The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems

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A R T I C L E   I N F O

A B S T R A C T

Formulations that are able to control the release of drug have become an integral part of the pharmaceutical industry. In particular oral drug delivery has been the focus of pharmaceutical research for many years. This type of drug delivery has been at the centre of research due to its many benefits over conventional dosage. The focus of this review is on matrix tablets due to their widely use and simplicity of the formulation. This includes the discussion of various types of matrix tablets and factors affecting the drug release from these formulations. The mechanism of drug release from HPMC matrices is also discussed.

Oral controlled release systems

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes (Chen *et al.* 2010, Gupta and Robinson 1992, Maderuelo *et al.* 2011, Tongwen and Binglin 1998). A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time (Chen *et al.* 2010, Nair *et al.* 2010, Rajput *et al.* 2010). The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels (Chen *et al.* 2010, Grundy and Foster 1996, Lordi 1986). Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms (Levina and Rajabi-Siahboomi 2004).

Controlled release systems can be influenced by physiological conditions such as motility, ions, pH and enzymes (Abrahamsson *et al.* 2004, Singh *et al.* 1968).

Hydrophillic matrix systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective (Prajapati and Patel 2010, The Dow Chemical Company 2000). The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion (Colombo 1993, Ishikawa *et al.* 2000, Siepmann and Peppas 2001a, Tiwari and Rajabi-Siahboomi 2008).

Advantages of oral controlled release formulations

This type of drug delivery has been at the centre of research due to its many benefits over conventional dosage forms, some of which are as follows:

- The frequency of dosing is reduced due to drug being released over a longer period of time unlike conventional tablets (Kojima *et al.* 2008). This is extremely valuable for patients with chronic illnesses which require the plasma concentrations of a drug to be within its therapeutic range to avoid breakthrough symptoms, for example, overnight management of pain in terminally ill patients (Aulton 2008).

- The reduction or avoidance of side effects due to high plasma drug concentrations or 'dose dumping' (Maderuelo *et al.* 2011).

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- Improvement in patient compliance due to reduced dosing (Maderuelo *et al.* 2011).
- Better control of therapeutic drug concentration;
- Cost effective manufacturing (Maderuelo *et al.* 2011) as the amount of tablets needed per patient would be reduced compared to its conventional form.

Disadvantages of oral controlled release formulations

Oral controlled release formulations like other formulations have several disadvantages. These include (DiMatteo and DiNicola 1982, Jayanthi *et al.* 2011, Kayser *et al.* 2005, Sansom 1999):

- *Development costs:* Expensive specialised equipment and inert ingredients may be required for some controlled release formulations.
- *Release rate:* The drug release rate can be altered by food and gastric transit time; as a result differences may arise in the release rate between doses.
- *Can not crush or chew products*: Controlled release products should not be crushed or chewed as it can lead to loss of the 'slow release' characteristics as well as toxicity.

The effect of drug properties in developing oral controlled release

Alongside the benefits and disadvantaged, sustained release dosage forms have also posed many challenges for pharmaceutical technologists (Khan 1996). In order for drug release to be manipulated and for the resulting product to possess the above mentioned characteristics there are many factors that need to be taken into consideration when designing such formulations. Some of these are as follows:

- Different drug solubility's need to be considered (Sudha *et al.* 2010) as highly soluble drugs will dissolve immediately after administration (Siahi *et al.* 2005). Reduced drug solubility increases the tendency of the tablet to erode due to particle displacement (Bettini *et al.* 2001).
- The drug should have a short half-life (Aulton 2008). If a drug has a long half-life then there is a risk of

accumulation as it will be eliminated at a slower rate compared to its absorption (Kim 2000).
- A drug that is tested *in-vitro* needs to be able to provide similar release characteristics once administered and is under pathophysiological or *in-vivo* conditions (Khan 1996, Diakidoua *et al.* 2009). A direct correlation of *in-vitro* data with *in-vivo* release is not possible without thorough and careful analysis (Khan 1996). For example, there is a difference in the availability of water in different parts of the gastrointestinal tract and such factors need to be considered when designing tablets for extended release (Khan 1996, Kojima *et al.* 2008).
- The dissolution characteristics should allow for drug to be released in a controlled manner, highlighting the importance for the correct selection of polymers according to their physical, mechanical and pharmacokinetic properties (Kim 2000).

