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Review Article

The use of hypromellose in oral drug delivery

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Abstract

Hypromellose, formerly known as hydroxypropylmethylcellulose (HPMC), is by far the most commonly employed cellulose ether used in the fabrication of hydrophilic matrices. Hypromellose provides the release of a drug in a controlled manner, effectively increasing the duration of release of a drug to prolong its therapeutic effect. This review provides a current insight into hypromellose and its applicability to hydrophilic matrices in order to highlight the basic parameters that affect its performance. Topics covered include the chemical, thermal and mechanical properties of hypromellose, hydration of the polymer matrices, the mechanism of drug release and the influence of tablet geometry on drug-release rate. The inclusion of drug-release modifiers within hypromellose matrices, the effects of dissolution media and the influence of both the external environment and microenvironment pH within the gel matrix on the properties of the polymer are also discussed.

Introduction

Hydrophilic matrices are compressed powder mixtures of drug and excipients including one, or more, water-swellable hydrophilic polymers. The matrices are typically compressed (Hogan 1989). Such matrices are commonly employed because of the advantages associated with their manufacture, including simple formulation, the use of existing tableting technologies and the low cost of polymers, which are generally regarded as safe (GRAS) excipients. Many swellable polysaccharides are available, allowing flexibility for the needs of an individual formulation. Hydrophilic matrices are erodible and therefore, unlike inert matrices, they reduce in size and dissolve following swelling as they pass through the gastrointestinal tract (GIT). Thus, these matrices avoid the expulsion of the exhausted 'ghosts' that are typical of many hydrophobic matrices. Swellable matrices are also suitable for other administration routes, including buccal, vaginal and rectal delivery. Swellable-soluble matrices are versatile as they can be formulated as mini-matrices or bilayer or even trilayer dosage units.

Hypromellose, formerly known as hydroxypropylmethylcellulose (HPMC), is by far the most common cellulose ether used to form swellable-soluble matrices. It is a water-soluble hydrophilic, non-ionic cellulose ether that gels, is stable over the pH range 3.0–11.0 and is enzyme resistant (Dow Commercial Information, 2002). Hypromellose is used to provide the release of a drug in a controlled manner. Its classification as GRAS by the FDA is one reason why the polymer is widely used.

The hypromellose patents US4369172 and US4389393 originally granted to Forest Laboratories Incorporated have now expired, however patent US5393765, entitled *Pharmaceutical compositions with constant erosion volume for zero order controlled release*, was granted to Hoffmann–La Roche Incorporated in 1995. This patent covers dosage forms with zero-order release using hypromellose and containing active substances having a solubility not greater than $80\,mg\,mL^{-1}$.

Dow Chemical Company have purchased worldwide rights to the patent and is allowing formulators and drug makers use of hypromellose (Methocel brand) covered in the patent without concern for future licensing or royalties.

Hydrophilic matrices effectively increase the duration of release of a drug to prolong its therapeutic effect. Following ingestion, it is important for the drug to be released in a controlled manner, consequently the dosage form should remain intact as it travels through the GIT, where chemical and mechanical challenges can potentially break up the dosage form. Such matrices are subjected to continuous peristalsis and shear forces, as well as a variety of pH environments for varying periods of time (Fallingborg 1999).

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The aim of this review is to provide a current insight into hypromellose and its applicability to hydrophilic matrices in order to highlight the basic parameters that affect its performance.

Chemical nature of hypromellose

Substitution types of hypromellose

Hypromellose has a polymeric backbone of cellulose and is produced by processing pulp cellulose with caustic soda, then reacting with methyl chloride and propylene oxide, leading to hydroxypropyl substitution on the anhydroglucose units (Chan et al 2003). The hydroxypropyl substituent group ($-OCH_2CH(OH)CH_3$) has a secondary hydroxyl group on the number 2 carbon and it is the ratio of hydroxypropyl and methyl substitution that gives a particular hypromellose its different characteristics (Figure 1).

Many commercial hypromelloses are identified by codes. For instance, in those manufactured by the Dow Chemical Company, the first part is a letter (E, F or K) that relates to the degree of substitution. The K grades (hypromellose 2208) have a methoxy substitution of 19–24% and a hydroxypropyl substitution of 7–12%. F grades (hypromellose 2906) have a methoxy substitution of 27–30% and a hydroxypropyl substitution of 4.0–7.5%. E grades (hypromellose 2910) have a methoxy substitution of 28–30% and a hydroxypropyl substitution of 7–12% (Dow Commercial Information 2002). This first letter is followed by an indication of the viscosity of their aqueous 2% w/w gels (in centiPoises) at 20°C, with a multiplier of 100 (denoted by the letter C) or 1000 (denoted by the letter M). A final suffix identifies the grade of the material, such as premium (P), low viscosity (LV), controlled release (CR), granular (G), surface treated (S) or food grade (FG). Controlled-release dosage forms mainly use the K or E grades of hypromellose (Dow Commercial Information 2002).

Viscosity types of hypromellose

Commonly used viscosity grades of hypromellose 2208 range from 100 to 100 000 cP. The commonly used hypromellose 2910 grades include those with viscosities of 4000 and 10 000 cP (Gustafsson et al 1999).

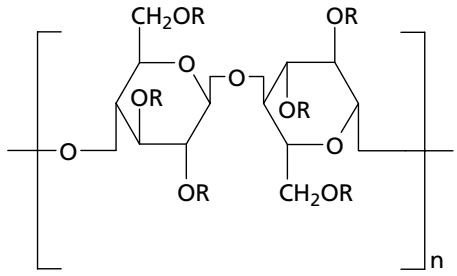

Figure 1 Chemical structure of hypromellose.

Thermal properties

Hydration of hypromellose is influenced by temperature, which has significant effects on the characteristics of its gels. Increasing the gel temperature causes a loss of the hydrating water that in turn leads to a decrease in relative viscosity; continued loss leads to polymer–polymer interactions of the methoxy substituents, leading to what is termed a gel point (Mitchell et al 1990). Another effect of increasing the temperature of hypromellose gels is precipitation. An incipient precipitation temperature may be recorded that corresponds to the commencement of visual precipitation of the polymer molecules (Sarkar 1979). Light transmittance can be used to identify incipient precipitation, which is normally defined by a 97.5% transmittance. The value when the transmittance reaches 50% is known as the cloud point (Sarkar 1979). However, a turbid solution can be achieved before reaching a cloud point, which makes the determination of a cloud point subjective (Mitchell et al 1990; Ford 1999). The cloud point is dependent on the concentration of hypromellose (Sarkar 1979). High concentrations can lead to a gel being formed before turbidity occurs but, on the other hand, at low concentration a turbid solution can be observed before gelation occurs (Mitchell et al 1990). Electrolytes may decrease both the thermal gelation temperature and the cloud point (Mitchell et al 1990).

