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Effect of ionic strength and pH of dissolution media on theophylline release from hypromellose matrix tablets—Apparatus USP III, simulated fasted and fed conditions

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ABSTRACT

The objectives of this study were to evaluate the effects of different media ionic concentration strengths and pH on the release of theophylline from a gel forming hydrophilic polymeric matrix. Theophylline extended release (ER) matrices containing hypromellose (hydroxypropyl methylcellulose (HPMC)) were evaluated in media with a pH range of 1.2–7.5, using an automated USP type III, Bio-Dis dissolution apparatus. The ionic concentration strength of the media was varied over a range of 0–0.4 M to simulate the gastrointestinal fed and fasted states and various physiological pH conditions. Sodium chloride was used for ionic regulation due to its ability to salt out polymers in the midrange of the lyotropic series. The results showed that the ionic concentration strength had a profound effect on the drug release from the K100LV matrices. At pH 1.2 theophylline releases increased significantly within the first hour from 28% in water to 48% in the medium with ionic strength of 0.49 M. The K4M, K15M and K100M tablets, however, withstood the effects of media to the same extend at all ionic concentration strengths investigated. The similarity factor f_2 was calculated using drug release in water as a reference. For the K100M matrices, f_2 values of 74 (pH media), 80 (0.2 M media) and 72 (0.4 M media) suggested that it was the most resilient of all the matrices studied here. DSC hydration results explained the theophylline release from their HPMC matrices. Despite an increase in the percentage of bound water for the tablets made with high viscosity polymers K4M, K15M and K100M, they were, however, resilient to the ionic concentration strength effects as they were still able to form a strong gel layer. This methodology can be used as a valuable tool for predicting potential ionic effects related to in vivo fed and fasted states on drug release from hydrophilic ER matrices.

1. Introduction

Hydroxypropyl methylcellulose (HPMC) has been a material of great importance in its use as a carrier in drug release systems (Colombo, 1993; Pham & Lee, 1994). It is the most popular hydrophilic polymer for extended release matrices because of its ability to provide robust formulations and desired release profiles for a wide range of drugs (Colombo, 1993; Tiwari, Murthy, Pai, Mehta, & Chowdary, 2003) due to its non-ionic nature, stability, global regulatory acceptance and cost effectiveness (Alderman, 1984; Li, Martini, Ford, & Roberts, 2005; Tiwari & Rajabi-Siahboomi, 2008).

Tablets made with HPMC swell once in contact with water and forms a gel layer around the matrix. The release of the drug from the matrix thus depends on the possible interactions between aqueous medium, polymer, drug and other tablet ingredients (Sasa, Odon, Stane, & Julijana, 2006). It is well known that food administration can affect the bioavailability of oral dosage forms as a result of interactions which may occur between the formulation and the food (Abrahamsson, Roos, & Sjogren, 1999; Phuapradit & Bolton, 1991). Researchers have demonstrated that the gel layer formed around hydrophilic matrices, upon its contact with gastro-intestinal (GI) fluids, is eroded allowing drug release. This erosion is the dominant release mechanism for poorly soluble drugs. The other mechanistic approach is that the soluble portion of drug is released through the diffusion process through the gel layer (Abrahamsson, Johansson, Torstensson, & Wingstrand, 1994; Johnson, Holinej, & Williams, 1993; Lindner & Lippold, 1995; Skoug, Mikelsons, Vigneron, & Stemm, 1993). The non-ionic nature of HPMC means

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when drug solubility is pH-independent, the matrices also exhibit pH-independent drug releases profiles. Generally, the higher the solubility of the drug, the faster its release. This is as a result of them having a higher diffusional driving force. An investigation into the effect of drug solubility on release using seven different drugs of varying solubility by Tahara, Yamamoto, and Nishihata (1996) showed that a decrease in the drugs solubility brought about an increase in the contribution of erosion to drug release. It has, however, been reported that when drug solubility is pH dependent as in the cases of acidic and basic drugs, the pH of the media may have an effect on the drug release profiles (Streubel, Siepmann, Dashevsky, & Bodmeier, 2000; Tatavarti & Hoag, 2006; Tatavarti, Mehta, Augsburger, & Hoag, 2004).

Two major properties of the GI fluids are pH and ionic strength. They vary greatly along the GI tract under fasting and fed conditions (Charman, Porter, Mithani, & Dressman, 1997; Wilson & Washington, 1989) and can affect the rate at which a drug is released from hydrophilic ER matrices (Bonferoni, Rossi, Ferrari, Bertoni, & Caramella, 1995; Hodsdon, Mitchell, Davies, & Melia, 1995; Johnson et al., 1993). The ionic concentration strength of the GI tract in man under both fasted and fed states and various physiological pH conditions cover a range of 0–0.4 M (Johnson et al., 1993). In a fasted stomach, ionic concentration strength has been estimated at approximately 0.11 M (Lindahl, Ungell, Knutson, & Lennernas, 1997). There is a variation in that value after a meal consumption dependant on the composition of the food. The ionic concentration strength in the intestinal tract has been estimated to be around 0.14 M (Lindahl et al., 1997). Cellulose ethers are susceptible to ion effect of the media in the following order: chloride < tartrate < phosphate and potassium < sodium. Sodium chloride is the midrange of lyotropic series and has the ability to salt out polymers, hence is often used as the agent for ionic regulation of dissolution media (Mitchell et al., 1990; Johnson et al., 1993).

Dissolution testing is a quality control procedure employed in pharmaceutical product development and is of a great importance in the selection and facilitation of candidate formulations for in vitro–in vivo correlations (IVIVC) (Grundy, Anderson, Rogers, & Foster, 1997; Yu, Schwartz, & Sugita, 1996). The IVIVC is achievable by the use of in vitro dissolution data for certain defined physiological and hydrodynamic conditions to help in the facilitation of possible bioequivalence testing, in vivo bioavailability and IVIVC (Pillay & Fassihi, 1998). As oral extended release formulations are subjected to different pH and ionic strength values along the gastrointestinal tract, it is important to evaluate their performance under those conditions.

Hydration water is classified into three types and they have different physical properties (Jhon & Andrade, 1973). Type I (freezing or free, bulk-like water) melts at the normal melting point of pure water (0 °C). Type II (freezing or bound water) weakly interacts with macromolecules and displays a lower melting point than pure water (<0 °C). These two types (I and II) can be both called free (freezable) water. Type III (bound water) strongly interacts with hydrophilic and ionic groups of the polymer and shows non-freezing behaviour. Aoki, Ando, Ishii, Watanabe, and Ozawa (1995) explained that during the initial stages of dissolution, water penetrates into the matrix and usually acts as non-freezing (bound) water. In the next stage, the water content of the matrix increases and freezable water is detected at levels that are related to drug release.

