Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 68 (2008) 795–801
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

# The role of solution calorimetry in investigating controlled-release processes from polymeric drug delivery systems

Stefania Conti [a,b], Simon Gaisford [a,*], Graham Buckton [a], Lauretta Maggi [b], Ubaldo Conte [b]

[a] The School of Pharmacy, University of London, London, UK
[b] Department of Pharmaceutical Chemistry, Pavia University, Pavia, Italy

Received 20 February 2007; accepted in revised form 4 June 2007
Available online 12 June 2007

**Abstract**

In this paper we investigate the potential role of solution calorimetry measurements in aiding the formulation of swellable matrices containing a mixture of HPMC and NaCMC, an ionic cellulose derivate. These polymers show a synergistic effect in their ability to modulate drug delivery rates; a matrix containing a 1:1 mixture of NaCMC and HPMC exhibits a significantly slower drug release rate than either polymer shows alone. The exact cause of this synergism is not clear and it is not an easy effect to examine using conventional means (such as dissolution testing). Here, we used solution calorimetry to study the system holistically. By comparing the measured response of a physical blend with a theoretical one (obtained by summation of the power–time data for each material), it was possible to assess if there was/was not any interaction which may explain the synergism. Furthermore, since a thermodynamic quantity was returned it was possible to establish if the interaction was favourable or unfavourable and so to obtain useful information to understand and predict the dissolution behaviour of polymeric systems containing the same materials.

An unfavourable interaction was noted between NaCMC and the model drug (Diltiazem HCl); no interaction was seen between HPMC and the drug; and a favourable interaction was recorded when both polymers were formulated with the drug. The trend was mirrored by the $t_{90}$ (the time required for 90% drug release) values determined from dissolution testing; NaCMC 10.8 h, HPMC 16.4 h, NaCMC and HPMC 19.1 h. The data suggest that solution calorimetry measurements can be used to aid the selection of polymeric excipients to design controlled-release drug delivery systems.


*Keywords:* Matrix tablets; Drug release kinetics; Controlled release; Solution calorimetry; Drug–polymer interactions

## 1. Introduction

The use of swellable materials for drug delivery applications has followed experimental and theoretical investigation of solvent and solute transport in polymeric systems, with several important observations and mathematical models developed describing transport behaviour in polymeric systems [1]. Hydrophilic matrices, in particular, are one of the most used controlled delivery systems, due to their simple technology and low cost. Their study is a difficult task because of their complex and disordered structure and the mechanism of drug release from these systems continues to be a matter of debate [2].

One method of fabricating controlled-release dosage forms is by incorporating a drug in a matrix containing a hydrophilic, rate controlling polymer. Commonly used polymers are cellulose derivates, which include hydroxypropylmethylcellulose (HPMC, [3]). Drug release from this type of system is controlled by hydration of the polymer, which forms a gelatinous barrier layer at the surface of the tablet through which the drug diffuses. The consistency and strength of the gel layer formed at the tablet surface are crucial factors in determining drug release mechanism and the rate of drug delivery from the polymeric system [4]. Mixtures of polymers, particularly cellulose ethers,

* Corresponding author. The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK. Tel.: +44 20 7753 5863; fax: +44 20 7753 5942.
*E-mail address:* simon.gaisford@pharmacy.ac.uk (S. Gaisford).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.06.002

are thus useful in regulating the drug release properties of a dosage form. In matrix tablets, polymer mixtures can be used to control the drug release rate by producing gel barriers of varying consistency. This effect is often due to interactions between the excipients that modify the matrix viscosity and/or polarity as well as the internal structure of the tablet through which the drug must diffuse [5].

When a matrix containing a swellable glassy polymer comes into contact with a solvent a progressive change from the glassy to the rubbery state leads to a swelling process. The individual chains, originally in a fixed state, absorb water, their end to end distance and radius of gyration expanding to a solvated state because of the lowering of the transition temperature of the polymer [6]. Macroscopically this phenomenon is evidenced by the formation of a thick gel layer at the tablet surface, which governs the drug release rate. In the gel phase, polymer chains begin slowly to unfold and gradually become solvated: however, the presence of physical entanglement between neighbouring chains hinders polymer dissolution. At the outer surface, the polymer is so diluted that the chains disentangle; the polymer no longer has structural integrity and dissolves as single molecules or as discrete agglomerates [7].