Different types of sustained release systems

There are several types of sustained release systems that are designed and categorised according to the mechanism they employ. These include diffusion controlled, dissolution controlled, erosion controlled, ion exchange controlled and transport control also known as osmotic pump systems (Aulton 2008).

Matrix systems

Diffusion controlled systems also known as matrix systems are very popular for sustained release formulations (Colombo *et al.* 2000). The can be divided up into different types of mechanisms by which they prolong drug release, these includes reservoir matrix systems, monolithic matrix systems and osmotic pump systems.

Reservoir matrix systems

This system involves a membrane which controls the release of drugs from the matrix system. The drug will eventually diffuse through the membrane and its release is kept constant by the diffusion distance that the drug particles have to cover (Fig. 1).
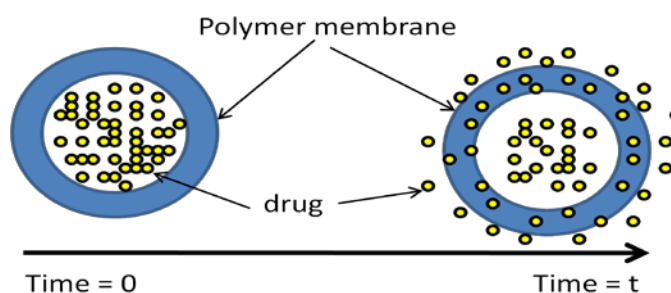

Fig. 1. Schematic representation of Reservoir matrix systems (The figure is adopted from Dash and Cudworth 1998).

Osmotic pump systems

Osmotic systems operate on osmotic pressure. They contain a core tablet that is surrounded by a semipermeable membrane coating which has an orifice. The core tablet has two layers to it, one containing the active ingredient/drug known as the active layer and the second containing the osmotic agent which is also known as the push layer (Allen 2005). Water enters the tablet through the semipermeable membrane causing the drug to dissolve and suspend. The increase in osmotic pressure causes the dissolved/suspended drug to be pumped out of the delivery orifice (Allen 2005). The rate of drug delivery can be changed by altering the size of the delivery orifice and the thickness of the semipermeable membrane (Allen 2005).

Monolithic matrix systems

These systems involve drug to be encapsulated or dispersed in a matrix (Kim 2000). These systems can be employed by forming hydrophobic matrices (Varshosaz *et al.* 2007) and/or hydrophilic matrices to allow for control or prediction of drug release (Colombo 1993, Nerurker *et al.* 2005, Thawatchai 2008). They can be divided into soluble/hydrophilic matrix systems which swell on hydration and dissolve to release drug and insoluble/hydrophobic matrix systems which release drug after being dissolved by a solvent (Fig. 2).

Hydrophobic matrix systems are formulated by waxes mainly and can be suitable for drugs which have a high solubility (Tiwari *et al.* 2003). Wax based matrices have been investigated to ascertain the factors that would affect the release of drug (Sudha *et al.* 2010). Drug release has been successfully modulated in hydrophobic matrices however, in a study conducted by Sudha and co-workers (2010) it was concluded that matrices which are based on waxes can modify release rate by increasing the amount of drug or wax concentration, as well as incorporating hydrophilic polymers which would enhance the release. Even though the hydrophobic matrix was able to modulate drug release, the processes that had to be carried out such as hot fusion and thermal treatment highlighted the length of the process that would be required to form such tablets. This can potentially be a deterrent for manufacturing companies who would prefer a more economical method of producing sustained release formulations.