In a recent study the influence of changing the agitation sequence during dissolution testing in a USP III Apparatus as a model for fed and fasted conditions on drug release from HPMC matrices were studied (Asare-Addo, Levina, Rajabi-Siahboomi, & Nokhodchi, 2010). The present work explores this methodology further to investigate the effect of ionic strength and pH of the media on theophylline release from HPMC matrices using the USP III Apparatus. This study also explores a differential scanning calorimetry (DSC) methodology to determine free and bound water to explain drug release in the different ionic strengths being investigated. DSC was also used to ensure there was no interaction going on between the drug and polymer mixtures. This methodology of dissolution testing could possibly indicate potential fed and fasted effects on drug release from hydrophilic extended release matrices.

2. Materials and methods

2.1. Materials

Hydrophilic matrix tablets were prepared using anhydrous theophylline (Sigma, UK) as the model drug and HPMC (METHOCEL™ Premium K100LV, K4M, K15M and K100M; Colorcon Ltd, UK) polymers as the hydrophilic matrix former.

Dissolution buffers were prepared according to the USP using the following materials: potassium chloride (Acros Organics, UK) and hydrochloric acid (Fisher Scientific, UK) for pH 1.2 and pH 2.2 and potassium phosphate monobasic-white crystals (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for pH 5.8, 6.8, 7.2 and 7.5 media.

2.2. Tablet preparation

Round cylindrical tablets with a diameter of 9.56 mm and the target weight of 250 mg were prepared by blending theophylline with HPMC in the ratio of 4:1 for 10 min in a Turbula™ (Type T2C, Switzerland) blender. The tablets were compressed using a single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 1500 psi (5.55 kN). The die wall was lubricated each time after tablet compression with a 1% (w/v) suspension of magnesium stearate (Fisher Scientific, UK) in acetone to enable easy ejection of the tablets from the die.

Tablet dimensions were obtained using an electronic digital calliper (Fisher Scientific, UK). The Ultrapycnometer 100 (Quantachrome Instruments, UK) was used in the determination of the true density of the powder mixtures. Tablet porosity was then calculated according to Eq. (1).

$$\text{tablet porosity} = 1 - \left[\frac{\text{tablet weight/tablet volume}}{\text{true density of powder}}\right] \times 100 \quad (1)$$

2.3. Dissolution test

An automated USP type III Bio-Dis (Varian, US) was used to carry out the dissolution tests. The dip rate used for the ionic strength evaluation was 20 dpm. The vessels contained 250 mL of the appropriate medium and the mesh on the top and bottom screens of the cylinder (the tablet holder) was fixed at 864 μm. Temperature was kept constant at 37 ± 0.5 °C. Theophylline released was measured at 271 nm using a UV/visible spectrophotometer (Varian, Cary 50).

The influence of media ionic concentration strengths on theophylline release from the METHOCEL K100LV, K4M, K15M and the K100M tablet matrices was studied. Sodium chloride was used to regulate the ionic concentration strength from 0 to 0.4 M in buffers with pH of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5.

All four theophylline HPMC (K100LV, K4M, K15M and K100M) formulations were tested using this methodology. This allowed discriminating the effect of the ionic concentration strength on the formulations where different grades of the HPMC were used. The transit times in the different pH used to simulate the digestive tract are presented in Table 1. As the tablet matrix starts at pH 1.2, it keeps dipping there for a period of 60 min before that same matrix

Table 1
Transit times and pH values mimicking the GI segment used in the study (table adapted from Klein et al., 2002; Asare-Addo et al., 2010). Transit times here are mimicked by the USP Apparatus III.

GI tract segment	pH value	Transit time (min)
Stomach	1.2	60
Stomach	2.2	60
Duodenum	5.8	10
Jejunum	6.8	120
Proximal ileum	7.2	30
Distal ileum	7.5	30

transfers to pH 2.2 and dips for another 60 min, it then transfers to pH 5.8 and dips for 10 min and so forth. The period of time the tablet matrix stays in a particular vial before transferring is what the authors have referred to as the transit time. The experiments were carried out in triplicate.

2.4. Similarity factor

To determine the similarity between the obtained drug release profiles f_2 factor (Moore & Flanner, 1996; Polli et al., 2004) was calculated according to Eq. (2):

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

This being a mathematical treatment of the dissolution data where n is the number of pull points for tested samples; w_t is the optional weight factor; R_t is the reference assay at time point t; T_t is the test assay at time point t.

Similarity factor was calculated using drug release profile in water as the reference. An f_2 value ranging from 50 to 100 suggests a similarity between two profiles. The closer the f_2 value is to 100, the more similar or identical the release profiles are. Also dissimilarity occurs with a decrease of the f_2 value (Pillay & Fassihi, 1998).

2.5. Differential scanning calorimetry (DSC)

Samples of physical mixtures of drug and polymer after the mixing described in Section 2.2 were placed in standard 40 μm aluminium crucibles and sealed. The aluminium crucibles were heated from 25 to 300 °C at 10 °C/min rate under nitrogen gas to identify any potential material interactions.

In order to investigate the effect of ionic strength on the drug release of HPMC tablets, flat faced 4 mm disks with target weights of 20 mg were produced from all four theophylline HPMC (K100LV, K4M, K15M and K100M) formulations and compressed using a single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 1500 psi (5.55 kN). The die wall was lubricated each time before tablet compression with a 1% (w/v) suspension of magnesium stearate in acetone.

The discs were hydrated for 5, 10, 15 and 20 min using 25 mg of purified water and the following buffers: pH 1.2, pH 1.2 (0.2 M ionic strength) and pH 1.2 (0.4 M ionic strength) in standard aluminium pans sealed with a lid. The aluminium pans were firstly cooled down from ambient temperature (25 °C) to −30 °C at 55 °C/min in order to freeze any unbound (free) water; then kept at −30 °C for 5 min for equilibration to occur and heated up again from −30 °C up to 50 °C at 10 °C/min under nitrogen gas to determine amount of free and bound water of the tablets using endotherm scanning of the melted free water. The reference standard using distilled water was prepared using 25 mg of purified water in standard aluminium pan sealed with a lid and allowing it to go through the same process as the hydrated disks. The integration of the endotherm represented 100% free water. From this deduction, bound and free water was determined. All these experiments were done in triplicate.