Hydration and *modus operandi* of hypromellose matrices

Hydration of matrix

Rapid uptake of water occurs on first contact of the dosage form with aqueous fluid. Liquid penetration into the spaces of the polymer causes hydration; chains gradually uncoil and extend but never form into linear coils. These events break polymer hydrogen bonds, making sites available for further hydrogen bonding with additional water molecules and leading to a mass of polymer entanglement (Ju et al 1995; Gao et al 1996; Kim & Fassihi 1997a, b) (Figure 2). As the water content increases, the polymer becomes hydrated and the layer takes on the full characteristics of a gel. This is followed by retardation of water uptake by the rest of the tablet due to the formation of this gel layer (Adler et al 1999). Gel layer thickness may be moderated by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion (Colombo et al 1996; Tahara et al 1996). For a good controlled-release matrix, quick hydration is necessary to form a protective gelatinous layer. This ensures that the drug and excipients in the matrix do not dissolve prematurely.

Viscosity effects

Generally hypromellose chains swell faster with an increase in polymer viscosity (Wan et al 1991). The pores of high-viscosity hypromellose block up quickly and inhibit further liquid uptake (Wan et al 1991). This in turn leads to the formation of a turbid gel, which resists dilution and erosion, subsequently resulting in slower drug diffusion and release rates (Wan et al 1991; Gao et al 1996; Talukdar et al 1996). Drugs that are charged or

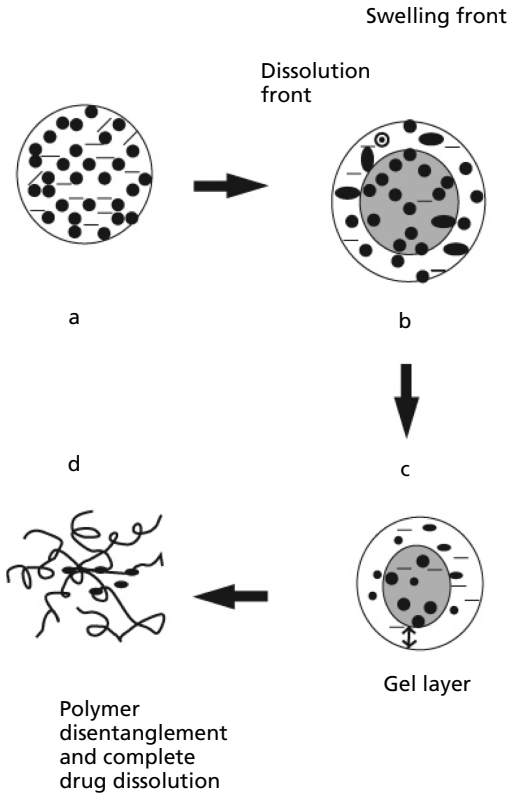

Figure 2 Schematic representation of drug distribution and matrix swelling during dissolution. (a–b) Water diffuses into the matrix, reaching a threshold value when the glassy matrix undergoes a phase transition to the rubbery state, (b–c) drug is released from the swollen system, which gradually erodes away and finally completely dissolves (d). Reprinted from Pharmaceutical Research, 14(10), Kim and Fassihi, A new ternary polymeric matrix system for controlled drug delivery of highly soluble drugs: I. Diltiazem hydrochloride, pp 1415–1421, Copyright (1997), with kind permission of Springer Science and Business Media.

possess long side-chains are less mobile because of interaction with the gel. This increases the time taken for such drugs to diffuse through the gel structure (Sung et al 1996; Fyfe & Blazek-Welsh 2000). One proposed advantage of using a high-viscosity polymer is that, because of the rapid hydration and formation of a gel, it is likely to prevent dose dumping (Nellore et al 1998).

Instances have been observed by Ford & Mitchell (1995) whereby gel layer thickness was similar despite differences in polymer viscosity grade. The viscosity grade of the polymer slightly affected the drug-release rate using hypromellose 2208 in matrices (Bettini et al 1994).

Mechanism of drug release

Drug release is controlled by diffusion through, and erosion of, the gel layer (Colombo et al 1996; Tahara et al 1996). Any drug present on the surface of the matrix is released as a 'burst' (Ford et al 1985a). This is followed by expansion of the gel layer due to water permeating into the tablet, increasing the thickness of the gel layer (Ford et al 1985a; Talukdar et al 1996). If a good gel layer is formed, the rate of drug release is reduced and becomes dependent on the rate at which the drug molecules diffuse through the gel, as well as the rate at which the barrier layer is mechanically removed by attrition and disentanglement of the matrix. In most cases, both diffusion and erosion occur simultaneously (Ju et al 1995; Gao et al 1996; Kim & Fassihi 1997b).

Three characteristics of swelling were observed from MRI images: the growth of the gel layer with time, a reduction in the size of the dry core of the polymer as more of the polymer becomes hydrated and, finally, an increase in the diameter of the matrix with time (Tritt-Goc & Pislewski 2002) (Figure 3).

The central mechanism of drug release is the gel layer, described by some as a rubbery polymer, which forms around the matrix. This gel layer prevents matrix disintegration and any further rapid water penetration (Colombo et al 1996). Gel layer dynamics are therefore an important factor. The swelling process is geometrically uniform and water penetration follows a gradient rate with decreasing speed on further penetration into the dosage form. The process is dependent on pH and is of great importance because the GIT varies from pH 1–3.5 in the stomach to pH 8 in the colon. Clearly such pH changes may result in differing levels of swelling, water penetration

