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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.

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

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release behaviour from hydrophilic matrices. Mechanistically both diffusion and erosion will be contributing factors in controlling drug release from a hydrophilic matrix tablet. In practical terms, however, 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).

During dissolution phenomena there are two processes fundamentally 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 Siepmann, 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, 2009b; Bettini et al., 2001; Cascone et al., 2014; Chirico et al., 2007; Lamberti et al., 2013; Tajarobi et al., 2009) but 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 assay 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 min (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 s 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 h 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 min 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 a 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 min. 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).