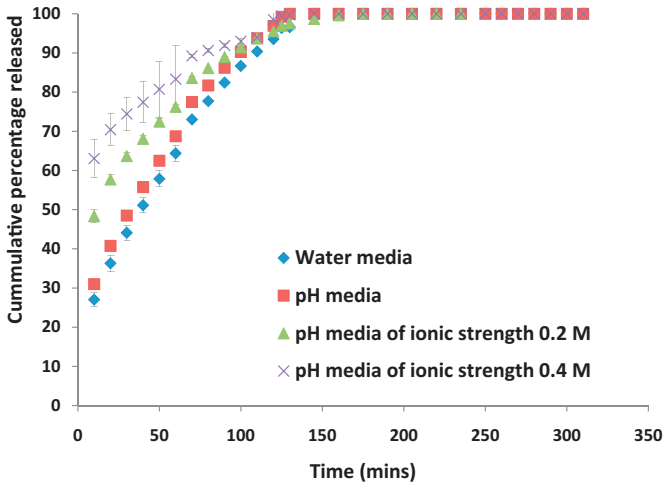

Fig. 1. The cummulative drug release profiles from the USP Apparatus III (pH 1.2–7.5) showing the effect of ionic concentration strength on drug release from HPMC K100LV matrices.

3. Results and discussion

Physical characterization of the compacts is presented in Table 2. All compacted tablets had similar volumes. The tablet porosities were also very similar (37%), with the exception of the K15M tablet matrices which had a porosity of 34%. The authors believe that due to the similarity of the porosity values, it does not have a considerable impact on drug release. Figs. 1–4 show the influence of ionic concentration strength on drug release from tablets made using HPMC grades with different viscosity, i.e., K100LV, K4M, K15M and K100M in the drug:polymer ratio of 4:1. These were obtained by plotting the cumulative drug releases in the individual vials with the different pH's together. The original buffers used in the experimentation of "pH media" have differ-

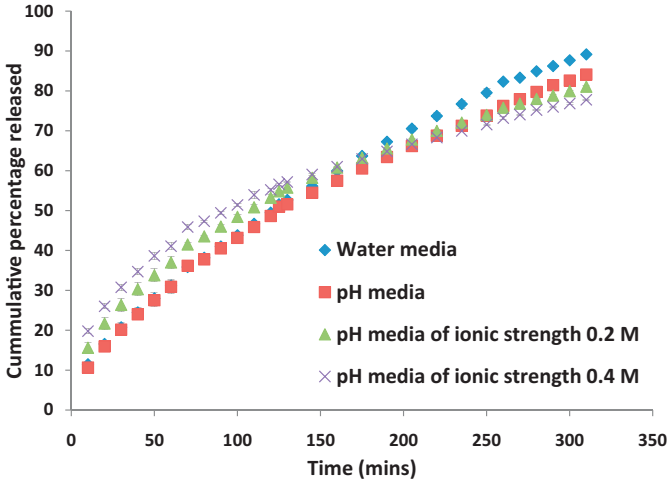

Fig. 2. The cummulative drug release profiles from the USP Apparatus III (pH 1.2–7.5) showing the effect of ionic concentration strength on drug release from HPMC K4M matrices.

Table 2
Physical characterization of the formulated tablets subjected to the USP Apparatus III for the dissolution study ($n = 5$).

Tablet characterization	Formulation			
	K100LV	K4M	K15M	K100M
Weight (mg)	250.47 ± 0.84	250.30 ± 0.54	251.52 ± 3.89	251.03 ± 0.88
Volume (cm^3)	0.267	0.270	0.265	0.270
Porosity (%)	36.91	36.77	33.57	37.18

Table 3
Amount of drug released (%) from HPMC matrices after 1 h in media of varying ionic concentration strengths.

Dissolution medium (ionic strength)	Formulation			
	K100LV (%)	K4M (%)	K15M (%)	K100M (%)
Water (0)	64.37 ± 2.13	31.19 ± 1.55	23.86 ± 0.06	21.22 ± 0.71
pH 1.2 (no NaCl)[a]	68.74 ± 0.90	30.91 ± 1.70	27.05 ± 1.21	21.34 ± 0.84
pH 1.2 (0.2 M NaCl)[b]	76.25 ± 0.72	37.02 ± 1.54	33.00 ± 3.17	24.61 ± 0.24
pH 1.2 (0.4 M NaCl)[c]	83.30 ± 8.60	41.09 ± 0.86	27.58 ± 0.12	26.46 ± 0.96

[a] Actual ionic concentration strength here is 0.14 M.
[b] Actual ionic concentration strength at pH (ionic strength 0.2) was 0.34 M.
[c] Actual ionic concentration strength at pH (ionic strength 0.4) was 0.54 M.

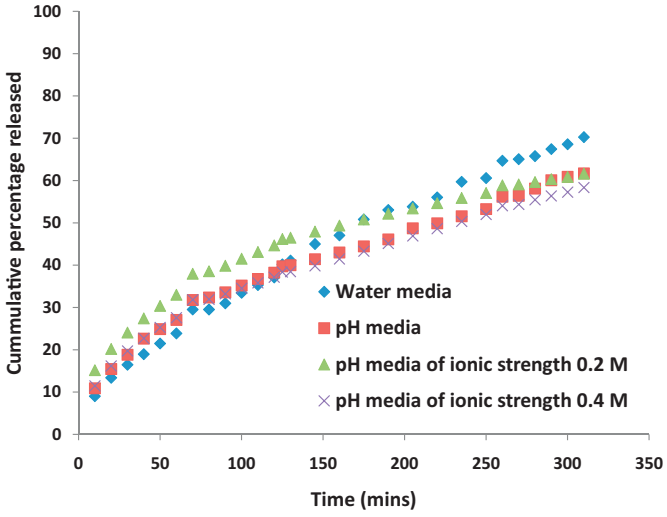

Fig. 3. The cummulative drug release profiles from the USP Apparatus III (pH 1.2–7.5) showing the effect of ionic concentration strength on drug release from HPMC K15M matrices.

ent ionic concentration strength levels. These ranged from 0.05 to 0.14 M. The use of sodium chloride at the 0.2 and 0.4 M ionic concentration strength levels in addition to the "pH media" meant that the actual ionic concentration strength at the 0.2 M level ranged between 0.25 and 0.34 M and for the 0.4 M ranged between 0.45 and 0.54 M. The increased amounts of the ionic concentration strength in media compositions had the most effect on the release of theophylline from the K100LV tablet matrices. Due to the reasoning that the substitution levels of the K chemistry did not differ significantly, its effects are not discussed in this study.