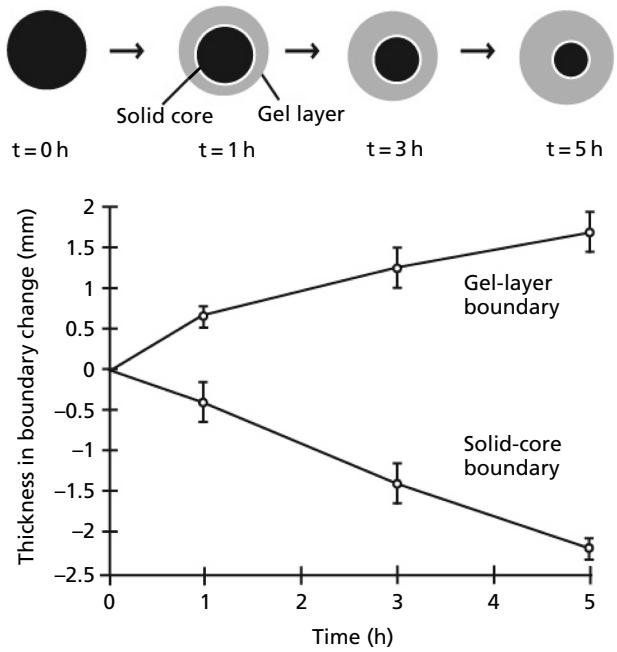

Figure 3 Schematics and actual changes in boundary regions of a 3:6 pectin:hypromellose matrix with time in deionized water. The zero position corresponds to the initial dimensions of the tablet. Reprinted from Journal of Pharmaceutical Sciences, Vol. 86, Kim and Fassihi, Application of a binary polymer system in drug release rate modulation. 1. Characterisation of release mechanism, pp 316–328, Copyright (1997), with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

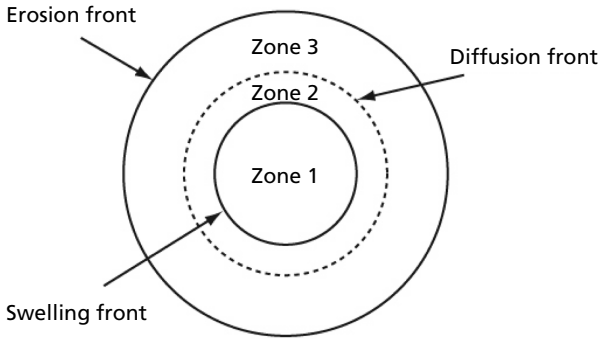

Figure 4 Schematic illustration of a swellable hypromellose-based matrix during drug release. The three distinct moving fronts are indicated. At all times the dissolved drug profile extends from the diffusion to the erosion front and the water profile from the swelling to the erosion front (i.e. the entire gel layer). Reprinted from Journal of Controlled Release, Vol. 90, Kiil & Dam-Johansen, Controlled drug delivery from swellable hydroxypropylmethylcellulose matrices: model based analysis of observed radial front movements, pp 1–21, Copyright (2003), with permission from Elsevier.

and hence drug release in different compartments of the GIT (Tritt-Goc & Pislewski 2002). The fed and fasted states of the GIT are different. The stomach fed state has a pH greater than 3, whereas the fasted state has a pH less than 3. Residence time is different depending on whether the individual is in the fed state or fasted state (Fallingborg 1999).

Three sharp fronts exist that separate different matrix states (Figure 4). The swelling front is the boundary between the still glassy polymer and its rubbery state. The hypromellose is regarded as glassy because water has yet to fully penetrate the matrix. The mobility of macromolecules is hence very low, which leads to low diffusion rates of water (Colombo et al 1996; Kiil & Dam-Johansen 2003). The erosion front is the boundary between the matrix and the dissolution medium. The mobility of the polymer chains is increased, leading to higher rates of diffusion (Colombo et al 1996; Kiil & Dam-Johansen 2003). The diffusion front is the boundary in the gel layer itself between solid and dissolved drug. Drug dissolution occurs at this diffusion front (Lee & Kim 1991). When the diffusion front is formed, the thickness of the dissolved drug–gel layer (i.e. the distance between the diffusion and the erosion front) is the main drive for drug release, not the whole gel layer thickness (i.e. the distance between the swelling and erosion fronts) (Colombo et al 1996).

Movement of the erosion front determines drug-release kinetics. If the polymer in the diffusion front is diluted to such an extent that the gel has no structural integrity, it dissolves and erodes away. A water-soluble drug is released by diffusion and erosion of the gel layer. If a drug is highly insoluble then the mechanism is predominantly erosion (Tahara et al 1995; Colombo et al 1996).

The internal dynamics of a tablet matrix have been visualized by applying the technique of tracking embedded fluorescent microspheres. Microspheres and air bubbles move linearly outwards from the core (Adler et al 1999) (Figure 5). Expansion of the polymer was observed deep into the tablet and at the outer gel layer.

Axial expansion of the core is not well characterized. Investigations into the differences between the swelling of the edge and face of a tablet have been carried out (Papadimitriou et al 1993). Axial relaxation was the result of the relief of the stresses involved during compaction of the dosage form (Papadimitriou et al 1993; Ford & Mitchell 1995). The dimensional changes resulting from increased axial swelling were nine-fold higher compared to radial swelling. This was attributed to the difference in the relative surface areas. The axial surface area was much greater and water was able to imbibe in the axial direction, causing the tablet to swell (Mitchell et al 1993a; Rajabi-Siahboomi et al 1994; Siepmann et al 1999a). The rate of growth of the gel was found to be similar in both the axial and radial directions (Rajabi-Siahboomi et al 1994).

Hydration state

Hypromellose is capable of taking up and retaining large amounts of water in its amorphous regions when exposed to water vapour (Zografi 1988), which affects its physical and chemical properties (Nokhodchi & Rubinstein 2001). Increasing the particle size of hypromellose generally results in a reduction in the internal absorption and an increase in the external absorption of water into the polymer. Water absorption is dependent on the surface area of the polymer particles (Nokhodchi et al 1997) (Figure 6).

It has been hypothesized that there is more than one state of water in the matrix gel. The water may be regarded as (a) tightly bound water that interacts with polymer chains and is non freezable, (b) free water that is freezable and (c) water in states between these two extremes (Ford & Mitchell 1995; McCrystal et al 1997, 2002; Nokhodchi et al 1997).

Nokhodchi et al (1997) predicted that hypromellose 2208 containing as much as ~31% w/w moisture would show no free water as all the moisture is tightly bound. Particle size and viscosity grade had no effect on this value (Nokhodchi et al 1997). The presence of hydrophobic or poorly water-soluble drugs or excipients, however, affects the disruption of the hydrogen bond network of the polymer and diminishes the amount of water bound to the polymer (Salsa et al 2003).

Mechanical properties of hypromellose (compaction)

The compression and compaction properties of hypromellose are affected by particle size, moisture content, compression force, compression speed, viscosity grade and substitution type (Nokhodchi & Rubinstein 2001). Frequently, the Heckel equation (Heckel 1961) is used to assess the rearrangement and packing of hypromellose particles and their deformation during tableting (Malamataris & Karidas 1994; Nokhodchi et al 1996a).

