Simultaneous Quantification of Drug Release and Erosion from Hypromellose Hydrophilic Matrices

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Abstract

Hypromellose, HPMC, is frequently used to control drug release from matrix tablet formulations. Drug is released by a combination of diffusion through and erosion of, the matrix and is usually measured *in vitro* by separate dissolution and swelling/erosion studies. The present study was designed to measure matrix erosion, polymer dissolution and drug release kinetics and their inter-relationship in a single experiment using a phenol-sulphuric acid assay to quantify dissolved HPMC alongside spectrophotometrical analysis of drug release. HPMC-based matrix tablets were manufactured containing two drugs at various drug:HPMC ratios. Drug release was determined and the degree of erosion was calculated by gravimetry. Results showed the matrix erosion rate and drug release were dependent on HPMC content and drug solubility, as expected. It was also apparent that the erosion rate was directly related to the drug release kinetics and comparative analysis of both matrix erosion techniques showed a high level of correlation. The findings show that a simple and inexpensive assay can be utilised not only to quantify HPMC but can also be used to calculate the degree of erosion of tablet matrices, negating the need for a separate study and providing a simplified practical approach that may be of use during product optimization.

Keywords: Hydroxypropyl methylcellulose; hydrophilic matrix; drug release; matrix erosion; phenol-sulphuric acid assay

1- Introduction

The use of hydrophilic matrices to develop extended release (ER) formulations has become progressively widespread because of their potential to control the release of wide range of active pharmaceutical ingredients (APIs) and to produce robust tablet formulations (Alderman, 1984). Hydrophilic matrices containing hypromellose, HPMC (hydroxypropyl methylcellulose), as the polymeric carrier have been extensively used in oral dosage forms (Maderuelo *et al*., 2011). The popularity of HPMC can be attributed to its non-toxic nature, availability in different grades, good compression properties, ability to give pH independent drug release profiles, good regulatory acceptance and amenability to high levels of drug loading (Li *et al*., 2005). On incorporation of HPMC into the tablet formulation, the tortuosity and porosity of matrix tablets can be altered and are intuitively expected to influence the rate and mechanism of drug release from monolithic HPMC-based devices (Reza *et al*., 2003).

Upon submersion in liquids, such as dissolution testing media or biological fluids, these hydrophilic matrices swell and polymer chains eventually disentangle which leads to the breakage of hydrogen bonds formed during tablet compaction. However, persistent liquid ingression and interaction between HPMC polymeric chains and the ingressing liquid can cause hydrogen bond formation accommodating water molecules (Gao *et al*., 1996). This leads to the formation of gel layer across the matrix tablet as HPMC passes from an amorphous to rubbery state. (Colombo et al., 1999; Colombo et al., 2000; Jiasheng et al., 2010). The polymeric chains present on the surface of matrix tablet hydrate quickly compared to those located inside the core and contact with liquid causes chain relaxation (swelling) which initiates erosion of the matrix. The relative rates of liquid uptake and

erosion of a polymer matrix play a critical role in controlling the rate of drug release. The swelling, matrix erosion, drug release mechanism and rate are dependent on the concentration and viscosity of HPMC being used in the hydrophilic matrices (Mitchell *et al*., 1993; Wan *et al*., 1991). HPMC has the potential to hydrate quickly enough to form a gel layer before the drug entrapped in the tablet matrix can dissolve. Moreover, the higher the viscosity and density of the gel layer, the more resistant the gel is to dissolution and/or erosion as it can retain integrity, thus increasing drug diffusion path length (Khamanga and Walker, 2006). Highly water soluble drugs diffuse through the gel layer before the matrix erodes but it is suggested that the presence of poorly soluble drugs can increase matrix erosion by imperilling the integrity of the gel layer (Bettini *et al*., 2001; Yang and Fassihi, 1997). So, the solubility of entrapped drugs is another key factor in determining the drug release behaviour from hydrophilic matrices. Mechanistically both diffusion and erosion will be contributing factors in controlling drug release from a hydrophilic matrix tablet, however, in practical terms, one process will often play a dominant role over the other depending on the HPMC level and solubility of other matrix tablet contents (Sinha Roy and Rohera, 2002).

Fundamentally during dissolution phenomena there are two processes involved by which polymer erosion from the hydrophilic matrices takes place. Firstly the disentanglement of individual polymeric chains at the surface of matrix tablets and secondly their subsequent transport to the surrounding bulk solution. The physical entanglement of the polymer chains precludes polymer dissolution but polymer present at the outermost surface is diluted by the bulk dissolution medium over time to a point when the polymeric network no longer has structural integrity. This eventually leads to polymer disentanglement and the matrix tablet starts to disappear (Colombo et al., 2000; Maderuelo et al., 2011; Miller-Chou and Koenig, 2003; Siepmann and Peppas, 2001; Wen et al., 2010) .

Various mathematical models have been reported including contributions from the role of water diffusion, polymer swelling, dissolution and degradation and drug diffusion (reviewed by Siepmann and Siepman, 2013). Similarly, there have been many techniques applied to determine the extent of water uptake and polymer erosion from hydrophilic matrices including photography, texture analysis, video recording and nuclear resonance (NMR) imaging (Barba et al., 2009 a and b; Bettini et al., 2001; Cascone et al., 2014; Chirico et al., 2007; Lamberti et al., 2013; Tajarobi et al., 2009) and gravimetric methods are the most commonly used technique to date (Chaibva et al., 2010; Dhopeshwarker and Zatz, 1993; Ebube et al., 1997; Franek et al., 2014; Ghimire et al., 2010; Khamanga and Walker, 2006; Ranga Rao et al., 1988; Sinha Roy and Rohera, 2002). Such measurements, however, can be relatively time consuming and laborious, requiring a significant amount of API and excipients. It has recently been shown that, for HPMC/lactose tablets, for example, that the choice of model for predicting drug release should be based on the desired accuracy and ease of application and often, simple equations may be adequate for the purpose (Siepmann et al., 2013).

A number of analytical techniques can be used to measure carbohydrate concentration including size exclusion chromatography (Viridén et al., 2009), capillary electrophoresis (Cortacero-Ramírez *et al*., 2004), infrared (IR) spectroscopy (Cadet, 1999), nuclear magnetic resonance (NMR) micro-imaging (Tajarobi et al., 2009) and light scattering detection (Zhang *et al*., 2008). Recently Viridén *et al*., (2009) successfully employed size exclusion chromatography to study HPMC tablet dissolution to determine the impact of HPMC heterogeneity on release. A phenol-sulphuric acid assay is commonly employed for analysing sugars in foods, including mono-, di- and polysaccharides and if successful would provide a simple method to study matrix erosion, negating requirements for separate

analytical equipment and associated costs and time (Albalasmeh et al., 2013; Brummer and Cui, 2005; Masuko et al., 2005) .

The aims of the present work were therefore multifold: firstly, to quantify HPMC in the dissolution medium by using novel application of a phenol-sulphuric acid alongside drug release studies. The Peppas and Korsmeyer model was applied to drug release profiles to attain mechanistic insight into the process (Korsmeyer et al., 1983). Secondly, the amount of dissolved HPMC and drug was used to calculate the degree and rate of erosion. Moreover, erosion was also determined using gravimetrical methods for comparative purposes; with an assumption that phenol-sulphuric acid assay will be an alternative option. Thirdly, the inter-relationship of HPMC erosion rate and drug release was studied. Fourthly, the impact of HPMC to drug ratio and the solubility of model drugs on matrix erosion, polymer dissolution and drug release kinetics were also studied, using theophylline (aqueous solubility, 7.3 g/L) and flurbiprofen (aqueous solubility, 8.0 mg/L) as model drugs (Yalkowsky et al., 2010).

2- Materials and methods

2.1- Materials

Flurbiprofen (FBP) and theophylline (THP) were purchased from Aesica Pharmaceutical Ltd, Cramlington, UK and Tokyo Chemical Industry Ltd, UK, respectively. Hydroxypropyl methyl cellulose, HPMC, (Methocel® K4M Premium) was a kind gift from Colorcon Ltd, Dartford, UK. Sulphuric acid, hydrochloric acid and phenol were purchased from Sigma-Aldrich, UK, and all were of analytical grade. Disodium hydrogen phosphate (Na_2HPO_4) and sodium dihydrogen phosphate (NaH_2PO_4) were purchased from Fisher Scientific, UK and used for the preparation of 0.2 M phosphate buffer (pH 7.2). All the materials were used as received.