Although drug-related parameters (such as solute size, solubility and loading) and polymer-related parameters (such as molecular weight, viscosity and concentration) have been shown to influence the drug release rate from swellable devices [8–12], the presence and the effect of potential drug–polymer interactions on polymer swelling and drug release kinetic are not well researched [13].

In a previous study we demonstrated that solution calorimetry has the potential to monitor the swelling of cellulose polymers by reporting the heat changes that occur following dispersion of the polymer into a solvent [14]. We also showed that there was the potential to gain some insight into the mechanism of swelling/dissolution by analysing data using a power law model, although the interpretation was limited by the fact that powdered samples were employed. The primary aim of this work is thus to extend the analysis to polymer compacts and to assess if mechanistic information can in fact be elucidated. Various compacts were prepared using individual polymers (HPMC E4M and sodium carboxymethylcellulose, NaCMC) and a polymer blend. It was observed (by dissolution testing) that the release profile of a model drug (Diltiazem HCl) from the polymer blend compact was significantly slower than from compacts containing a single polymer. Thus, a further aim of the present study was to determine whether calorimetric monitoring could detect any interactions between the species which may explain the observed release data.

## 2. Materials and methods

Diltiazem HCl was supplied by Profarmaco S.p.A. (Milan, Italy). Hydroxypropylmethylcellulose (Methocel E4M, $\eta = 4000$ cP) was donated by Colorcon Ltd., Orpington, UK, and sodium carboxymethylcellulose (Blanose 7HXFPH) was donated by Hercules, Wilmington, DE. All materials were used as received without further purification. Buffer solutions were prepared in accordance with the Pharmaceutical Codex [15]. Dissolution tests were conducted in an acetate buffer (pH 6.8, 30 mM) using ammonium acetate (>98%) and acetic acid (>99%), both from Sigma Ltd. (UK). Calorimetric experiments were conducted in a McIlvaine buffer (pH 6.8) using citric acid (>99%) and disodium hydrogen phosphate dodecahydrate (>99%), both from Sigma Ltd. (UK).

### 2.1. Dissolution studies

#### 2.1.1. Tablet preparation

Drug and polymer powders were sieved and then mixed together in a Turbula apparatus (Turbula T2A, Bachofen, Basel, CH) for 10 min. The percentage composition of each formulation is reported in Table 1. Drug and polymer mixtures were directly compressed with a single die tabletting machine (Kilian, Coln, D) equipped with a piezoelectric load washer (Kistler, Winterthur, CH) for compression force measurements and fitted with flat-faced 9.8 mm punches. A compression force of about 2500 kg was recorded. The mean weight of the cylindrical tablets obtained was 329 mg.

Dissolution tests (six replicates) were performed in acetate buffer pH 6.8 (37 °C, 1 L) using USP30 (2007) Apparatus 2 with paddles rotating at 100 rpm. The amount of drug released as a function of time was determined by UV (Spectracomp 602, Advanced Products S.r.l., Milan, Italy) at 246 nm.

The dissolution data were fitted to the well-known power law model (Eq. (1)), which is frequently employed to describe the drug release behaviour of polymeric systems [16].

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where $M_t/M_\infty$ is the fraction of drug released at time $t$, $k$ is a proportionality constant accounting for structural

Table 1
Percentage composition of matrix tablets containing Diltiazem HCl and HPMC E4M, NaCMC and HPMC/NaCMC (1:1)

| Formulation name | Component (% w/w composition) |
|---|---|
| HPMC | Diltiazem HCl (36.5)<br>HPMC (Methocel E4M) (63.5) |
| NaCMC | Diltiazem HCl (36.5)<br>NaCMC (Blanose 7H4XFPh) (63.5) |
| HPMC/NaCMC | Diltiazem HCl (36.5)<br>HPMC (Methocel E4M) (31.75)<br>NaCMC (Blanose 7H4XFPh) (31.75) |

and geometrical properties of the matrix and $n$ is an exponent which describes the mechanism of drug release. According to the criteria for release kinetics from swellable systems, release exponent values $n = 0.45$, $0.45 < n < 0.89$ and $0.89 < n < 1.0$ indicate, respectively, Fickian (Case I) diffusion, non-Fickian (anomalous) diffusion and zero-order (Case II) transport [17].