The tensile strengths of tablets made from hypromelloses are dependent on the substitution types of those hypromelloses. The methoxy groups are hydrophobic,

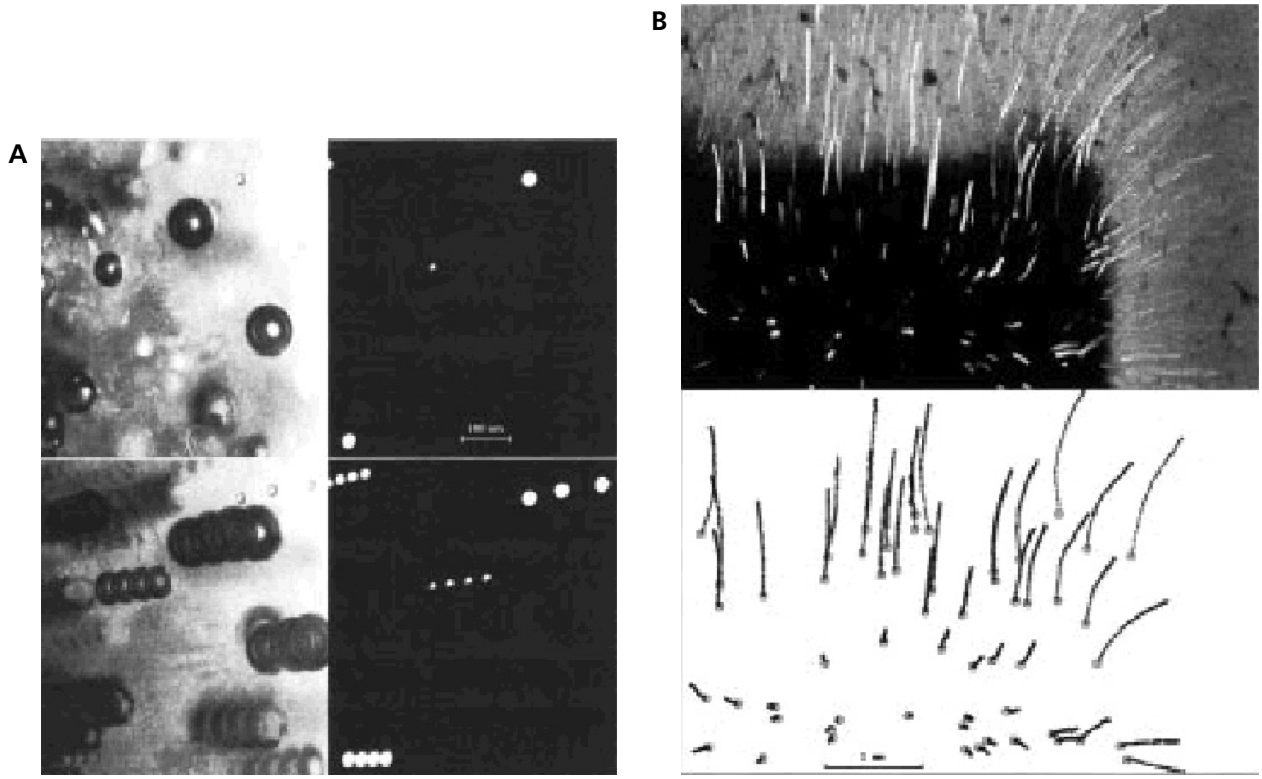

Figure 5 Microspheres and air bubbles tracked moving through the gel layer of a hypromellose tablet. (A) The left-hand panels show (transmitted light image) air bubbles and microspheres, and the right-hand panels (fluorescence image) microspheres only, in the gel layer of a hypromellose tablet. The lower panels show a superimposed sequence of four images, showing movement. (B) The expansion of a bisected hypromellose tablet after hydration. The upper panel is an image showing the paths followed by microspheres following hydration. The lower panel shows the mapped tracks of identified microspheres, starting from their original locations. Axial movements are in the vertical plane and radial movements in the horizontal plane. Reprinted from Journal of Pharmaceutical Sciences, Vol. 88, Adler et al, A method for quantifying differential expansion within hydrating hydrophilic matrices by tracking embedded fluorescent microspheres, pp 371–377, Copyright (1999), with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

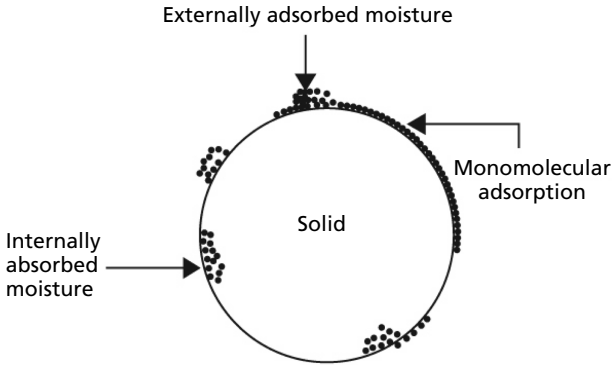

Figure 6 Diagrammatic representation of different states of moisture around a hypromellose particle. Reprinted from Journal of Pharmaceutical Sciences, Vol. 86, Nokhodchi et al, Studies on the interaction between water and (hydroxypropyl)methylcellulose, pp 608–615, Copyright (1997), with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

decreasing hydrogen bonding within and between particles of close proximity and thereby reducing compact strength (Gustafsson et al 1999; Nokhodchi & Rubinstein 2001). Increasing the compaction force increases the density of hypromellose tablets (Ford et al 1985b) but this has little effect on the drug-release characteristics (Nokhodchi et al 1996b).

Nokhodchi et al (1995) considered that the relationship between particle size, tensile strength and the viscosity grade of HPMC was complex. Using different hypromellose 2208 viscosity grades (Methocel K100, K4M, K15M and K100M), Nokhodchi et al (1995) showed that for <45 and 45–125 μm size ranges an increase in viscosity grade caused a reduction in the tensile strength of compacts composed solely of the polymer. The tensile strength of compacts decreased with an increase in viscosity grade up to K15M for larger particle sizes (125–180, 180–250 and 250–350 μm) (Nokhodchi et al 1995). The compressibility indices increased by ~50–75% as the particle size was reduced from 250–350 μm to <45 μm, indicating that the interparticle frictional and cohesive forces increased with decreasing particle size. Additionally, the tensile

strength of compacts made of the smallest particle size (< 45 μm) fraction were > 300% higher than those of compacts made from the 250–350 μm fraction. Nokhodchi et al (1995) considered that particle size was the single most important factor in controlling the tensile strengths of HPMC tablets. Heckel analysis showed that the mean yield pressure to induce plastic deformation was lowest for HPMC K100. A decrease in particle size generally causes an increase in the tensile strengths of hypromellose matrices. The mean yield pressures of various hypromellose 2208 viscosity grades were independent of particle size (Nokhodchi & Rubinstein 2001). Increased compression speed generally decreased the tensile strengths of the tablets (Nokhodchi et al 1996c). Those of Methocel HPMC K100 tablets were more sensitive to changes in compression speed than those of the other grades. An increase in compression speed caused an increase in the mean yield pressure of hypromellose 2208 (Nokhodchi et al 1996c).