2.2- Methods

2.2.1- Preparation of matrix tablets

All the powder mixtures comprising different HPMC to drug ratios (flurbiprofen or theophylline, Table 1) were blended for 15 minutes (Turbula shaker-mixer). To evaluate the mixing efficiency, samples were removed from each powder mixture, theophylline and flurbiprofen content were determined by using the linear regression equation obtained from their respective UV standard calibration curves at 272 nm and 247 nm for theophylline and flurbiprofen, respectively. The final powder blends, having drug content between 95-105 %, were compacted using a manual hydraulic press equipped with 13.00 mm die set (Specac® Ltd, UK). The compact weight was maintained at 500 ± 2.5 mg each and was compressed at 20 KN with a 20 second dwell time. At least 20 tablets for each batch of powder blend were made and assayed for theophylline and flurbiprofen using UV spectrophotometry as described above. Each determination was carried out in triplicate and mean results were reported. All the matrix tablets were stored in an air-tight container over silica gel for 24 hours before further investigation.

2.2.2- *In vitro* release studies

2.2.2.1- Drug release studies

In vitro drug release studies were performed on all the hydrophilic matrices, except those containing 100 % HPMC, using USP dissolution apparatus I, SR II 6-flask, basket apparatus, (Hanson Research, USA) at 100 rpm. pH 7.2 sodium phosphate buffer (900 ml) was used as the release medium and was maintained at 37.5 ± 0.5 $^{\circ}$C. Aliquots of dissolution media (5 ml) were withdrawn manually after 30, 60, 120, 360, 740 and 1440 minutes and

replaced with an equal amount of fresh dissolution medium. The dissolution samples were then analysed for drug content as before.

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2.2.2.2- HPMC dissolution studies

HPMC dissolution was studied for all the hydrophilic matrix tablets. Dissolved HPMC was quantified using phenol-sulphuric acid assay alongside drug analysis on the removed samples described previously. Filtered samples (1 ml) were added to 1 ml of 5% phenol in
185 0.1 M hydrochloric acid, followed by 5 ml of concentrated sulphuric acid. The resultant solution was mixed vigorously for 10 minutes and placed in a water bath at 25-30 $^{\circ}$C for 20 minutes. Absorbance was measured at maximum wavelength (λ_{max}) 490 nm and dissolved HPMC content was calculated from a standard calibration curve (Brummer and Cui, 2005; Dubois et al., 1956;).

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2.2.3- Erosion studies

2.2.3.1- Gravimetrical method (GM)

Erosion of matrix tablets was determined by a gravimetric technique (Chaibva *et al*., 2010; Dhopeshwarker and Zatz, 1993; Ebube *et al*., 1997; Ranga Rao *et al*., 1988; Sinha Roy and
195 Rohera, 2002). The study was conducted using USP apparatus I, SR II 6-flask (Hanson Research, USA) at 100 rpm. The dry hydrophilic matrix tablets were accurately weighed and placed in baskets prior to immersion in dissolution media (pH 7.2 sodium phosphate buffer) which was maintained at 37 ± 0.5 $^{\circ}$C. Tablets were removed at 30, 60, 120, 360, 720 and 1440 minutes and lightly blotted dry with 125 mm filter paper (Whatman®) to remove
200 excess water. They were subsequently dried in a convection oven at 50 °C. After 24 hours, the tablets were cooled to ambient temperature and then weighed until a constant weight

had been achieved and this was termed the dried weight. All studies were conducted in triplicate. The degree of erosion (E) was calculated using equation 1.

$$Matrix\ Erosion\ (E) = \frac{Wi - Wf}{Wi} \times 100 \quad (1)$$

Where, *Wi* is the initial weight of the matrix tablets and *Wf* is the weight of the dried matrices at specific sampling times. Water uptake can also be calculated using difference in weight between the tablet wet weight and the dried weight using this method.

2.2.3.2- Combined dissolution method

Matrix tablet erosion was also determined by using the collective amount of drug and polymer dissolved during dissolution and the percentage erosion was calculated at each sampling time using equation 2, and this method is subsequently termed sugar analysis technique (SA) in this paper.

$$Matrix\ Erosion\ (E) = \frac{Wd + Wp}{Wi} \times 100 \quad (2)$$

where, *Wd* is amount of drug released (mg) and *Wp* is amount of HPMC dissolved (mg), determined using the phenol-sulphuric assay method in the dissolution medium at specific sampling times while W_i is the initial weight of matrix tablet. Moreover, the HPMC degree of erosion (H_e) was also calculated by using the equation 3.

$$HPMC\ Erosion\ (He) = \frac{Wp}{Wpi} \times 100 \quad (3)$$

where, *Wp* is amount of dissolved HPMC (mg) and *Wpi* is the initial amount of HPMC in the matrix tablet.

A graph was plotted between percentage matrix or HPMC erosion and time (up to 720 minutes) for all the matrix tablets and simple linear regression was applied representing slope as an erosion rate (k, % min^{-1}).

2.2.4- Modelling of drug release profiles

The mechanism and kinetics of drug release were deduced by fitting respective dissolution data to the Korsmeyer– Peppas model, equation 4 (Korsmeyer et al., 1983). The goodness of fit was established using the adjusted coefficient of determination where the closer the value is to 1, the better the data fit to the model. The value of diffusional exponent (*n)* is dependent on the mechanism of drug release and geometrical shape of the matrix that is being assessed and was further used to describe drug release patterns (Siepmann and Peppas, 2001).

$$\frac{Mt}{M\infty} = Kt^n \qquad (4)$$

Where, $\frac{Mt}{M\infty}$, is the fraction of drug released at time t while K is a drug release constant incorporating the geometrical characteristics of matrix tablet, and *n* is diffusional exponent of drug release and used to elucidate the drug release mechanism. For cylindrical hydrophilic matrices, the *n* values of 0.45 are indicative drug release through Fickian

diffusion and the values between $0.45 < n < 0.89$ means drug is being released through anomalous transport.

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3- Results and discussion

3.1- Theophylline and flurbiprofen release studies

HPMC present on the surface of matrix tablets initially hydrates during dissolution and forms an outer gel layer on matrix tablet surface. Progressive contact with the medium leads
255 to subsequent bulk hydration of the matrix. Eventually, this leads to HPMC chain relaxation, followed by erosion of the matrix. The drug release rate and mechanism is controlled by the matrix swelling, diffusion of drug through the gel layer and/or matrix erosion.

It was observed that the HPMC to drug ratio played an important role in regulating the
260 release behaviour of theophylline and flurbiprofen from the hydrophilic matrix system. Theophylline and flurbiprofen release profiles are shown in Figure 1 (a and b), and for both drugs, HPMC ratio significantly affected the release rates, both decreasing with increasing HPMC content as polymer chain disentanglement slows (Li *et al*., 2005; Maderuelo *et al*., 2011). At higher levels of HPMC the increased concentration leads to chain entanglement
265 which increases the tortuosity of matrix tablets (Chaibva *et al*., 2010; Mitchell *et al*., 1993) and can be considered a decisive feature impeding the diffusion of drug from the matrix gel layer during dissolution. An additional factor can be a lower porosity, as higher amount of HPMC corresponds to low matrix tablet porosity which exhibits low liquid movement across the surface of matrix tablet and leads to slower drug release rates (Reza *et al*., 2003).

270 A markedly faster drug release was determined for hydrophilic matrices containing 20% HPMC, and the release rates from matrices containing theophylline were faster than those

with flurbiprofen. The t_{60} and t_{120} of theophylline-containing matrices were higher than flurbiprofen matrices (Table 1). Rapid gel layer formation around the matrix tablet is an essential feature that can dictate drug release regardless of solubility of drug. Higher amounts of HPMC form a quicker but stronger gel layer which is more resistant to diffusion and/or erosion (Mitchell *et al*., 1993) .

The mechanism by which drugs are released from hydrophilic systems can possibly be; (a) (diffusion- Fickian release), (b) non- Fickian or anomalous transport (c) zero-order release or case II mechanism. Soluble drugs can act as pore formers in matrix tablets and have the capacity to form micro-cavities thus making the gel layer more porous increasing liberation into the bulk dissolution media through diffusion (Yang and Fassihi, 1997). Furthermore, poorly soluble drug (flurbiprofen) particles can be translocated through the gel layer with a spring-like action caused by transition of the polymer chains from a glassy to a rubbery state, which disrupts the gel layer structure (Bettini *et al*., 2001) and can result in exposure of drug particles to water. To determine the mechanism of drug release, dissolution profiles were characterised using Korsmeyer-Peppas model (equation 4). The diffusional exponent (n) of drug release is used to characterize the type of release mechanism during dissolution testing. The matrix tablets demonstrated a linear relationship with correlation coefficient within range 0.995 - 0.999 (Fig. 1 (a and b) and Table 1).

Referring to the criteria of release kinetics from swellable cylindrical (Siepmann and Peppas, 2001) all tablet matrices, regardless of the drug, resulted in non-Fickian release (anomalous transport) mechanism (Table 1). The concentration of HPMC and drug in the matrices affect the diffusional exponent (n). With the gradual increase of HPMC, the n values decreased from 0.75 to 0.50 and 0.88 to 0.62, respectively for theophylline- and flurbiprofen-containing hydrophilic matrices. This indicates that the mechanism of release is a mixture of diffusion and erosion, however depending on the n values it can be predicted

that the diffusion was the dominating mechanism for theophylline matrices whilst erosion dominated for flurbiprofen matrices.