### 2.2. Calorimetric studies

#### 2.2.1. Tablet preparation

Tablets (2 mm diameter) were kindly prepared by Pharmaceutical Development Services (Guildford, Surrey). The mean tablet weight was $5.09 \pm 0.45$ mg and the compression forces used were 185 kg (HMPC), 190 kg (NaCMC) and 160 kg (1:1 mixture of HPMC and NaCMC).

#### 2.2.2. Solution calorimetry

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 [18]. Briefly, 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 (17 mL) into which the cartridges are introduced. Once thermal equilibrium has been attained (indicated by a zero baseline signal) the cartridges are pushed into the solvent (either sequentially or simultaneously) where they fall apart, dispersing the solid sample which subsequently dissolves into the solvent. The vessel was filled with either distilled, deionised water or buffer (15 mL).

The power associated with the introduction of the empty cartridge into the solution was determined in a separate control experiment and was used to correct the experimental data. Tablets or polymer samples (between 1 and 6 mg) were weighed on a Sartorious microbalance (accurate to ±0.01 mg) and were loaded into one of the three cartridges. The instrument was maintained at 298 K using a precision water bath (TAM, accurate to ±0.0001 °C) and left to reach thermal equilibrium. The cartridge was then broken into the solvent, dispersing the polymer sample into the dissolution medium. The vessel's contents were stirred at 120 rpm with a turbine stirrer. Power data were recorded (every second) with the dedicated 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 (15 mL) was used as a reference. 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 (SD, $\sigma_{n-1}$). In accordance with the manufacturer's settings, exothermic data are plotted as positive values.

## 3. Results and discussion

### 3.1. Dissolution studies

The in vitro sustained release of Diltiazem HCl from the tablets prepared as above was examined by performing dissolution tests at pH 6.8. The results of the release tests are shown in Fig. 1. The graph reports the percentage of drug release as a function of time from systems containing Diltiazem HCl incorporated in NaCMC, HPMC and a 1:1 blend of HPMC and NaCMC, respectively. Table 2 reports the values of the exponent $n$, indicative of the mechanism of drug release, and of $t_{90}$, indicative of the rate of drug release from the system, determined by fitting the dissolution data to Eq. (1).

HPMC tablets release the drug with an anomalous non-Fickian mechanism ($n$ is 0.71) indicating an influence both of diffusion of the drug through the gel layer and erosion of the whole hydrated and gelled tablet from the outer surface. Total drug release is achieved within 24 h ($t_{90}$ is 16.40 h). A burst effect can be noticed at the beginning of the dissolution test. This arises because the hydration rate of the drug is faster than the hydration rate of the polymer; thus, initially at least, drug release is instantaneous because the rate-limiting gel layer formed by the hydrated polymer requires a finite time to form.

A sigmoidal drug release profile is observed for NaCMC tablets. The profile is characterised by an initial lag phase; after this short period, the drug release rate increases (the $t_{90}$ value being the lowest of the three formulations, 10.8 h). Upon exposure to the dissolution fluid, the tablets hydrate quickly and the polymer becomes immediately effective in controlling the drug release rate from the tablet. The mechanism of drug delivery seems to be mainly associated to the erosion of the tablet ($n$ is 1.43) due to the high solubility of the polymer (NaCMC) at this pH value.

Linearisation of the drug release profile is achieved by using a mixture of the two polymers as functional excipients in the formulation ($n$ is 0.98). At the beginning of the test, the profile lies between the profiles of the single

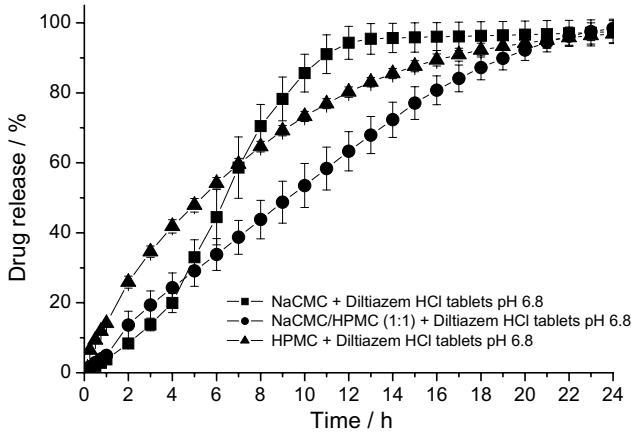


Fig. 1. Drug release profiles of the three formulations at pH 6.8.