Hydrophilic matrix systems tend to be more popular in tablet manufacture for controlled release drug delivery systems due to their low manufacturing cost (Tiwari 2003). On contact with water a hydrophilic matrix increases in size due to the entry of the solvent. This then allows the polymer to swell up forming a barrier to drug release. The drug particles would then move through this gel layer via diffusion or erosion of the gel eventually allowing drug to be released (Maderuelo *et al.* 2011). There has been a lot of research into the mechanisms of drug release from hydrophilic matrices and the critical factors that influence the release rate (Colombo *et al.* 2000, Maggi *et al.* 2002, Siahi 2005, Conti *et al.* 2007, Thawatchai 2008, Maderuelo *et al.* 2011, Siahi-Shadbad *et al.* 2011).

These swellable matrices have more than one 'front' as a part of its release mechanism (Colombo *et al.* 2000). This has been shown in Fig. 3.
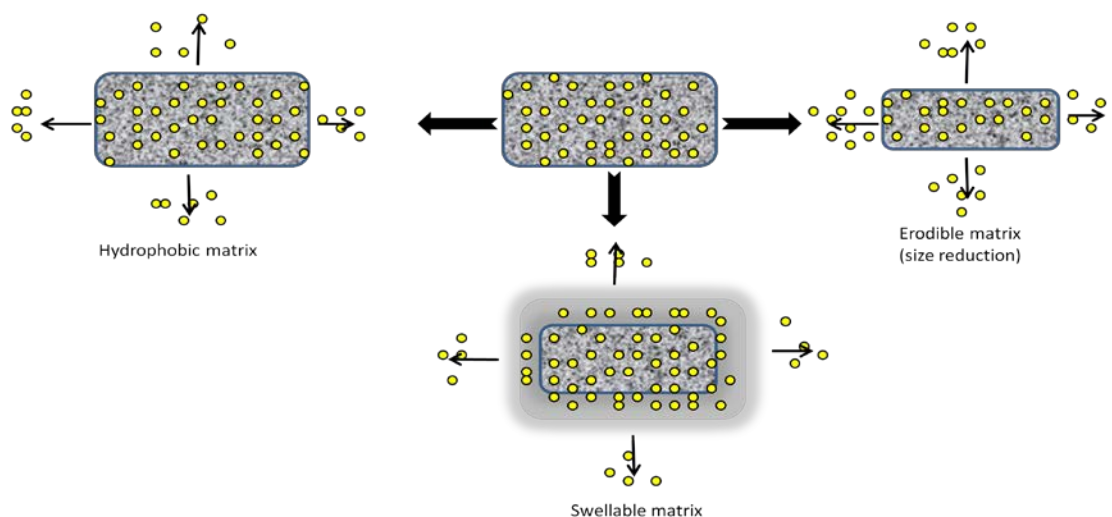

Fig. 2. Schematic representation of drug release from different types of matrix tablets.
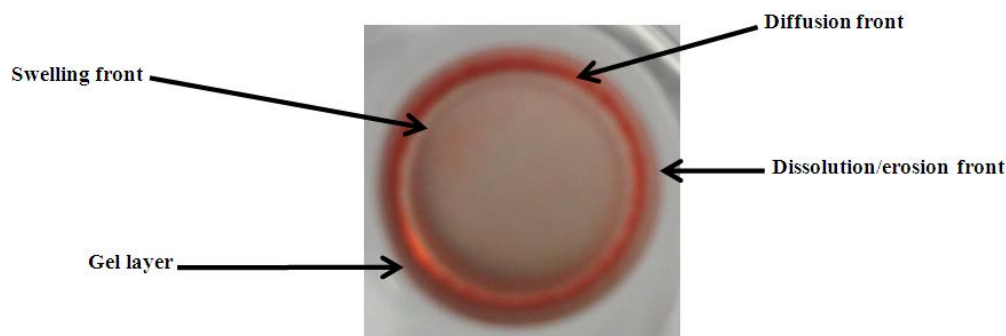
Fig. 3. Different front within a matrix tablet containing colouring agent to distinguish different swelling fronts.

