Simultaneous Quantification of Drug Release and Erosion from Hypromellose Hydrophilic Matrices

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Abstract

Hypermellose, 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., 2009a 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 gravimetical 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 (\( \text{Na}_2\text{HPO}_4 \)) and sodium dihydrogen phosphate (\( \text{NaH}_2\text{PO}_4 \)) 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 °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.

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 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 °C for 20 minutes. Absorbance was measured at maximum wavelength ($\lambda_{\text{max}}$) 490 nm and dissolved HPMC content was calculated from a standard calibration curve (Brummer and Cui, 2005; Dubois et al., 1956;).

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 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 °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 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.

\[
Matrix \ Erosion \ (E) = \frac{W_i - W_f}{W_i} \times 100 \quad (1)
\]

Where, \( W_i \) is the initial weight of the matrix tablets and \( W_f \) 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.

\[
Matrix \ Erosion \ (E) = \frac{W_d + W_p}{W_i} \times 100 \quad (2)
\]

where, \( W_d \) is amount of drug released (mg) and \( W_p \) 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.

\[
HPMC \ Erosion \ (He) = \frac{W_p}{W_{pi}} \times 100 \quad (3)
\]
where, $W_p$ is amount of dissolved HPMC (mg) and $W_{pi}$ 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 ($k, \% \text{ min}^{-1}$).

### 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).

\[
\frac{M_t}{M_\infty} = Kt^n \tag{4}
\]

Where, $\frac{M_t}{M_\infty}$, 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.

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 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 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 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).

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 ($\lambda_{\text{max}} = 490 \text{ nm}$).

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 lipids 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-stoichiometric 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.

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

- Theophylline matrix tablets
- Flurbiprofen matrix tablets

Erosion rate ($k$, % min$^{-1}$) by gravimetric method.

Erosion rate ($k$, % min$^{-1}$) by sugar assay.
Figure 6. Comparative analysis of degree of erosion calculated using both techniques, theophylline matrices (a) and flurbiprofen matrices (b).
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Table 1, HPMC and drug release kinetics parameters of theophylline and flurbiprofen matrix tablets (standard deviation are in parenthesis)

<table>
<thead>
<tr>
<th>HPMC:Theophylline</th>
<th>HPMC:Flurbiprofen</th>
<th>Drug release kinetics parameters</th>
<th>( t_{60} ) (%)*</th>
<th>( t_{120} ) (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( n )</td>
<td>( R^2 )</td>
<td>Drug</td>
</tr>
<tr>
<td>100:0</td>
<td>100:0</td>
<td>-</td>
<td>-</td>
<td>20.57 (1.02)</td>
</tr>
<tr>
<td>80:20</td>
<td>-</td>
<td>0.50</td>
<td>0.999</td>
<td>2.50 (0.12)</td>
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<tr>
<td>60:40</td>
<td>-</td>
<td>0.61</td>
<td>0.990</td>
<td>25.38 (1.26)</td>
</tr>
<tr>
<td>40:60</td>
<td>-</td>
<td>0.66</td>
<td>0.997</td>
<td>33.58 (2.43)</td>
</tr>
<tr>
<td>20:80</td>
<td>-</td>
<td>0.75</td>
<td>0.999</td>
<td>48.69 (1.67)</td>
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<tr>
<td>-</td>
<td>80:20</td>
<td>0.62</td>
<td>0.997</td>
<td>13.65 (0.68)</td>
</tr>
<tr>
<td>-</td>
<td>60:40</td>
<td>0.64</td>
<td>0.994</td>
<td>20.64 (1.03)</td>
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<tr>
<td>-</td>
<td>40:60</td>
<td>0.83</td>
<td>0.999</td>
<td>25.36 (1.26)</td>
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<tr>
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<td>20:80</td>
<td>0.88</td>
<td>0.995</td>
<td>40.31 (2.01)</td>
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</table>

\( t_{60} \) * = 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.**

<table>
<thead>
<tr>
<th>HPMC:Theophylline</th>
<th>HPMC:Flurbiprofen</th>
<th>Erosion rates (k, %min⁻¹)</th>
<th>SA*</th>
<th>R²</th>
<th>GM**</th>
<th>R²</th>
<th>Hₑ***</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>100:0</td>
<td>100:0</td>
<td></td>
<td>0.011</td>
<td>0.918</td>
<td>0.011</td>
<td>0.915</td>
<td>0.011</td>
<td>0.918</td>
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<tr>
<td>80:20</td>
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<td></td>
<td>0.028</td>
<td>0.989</td>
<td>0.033</td>
<td>0.996</td>
<td>0.018</td>
<td>0.970</td>
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<td>0.946</td>
<td>0.049</td>
<td>0.937</td>
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<td>0.997</td>
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<td>0.083</td>
<td>0.917</td>
<td>0.078</td>
<td>0.939</td>
<td>0.051</td>
<td>0.990</td>
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<tr>
<td>20:80</td>
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<td>0.089</td>
<td>0.716</td>
<td>0.088</td>
<td>0.716</td>
<td>0.099</td>
<td>0.903</td>
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<tr>
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<td>80:20</td>
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<td>0.028</td>
<td>0.952</td>
<td>0.027</td>
<td>0.931</td>
<td>0.024</td>
<td>0.979</td>
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<tr>
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<td>0.047</td>
<td>0.874</td>
<td>0.047</td>
<td>0.899</td>
</tr>
<tr>
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<td>0.081</td>
<td>0.890</td>
<td>0.080</td>
<td>0.833</td>
<td>0.080</td>
<td>0.976</td>
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<tr>
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<td>20:80</td>
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<td>0.104</td>
<td>0.734</td>
<td>0.100</td>
<td>0.710</td>
<td>0.112</td>
<td>0.853</td>
</tr>
</tbody>
</table>

*SA = Sugar assay technique, **GM = Gravimetric method, ***Hₑ = 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 gravimetical and sugar assay from residual plots.

<table>
<thead>
<tr>
<th>Type of matrices</th>
<th>Adjusted $R^2$</th>
<th>Standard error</th>
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</thead>
<tbody>
<tr>
<td>Flurbiprofen matrices</td>
<td>0.998</td>
<td>0.0016</td>
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<tr>
<td>Theophylline matrices</td>
<td>0.988</td>
<td>0.0034</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>HPMC:Theophylline</th>
<th>HPMC:Flurbiprofen</th>
<th>Correlation co-efficient $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100:0</td>
<td>100:0</td>
<td>0.998 (0.18)</td>
</tr>
<tr>
<td>80:20</td>
<td>-</td>
<td>0.986 (1.45)</td>
</tr>
<tr>
<td>60:40</td>
<td>-</td>
<td>0.988 (1.99)</td>
</tr>
<tr>
<td>40:60</td>
<td>-</td>
<td>0.991 (2.53)</td>
</tr>
<tr>
<td>20:80</td>
<td>-</td>
<td>0.998 (1.17)</td>
</tr>
<tr>
<td>-</td>
<td>80:20</td>
<td>0.994 (0.86)</td>
</tr>
<tr>
<td>-</td>
<td>60:40</td>
<td>0.997 (0.87)</td>
</tr>
<tr>
<td>-</td>
<td>40:60</td>
<td>0.986 (3.57)</td>
</tr>
<tr>
<td>-</td>
<td>20:80</td>
<td>0.995 (2.68)</td>
</tr>
</tbody>
</table>