3.2- HPMC dissolution studies

In this study, its release from matrix tablets containing varying concentrations of drug (theophylline or flurbiprofen), ranging from 0% to 80 % was quantified using the phenol-sulphuric acid colorimetric assay. HPMC contains glucose monomers with different levels of methoxyl (%) and hydroxypropoxyl (%) substitution groups, so, it was expected that the phenol-sulphuric acid assay which is classically used to measure carbohydrate content in foods and beverages (Brummer and Cui, 2005) could be applied to quantify HPMC dissolution from tablets. UV-Vis spectrum scanning for both theophylline and flurbiprofen showed there was no interference with the assay at the wavelength of interest (λ_{max} = 490 nm).

It can be seen in Figure 2 (a and b), that the rate and extent of HPMC dissolution fell with increasing HPMC content. This is attributed to a thicker, more durable gel layer on the matrix surface at higher concentrations. The release rates were concentration dependant and a similar trend was seen for both the formulations containing theophylline and flurbiprofen, i.e. 20 > 40 > 60 > 80 > 100%. Despite HPMC being relatively soluble at pH 7.2, the mobility of the macromolecule is decreased with increasing HPMC levels. Methocel® K4M Premium, which is used in this study, has a high molecular weight and viscosity; therefore it is relatively resistant to polymer erosion compared to lower molecular weight and viscosity grades. The concentration of HPMC necessary to develop a rapid and strong gel layer around the matrix tablet is termed the critical concentration and indicates an ability to withstand the influence of different factors during dissolution or hydration. This is a desirable property of a polymer in controlled drug delivery system and the critical

concentration is related to the thickness of the gel layer that forms and specific to each polymer (Maderuelo *et al*., 2011). It can be seen from Figure 2 (a and b) and Table 1 (t_{60} and t_{120}), that HPMC dissolution from flurbiprofen-containing matrices was higher than corresponding theophylline formulations because flurbiprofen is a poorly soluble drug and expected to jeopardise the integrity of gel layer, which can lead to faster HPMC dissolution. The presence of poorly soluble particles in the gel layer hinders the expansion of the polymer and decreases the resistance of the system to erosion, which increases the rate of release of the drug via erosion mechanisms (Table 1).

3.3- Matrix tablets erosion studies

In the hydrated gel layer on the matrix tablet surface, water exists in three distinct states; type I (freezable free or bulk water), type II (freezable bound water) and type III (bound water) (Asare-Addo *et al*., 2013a; Jhon and Andrade, 1973) and there is a moisture gradient which is present from the outer surface which is in contact with liquid to the inner dry polymeric matrix core (McCrystal *et al*., 1997). Once the polymer outer surface completely hydrates, the polymeric chains start to dissolve and this leads to matrix erosion. The erosion and drug dissolution rate are significantly influenced by the presence of drugs, viscosity, chemistry, ionic strength and particle size of drug and polymer (Asare-Addo *et al*., 2013a; Asare-Addo *et al*., 2013b; He *et al.,* 2001; Li *et al*., 2005; Maderuelo *et al*., 2011).

The degree of matrix erosion is shown in Figure 3 and 4, reported as % matrix erosion (E) and reflects the collective amount of polymer and drug dissolved. In the present study, the mass loss from the matrices increased gradually over time. The matrices prepared with 100 % HPMC eroded slowly compared to those containing drugs (theophylline or flurbiprofen). Both methods for determining erosion, GM and SA, gave similar results, with the erosion rate of 100% HPMC matrices being 0.011 % min^{-1} (Table 2). The matrices prepared with

80:20, HPMC: THP have slowest erosion rate (GM = 0.033 and SA = 0.028 % min^{-1}) and the rate tends to increase as HPMC content decreases. The erosion rate of matrices containing 20:80, HPMC: THP was 0.089 and 0.088 % min^{-1} respectively with SA and GM methods. Similarly the erosion rate of, 80:20, HPMC:FBP was lower (GM = 0.027 % min^{-1} SA = 0.028 % min^{-1}) increasing to 0.104 and 0.100 % min^{-1} respectively with both SA and GM methods as the HPMC levels declined in the matrix tablets, suggesting that these matrices have reduced resistance to erosion. Moreover, it was obvious that erosion increased as the drugs were incorporated in the matrices (Table 2), with erosion rates being slower for the more water-soluble theophylline as described before.

3.4- Quantitative relationship between GM and SA

The validity of the phenol-sulphuric acid assay to study polymer dissolution and matrix erosion was determined by comparison with the more established gravimetric method. Mass balance was achieved in all cases and the matrix erosion rates and degree of matrix erosion (%) calculated using both techniques are reported in Table 2 and Figures 3 and 4, respectively. There was a high correlation between the results from both techniques (Figure 5), with adjusted R^2 of 0.998 and 0.988 for flurbiprofen and theophylline respectively (supplementary data). Furthermore, matrix erosion (%) over time showed a higher degree of correlation when both methods were compared (Figure 6, a and b), with residual R^2 ranging between 0.986-0.998 and analysis of residuals showed random distribution about the horizontal axis (supplementary data). The PSA assay can be used for determining neutral sugars in oligosaccharides, polysaccharides, proteoglycans, glycoproteins and protein lipds and can be scaled down to a microplate retaining sensitivity, with potential for high throughput screening, down to 1 nmol for some sugars (Masuko et al., 2005). This method determines the total sugars present as the sulfuric acid causes all non-reducing

sugars to be converted to reducing sugars, so it is non-stoichemetric and therefore necessary to prepare a calibration curve using a series of standards of known carbohydrate concentration. The assay can provide a simple, cheap, robust and rapid analysis, and has been successfully applied in this study to determine dissolved HPMC and to characterise matrix erosion of hydrophilic matrices in *in vitro* dissolution studies.

3.5- Inter-relationship between HPMC erosion and drug release kinetics

It is apparent from results shown in Table 1 that as the HPMC to drug ratio in a matrix tablet varies, the drug release diffusional co-efficient (*n*) values change. It can be predicted from the *n* values (Table 1) that both diffusion and erosion are involved during drug release. It has reported in previously that water soluble drugs were released dominantly by diffusion through the gelatinous layer and poorly soluble drugs by erosion of the matrix tablet (Bettini et al., 2001; Yang and Fassihi, 1997). This is corroborated in this study with erosion dominating when flurbiprofen was released and diffusion in the case of theophylline release. Figure 7 shows the relationship between the diffusional co-efficient (*n*) values of drugs and HPMC erosion rate (k), with a simple regression analysis applied to model the relationship. It is apparent that there is a linear relationship between the *n* values and HPMC erosion rate (k); the diffusional exponents are lower for the less water soluble drug, flurbiprofen, at all drug;polymer ratios, indicating that they are less dependent on diffusional drug release and thus a better correlation was apparent between n and polymer erosion rate. Poorly soluble drugs have the ability to disrupt the gel layer structure leading to higher degree of matrix erosion.

Conclusion

Although drug release from HPMC matrix devices is complex and multifaceted, this simplified practical approach can be used to assess the impact of formulation parameters on drug release during product development and optimisation. Hydrophilic matrices containing HPMC as the polymer and different drugs, theophylline and flurbiprofen, were evaluated for drug content, degree of matrix erosion, HPMC and drug release properties.

A phenol-sulphuric acid assay was successfully adopted for the quantification of dissolved HPMC in the dissolution media. The HPMC dissolution rate increased as the level of HPMC decreased in the matrix tablets. Thus it leads to a conclusion that HPMC levels and solubility of drugs are important factors to consider during the designing of hydrophilic matrix tablet formulations.

The release of FBP and THP was through an anomalous transport mechanism, however, Fickian diffusion and erosion dominated in THP and FBP matrices, respectively. The phenol-sulphuric acid assay also identified an inter-relationship between HPMC erosion rates (H_e) and Korsmeyer– Peppas parameter, *n*,

The matrix erosion results obtained from newly adopted method, phenol-sulphuric acid assay confirm that the solubility of drug and levels of HPMC in a particular matrix tablet significantly affect the matrix erosion rate and results were similar to those determined using the much more labour-intensive gravimetric method. Moreover, the combination of conventional UV drug analysis technique and phenol-sulphuric acid assay can be used to simultaneously quantify the matrix erosion, polymer dissolution and drug release kinetics in a single set of experiments avoiding the need for separate studies.

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6- References

Albalasmeh, A.A., Berhe, A.A., Ghezzehei, T.A., 2013. A new method for rapid determination of carbohydrate and total carbon concentrations using UV spectrophotometry. Carbohydrate Polymers 97, 253-261.

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.

Asare-Addo, K., Conway, B.R., Larhrib, H., Levina, M., Rajabi-Siahboomi, A.R., Tetteh, J., Boateng, J., Nokhodchi, A., 2013a. The effect of pH and ionic strength of dissolution media on in-vitro release of two model drugs of different solubilities from HPMC matrices. Colloids and Surfaces B: Biointerfaces 111, 384-391.