Table 1. Examples of a few polymers used in formulation of controlled release dosage forms

Hydrophilic Polymers	Methylcellulose, Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Ethylhydroxyethylcellulose (E-HEC), Sodium-carboxymethylcellulose (Na-CMC)
Non-cellulosic	Sodium alginate, Xanthan gum, Carrageenan, Chitosan, Guar gum, Pectin, Polyethylene oxide
Hydrophobic Polymers	Ethylcellulose, Hypromellose acetate succinate, cellulose acetate, cellulose acetate propionate

The area of dissolved drug and un-dissolved drug are separated by two types of "fronts" from the swollen gel region. They have a diffusion front which is located in between the swelling and erosion front (Colombo *et al.* 2000, Maderuelo *et al.* 2011). Drug release can occur by many mechanisms such as erosion, diffusion, polymer relaxation or a combination. Modulation of drug release from geomatrix multi-layered tablets was proposed by Conti and Maggi (1996) and they found that a swellable barrier around an active core provides greater modulation for soluble drugs.

Polymers in sustained release formulations

Polymers are chains of covalently bound monomers. They are used throughout the pharmaceutical industry and in relation to oral drug delivery systems they are used as carriers for the drug (Colombo *et al.* 2000). Polymers are used as a backbone in conventional and controlled release formulations (Kim 2000). For sustained release formulations the polymers need to have certain characteristics to control and maintain the rigidity of the matrix over a prolonged period (Kim 2000). There are a large number of polymers that are used in sustained release drug delivery (Table 1) (Maderuelo *et al.* 2011):

For the purpose of this study, the polymers that will be discussed are hydroxypropyl- methylcellulose, sodium carboxymethylcellulose and sodium alginate.

Hydroxypropylmethyl cellulose (HPMC)

HPMC is a non-ionic derivative of cellulose ether (Kamel *et al.* 2008), it is stable over pH range 3.0-11

(Lee *et al.* 2005). Hydroxypropylmethlcellulose (HPMC) is a semi-synthetic polymer (Colombo 1993, Ferrero-Rodriquez *et al.* 2000, Siepmann and Peppas 2001a). It is used as first choice for the formulation of hydrophilic matrix systems as it provides a robust mechanism for controlled release of drugs and choice of viscosity grades. Its non ionic nature minimises interaction problems when used in acidic, basic or electrolytic systems and provides reproducible release profiles. It is also cost effective (Bettini *et al.* 1995, Colorcon 2005, Conti *et al.* 2007). Matrices containing HPMC are not affected by the pH of fluid (Conti *et al.* 2007). Nokhodchi *et al.* (1995) found that the best grades to use for sustained release formulations are K4M and K100M due to their high tensile strength. When hydrated the polymer chains disentangle from the matrix (Kamel *et al.* 2008). HPMC matrix systems are classed as swelling controlled systems and are controlled by the rate of penetration of media and erosion of the matrix (Tahara *et al.* 1995). In hydrophilic polymers the rate of swelling determines the presence of different fronts within the matrix and when the movement of these front is synchronised then the drug release rate is constant (Colombo 1993).

HPMC is a mixture of alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups (Fig. 4). The rate of hydration of HPMC depends on the nature of the substituent's that form the polymer e.g. molecular structure, degree of substitution (Alderman 1984). The percentage of methoxyl and hydroxypropoxyl for different chemistry of HPMC are listed in Table 2.
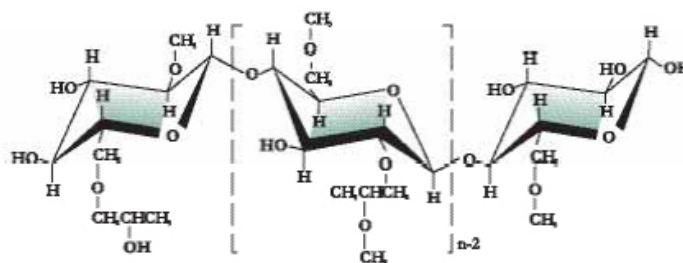
Fig. 4. The structure of hydroxypropyl methylcellulose (taken from The Dow Chemical Company 2000).