It is important that the formation of a gel layer occurs quickly enough to prevent fast water penetration inside the tablet core and potential matrix disintegration (Asare-Addo et al., 2010; Siepmann and Peppas, 2001; Wan et al., 1995). It was, however, observed that for the matrices that contained HPMC K100LV, once in media with the applied agitation, fragments of the tablet were eroded from the matrix surface into the media before a full gelatinous layer was formed. None of the tablets that were subjected to the various levels of ionic concentration strength of the media, disintegrated. Drug release was in the order of K100LV > K4M > K15M > K100M (Table 3).

The Food and Drug Administration (FDA) have approved the concept of the similarity factor, f_2, for the comparison of dissolution profiles. These calculated f_2 values are presented in Table 4. Due to the quick release of theophylline from the K100LV matrices, f_2 values were not obtained for them. It is evident that ionic concentration strength had a significant effect on drug release patterns from matrices containing K100LV (Fig. 1, Tables 3 and 4). A critical look at the drug release profiles from the K4M, K15M and K100M in the "water media" and "pH media" shows that the difference in their release profiles which is more evident after the 200 min time point is due to the effect of the phosphate ionic species. This increase in drug release in the pH media is attributed to the phosphate exert-

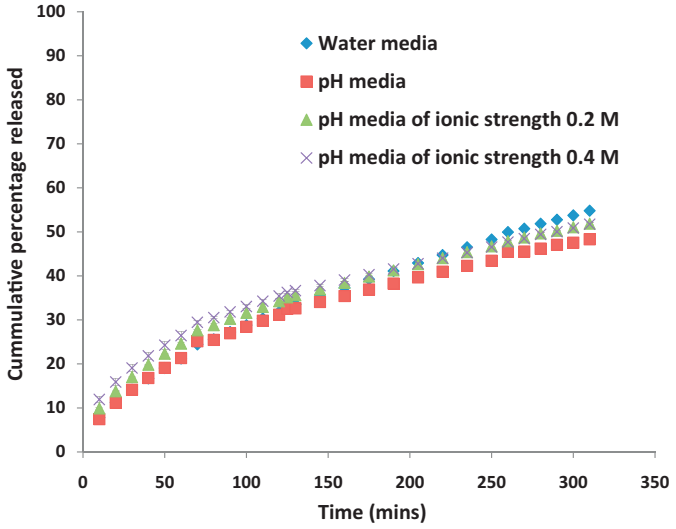

Fig. 4. The cummulative drug release profiles from the USP Apparatus III (pH 1.2–7.5) showing the effect of ionic concentration strength on drug release from HPMC K100M matrices.

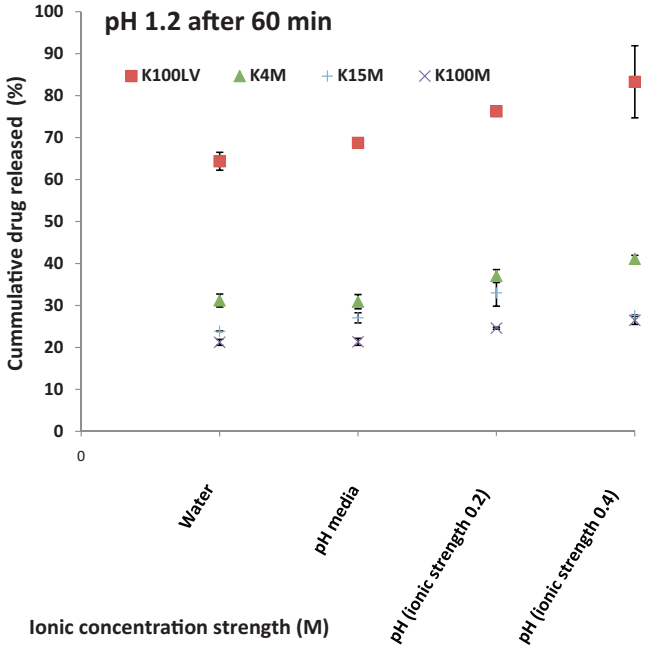

Fig. 5. The cummulative amount of drug release from matrices made from different HPMC grades after 60 min of being in the first vial represented as a single point in the varying ionic strengths (pH was 1.2 except for water medium). Actual ionic concentration strength were: at pH media was 0.14 M, at pH (ionic strength 0.2) was 0.34 M and at pH (ionic strength 0.4) was 0.54 M.

Table 4
F2 similarity factor for the theophylline drug release curves from the different HPMC matrices.

Ionic strength	Formulation			
	K100LV	K4M	K15M	K100M
pH media	–	74	64	74
Ionic strength 0.2 M	–	66	59	80
Ionic strength 0.4 M	–	56	58	72

>50 means similar and <50 means not similar.

ing a strong ionic effect and thus bringing about a change in the hydration properties of the gel. This shows that despite HPMC being a non-ionic polymer, the medium ionic composition can influence its behaviour (Kavanagh & Corrigan, 2004). Similarity values for the K4M, K15M and K100M in the "pH media" with the "water media" as a reference showed similarity at all the values (f_2 = 64–74). This showed how resilient these polymers were to the effect of pH. Despite the decrease in f_2 values as ionic concentration strength was increased, all formulations for K4M, K15M and K100M showed similarity. The K100M matrices were the most robust with f_2 values of 80 and 72 in the media with ionic concentration strengths 0.2 and 0.4, respectively (Table 4). For the purposes of this study, the similarity values obtained and the little variability in the actual values show that even with such high ionic strengths such as maybe experienced in the GI tract, HPMC, K4M, K15M and K100M are able to withstand such effects and therefore could be excellent candidates for producing drug dissolution profiles less affected by foods rich in ion contents.

Fig. 5 where the ionic strength was plotted against the drug release after 60 min in the first vials containing the different media tested showed that with an increase in the ionic concentration strength there was an increase in the theophylline release from the HPMC matrices. This general positive slope in Fig. 5 also indicates that there was an increasing tablet erosion taking place as the ionic concentration strength of the medium was increased. In Table 3 and in Fig. 6 where the cumulative amount of drug released is plotted against its respective media of differing ionic concentration strength, is the proof that erosion was higher for the polymers with lower molecular weight. For K100LV matrices, drug release also rose from 64% in water media to 83% in the medium with ionic concentration strength 0.4 M (actual value is 0.54 M) after 60 min. Although the ionic concentration strengths increased drug release from matrices with high molecular weight HPMC, this increase was not as significant as for matrices made of K100LV. For example, 31%, 24% and 21% of drug was released in water media and when the ionic concentration strength was increased to 0.2 M (actual being 0.34 M), the amount of drug released increased to 37%, 33% and 25% for the K4M, K15M and K100M, respectively. The results showed that a further increase in drug release occurred when the ionic concentration strength of the medium was increased from 0.2 M to 0.4 M (Table 3). The amount of bound and free water is used to explain these observations later. At higher ionic concentration strengths, a loss of gel integrity of the K100LV matrices may have occurred hence the increase in drug release. Also the relatively higher amount of drug released in the first 60 min could be due to drug dissolution and release from near the surface of the tablet before the gel layer was formed (Fig. 6). K4M produced a higher drug release as compared to the K15M and K100M.