Asare-Addo, K., Kaialy, W., Levina, M., Rajabi-Siahboomi, A., Ghori, M.U., Supuk, E., Laity, P.R., Conway, B.R., Nokhodchi, A., 2013b. The influence of agitation sequence and ionic strength on in vitro drug release from hypromellose (E4M and K4M) ER matrices-The use of the USP III apparatus. Colloids and Surfaces B: Biointerfaces 104, 54-60.

Barba, A.A., D'Amore, M., Cascone, S., Chirico, S., Lamberti, G., Titomanlio, G., 2009a. On the behavior of HPMC/theophylline matrices for controlled drug delivery. Journal of Pharmaceutical Sciences 98, 4100-4110.

Barba, A.A., d'Amore, M., Chirico, S., Lamberti, G., Titomanlio, G., 2009b. Swelling of cellulose derivative (HPMC) matrix systems for drug delivery. Carbohydrate Polymers 78, 469-474.

Bettini, R., Catellani, P.L., Santi, P., Massimo, G., Peppas, N.A., Colombo, P., 2001. Translocation of drug particles in HPMC matrix gel layer: Effect of drug solubility and influence on release rate. Journal of Controlled Release 70, 383-391.

Brummer, Y., Cui, S.W., 2005. Understanding carbohydrate analysis, in: Cui, S.W. (Ed.), Food Carbohydrates : Chemistry, Physical Properties, and Applications. Taylor & Francis Group Boca Ranton FL (USA).

Cadet, F., 1999. Measurement of sugar content by multidimensional analysis and mid-infrared spectroscopy. Talanta 48, 867-875.

Cascone, S., Lamberti, G., Titomanlio, G., d'Amore, M., Barba, A.A., 2014. Measurements of non-uniform water content in hydroxypropyl-methyl-cellulose based matrices via texture analysis. Carbohydrate Polymers 103, 348-354.

Chaibva, F.A., Khamanga, S.M.M., Walker, R.B., 2010. Swelling, erosion and drug release characteristics of salbutamol sulfate from hydroxypropyl methylcellulose-based matrix tablets. Drug Development and Industrial Pharmacy 36, 1497-1510.

Chirico, S., Dalmoro, A., Lamberti, G., Russo, G., Titomanlio, G., 2007. Analysis and modeling of swelling and erosion behavior for pure HPMC tablet. Journal of Controlled Release 122, 181-188.

Colombo, P., Bettini, R., Peppas, N.A., 1999. Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug. Journal of Controlled Release 61, 83-91.

Colombo, P., Bettini, R., Santi, P., Peppas, N.A., 2000. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharmaceutical Science & Technology Today 3, 198-204.

Cortacero-Ramírez, S., Segura-Carretero, A., Cruces-Blanco, C., Hernáinz-Bermúdez De Castro, M., Fernández-Gutiérrez, A., 2004. Analysis of carbohydrates in beverages by capillary electrophoresis with precolumn derivatization and UV detection. Food Chemistry 87, 471-476.

Dhopeshwarker, V., Zatz, J.L., 1993. Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Development and Industrial Pharmacy 19, 999-1017.

Dubois, M., Gilles, K.A., Hamilton, J.K., Rebers, P.A., Smith, F., 1956. Colorimetric method for determination of sugars and related substances. Analytical Chemistry 28, 350-356.

Ebube, N.K., Hikal, A.H., Wyandt, C.M., Beer, D.C., Miller, L.G., Jones, A.B., 1997. Sustained release of acetaminophen from heterogeneous matrix tablets: Influence of polymer ratio, polymer loading, and co-active on drug release. Pharmaceutical Development and Technology 2, 161-170.

Franek, F., Holm, P., Larsen, F., Steffansen, B., 2014. Interaction between fed gastric media (Ensure Plus®) and different hypromellose based caffeine controlled release tablets: Comparison and mechanistic study of caffeine release in fed and fasted media versus water using the USP dissolution apparatus 3. International Journal of Pharmaceutics 461, 419-426.

Gao, P., Skoug, J.W., Nixon, P.R., Robert Ju, T., Stemm, N.L., Sung, K.-C., 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Journal of Pharmaceutical Sciences 85, 732-740.

Ghimire, M., Hodges, L.A., Band, J., O'Mahony, B., McInnes, F.J., Mullen, A.B., Stevens, H.N.E., 2010. In-vitro and in-vivo erosion profiles of hydroxypropylmethylcellulose (HPMC) matrix tablets. Journal of Controlled Release 147, 70-75.

He, P.S.W., Chan, L.W., Easterbook, M.G., Li, X. 2001. Investigation of the influence of mean HPMC particle size and mumber of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. Journal of Controlled Release, 76, 39-49.

Jhon, M.S., Andrade, J.D., 1973. Water and hydrogels. Journal of Biomedical Materials Research 7, 509-522.

Jiasheng, T., Shen, Y., Ravichandran, M., Bhaskara, J., Xiaoling, L., 2010. Polymers in oral modified release systems, in: Wen, H., Park, K. (Eds.), Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons.

Khamanga, S.M., Walker, R.B., 2006. Evaluation of rate of swelling and erosion of verapamil (VRP) sustained-release matrix tablets. Drug Development and Industrial Pharmacy 32, 1139-1148.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics 15, 25-35.

Lamberti, G., Cascone, S., Cafaro, M.M., Titomanlio, G., D'Amore, M., Barba, A.A., 2013. Measurements of water content in hydroxypropyl-methyl-cellulose based hydrogels via texture analysis. Carbohydrate Polymers 92, 765-768.

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.

Maderuelo, C., Zarzuelo, A., Lanao, J.M., 2011. Critical factors in the release of drugs from sustained release hydrophilic matrices. Journal of Controlled Release 154, 2-19.

Masuko, T., Minami, A., Iwasaki, N., Majima, T., Nishimura, S.-I., Lee, Y.C., 2005. Carbohydrate analysis by a phenol–sulfuric acid method in microplate format. Analytical Biochemistry 339, 69-72.

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.

Miller-Chou, B.A., Koenig, J.L., 2003. A review of polymer dissolution. Progress in Polymer Science 28, 1223-1270.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C., Hogan, J.E., 1993. The influence of concentration on the release of drugs from gels and matrices containing Methocel®. International Journal of Pharmaceutics 100, 155-163.

Ranga Rao, K.V., Padmalatha Devi, K., Buri, P., 1988. Cellulose matrices for zero-order release of soluble drugs. Drug Development and Industrial Pharmacy 14, 2299-2320.

Reza, M.S., Quadir, M.A., Haider, S.S., 2003. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. Journal of Pharmacy and Pharmaceutical Sciences 6, 282-291.

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.

Siepmann, J., Karrout, Y., Gehrke, M., Penz, F.K., Siepmann F., 2013. Predicting drug release frim HPMC/lactose tablets. International Journal of Pharmaceutics 441, 826-834.

Siepmann, J., Siepmann, F., 2013. Mathematical modeling of drug dissolution. International Journal of Pharmaceutics 453, 12-24.

Sinha Roy, D., Rohera, B.D., 2002. Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. European Journal of Pharmaceutical Sciences 16, 193-199.

Tajarobi, F., Abrahmsén-Alami, S., Carlsson, A.S., Larsson, A., 2009. Simultaneous probing of swelling, erosion and dissolution by NMR-microimaging-Effect of solubility of additives on HPMC matrix tablets. European Journal of Pharmaceutical Sciences 37, 89-97.

Viridén, A., Wittgren, B., Andersson, T., Larsson, A., 2009. The effect of chemical heterogeneity of HPMC on polymer release from matrix tablets. European Journal of Pharmaceutical Sciences 36, 392-400.

Wan, L.S.C., Heng, P.W.S., Wongh, L.F., 1991. The effect of hydroxypropylmethylcellulose on water penetration into a matrix system. International Journal of Pharmaceutics 73, 111-116.

Wen, X., Nokhodchi, A. Rajabi-siahboomi, A., 2010. Oral extended release hydrophilic matrices: formulation and design, in: Wen, H., Park, K. (Eds.), Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons.

Yalkowsky, S.H., He, Y., Jain, P., 2010. Handbook of Aqueous Solubility Data, Second Edition. Taylor & Francis.

Yang, L., Fassihi, R., 1997. Examination of drug solubility, polymer types, hydrodynamics and loading dose on drug release behavior from a triple-layer asymmetric configuration delivery system. International Journal of Pharmaceutics 155, 219-229.

Zhang, M.L., Sheng, G.P., Yu, H.Q., 2008. Determination of proteins and carbohydrates in the effluents from wastewater treatment bioreactors using resonance light-scattering method. Water Research 42, 3464-3472.