There are also different viscosity grades of HPMC available. And an example is shown in Table 2 for K chemistry. The initial letter identifies the chemistry of the type of cellulose ether; 'K' identifies different HPMC products. METHOCEL K is one of the most widely used for controlled release drug formulations (The Dow Chemical Company 2000). The number that follows the initial letter identifies the viscosity grade in millipascal-seconds (m.Pa.s) for the product measured in 2% aqueous solution at 20°C. Millipascal-second is equivalent to centipoises (cPs). The letter followed by the number identifies the viscosity. The letter 'M' suggests the value is multiplied by 1000 and the abbreviation 'LV' represents special low viscosity products. The abbreviation 'CR' denotes controlled release grades (The Dow Chemical Company 2000).

All these have been summarized in Fig. 5. Many studies have demonstrated the drug release profile from a hydrophilic matrix tablet is influenced by the viscosity of the gel layer formed by HPMC (Alderman 1984, Colombo 1993, Lee 1985).

Table 2. Various grades of HPMC (taken from The Dow Chemical Company 2000)

HPMC type*	Methoxy (%)	Hydroxypropoxy	other names
K	19-24	4-12	Hypromelose 2208
E	28-30	7-12	Hypromelose 2910
F	27-30	4-7.5	Hypromelose 2906

*Different viscosity grades are available on the market (e.g. for K series HPMC K100LV, HPMC K4M, HPMC K15M and HPMCK100M).
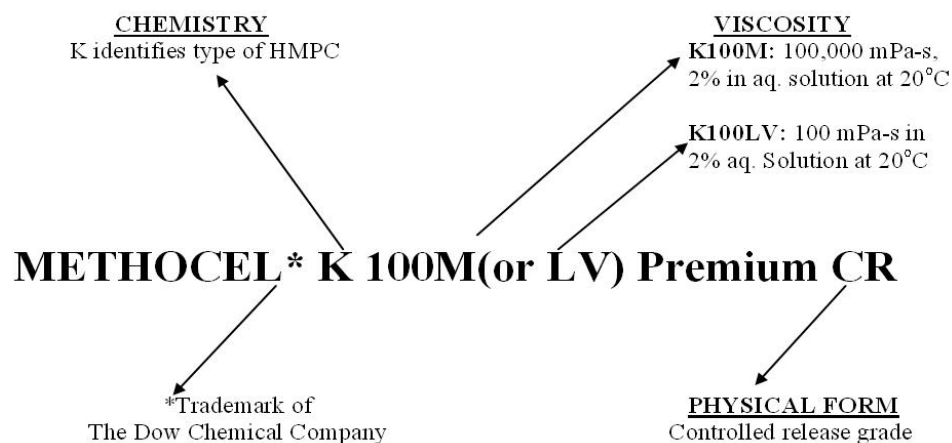

Fig. 5. Summary of nomenclature for METHOCEL K cellulose ether (adapted from The Dow Chemical Company 2000).

Compared to other swellable polymers used to prolong drug release, HPMC is said to have been the most widely used due to its rapid hydration, good compression and gelling characteristics. In addition it has very low toxicity and is generally widely available for use (Alderman 1984, Colombo 1993, Lee 1985, Wan *et al.* 1995). Hence it has been a material of great importance when used as a carrier in drug release systems.

Mechanism of drug release

Alderman (1984) describes a gel layer being formed around a tablet (Fig. 6); this is because when hydrophilic matrices are immersed in aqueous media i.e. Gastro-intestinal fluids, the polymer hydrates and swells resulting in an increase in size. After some time the matrix dissolves or erodes allowing drug release (Lee 1980, Peppas *et al.* 1980). The soluble portion of the drug is released by the process of diffusion through the gel layer while the insoluble portion is released through tablet erosion (Johnson *et al.* 1993, Lindner and Lippold 1995, Skoug *et al.* 1993, The Dow Chemical Company 2000). Studies have shown that drug release from swellable hydrophilic matrices is dependent on the thickness of the hydrated layer that is formed during polymer hydration. The degree of swelling determines the rate of drug release; the thicker the gel layer, the slower the rate of drug release (Johnson *et al.* 1993, Skoug *et al.* 1993, Sujja-areevath *et al.* 1998).