Fig. 7 shows DSC thermograms for the HPMC polymers, drug and their physical mixtures. The physical mixtures of different formulations exhibited single endotherms which were representative of the drug. The HPMC peaks were not present due to a low intensity of this peak in pure sample and also low concentration of polymer in the formulation. No material interactions were observed in this study.

Fig. 8, shows the thermographs obtained for the different tablet formulations of drug:polymer in their 4:1 ratio hydrated with the different media used to obtain the values of bound and free water as explained in Section 2.5. Table 5 shows the amount (%) of bound water for different grades of HPMC after 10 min hydration. There was a general increase in the amount of water uptake

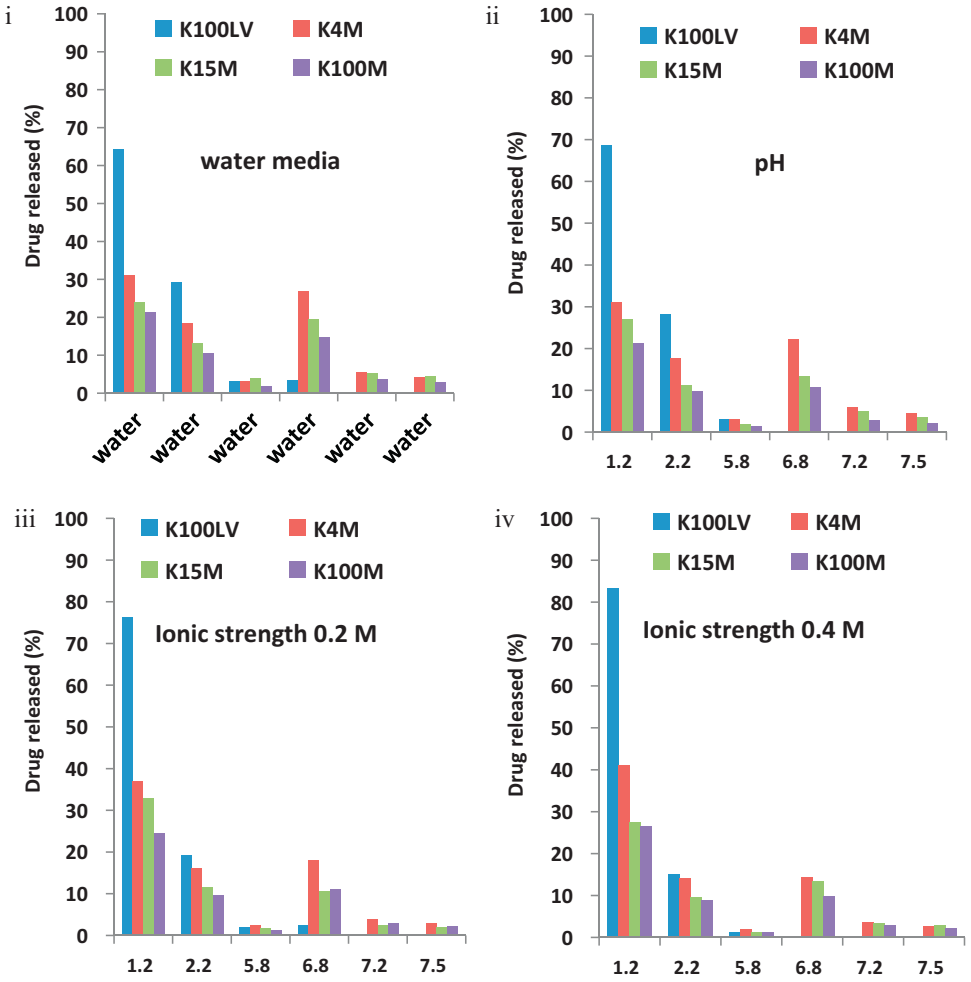

Fig. 6. Graph showing the drug release contributions from matrices made from the different HPMC grades in their respective medium (pH 1.2–7.5) at the varying ionic concentration strengths after transit times as mimicked in Table 1.

Table 5
Amount (%) of bound water for different grades of HPMC resulting after 10 min hydration with the relevant media of different ionic concentration strengths.

Dissolution medium (ionic strength)	Formulation			
	K100LV (%)	K4M (%)	K15M (%)	K100M (%)
Water (0)	23.63 ± 0.81	20.52 ± 0.43	18.77 ± 0.21	18.43 ± 0.30
pH 1.2 (no NaCl)[a]	26.77 ± 0.21	22.41 ± 0.25	25.86 ± 0.41	22.12 ± 0.37
pH 1.2 (0.2 M NaCl)[b]	43.04 ± 0.11	33.16 ± 0.60	32.03 ± 0.19	33.72 ± 1.63
pH 1.2 (0.4 M NaCl)[c]	41.95 ± 1.39	41.88 ± 0.19	40.84 ± 1.01	46.45 ± 2.88

[a] Actual ionic concentration strength here is 0.14 M.
[b] Actual ionic concentration strength at pH (ionic strength 0.2) was 0.34 M.
[c] Actual ionic concentration strength at pH (ionic strength 0.4) was 0.54.

for all the HPMC polymers tested over the 20 min period (results not included). This increase over the 20 min period was slightly higher for the higher molecular HPMC grades. This was consistent with the results reported by Wan et al. (1995). They attributed this phenomenon to the larger hydrodynamic volume occupied by the chains of the hydrated polymers with higher molecular weight Due to the first time point in the dissolution studies being at 10 min, the focus of the water uptake in this section is also at 10 min. Also this explained the release pattern.

It is generally known that as the ionic concentration in a solution is increased, the solubility of the polymer decreases thus reducing the amount of available water for polymer hydration (Johnson et al., 1993). For K100LV formulation, after 10 min in the relevant media approximately 24%, 27%, 43% and 42% uptake of bound water had occurred in water, pH 1.2 (actual ionic strength being 0.14 M), pH 1.2 (0.2 M, actual ionic strength being 0.34 M) and pH 1.2 (0.4 M, actual ionic strength being 0.54 M), respectively. The K100LV tablets bound more to any of the tested media as compared to other HPMC formulations at 10 min (Table 5) indicating that they are more prone to potential food effect. This suggested that the penetration of the relevant media into the K100LV wafers happened more easily and thus could explain the faster drug release.