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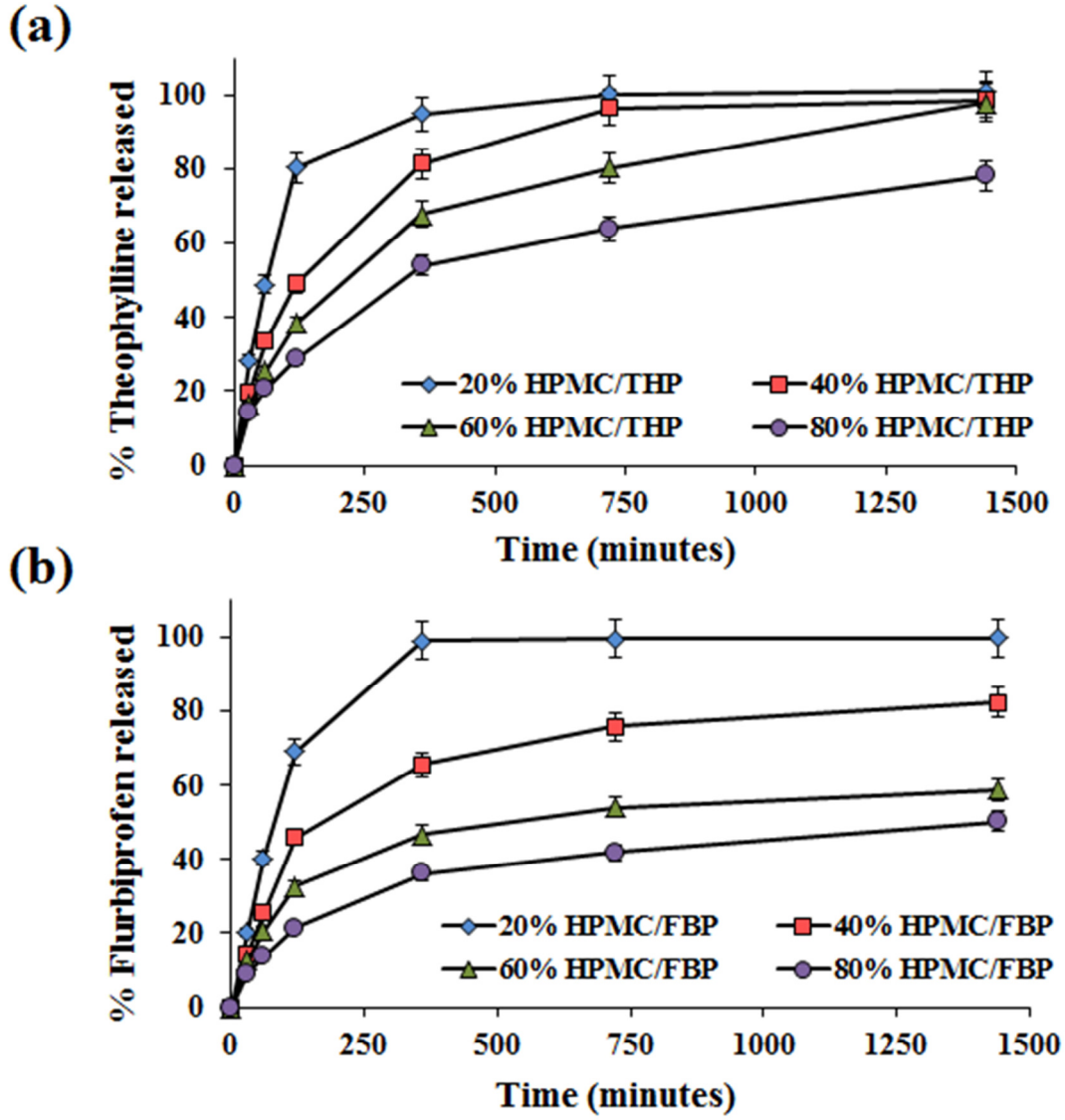

Figure 1. Effect of HPMC concentration on the theophylline (a) and flurbiprofen (b) release from matrix tablets.

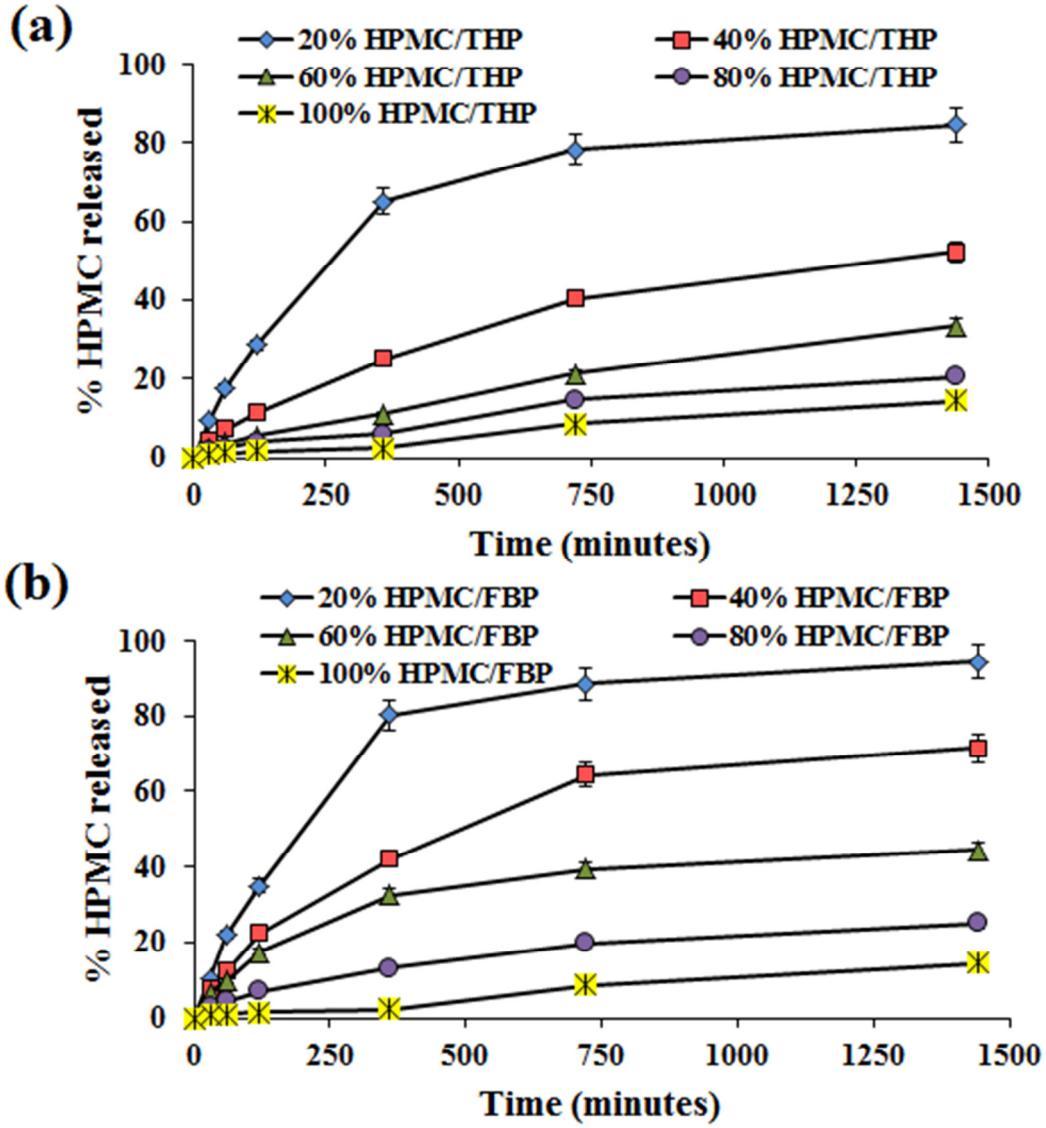

Fig. 2. Effect of HPMC concentration on the HPMC dissolution from theophylline (a) and flurbiprofen (b) containing matrix tablets.