Physiological factors of the gastro-intestinal (GI) tract can affect the release of drugs. This includes pH, GI transit time, intestinal motility, and GI contents, for example fed and fasted states (Charman *et al.* 1997, Grundy and Foster 1996, Streubel *et al.* 2000).

Factors affecting drug release

Effect of viscosity

Viscosity is defined as a measure of resistance of a fluid to flow. In relation to polymer solutions, viscosity is dependent upon the molecular weight of the polymer (Indian Academy of Sciences 2010). Viscosity of polymer solutions is the result of polymer chain hydration through hydrogen bonding of oxygen atoms in ether linkages, causing them to extend and form relatively open random coils. The hydrated coils continue to hydrogen bond to additional water molecules causing entrapment within the coils (The Dow Chemical Company 2000). Viscosity can therefore affect the extent of drug release from hydrophilic matrices.
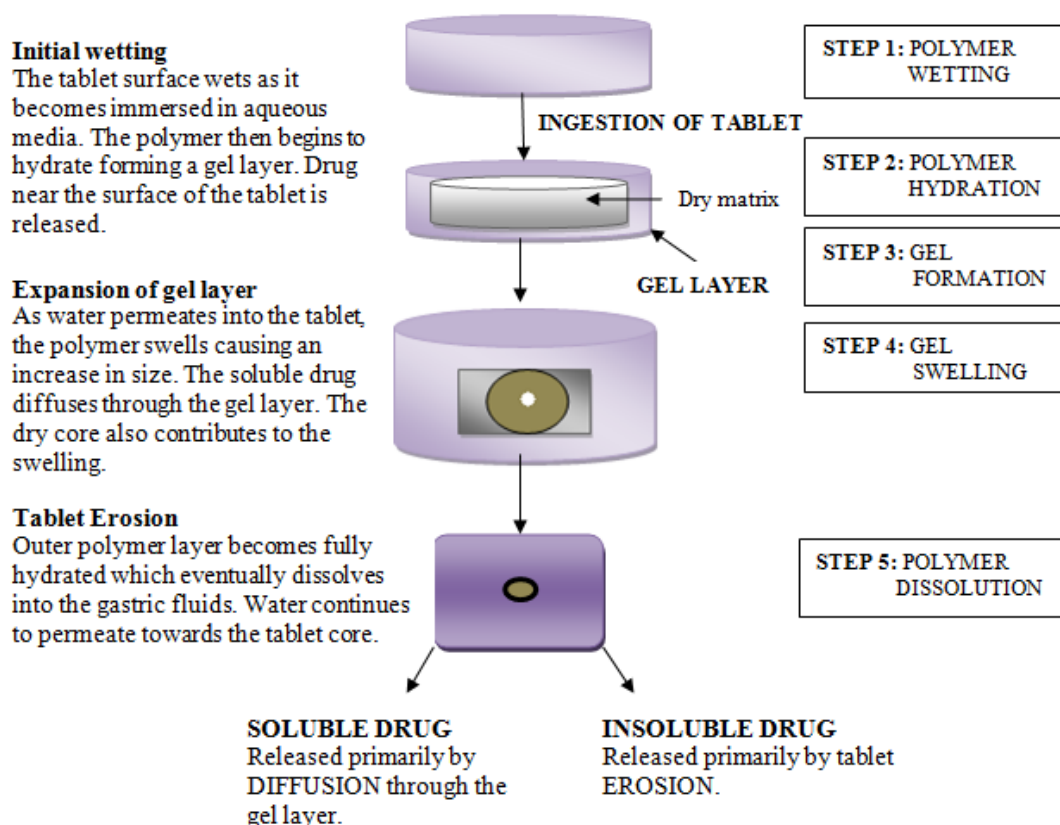
Initial wetting
The tablet surface wets as it becomes immersed in aqueous media. The polymer then begins to hydrate forming a gel layer. Drug near the surface of the tablet is released.