Table 2
Values for $t_{90}$ (h) and $n$ values obtained from the dissolution tests at pH 6.8 for matrix tablets [HPMC E4M, NaCMC and HPMC/NaCMC (1:1)] containing Diltiazem HCl

| Tablets formulations | $t_{90}$ (h) | $n$ |
|---|---|---|
| NaCMC + DTZ HCl | 10.8 ± 1.15 | 1.43 ± 0.09 |
| HPMC E4M + DTZ HCl | 16.40 ± 1.12 | 0.71 ± 0.02 |
| HPMC E4M + NaCMC + DTZ HCl | 19.10 ± 0.70 | 0.98 ± 0.02 |

Table 3
The values of $n$ and $k$ derived from $\log q_t/Q$ versus $t$ plots for the swelling of tablets containing NaCMC, HPMC and a mixture 1:1 of NaCMC and HPMC

| Formulation | pH | $n$ | $-\log k$ | $R^2$ |
|---|---|---|---|---|
| NaCMC | 6.8 | 1.3 ± 0.04 | 1.1 ± 0.14 | 0.988 |
| NaCMC/HPMC (1:1) | 6.8 | 1.0 ± 0.03 | 1.2 ± 0.01 | 0.985 |
| HPMC | 6.8 | 0.8 ± 0.04 | 1.2 ± 0.05 | 0.990 |

The linear regression $R^2$ values are also shown.

polymer tablets. Surprisingly $t_{90}$ is 19.10 h, meaning that the system containing the polymer blend shows a synergistic effect in controlling and modulating the drug release rate. This could be due to an interaction between the two polymers and/or between the polymer/s and the drug.

### 3.2. Calorimetric studies

We demonstrated in an earlier publication [14] that swelling/dissolution can be investigated using a solution calorimetric method. The heat output is determined by integrating the power–time data to a specific time point. It is assumed that the total heat output following dispersion of the sample ($Q$) represents total swelling/dissolution while the heat output to any time $t$ ($q_t$) represents the fraction of swelling/dissolution that has occurred to this point. Hence a plot of $q_t/Q$ versus time is analogous to a dissolution profile and can be fitted to the power law model defined earlier if the assumption is made that:

$$\frac{M_t}{M_\infty} = \frac{q_t}{Q} = kt^n \tag{2}$$

The dissolution profiles constructed from the calorimetric data for HPMC, NaCMC and HPMC/NaCMC tablets are shown in Fig. 2. It is immediately apparent that the profiles differ for each system. From Eq. (2) it is evident that a plot of $\log q_t/Q$ versus $\log t$ should be linear, the slope giving the value of $n$ directly. These values of $n$ determined in this way are shown in Table 3.

Encouragingly, the values of $n$ obtained calorimetrically agree very well with those obtained from dissolution testing (0.81 and 0.71 for HPMC; 1.43 and 1.28 for NaCMC; 1.04 and 0.98 for HPMC/NaCMC, respectively). The small differences in the values can be ascribed to two factors; the fact that the tablets used in the two studies had different geometries (necessitated by the limited size of the cartridges and dissolution medium volume in the solution calorimeter relative to the dissolution apparatus) and the fact that different buffer components were employed. The power law model is empirical and was originally developed for slab geometry; hence, slight variations in the values of the exponential term can be expected for other tablet shapes. We have discussed the limitations and assumptions of this approach fully in our earlier study [14] and readers are referred there for further clarification of issues regarding the interpretation and meaning of these values.