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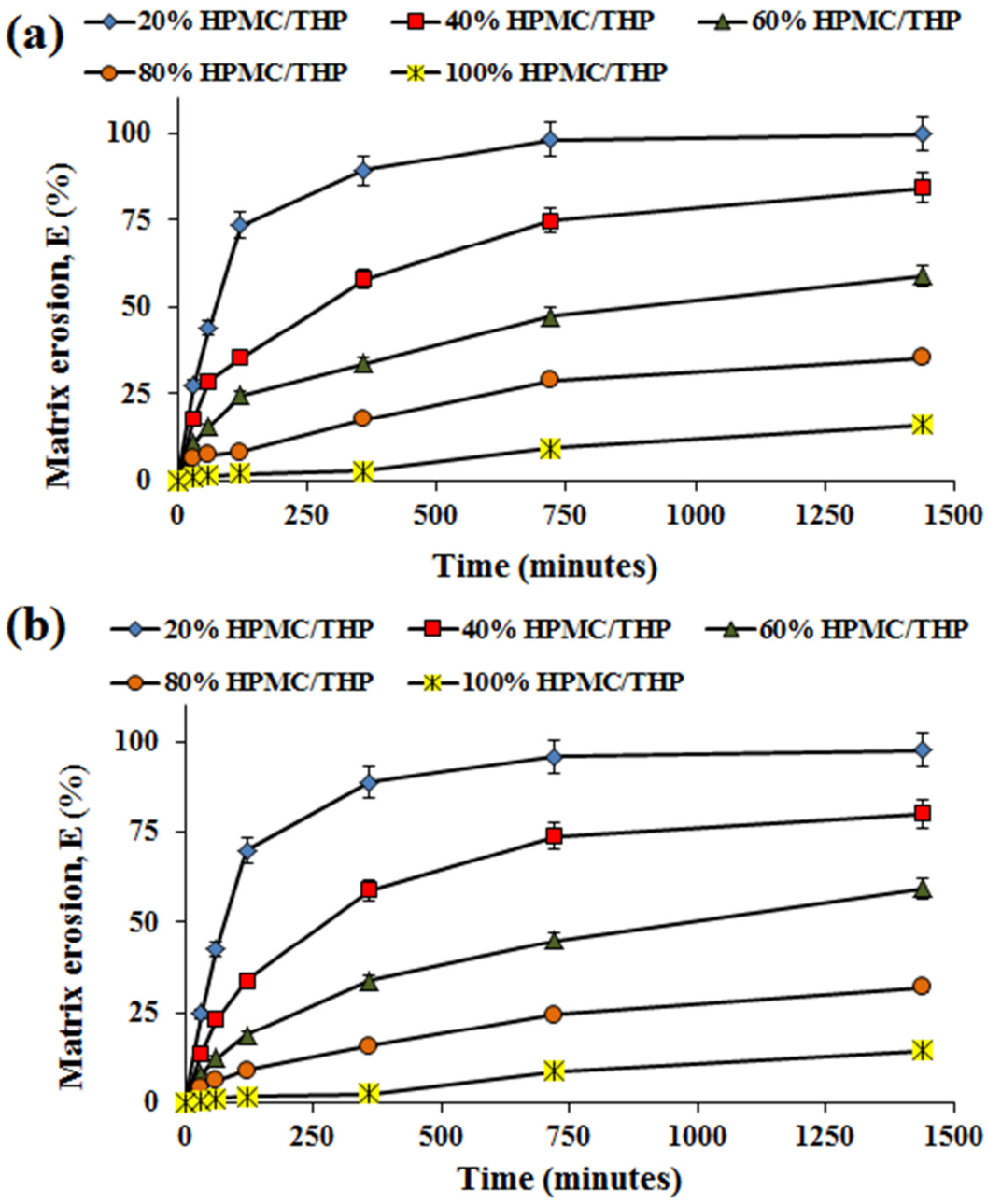

Fig. 3, Matrix erosion profiles of HPMC/THP matrix tablets, gravimetrical technique (a) and phenol-sulphuric acid assay method (b).

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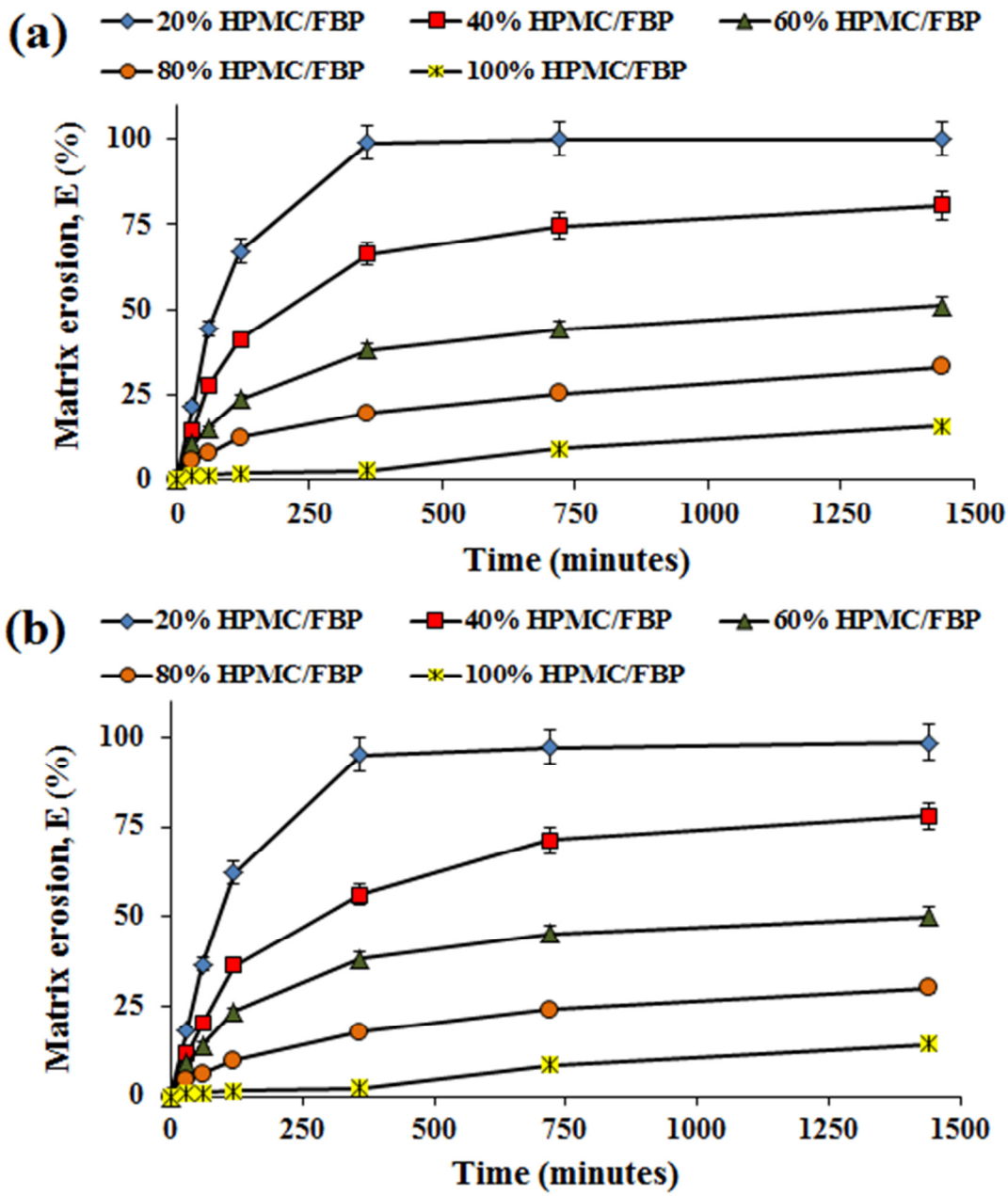

685 **Figure 4, Matrix erosion profiles of HPMC/FBP matrix tablets, gravimetrical technique (a) and phenol-sulphuric acid assay method (b).**

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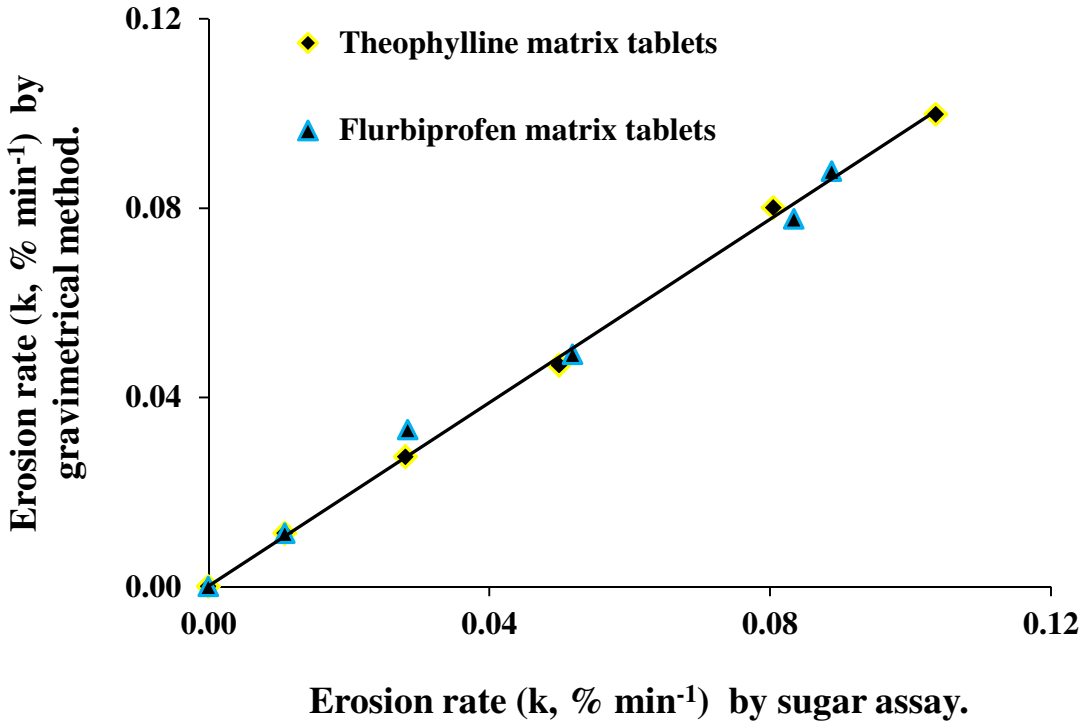

Figure 5. Comparative analysis of erosion rates calculated from both techniques.