Residual water may be present from before compaction (i.e. in the raw material) or be sorbed from the atmosphere (Mosquera et al 1996). Initial uptake of moisture to ~6% w/w is in the form of tightly bound moisture; higher moisture uptake causes a decrease in tensile strength due in part to weakened interparticulate bonding caused by softening of the hypromellose (Malamataris & Karidas 1994). The consequence of increasing the amount of water during wet granulation is the production of larger granules that are intrinsically hard yet yield softer tablets because of insufficient intergranular bonding.

Increasing moisture content markedly affects the compaction of hypromellose 2208. The thickness of Methocel K4M compacts decreased as the moisture content increased from 0 to 14.9% w/w (Nokhodchi et al 1996b), which also resulted in a marked increase in the tensile strength of the tablets. The increase in moisture content reduced the elastic recovery of the compacts because of greater tablet consolidation.

The influence of moisture content on the Heckel analysis, energy analysis and strain-rate sensitivity of hypromellose 2208 was also evaluated. An increase in moisture content from 0 to 14.9% w/w decreased the mean yield pressure, probably because of a plasticising effect of moisture that reduced the resistance of particles to deformation (Nokhodchi et al 1996a). The strain-rate sensitivity increased from 21.6 to 50.7% as the moisture content increased from 0 to 14.9% w/w, indicating that the plasticity of HPMC increased with an increase in moisture content (Nokhodchi et al 1996a). The distribution of externally adsorbed and normally condensed moisture may account for many of these observations (Malamataris & Karidas 1994). The compression characteristics of powdered HPMC polymers, namely particle packing and deformation, are related to differences in moisture distribution due to differences in particle size and, to some extent, in the methoxy/hydropropoxy substitution (Nokhodchi & Rubinstein 2001).

Gustafsson et al (1999) assessed the effects of this substitution on the particle characteristics and compaction behaviour of hypromellose obtained from two different suppliers. Low, medium and high substitution ratios were studied using Methocel K4M, E4M and F4M (hypromellose 2208, 2910 and 2906, respectively) and compared with Metolose 90 SH 4000, 60 SH 4000 and 65 SH 4000 (hypromellose 2208, 2910 and 2906, respectively), respectively. Differences in drug release from Methocel E4M matrices compared with the other two Methocel products were related to a lower powder surface area, differing particle morphology and lower fragmentation propensity (Gustafsson et al 1999). Additionally, its compacts were weaker and had different porosity and elastic recovery properties. There were no differences between the polymers in degree of disorder, as evaluated by solid-state NMR spectroscopy (Gustafsson et al 1999). The different behaviour of Methocel E4M could, however, be related to the overall higher total degree of substitution of this polymer and in particular the high content of hydrophobic methoxy groups, which may change the particulate and mechanical properties of the powder. The high content of methoxy groups might also decrease the development of inter- and intraparticulate hydrogen bonds during compaction. Rajabi-Siahboomi & Nokhodchi (1999) found that the tensile strength of tablets made from hypromellose was affected by the substitution level. Hypromellose 2906 produced tablets with higher tensile strength and lower mean pressure compared to hypromellose 2208 and 2910, indicating a greater compressibility of hypromellose 2906.

Influence of compression speed

Compression speed affects the tensile strength of hypromellose tablets (Nokhodchi et al 1996a–c). Increasing compression speed leads to a decrease in the tensile strength of hypromellose matrices and better quality matrices may be produced at low compression speeds (Nokhodchi et al 1996a–c). Huang et al (2003) suggested that the drug-release profiles may be made less sensitive to the effects of the manufacturing process, for example hardness, by introducing a small amount of intergranular hypromellose. This also reduced the effects of over-granulation (Huang et al 2003). The authors considered that water added during wet granulation has a significant impact on dissolution by allowing the production of a more dense compact, which reduces the permeability of the tablets.

Polymer factors affecting release from hypromellose matrices

Hypromellose polymer level

The initial 5 min of contact of the matrix with aqueous fluids is the most important time for the gel structure to form, after which, if the structure has not formed, the matrix may erode too quickly to provide controlled release (Campos-Aldrete & Villafuerte-Robles 1997; Kim & Fassihi 1997a, b; Nellore et al 1998). High polymer contents result in the formation of a strong gel; at low polymer levels the gel does not form quickly. As hypromellose content is increased, the resulting gelatinous

diffusion layer becomes stronger and more resistant to diffusion and erosion (Xu & Sunada 1995; Dabbagh et al 1996).

Once a particular polymer level is reached, the effects from characteristics such as viscosity, burst effect and particle size are less evident. A polymer content of 30–40% appears to be the level at which similar drug-release profiles are obtained from differing grades of hypromellose (hypromellose 2208, 2906, 2910) (Ford et al 1985a; Nellore et al 1998).

The drug-to-polymer ratio has been investigated since this has a major effect on the drug-release rate. Drug release deviated from linearity after 70% of the drug had been released. This indicated that the drug had been depleted from the matrix and the final drug release was dependent on attrition (Ford et al 1985a). When replacing hypromellose with lactose, higher drug-release rates were observed with lower hypromellose/lactose ratios (Gao et al 1995; Sung et al 1996). However, care must be taken when adding excipients to the dosage form. Misinterpretation can arise when adding an excipient that has an apparent effect on drug release but in fact may merely be changing the hypromellose:excipient ratio. It is known that on addition of any amount of diluent or filler, the drug-release rate will increase. The inclusion of Avicel increased the drug-release rate from matrices containing up to 30% hypromellose. The inclusion of Emcompress gave lower drug-release rates (Vargas & Ghaly 1999). Formulations containing 30 and 40% hypromellose gave similar release profiles irrespective of the diluent used (Vargas & Ghaly 1999).

Substitution-type effect on matrix

Drug-release rates are dependent on substitution type if the polymer level is kept low, such that polymer content is not the overriding factor controlling drug-release rate. The hydrophobic methoxy groups decrease hydrogen bonding within and between particles of close proximity, in particular in the dry regions closest to the tablet core where the level of water is lowest (Malamataris & Karidas 1994). This can retard the drug-release rate and was confirmed with NMR imaging when different substitution levels gave rise to different water mobilities, leading to differing drug-release characteristics (Rajabi-Siahboomi et al 1996). The amount of water that attaches to the polymer and the amount of tightly bound water depends on the degree of substitution (McCrystal et al 1999).