The principal aim of this work was to determine whether the calorimeter could monitor drug release as well as swelling/dissolution. The power–time data for the three types of drug-loaded tablet are shown in Fig. 3. Again, there are significant differences in behaviour between the three systems; most notable is the case of NaCMC tablets, which shows a complex signal comprising exo- and endothermic phases. It is true that sometimes calorimetric techniques are not as widely used as might be expected because the data can be difficult to interpret. Here, the logical analysis would be to subtract the power–time data obtained for the

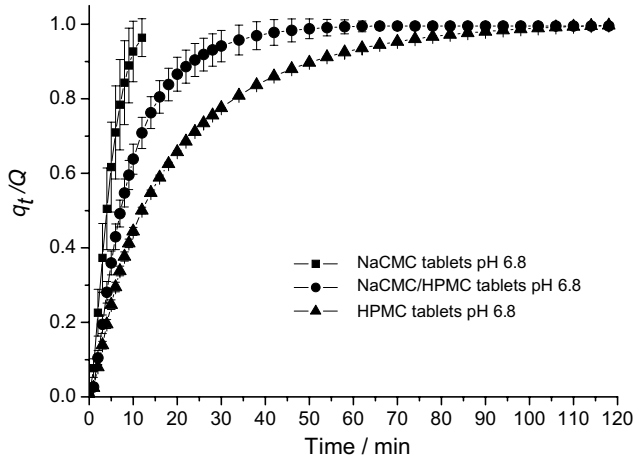


Fig. 2. Plots of $q_t/Q$ versus time for polymer tablets (containing no drug).

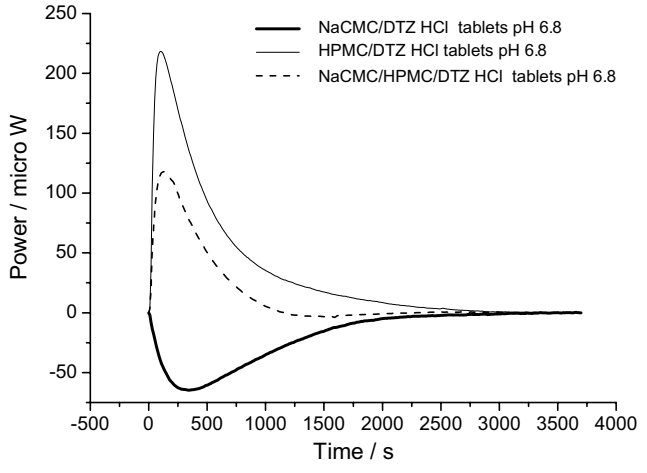


Fig. 3. Power–time data for the dissolution of drug-loaded polymer tablets.

tablets with and without drug. The difference should, in principle, contain information on the drug release process(es). However, this is not as straightforward as it appears. This is because the compositions of the tablets with and without drug differed considerably, the drug-loaded tablets containing 2 mg of active and 3 mg of polymer. The significant heats associated with both polymer and drug dissolution thus meant that it was impossible to construct an experiment to give a suitable blank (i.e., the ideal blank would be a 3 mg polymer tablet, not a 5 mg tablet, but this would have different dissolution behaviour because of its altered geometry).

Accepting this limitation, we decided to conduct further experiments using powdered samples in order to ascertain whether interactions between the drug and polymer could account for the observed dissolution behaviour. Using powdered samples meant that appropriate blank experiments could be performed. The experimental series was thus; data were measured for drug alone (2 mg), polymer alone (3 mg) and then a drug/polymer physical mixture (comprising 2 mg drug and 3 mg polymer). To assess whether any interactions were present, the data for the individual species were summed and compared with the data for the physical mixture; any differences inferred an interaction.

Dealing with interactions between the polymers first, Fig. 4 shows the summed data for HPMC and NaCMC and the data for a physical blend (prepared in a 1:1 ratio). Although the shapes of the curves vary slightly, the areas were equal within experimental error ($-40.6 \pm 10.4$ and $-34.9 \pm 5.6$ J g$^{-1}$, respectively), which implies there was no interaction between the polymers. In other words, the polymers hydrate, swell and dissolve in combination in exactly the same way as they do individually.