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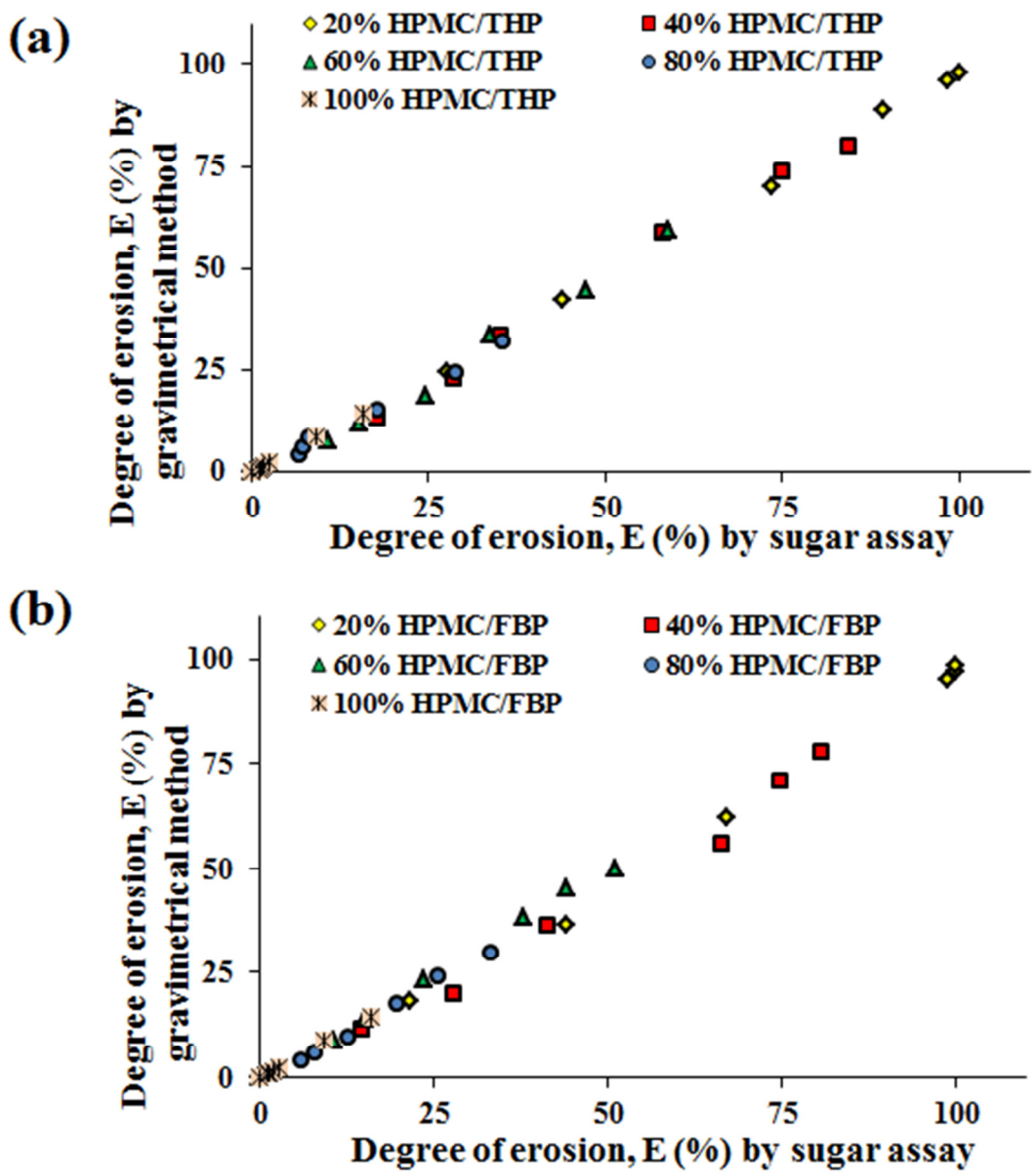

725 **Figure 6. Comparative analysis of degree of erosion calculated using both techniques, theophylline matrices (a) and flurbiprofen matrices (b).**

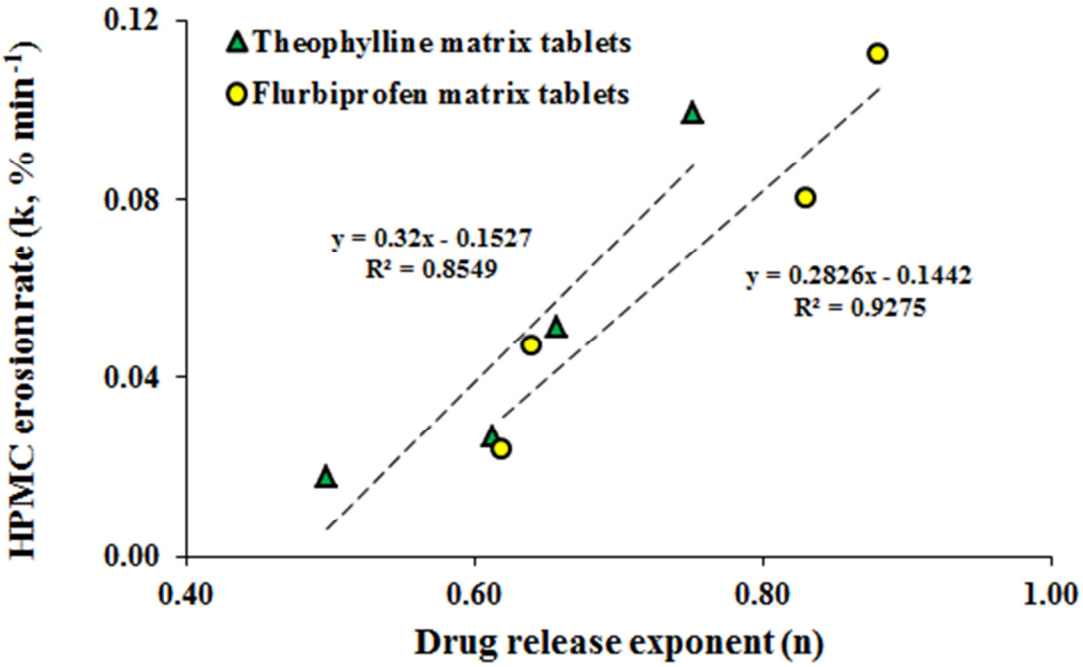

Figure 7. **Comparative analysis of HPMC erosion rate (k) and drug release diffusional exponent (*n*).**

Table 1, HPMC and drug release kinetics parameters of theophylline and flurbiprofen matrix tablets (standard deviation are in parenthesis)

HPMC:Theophylline	HPMC:Flurbiprofen	Drug release kinetics parameters		t_{60} (%)*		t_{120} (%)**	
		n	R^2	Drug	HPMC	Drug	HPMC
100:0	**100:0**	-	-	-	1.05	-	1.56
80:20	**-**	0.50	0.999	20.57 (1.02)	2.50 (0.12)	28.64 (1.43)	3.85 (0.19)
60:40	**-**	0.61	0.990	25.38 (1.26)	3.58 (0.17)	38.31 (1.91)	5.50 (0.27)
40:60	**-**	0.66	0.997	33.58 (2.43)	7.30 (0.36)	48.95 (2.44)	11.20 (0.56)
20:80	**-**	0.75	0.999	48.69 (1.67)	17.67 (0.88)	80.32 (4.01)	28.52 (1.42)
-	**80:20**	0.62	0.997	13.65 (0.68)	4.33 (0.21)	21.37 (1.06)	6.98 (0.34)
-	**60:40**	0.64	0.994	20.64 (1.03)	9.65 (0.48)	32.68 (1.63)	17.32 (0.86)
-	**40:60**	0.83	0.999	25.36 (1.26)	12.36 (0.61)	45.87 (2.29)	22.36 (1.11)
-	**20:80**	0.88	0.995	40.31 (2.01)	21.98 (1.09)	68.96 (3.44)	34.89 (1.74)

t_{60} * = Percent drug/HPMC release at 60 minutes, t_{120} ** = Percent drug/HPMC release at 120 minutes

Table 2, Matrix erosion kinetics parameters of theophylline and flurbiprofen matrix tablets.

