 ± 0.07 for NaCMC alone, HPMC E4M alone and the mixture, respectively), all being higher than 1, again indicating a swelling mechanism mainly associated with the dissolution of the polymer from the surface exposed to the fluid. To highlight and quantify the differences between the samples, the initial swelling rates were determined by taking the slope of the first part of the curve (Table 2). It is clear that the hydration and swelling processes of NaCMC are faster compared with the other samples. HPMC E4M shows the lowest rate and the rate of the sample containing the polymer blend lies between the rate of each individual material.

Previous dissolution studies, on drug loaded tablets prepared by direct compression of the two polymers and a model drug,

Table 2
The initial rate values determined for HPMC E4M and NaCMC both alone and in combination at pH 2.2 and 6.8

	Initial rate (min^{-1})	R^2
NaCMC (45–53 μm) pH 2.2	0.099 ± 0.002	0.9939
HPMC E4M (45–53 μm) pH 2.2	0.066 ± 0.003	0.9938
EM4B (45–53 μm) pH 2.2	0.080 ± 0.007	0.9946
NaCMC (45–53 μm) pH 6.8	0.069 ± 0.006	0.9981
HPMC E4M (45–53 μm) pH 6.8	0.064 ± 0.003	0.9885
EM4B (45–53 μm) pH 6.8	0.054 ± 0.004	0.9881

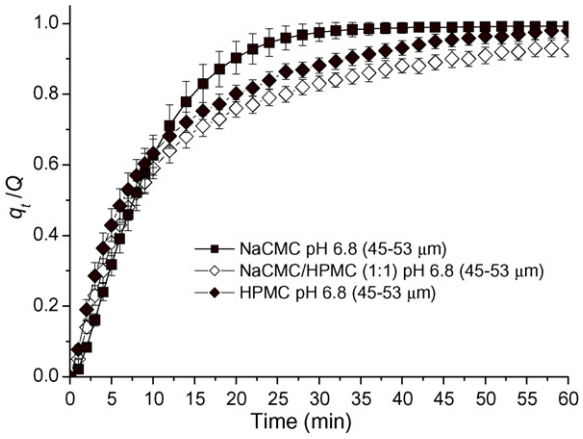

Fig. 6. The swelling response for HPMC E4M and NaCMC, both alone and in combination at pH 6.8.

showed that when formulated in combination these polymers exhibited a synergistic effect at pH 6.8, releasing loaded drug more slowly than was observed when either polymer was used alone [14]. The time to release of 90% of the loaded drug (t_{90}) was 16.4 h for an HMPC E4M matrix and 10.8 h for a NaCMC matrix. This value increased to 19.10 h when the two polymers were formulated in combination. No synergistic effects were noted at lower pHs.

The calorimetric responses of the two polymers both alone and in combination at pH 6.8 (Fig. 6) show trends which are similar to the dissolution profiles noted above for matrix tablets containing the same polymers and a model drug. In fact the time required for the total release of heat by NaCMC is faster compared with both HPMC and the mixture. This means that the swelling process, including hydration, swelling, gelling and dissolution, occurs fastest for this polymer. The presence of carboxylic acid groups on the main chain of NaCMC appears to confer this polymer with a higher affinity to water compared with HPMC. The higher hydrophilicity of the NaCMC leads to a higher hydration rate and a faster swelling and dissolution process and, when the polymer is formulated in a drug loaded matrix tablet, to a faster drug release profile. The data for the HPMC E4M sample suggest a slower swelling process compared with NaCMC. This is in agreement with the t_{90} value calculated from dissolution profiles of matrices containing the same polymer noted above.

The polymer mixture showed the slowest swelling process while the t_{90} values for tablets containing this polymer blend were the longest. This could attest to an interaction between the two polymers, which leads to a slower hydration, swelling, gelling and dissolution process. The n values for these samples (1.61 ± 0.08, 1.09 ± 0.04 and 1.32 ± 0.10 for NaCMC alone, HPMC E4M alone and the mixture, respectively) were significantly different. The swelling mechanism for NaCMC seems to be highly determined by polymer dissolution from the surface exposed to the fluid. This phenomenon is less marked for HPMC E4M while the sample containing the two polymers shows an intermediate n value showing an intermediate mechanism. No significant differences can be noticed in the initial rate of NaCMC and HPMC E4M, but a slower rate is clearly shown by the mixture.

4. Summary

The objective of this work was to determine whether solution calorimetry could be used to monitor the swelling of polymers and, if so, whether comparative parameters could be recovered from the data. It has been demonstrated that both are feasible. Conversion of the raw power versus time data to q_t/Q versus time data results in swelling responses that are comparable to those obtainable via conventional techniques such as dissolution testing. As such, the data were amenable to analysis via a modified form of the power-law model, allowing the model parameter n to be determined. The values of n were all found to be greater than 1, which is likely to be a result of the fact that powdered samples were employed.

A further aim was to demonstrate the sensitivity of calorimetric measurement to changes in polymer composition and experimental conditions. Changes in both particle size distribution and dissolution medium pH were observed to vary the swelling responses. Moreover, the swelling response of a two component formulation was observed to be slower than that of either component alone, indicating that a change in swelling of the polymer network, rather than a change in diffusion rate of the drug, was responsible for the negative synergy previously noted for this system.

As well as being sensitive to small changes in swelling, solution calorimetry affords the opportunity to measure the swelling of polymers non-invasively. This obviates the need to manipulate the system to facilitate measurement (such as by using highly soluble drugs) and means that any system can (potentially) be studied. Moreover, since the calorimeter does not rely on an optical measurement its use is not dependent on maintaining a high degree of optical clarity in the dissolution medium, which means that swelling can be measured in representative bodily fluids (such as fed and fasted simulated intestinal fluids), which are often opaque. The resulting data would allow better in vitro:in vivo correlations (IVIVC) to be drawn.

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