Comparable data are shown in Fig. 5 for mixtures of HPMC and drug; again, it is clear that the summed

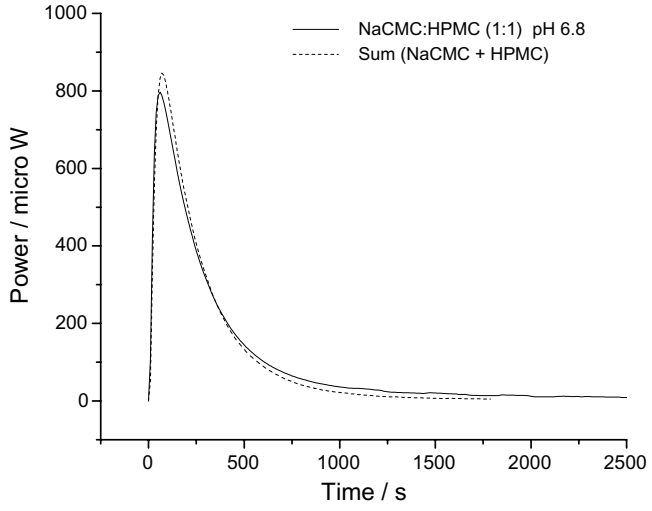


Fig. 4. Power–time data for the dissolution of the mixture of NaCMC and HPMC (1:1) compared to the theoretical power–time data obtained by summing the calorimetric response of NaCMC and HPMC alone.

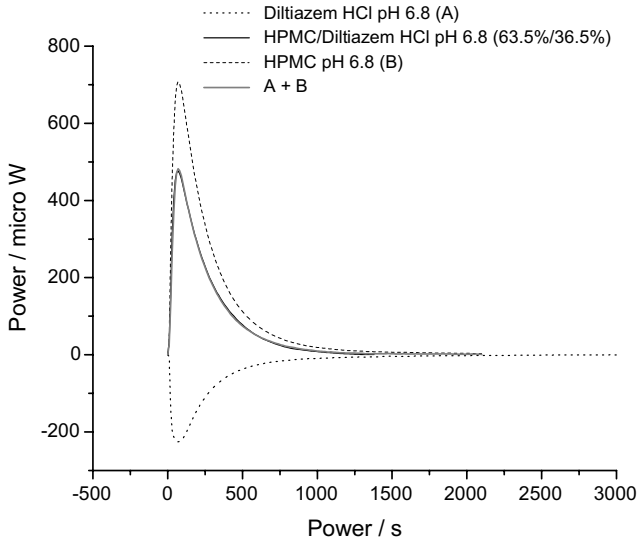


Fig. 5. Power–time data for the dissolution of Diltiazem HCl (A), HPMC (B) and the physical mixture of HPMC/Diltiazem HCl. Also shown are the theoretical power–time data obtained by summing the calorimetric response of Diltiazem HCl and HPMC (A + B).

response is identical to the physical mixture, confirming that there is no interaction between these two species. The response of HPMC is exothermic ($-68.1 \pm 18.6$ J g$^{-1}$) while that of Diltiazem HCl is endothermic ($22.3 \pm 1.0$ J g$^{-1}$). This balance of exo- and endothermic events explains the complex shape of the data obtained for drug-loaded tablets. In combination the response is net exothermic ($-26.2 \pm 4.2$ J g$^{-1}$). The theoretical enthalpy ($-24.2$ J g$^{-1}$) is thus equivalent, within error, to the measured enthalpy.

The remaining cases (NaCMC/drug and HPMC/NaCMC/drug) are more interesting; the power–time data for these systems are presented in Figs. 6 and 7, respectively. In the case of NaCMC/drug it can be observed that the response of NaCMC is less exothermic ($-13.2 \pm 2.2$ J g$^{-1}$) than that noted above for HPMC, the result of which is that the endothermic response of the drug dominates the observed signal and a net endothermic event is recorded. However, in addition the data for the real mixture do not overlay those of the summed responses; there is a significant endothermic heat in the real mixture ($7.6 \pm 1.7$ J g$^{-1}$) over and above that of the summed response (5.23 J g$^{-1}$). The fact that this interaction is endothermic implies that it is thermodynamically unfavoured.

The opposite behaviour is seen for the NaCMC/HPMC/drug system. Here the real mixture of components gave a heat change that was more exothermic ($10.8 \pm 2.7$ J g$^{-1}$) than the summed response (6.42 J g$^{-1}$), which implies a favourable interaction.