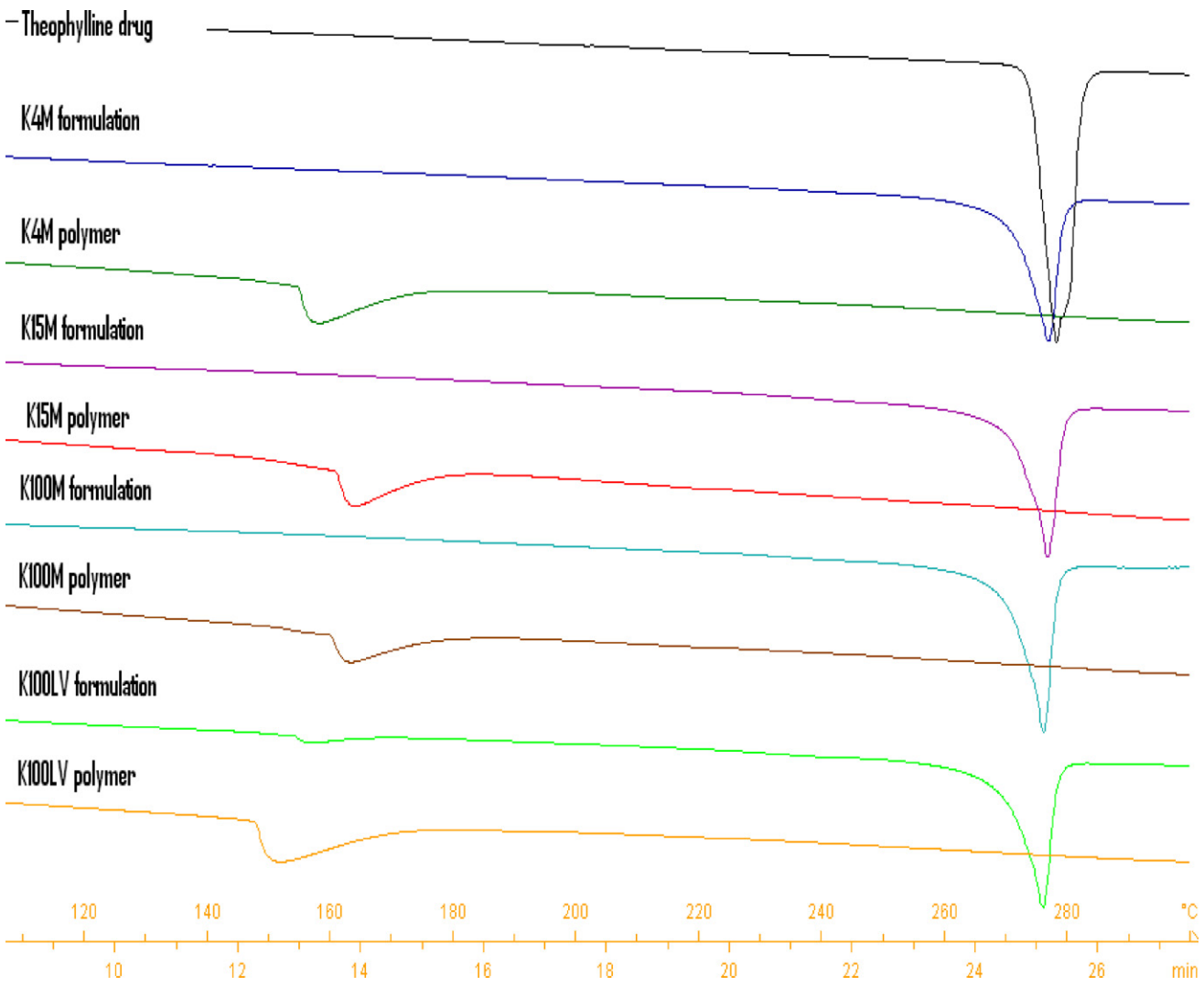

Fig. 7. DSC thermographs of the theophylline drug, K chemistry polymers used and their physical mixtures with drug:polymer in the ratio of 4:1 to show no material interaction occurring.

It was also noticed that an increase in ionic strength of the media caused an increase in the amount of the bound water (Table 5). This suggests that there was less free water available for polymer hydration to form the gel layer necessary for controlling the drug release. This is in agreement with work done by Aoki et al. (1995) who found that transport of solutes mainly occurred through the free water and that only little transport took place through bound water. Study conducted by Yoshioka, Aso, and Terao (1992) also established after studying hydrophilic polymeric gelatin gels that bound water did not contribute significantly to the hydration process and that the water uptake rate was dependant mainly on the amount of the free water present in the system.

Amount of the drug released at the 10 min time point for all the samples in the dissolution studies also correlated with the DSC hydration experiments. It was observed that as the ionic concentration strength increased, the theophylline release also increased. In the highest ionic concentration strength medium, the amount of bound water was similar for all the formulations suggesting that the strength of the gel played an important role also in the drug release pattern.

The results show that the first few minutes of hydration are the most important because this period corresponds to the time when the protective gel layer is formed around the matrix (Ford & Mitchell, 1995; McCrystal, Ford, & Rajabi-Siahboomi, 1997). Fig. 1 shows that at higher ionic strengths drug release from K100LV matrices increased dramatically. Similarity values for all K4M, K15M and K100M matrices in the varying ionic strengths suggest that these polymers could be less affected by potential food effects.

Asare-Addo et al. (2010) developed a methodology of varying agitation in ascending and descending sequences as a systematic process for potentially discriminating fasted and fed states. This was done by firstly: agitation was kept constant at 5, 10, 15, 20 or 30 dpm in all the vials at the varying pH. Then in the second part of the study agitation was increased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 5 dpm, in pH 2.2 – 10 dpm, in pH 5.8 – 15 dpm, in pH 6.8 – 20 dpm, in pH 7.2 – 25 dpm and in pH 7.5 – 30 dpm. The reverse was done as well when the agitation was decreased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 30 dpm, in pH 2.2 – 25 dpm, in pH 5.8 – 20 dpm, in pH 6.8 – 15 dpm, in pH 7.2 – 10 dpm and in pH 7.5 – 5 dpm. The evaluation of ionic strength in this experimentation could be an additional tool in allowing for foods with differing salt contents to be screened also.