INGESTION OF TABLET

Dry matrix

GEL LAYER

STEP 1: POLYMER WETTING

STEP 2: POLYMER HYDRATION

STEP 3: GEL FORMATION

STEP 4: GEL SWELLING

Expansion of gel layer
As water permeates into the tablet, the polymer swells causing an increase in size. The soluble drug diffuses through the gel layer. The dry core also contributes to the swelling.

Tablet Erosion
Outer polymer layer becomes fully hydrated which eventually dissolves into the gastric fluids. Water continues to permeate towards the tablet core.

STEP 5: POLYMER DISSOLUTION

SOLUBLE DRUG
Released primarily by DIFFUSION through the gel layer.

INSOLUBLE DRUG
Released primarily by tablet EROSION.

Fig. 6. Mechanism of drug release from a hydrophilic matrix tablet (adapted from The Dow Chemical Company 2000).

Rahman *et al.* (2011) explored viscosity grades of HPMC matrix systems as oral controlled release drug delivery systems using a non-steroidal anti-inflammatory drug, diclofenac sodium (Fig. 7). All viscosities of HPMC were used which included K100M, K15M, K4M and K100LV. The results demonstrated significant differences among the drug release profile from different matrices. The drug release from the higher viscosity grade K100M was slower compared to the lower viscosity grade K100LV (Fig. 7). As the release of diclofenac sodium from the HPMC K100M matrix was prolonged, it was able to avoid gastro-intestinal adverse effects. The release rate was considerably dependent on the viscosity grade of HPMC as it showed a statistically significant increase in drug release with low viscosity HPMC ($P<0.05$).
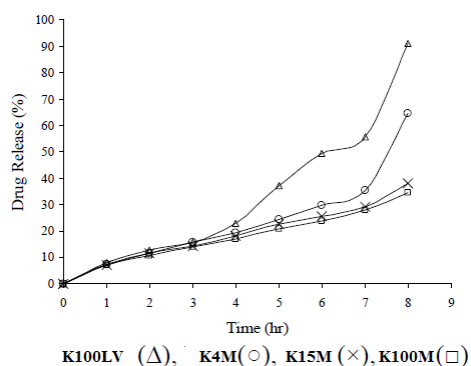

K100LV ($\triangle$), **K4M** ($\bigcirc$), **K15M** ($\times$), **K100M** ($\square$)

Fig. 7. A zero order plot showing the release kinetics of diclofenac sodium matrix tablets (taken from Rahman *et al.* 2011).

It can be concluded the higher viscosity grade of HPMC (K100M) can strengthen the gel layer and retard the penetration of water into the dry matrix core. This results in decreased release of water soluble and water insoluble drugs (Alderman 1984).

Effect of pH

The gastro-intestinal (GI) pH is one of the major properties of GI fluids and varies greatly along the digestive tract under fed and fasted conditions (Charman *et al.* 1997). It has an influence on the dynamics of HPMC hydrophilic matrix systems and can affect the gel layer formation (Tritt-Goc *et al.* 2005). Due to its non ionic nature, the viscosities of HPMC polymers are generally stable over a wide pH range of 3-11. This means if drug solubility is pH dependent, the drug release from the HPMC matrix will also be pH

dependent (Asare-Addo *et al.* 2011). The transit time explains the time taken for food to move through the different segments of the GI tract (Table 3).