These observations correlate very well with the $t_{90}$ values determined by dissolution testing. The NaCMC/drug system showed an unfavourable interaction by calorimetry and had the fastest $t_{90}$ (10.8 h) while the NaCMC/HPMC/drug system showed a favourable interaction and had the longest $t_{90}$ (19.1 h). The HPMC/drug system

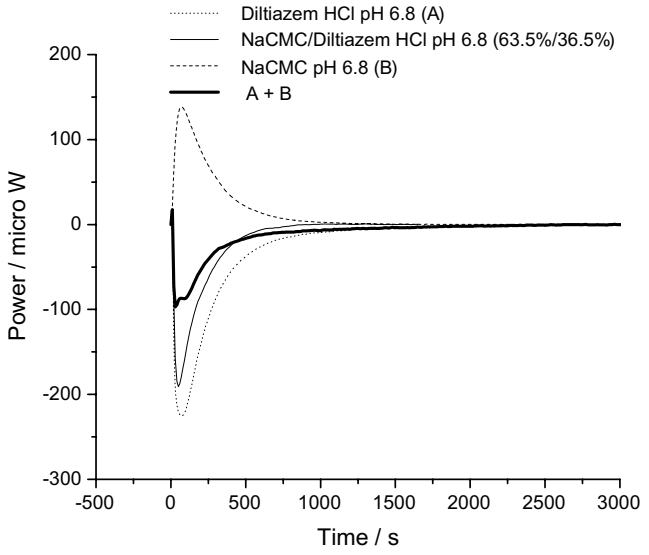


Fig. 6. Power–time data for the dissolution of Diltiazem HCl (A), NaCMC (B) and the physical mixture of NaCMC/Diltiazem HCl. Also shown are the theoretical power–time data obtained by summing the calorimetric response of Diltiazem HCl and NaCMC (A + B).

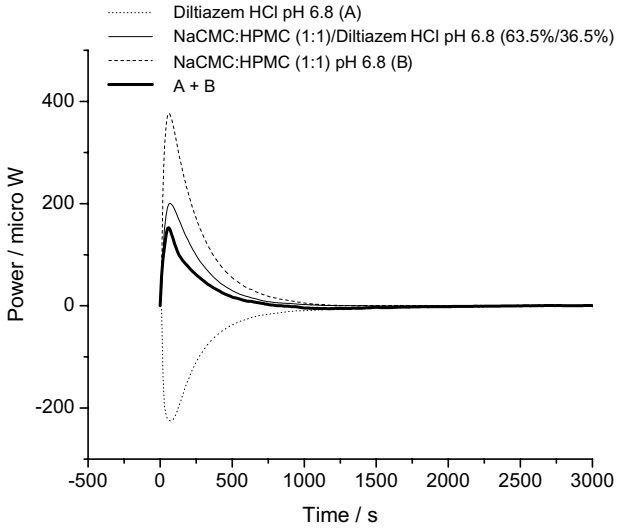


Fig. 7. Power–time data for the dissolution of Diltiazem HCl (A), HPMC/NaCMC (1:1) (B) and the physical mixture of HPMC/NaCMC/Diltiazem HCl. Also shown is the theoretical power–time data obtained by summing the calorimetric response of Diltiazem HCl and HPMC/NaCMC (A + B).

showed no interaction and had an intermediate $t_{90}$ value (16.4 h). Thus, it appears that interactions between the drug and the polymer, and not between the two polymers, are the principal cause of the delayed release kinetics observed when the drug is formulated with both polymers. Thus, while its nature means that calorimetry cannot give any mechanistic insight into the nature of these interactions, its ability to monitor processes in complex systems means that it certainly has the potential to screen and optimise tablet formulations, by examination of powder blends, without the need to manufacture batches of tablets.

## 4. Conclusion

The aim of this paper was to assess the feasibility of the application of solution calorimetry to the study of dissolution behaviour and formulation of hydrophilic matrix tablets. In particular, calorimetry has been used to assess the presence of interactions between the polymer/s and the drug. By comparison of theoretical and experimental power–time profiles, it was possible to classify the interaction as favourable or unfavourable and a correlation with the dissolution data could be drawn.