HPMC:Theophylline	HPMC:Flurbiprofen	Erosion rates (k, %min^{-1})					
		SA*	R^2	GM**	R^2	H_e***	R^2
100:0	**100:0**	0.011	0.918	0.011	0.915	0.011	0.918
80:20	**-**	0.028	0.989	0.033	0.996	0.018	0.970
60:40	**-**	0.052	0.946	0.049	0.937	0.027	0.997
40:60	**-**	0.083	0.917	0.078	0.939	0.051	0.990
20:80	**-**	0.089	0.716	0.088	0.716	0.099	0.903
-	**80:20**	0.028	0.952	0.027	0.931	0.024	0.979
-	**60:40**	0.050	0.874	0.047	0.874	0.047	0.899
-	**40:60**	0.081	0.890	0.080	0.833	0.080	0.976
-	**20:80**	0.104	0.734	0.100	0.710	0.112	0.853

***SA = Sugar assay technique, **GM = Gravimetrical method, ***H_e = HPMC erosion rate**

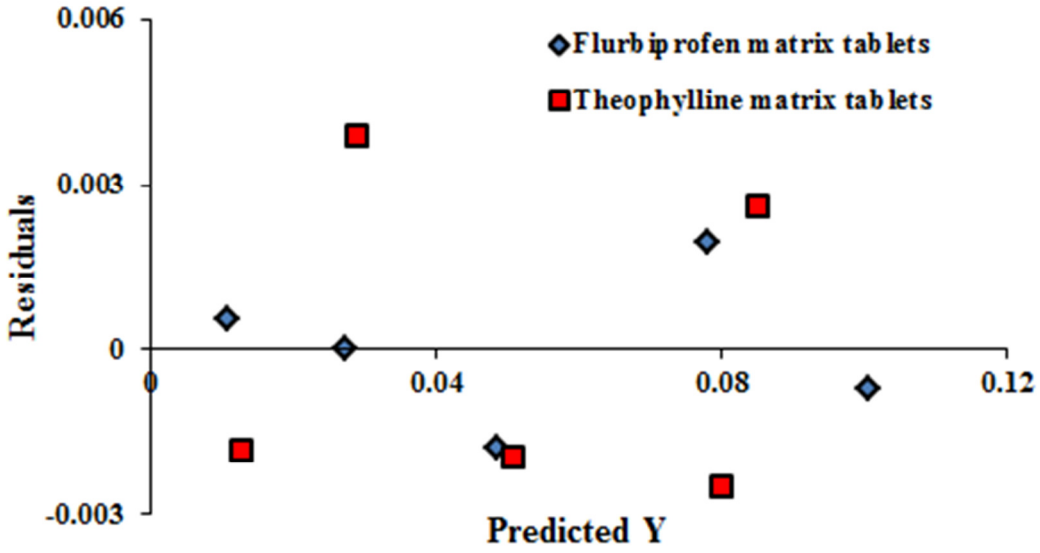

Figure 1, Residual plot of erosion rate, a comparison between GM and SA techniques.

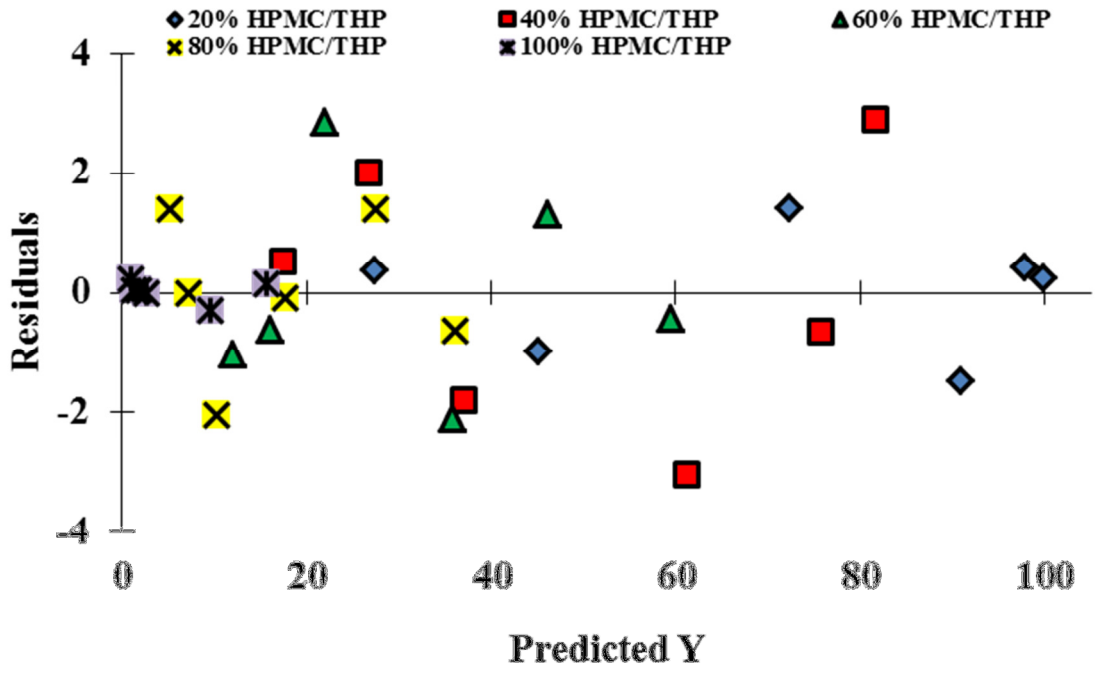

Figure 2, Residual plot of comparative degree of erosion between GM and SA, theophylline matrices.

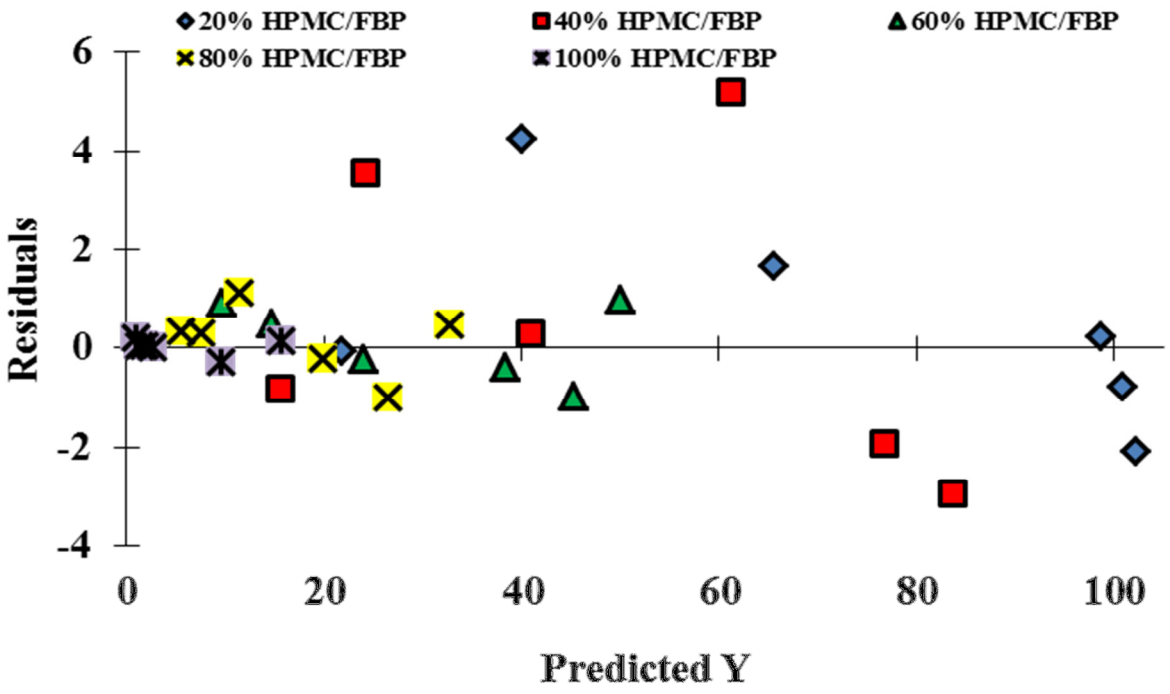

Figure 3, Residual plot of comparative degree of erosion between GM and SA, flurbiprofen matrices

Table 1, Comparison of erosion rates of matrix tablets from gravimetrical and sugar assay from residual plots.

Type of matrices	Adjusted R^2	Standard error
Flurbiprofen matrices	0.998	0.0016
Theophylline matrices	0.988	0.0034

Table 2, Comparison of degree of erosion (%) of matrix tablets from gravimetrical and sugar assay from residual plots (standard error is in parenthesis).

HPMC:Theophylline	HPMC:Flurbiprofen	Correlation co-efficient
		R^2
100:0	**100:0**	0.998 (0.18)
80:20	**-**	0.986 (1.45)
60:40	**-**	0.988 (1.99)
40:60	**-**	0.991 (2.53)
20:80	**-**	0.998 (1.17)
-	**80:20**	0.994 (0.86)
-	**60:40**	0.997 (0.87)
-	**40:60**	0.986 (3.57)
-	**20:80**	0.995 (2.68)