Hypromellose particle size

Hypromellose particle size and size distribution have significant effects on the hydration rate of the polymer and play an important role in moderating drug release from hypromellose matrices (Heng et al 2001). For hypromellose 2208, a threshold was identified at 113 μm. Values greater than this resulted in faster release rates (Heng et al 2001).

Particles of increased size require increased time for hydration to take place. Swelling hypromellose particles cannot effectively bind with adjacent ones so the polymer characteristics tend to lead to disintegration (Campas-Aldrete & Villafuerte-Robles 1997). The polymer particles tended to dissolve slowly and failed to provide adequate controlled release. The use of larger sized hypromellose K15M particles ($>355\,\mu$m) left a larger pore size that decreased the stability of the gel structure (Mitchell et al 1993b). However, hypromellose concentration in a matrix may override the effects of particle size and therefore any particle size-induced effects may only be observed at polymer levels of less than 10% (Campas-Aldrete & Villafuerte-Robles 1997). From a purely physical standpoint, decreasing particle size may achieve a matrix that has a higher tensile strength, since smaller particles allow greater packing density and contact points between particles, which allow better interparticle bonding (Velasco et al 1999; Nokhodchi & Rubinstein 2001).

Different hypromelloses may have different morphologies. More fibrous-shaped particles may lead to a decreased drug-release rate along with a reduced initial drug burst effect (Bonferoni et al 1996). Interlocking fibres therefore produce stronger matrices and perhaps alter the swelling characteristics of the matrix (Bonferoni et al 1996).

Manufacturing

Typically tablets are made by direct compression or compression of granules prepared by wet granulation. As discussed, particle size and size distribution are important and it might be considered prudent to control the particle size of the hypromellose undergoing compression. Granulating chlorpheniramine maleate with hypromellose may lead to the generation of particles of uniform size (Shah et al 1996). However, granulating with water can lead to irregular wetting with the production of lumps and unwetted areas. The use of a hydro-alcoholic granulation can overcome these problems because of an enhanced penetration of liquid into the powder bed, giving a uniform, non-lumpy final product (Shah et al 1996).

Non-polymer factors affecting release from hypromellose matrices

Drug factors

Drug solubility. Drug solubility is a very important factor which needs careful consideration on a case-by-case basis. Different drug characteristics, such as high or low solubility, affect gel characteristics and drug release (Conte & Maggi 1996; Gao et al 1996; Kim 1999; Reynolds et al 2002). High-solubility drugs can dissolve by diffusing through the gel matrices and this is considered to be the main pathway for their release. However, release also occurs through erosion of the gel matrix. It is said that highly soluble drugs also act as pore formers with the formation of micro-cavities and make the gel structure more porous and weaker, hence leading to increased drug-release rates (Yang & Fassihi 1997).

Poorly soluble drugs will be released predominantly by erosion of the gel matrix, giving rise to a dosage form that may release a later pulse of drug (Bettini et al 2001). Drug particle translocation has been observed whereby particles move through the gel layer with a spring-like action. This

is of particular interest at the end of the dissolution process, when the core is fully hydrated and the gel becomes fragile. This breakdown may explain the abrupt change in release rate towards the end of the drug-release curve (Bettini et al 2001).

Drug particle size. With highly soluble drugs, particle size is an important factor to consider. As the drug loading is increased, the drug-release rate increases due to greater channel formation in the swollen matrix. The channel size is dependent on drug particle size and leads to promotion of complete release (Kim & Fassihi 1997a; Kim 1999). With poorly soluble compounds, particle size affects drug release because erosion is the predominant release mechanism (Ford et al 1985a; Hogan 1989). However, the effect of drug particle size on drug release from hypromellose matrices was considered minimal and only apparent at lower hypromellose levels in the matrices, which would have inherent low tortuosity and high porosity characteristics (Ford et al 1985a; Hogan 1989; Mitchell et al 1993c; Velasco et al 1999).

Chirality

Hypromellose 2208 is a chiral excipient that Duddu et al (1993) investigated using propanolol hydrochloride, which is a racemic mixture. Hypromellose exhibited stereo-selective release of the *R* and *S* isomers of propanolol. A chiral interaction of hypromellose 2208 with *S* isomers of salbutamol and ketoprofen exists (Solinis et al 2002a, b). The mechanism for chiral interaction was not fully characterized and to enable easier understanding of the interaction, studies were performed in gels rather than tablets so that the erosion of the matrix did not confound any enantiomeric reaction (Solinis et al 2002a, b).

Lubricants

The inclusion of lubricants may affect tensile strength, friability and drug-release rates. This depends on the type of lubricant used, its quantity, the method of addition, the type of blender and the blending time (Ford et al 1985a; Lee et al 1999).

Tablet shape and modifications

Another factor affecting the drug-release rate from hypromellose matrices is the surface area-to-volume ratio. Tablet geometry or shape may affect drug release and in many cases the relationship between release rate and surface area is linear (Cobby et al 1974; Ford et al 1987; Reynolds et al 2002). A relationship can be established such that drug release can be predicted by using this surface area-to-volume ratio. It is possible to characterize drug-release profiles and optimize tablet shape, size and drug levels. Indications are that the optimum tablet shape is spherical (Ford et al 1987; Hogan 1989). Analysis of half tablets compared with whole tablets demonstrated that the increase in surface area led to increased drug dissolution rate (Skoug et al 1991). Small tablets required a higher polymer level to achieve the same drug-release profile when compared with larger tablets. The diffusion pathways are longer with larger tablets, which is why slower drug release is observed (Siepmann et al 1999a, b, 2000).

Many different types of novel-shaped dosage forms (doughnut-shaped tablets, perforated matrices, Geomatrix tablets, Smartrix tablets and bilayer caplets) have been developed and all use the basis of modifying surface area-to-volume ratios. Some examples follow.

Core in cup. Core-in-cup technology (Danckwerts 1994) involves an insoluble cup and soluble core that allow varying drug-release rates controlled by a matrix. The two parts are compressed together to form one unit. Polymer level, substitution and viscosity grade of hypromellose and surface area of one face of the tablet affect the release rate of the drug (Danckwerts 1994).