In this investigation the dissolution profiles of matrix tablets containing HPMC, NaCMC and a combination of both polymers with a model soluble drug were studied. HPMC tablets released the active with an anomalous non-Fickian mechanism mainly driven by diffusion while NaCMC delivered the drug mainly by erosion from the tablet surface. The tablets containing both polymers released the drug with zero-order kinetics and, surprisingly, a synergistic effect in controlling the rate of drug delivery was observed.

Calorimetric studies played an important part in understanding the mechanism and the rate of drug release from these dosage forms. Where no interaction was observed between the drug and the polymer the mechanism of drug delivery was mainly associated with the drug crossing the gel layer on tablet surface (diffusion controlled mechanism). An energetically favourable drug–polymer interaction was seen to promote a reduction in the drug release rate. Conversely, energetically unfavourable interactions drive the drug to be released faster from the polymeric matrix.

## References

[1] S.C. Brazel, N.A. Peppas, Dimensionless analysis of swelling of hydrophilic glassy polymers with subsequent drug release from relaxing structures, Biomaterials 20 (1999) 721–730.
[2] A. Miranda, M. Millan, I. Caraballo, Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery, Int. J. Pharm. 311 (2006) 75–81.
[3] C.D. Melia, Hydrophilic matrix sustained release systems based on polysaccharide carriers, Crit. Rev. Ther. Drug Carrier Syst. 8 (1991) 395–421.
[4] M.V. Velasco, J.L. Ford, P. Rowe, A.R. Rajabi-Siahboomi, Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets, J. Control. Release 57 (1999) 75–85.
[5] C.R. Young, C. Dietzsch, M. Cerea, T. Farrell, K.A. Fegely, A. Rajabi-Siahboomi, J.W. McGinity, Physicochemical characterization and mechanisms of release of theophylline from melt-extruded dosage forms based on a methacrylic acid copolymer, Int. J. Pharm. 301 (2005) 112–120.
[6] J. Siepmann, N.A. Peppas, Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC), Adv. Drug Deliv. Rev. 48 (2001) 139–157.
[7] L. Maggi, L. Segale, M.L. Torre, M.E. Ochoa, U. Conte, Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study, Biomaterials 23 (2002) 1113–1119.

[8] S. Furlanetto, M. Cirri, F. Maestrelli, G. Corti, P. Mura, Study of formulation variables influencing the drug release rate from matrix tablets by experimental design, Eur. J. Pharm. Biopharm. 62 (2006) 77–84.
[9] A. Frank, S.K. Rath, S.S. Venkatraman, Controlled release from bioerodible polymers: effect of drug type and polymer composition, J. Control. Release 102 (2005) 333–344.
[10] Y. Huang, K.H. Khanvilkar, A.D. Moore, M. Hillard-Lott, Effects of manufacturing process variables on in vitro dissolution characteristics of extended-release tablets formulated with hydroxypropyl methylcellulose, Drug Dev. Ind. Pharm. 1 (2003) 79–88.
[11] U. Conte, L. Maggi, Modulation of the dissolution profiles from Geomatrix multi-layer matrix tablets containing drugs of different solubility, Biomaterials 9 (1996) 889–896.
[12] V.M. Rao, J.L. Hashlam, V.J. Stella, Controlled and complete release of a model poorly water-soluble drug, prednisolone, from hydroxypropyl methylcellulose matrix tablets using (SBE)(7m)-beta-cyclodextrin as a solubilizing agent, J. Pharm. Sci. 90 (2001) 807–816.
[13] D.C. Coughlan, O.I. Corrigan, Drug–polymer interactions and their effect on thermoresponsive poly (*N*-isopropylacrylamide) drug delivery systems, Int. J. Pharm. 313 (2006) 163–174.
[14] S. Conti, S. Gaisford, G. Buckton, U. Conte, Solution calorimetry to monitor swelling and dissolution of polymers and polymer blends, Thermochim. Acta 450 (2006) 56–60.
[15] W. Lund (Ed.), The Pharmaceutical Codex: Principles and Practice of Pharmaceutics, twelfth ed., Pharmaceutical Press, London, 1994. ISBN 0-8536-9290-4.
[16] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.
[17] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices, J. Control. Release 5 (1987) 37–42.
[18] M. Bastos, G. Bai, E. Qvarnström, I. Wadsö, A new dissolution microcalorimeter: calibration and test, Thermochim. Acta 405 (2003) 21–30.