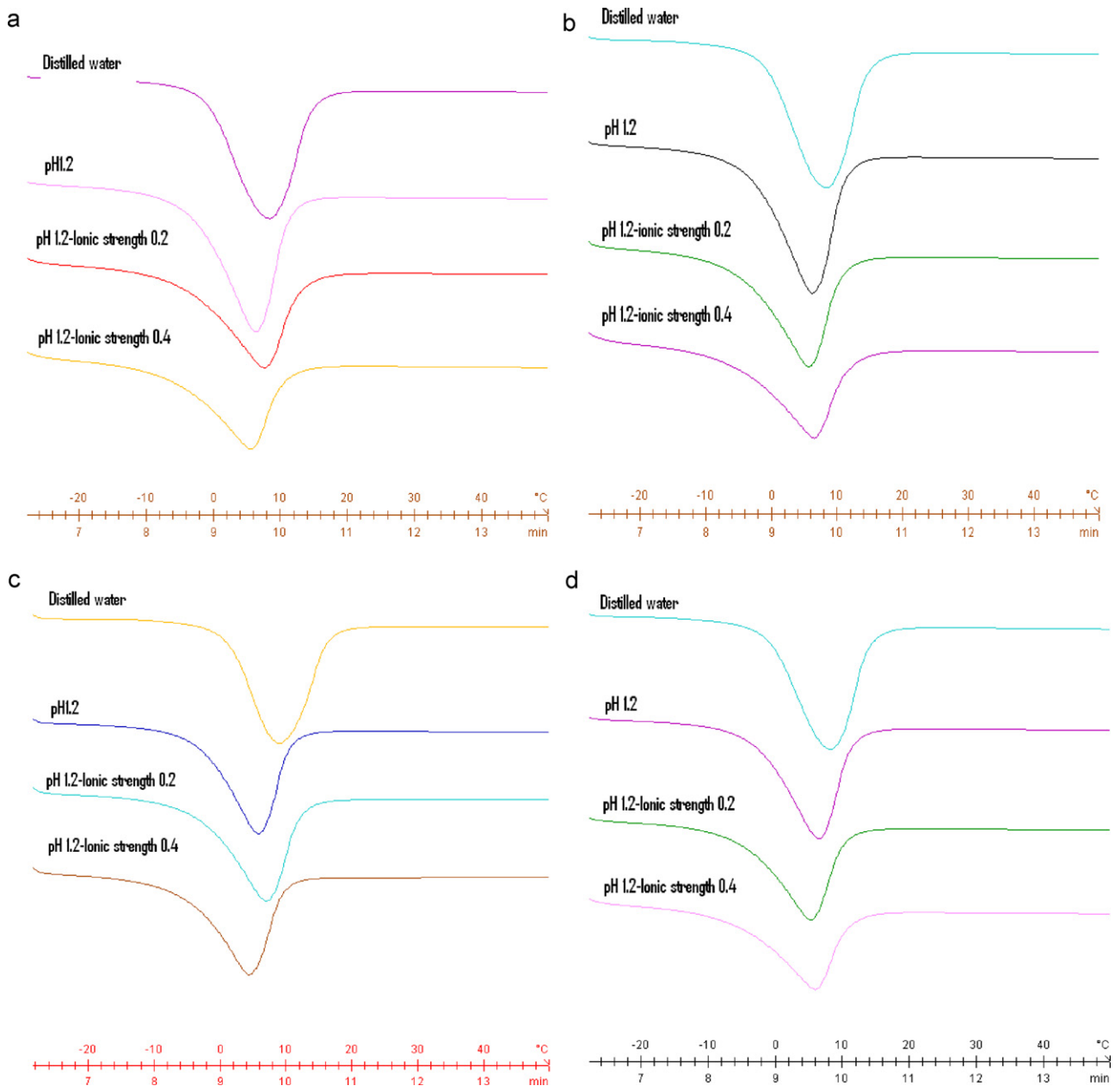

Fig. 8. DSC thermographs taken after 10 min hydration in relevant media of the matrices made from the K chemistry HPMC polymers with 4:1 drug:polymer ratio (a) K100LV, (b) K4M, (c) K15M and (d) K100M. Actual ionic concentration strength were: at pH media was 0.14 M, at pH (ionic strength 0.2) was 0.34 M and at pH (ionic strength 0.4) was 0.54 M.

4. Conclusion

Ionic concentration strengths had a significant effect on the release patterns of K100LV matrices. K4M, K15M and K100M were, however, resilient to the influence of media ionic concentration strength. K100M matrices produced the lowest drug release rate as compared to K4M and K15M. Additionally, the developed method allowed evaluation of the ionic strength effects on ER matrices and showed that the higher viscosity grades of HPMC polymers (K4M, K15M and K100M) produced resilient gel layers around their matrices that might be the best candidates in for producing release profiles less affected by potential food effects. The DSC hydration method also proved useful in explaining the theophylline release from the HPMC matrices. The use of systematic change of agitation method and ionic concentration strength evaluation may be used to indicate potential fed and fasted effects on drug release from hydrophilic matrices.

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References

Abrahamsson, B., Roos, K., & Sjogren, J. (1999). Investigation of prandial effects on hydrophilic matrix tablets. *Drug Development and Industrial Pharmacy*, *25*, 765–771.

Abrahamsson, B., Johansson, D., Torstensson, A., & Wingstrand, K. (1994). Evaluation of solubilizers in the drug release testing of hydrophilic matrix extended-release tablets of felodipine. *Pharmaceutical Research*, *11*, 1093–1097.

Alderman, D. A. (1984). A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *International Journal of Pharmaceutical Technology and Product Manufacture*, *5*, 1–9.

Aoki, S., Ando, H., Ishii, M., Watanabe, S., & Ozawa, H. (1995). Water behavior during drug release from a matrix as observed using differential scanning calorimetry. *Journal of Controlled Release*, *33*, 365–374.

Asare-Addo, K., Levina, M., Rajabi-Siahboomi, A. R., & Nokhodchi, A. (2010). Study of dissolution hydrodynamic conditions versus drug release from hypromellose matrices. The influence of agitation sequence. *Colloids and Surfaces B: Biointerfaces*, *81*, 452–460.

Bonferoni, M. C., Rossi, S., Ferrari, F., Bertoni, M., & Caramella, C. (1995). Influence of medium on dissolution–erosion behavior of Na carboxymethylcellulose and on viscoelastic properties of gels. *International Journal of Pharmaceutics*, *117*, 41–48.

Charman, W. N., Porter, C. J. H., Mithani, S., & Dressman, J. B. (1997). Physicochemical and physiological mechanisms for the effects of food on drug absorption: The role of lipids and pH. *Journal of Pharmaceutical Sciences*, *86*, 269–282.