Geomatrix. Geomatrix tablet technology from Skypharma (Conte & Maggi 1996) uses a multilayer tablet design. The unit is effectively a two- or three-layer tablet that has a layer containing the drug. Release of the drug is controlled by a hydrophilic polymer matrix including hypromellose. Either or both faces of the core are covered by a barrier layer that does not contain the drug and may comprise permeable, semi-permeable or erodible polymers (Figure 7). Hypromellose is used in the core or barriers for its ability to swell and gel quickly and prevent further hydration of the barrier layer, which hinders water ingress and exposure of the tablet surface area for dissolution. Drug is released from the side walls of the tablet and from the faces if the barrier layer detaches (Conte & Maggi 1996).

Bilayer caplets. Bilayer caplets are used to deliver an immediate dose followed by a prolonged release of drug. Hypromellose is used in the prolonged-release layer because of its good, strong gel characteristics (Maggi et al 1999). A similar matrix containing a high level of polymer was resistant to the effects of mechanical shear

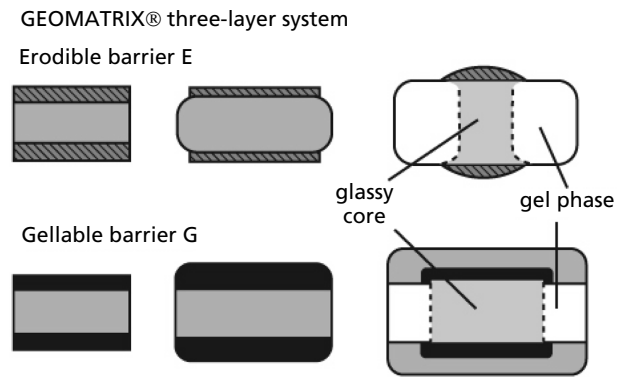

Figure 7 Swelling behaviour of the Geomatrix three-layer system with erodible or gellable types of barrier coatings. Reprinted from Biomaterials, Vol. 17, Conte and Maggi, Modulation of the dissolution profiles from Geomatrix® multilayer matrix tablets containing drugs of different solubility, pp 889–896, Copyright (1996), with permission from Elsevier.

when performing in-vitro dissolution testing in the presence of beads. This indicated that the dosage form would provide controlled release and be resistant to the shear generated in the GIT (Ohmori & Makino 2000).

Salting in and out

The ions of inorganic salts, which have a greater affinity for water, can remove water of hydration from a polymer, thereby dehydrating and 'salting out' the polymer (Heyman et al 1938; Lapidus & Lordi 1968). At low ionic strength the gel is unaffected, but intermediate ionic strength leads to a loss of gel integrity and disintegration of the matrix may be observed. Examination of the disintegrating particles confirmed that the particles formed a gel layer as they were released from the matrix, leading to retardation but not control of release (Lapidus & Lordi 1968).

Even the drug component itself can affect the gel structure by salting in or salting out the hypromellose 2208, leading to a potential weakening or strengthening of the gel structure (Mitchell et al 1993c; Hino & Ford 2001). Nicotinamide salts in hypromellose and increases its solubility. This was achieved by preventing the dehydration of hypromellose by hydrogen bonding to the hydrophilic groups of hypromellose and inhibiting the entanglement of polymer molecules (Hino & Ford 2001).

Electrolytes such as sodium chloride and potassium chloride may affect the drug-release rate. It is possible to alter the release of diclofenac sodium by the use of sodium chloride since drug release slowed in the presence of sodium chloride. The release was inversely proportional to salt content and sodium chloride had the greatest effect (Sheu et al 1992) because it salts out the diclofenac sodium as a result of the common ion effect, which contributes to a lower dissolution rate (Sheu et al 1992).

Matrices containing drug-release modifiers

Soluble and insoluble components. Replacing hypromellose with an insoluble excipient may increase the drug dissolution rate. However, such conclusions were only made when the hypromellose content was reduced to 50% (Lapidus & Lordi 1966, 1968). The presence of as little as 10% fibrous insoluble excipients may disturb the formation of the gel layer and prevent uniform swelling (Lapidus & Lordi 1968; Wan et al 1995; Bonferoni et al 1996; Zuleger & Lippold 2001; Williams et al 2002; Zuleger et al 2002).

Increased drug-release rate is observed with the addition of superdisintegrants, such as Explotab and Ac-Di-Sol. Rapid uptake of water occurs followed by swelling and wicking. The matrix is left highly porous and weak, giving rise to disintegration of the matrix (Lee et al 1999). Avicel, on the other hand, is not a superdisintegrant and has the effect of decreasing the drug-release rate and merely physically obstructing drug release (Xu & Sunada 1995; Lee et al 1999).

Buffers (pH and microenvironmental pH). Hypromellose is claimed to be stable over the pH range 3–11. However, pH changes may affect the ability of the polymer to swell. This applies to the external environment surrounding the tablet and gel as well as the microenvironment within the gel matrix (Perez-Marcos et al 1996). Katzhendler et al (2000) investigated the gel matrix microenvironment to determine its role in drug release. The gel matrix was unable to preserve a neutral environment inside the matrix and the pH observed was lower than with buffer ions in the surrounding media. It is likely that there was a pH gradient across the gel structure, with the outermost layer having a higher pH than the layer closer to the tablet core. Addition of sodium bicarbonate in the tablet, as a buffer, maintained a gel pH greater than 8, but without the buffer the internal matrix was essentially maintained at a similar pH to the surrounding media (Pillay & Fassihi 1999).

If an acidic drug is buffered to a pH above its pKa and is ionized, the drug may have a greater solubility, resulting in faster drug-release rates (Solinis et al 2002b). This emphasizes the importance of the state of the drug in the gel matrix and the potential use of pH modifiers to alter drug solubility. Such solubility factors may even cause the drug to precipitate, which could, potentially, lead to changes in the crystal structure and physicochemical characteristics of a drug. It should be apparent, therefore, that if a drug is included in the matrix in a soluble form, it may change to an insoluble form and interfere with the hypromellose matrix. Attempts should be made to ensure that the drug does not change to a less favourable form by introducing buffering agents to the matrix.

Acidification of the matrix core stabilizes the gel pH microenvironment such that a particular pH is maintained within the matrix core. This potentially stabilizes the drug-release profiles of drugs of pH-dependent solubility (Streubel et al 2000).

Surfactants. The presence of surfactants can enhance the drug-release rate by controlling wettability. An interaction of propranolol hydrochloride with sodium dodecyl sulfate (SDS) formed propanolol dodecyl sulfate within hypromellose matrices. This complex is poorly soluble and reduced the drug-dissolution rate in comparison with cetrimide, which did not (Ford et al 1991).