Colombo, P. (1993). Swelling-controlled release in hydrogel matrices for oral route. *Advanced Drug Delivery Reviews*, *11*, 37–57.

Ford, J. L., & Mitchell, K. (1995). Thermal analysis of gels and matrix tablets containing cellulose ethers. *Thermochimica Acta*, *248*, 329–345.

Grundy, J. S., Anderson, K. E., Rogers, J. A., & Foster, R. T. (1997). Studies on dissolution testing of the nifedipine gastrointestinal therapeutic system. I. Description of a two-phase in vitro dissolution test. *Journal of Controlled Release*, *48*, 1–8.

Hodsdon, A. C., Mitchell, J. R., Davies, M. C., & Melia, C. D. (1995). Structure and behavior in hydrophilic matrix sustained-release dosage forms. 3. The influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices. *Journal of Controlled Release*, *33*, 143–152.

Jhon, M. S., & Andrade, J. D. (1973). Water and hydrogels. *Journal of Biomedical Materials Research*, *7*, 509–522.

Johnson, J. L., Holinej, J., & Williams, M. D. (1993). Influence of ionic strength on matrix integrity and drug release from hydroxypropyl cellulose compacts. *International Journal of Pharmaceutics*, *90*, 151–159.

Kavanagh, N., & Corrigan, O. I. (2004). Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—Influence of agitation rate and dissolution medium composition. *International Journal of Pharmaceutics*, *279*, 141–152.

Klein, S., Rudolph, M. W., & Dressman, J. B. (2002). *Dissolution technologies-nov 2002 article 1*.

Li, C. L., Martini, L. G., Ford, J. L., & Roberts, M. (2005). The use of hypromellose in oral drug delivery. *Journal of Pharmacy and Pharmacology*, *57*, 533–546.

Lindahl, A., Ungell, A. L., Knutson, L., & Lennernas, H. (1997). Characterization of fluids from the stomach and proximal jejunum in men and women. *Pharmaceutical Research*, *14*, 497–502.

Lindner, W. D., & Lippold, B. C. (1995). Drug-release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress. *Pharmaceutical Research*, *12*, 1781–1785.

McCrystal, C. B., Ford, J. L., & Rajabi-Siahboomi, A. R. (1997). A study on the interaction of water and cellulose ethers using differential scanning calorimetry. *Thermochimica Acta*, *294*, 91–98.

Mitchell, K., Ford, J. L., Armstrong, D. J., Elliott, P. N. C., Rostron, C., & Hogan, J. E. (1990). The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrix tablets. *International Journal of Pharmaceutics*, *66*, 233–242.

Moore, J. W., & Flanner, H. H. (1996). Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. *Pharmaceutical Technology*, *20*, 64–74.

Pham, A. T., & Lee, P. I. (1994). Probing the mechanisms of drug-release from hydroxypropylmethyl cellulose matrices. *Pharmaceutical Research*, *11*, 1379–1384.

Phuapradit, W., & Bolton, S. (1991). The influence of tablet density on the human oral absorption of sustained-release acetaminophen matrix tablets. *Drug Development and Industrial Pharmacy*, *17*, 1097–1107.

Pillay, V., & Fassihi, R. (1998). Evaluation and comparison of dissolution data derived from different modified release dosage forms. An alternative method. *Journal of Controlled Release*, *55*, 45–55.

Polli, J. E., Yu, L. X., Cook, J. A., Amidon, G. L., Borchardt, R. T., Burnside, B. A., et al. (2004). Summary workshop report: Biopharmaceutics classification system—Implementation challenges and extension opportunities. *Journal of Pharmaceutical Sciences*, *93*, 1375–1381.

Sasa, B., Odon, P., Stane, S., & Julijana, K. (2006). Analysis of surface properties of cellulose ethers and drug release from their matrix tablets. *European Journal of Pharmaceutical Sciences*, *27*, 375–383.

Siepmann, J., & Peppas, N. A. (2001). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Advanced Drug Delivery Reviews*, *48*, 139–157.

Skoug, J. W., Mikelsons, M. V., Vigneron, C. N., & Stemm, N. L. (1993). Qualitative evaluation of the mechanism of release of matrix sustained-release dosage forms by measurement of polymer release. *Journal of Controlled Release*, *27*, 227–245.

Streubel, A., Siepmann, J., Dashevsky, A., & Bodmeier, R. (2000). pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. *Journal of Controlled Release*, *67*, 101–110.

Tahara, K., Yamamoto, K., & Nishihata, T. (1996). Application of model-independent and model analysis for the investigation of effect of drug solubility on its release rate from hydroxypropyl methylcellulose sustained-release tablets. *International Journal of Pharmaceutics*, *113*, 17–27.

Tatavarti, A. S., & Hoag, S. W. (2006). Microenvironmental pH modulation based release enhancement of a weakly basic drug from hydrophilic matrices. *Journal of Pharmaceutical Sciences*, *95*, 1459–1468.

Tatavarti, A. S., Mehta, K. A., Augsburger, L. L., & Hoag, S. W. (2004). Influence of methacrylic and acrylic acid polymers on the release performance of weakly basic drugs from sustained release hydrophilic matrices. *Journal of Pharmaceutical Sciences*, *93*, 2319–2331.

Tiwari, S. B., & Rajabi-Siahboomi, A. R. (2008). Extended-release oral drug delivery technologies. Monolithic matrix systems. *Methods in Molecular Biology*, 217–243.

Tiwari, S. B., Murthy, T. K., Pai, M. R., Mehta, P. R., & Chowdary, P. B. (2003). Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. *AAPS Pharmaceutical Sciences Technology*, *4*, E31.

Wan, L. S. C., Heng, P. W. S., & Wong, L. F. (1995). Matrix swelling—A simple-model describing extent of swelling of HPMC matrices. *International Journal of Pharmaceutics*, *116*, 159–168.

Wilson, C. G., & Washington, N. (1989). The stomach: Its role in drug delivery. In *Physiological pharmaceutics. The stomach: Its role in drug delivery*. Chichester: Ellis Horwood Ltd., pp. 47–68.

Yoshioka, S., Aso, Y., & Terao, T. (1992). Effect of water mobility on drug hydrolysis rates in gelatin gels. *Pharmaceutical Research*, *9*, 607–612.

Yu, Z. L., Schwartz, J. B., & Sugita, E. T. (1996). Theophylline controlled-release formulations: In vivo in vitro correlations. *Biopharmaceutics and Drug Disposition*, *17*, 259–272.