Other polymers. Carbopol is a commonly used polymer in matrices and the performance of carbopol 940 is variable with fluctuations of release. However, with the incorporation of hypromellose, a polymer–polymer interaction between the two different polymers, through the carboxyl group of carbopol and the hydroxyl group of hypromellose, produces an interaction that leads to stable release and the ability to decrease the size and weight of matrix tablets if used independently of each other (Samani et al 2003). This was not always the case as addition of mixtures of different polymers, such as guar gum, gum arabic, carageenan or corn starch, to hypromellose did not provide an extended release because of rapid partial disintegration of the dosage form and/or slower swelling of these polymers (Streubel et al 2003).

Ion-exchange resins have been used successfully in matrices. They are cross-linked water-insoluble polymers with ionizable functional groups. When a drug–resin

complex is formed, a counter ion must be found to replace the drug ion from the resin within the gel matrix. Ion-exchange resins have been used to modify the release of oppositely charged drugs. Drug release from hypromellose matrix tablets containing a drug–resin complex was slower (Sriwongjanya & Bodmeier 1998). The drug–resin complex forms in the gel layer in situ and a fast-forming gel layer is essential.

Mathematical models of matrix performance and drug release

It is not the aim of this paper to review mathematical models in depth. Recent work by Siepmann and various colleagues provides a wealth of information on such models. A large number of mathematical models has been developed and used to apply an algorithm that predicts the drug-release profile produced from a particular formulation (Siepmann & Peppas 2001). This is the key to decreasing the development time of a dosage form, decreasing cost and making the dosage form cheaper and more quickly available to the marketplace (Gao et al 1995).

The basis of the mathematical models started with Higuchi (1963), who derived a simple relationship between the release rate of the drug and the square root of time. Lapidus & Lordi (1966, 1968) found this equation to be highly applicable to hypromellose and modified it to describe the release of soluble drugs from a matrix system. These complex mathematical interpretations and relationships are being continually developed (Ford et al 1985a) and are now able to give an insight into the release mechanism of hypromellose matrices with different drugs. They can be used to predict the desirable tablet shape and dimensions of drug delivery dosage forms (Siepmann et al 1999a, b). Continued development and validation of these models is making good progress in providing predictability for polymers, drug release and tablet compositions (Siepmann & Peppas 2000; Siepmann et al 2002; Kosmidis et al 2003), which may then be used to optimize pharmaceutical dosage forms.

There are always limitations to models, for example the Higuchi model can only process the data in up to 60% of the release curve reliably. Continual research has led to the development of the other models, such as the 'power' law, which can be used to model the entire release curve of drug release and as these models develop they will be invaluable to researchers (Rinaki et al 2003).

Novel matrix formulations

Floating matrices

Generally the higher viscosity hypromelloses perform better in floating dosage forms than the lower viscosity analogues; different substitution grades of similar viscosity, e.g. Methocel K4M and E4M show little difference in floating properties. Hydrophobic additives, such as magnesium stearate, significantly improve floating capacity (Li et al 2002). Methocel K4M (Hypromellose 2208) is a good polymer for floating dosage forms. However, a high level of drug loading affects its capability to float and the drug:polymer ratio is critical. Crushing strength has a significant effect on buoyancy (Nur & Zhang 2000) and excessively hard tablets adversely affect the ability to float. An important factor is to achieve a density of less than 1 (Baumgartner et al 2000). Mixtures of different polymers with hypromellose, such as carbopol 934, have been used successfully to produce good floating delivery systems (Li et al 2003; Streubel et al 2003). Incorporation of highly porous foam powders also provides successful floating matrices (Streubel et al 2003).

Mucoadhesive formulations

Hypromellose 2208 (hypromellose K4M) demonstrates mucoadhesive properties showing maximum bioadhesion between pH 5 and 6 (Chary et al 1999). Other polymers that have been considered include lower viscosity grades of hypromellose, guar gum, polyvinylpyrrolidone, carbopol 934 and sodium carboxymethylcellulose, but Methocel K4M demonstrated the best mucoadhesive properties (Chary et al 1999). Adhesion was observed in the duodenum, jejunum and ileum and in these cases the progression of the dosage form through the GIT was retarded.

Drug release from these polymers is characteristically dependent on viscosity and the concentration of polymer used. Tablets of different hardness demonstrated no difference in drug release (Huber & Christenson 1968) and, more interestingly, the stir speed of dissolution equipment had no effect on drug-release rate (Nur & Zhang 2000).

Stability of hypromellose formulations

Hypromellose is stable to high-intensity UV light exposure, unlike other polymers such as polyethylene oxide, making it a good polymer of choice for incorporation of photo-labile drugs (Maggi et al 2003). Use of ion-exchange resins (Sriwongjanya & Bodmeier 1998) is an area of interest for potential controlled release with a potential for stability enhancement of unstable drugs in the GIT.

Dissolution testing of hypromellose matrices

Apparatus type

Many different types of dissolution apparatus are available; the choice of apparatus should be based on the knowledge of the formulation design. It is well known that compendial dissolution methods do not truly reflect the in-vivo environment in terms of gastrointestinal fluids, mechanical propulsion forces, grinding, retropulsion and gastrointestinal motility (Yang & Fassihi 1997). Factors such as sticking to paddles and clogging of meshes adversely affect results and although some degree of flexibility is observed with USP 3 and USP 4 apparatus types, these still do not represent the true in-vivo environment. One way forward may be novel technology such as the TNO Gastro-Intestinal Model, which is able to simulate body temperature, pH, salivary, gastric and intestinal mixing, transport by peristaltic movements, gastrointestinal secretion, and absorption of water (TNO Nutrition and Food Research).

Trapped air

During the compression process, air is trapped between particles and interparticular spaces are presented as air spaces. When the dosage form is placed in aqueous media, it swells and as a result air becomes trapped in the hydrated hypromellose matrix (Fyfe & Blazek 1998). During dissolution studies, air bubbles may appear attached to the tablet surface, making the dosage form more buoyant. This is a problem in small lightweight dosage forms, which may move about in a non-reproducible manner in the hydrodynamic flow and give erroneous results. The release of a bubble may disrupt the gel structure itself and alter the drug-release profile, leading to incorrect reporting of results (Melia et al 1993).

Conclusions

To date, many different techniques have been used to investigate the mechanism of drug release from hypromellose matrices. Attempts to characterize this polymer over the last four decades have multiplied, yet many questions remain unanswered. As technology evolves, there will be further methods that can characterize hypromellose in a non-invasive manner. Hypromellose is growing ever more popular as the controlled release polymer of choice and microenvironmental changes in the hypromellose gels must be fully understood to characterize how they affect drug release.

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