Table 3. Transit time and pH values used to mimic the GI tract (taken from Asare-Addo *et al.* 2011)

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

Asare-Addo *et al.* 2011 explored the effects of pH on theophylline release from HPMC matrix tablets. The results indicated higher drug release from low viscosity HPMC in acidic pH 1.2 which continued to decrease as the pH increased to alkaline (Fig. 8).
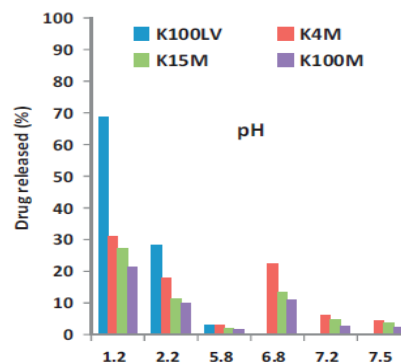

Fig. 8. A graph showing the drug release contribution from matrices made from different HPMC grades in pH media (taken from Asare-Addo *et al.* 2011).

In addition a study carried out by Tritt-Goc and Kowalczuk (2005) investigated the effects of pH and molecular mass on the hydration of HPMC. The study used magnetic resonance imaging (MRI) to generate images of HPMC swelling at different times. Fig. 9 shows the images of HPMC grades in acidic conditions. It shows the growth of the gel layer with time hence an increase in the diameter of the polymer and a reduction of the dry core. This study therefore supports the fact that drug release is higher in acidic conditions (i.e. stomach) for low viscosity HPMC as the gel layer is thinner thus allowing penetration of water.
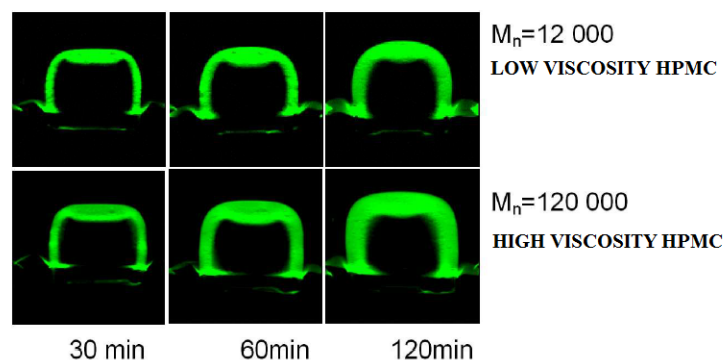
Fig. 9. Atypical two-dimensional MR images of swollen HPMC tablets after different times of swelling (pH = 2) (taken from Tritt-Goc and Kowalczuk 2005).

Effect of ionic strength

Ionic strength is also a major property of GI fluids and can affect the rate of drug release from HPMC matrices (Asare-Addo *et al.* 2011, Charman *et al.* 1997). In fasted conditions the ionic strength is approximately 0.11 M, however variability can be expected in the fed state depending on food composition. The ionic concentration is maintained at a constant level in the jejunum due to water and ion secretion and the remainder of the intestinal tract is estimated to be approximately 0.14 M in fasted conditions (Asare-Addo *et al.* 2011, Bonferoni *et al.* 1995, Lindhal *et al.* 1997). Generally the ionic concentration strength of the GI tract under both fed and fasted states is a range of 0-0.4 M (Johnson *et al.* 1993).

A study by Asare-Addo *et al.* (2011) investigated the effects of ionic strength on theophylline release from HPMC matrix tablets. It was observed that as the ionic strength increased, the amount of theophylline released also increased. The ionic concentration strengths mimicked the potential effects of food, 0.2 M: low content of food and 0.4 M: high content of food. The results indicated ionic concentration had a significant effect on the release pattern of K100LV matrices (Fig. 10). K100M matrices had the lowest drug release rate and produced a strong gel layer suggesting high viscosity grades are the best candidates for producing controlled release profiles that are less affected by food.

Sodium carboxymethyl cellulose (NaCMC)

This is a polyelectrolyte ionic cellulose derivative which is sensitive to changes in pH (Rimmer 2005). On hydration, polymer chains of NaCMC sell and untangle forming a viscous gel layer on the surface (Saeedi *et al.* 2009). The influence of NaCMC on drug release has been studied by many people (Bonferoni *et al.* 1995, Conti *et al.* 2007, Mohammadi *et al.* 2009, Saeedi *et al.* 2009). Erosion of the gel has been found to be one of main mechanisms by which this polymer releases drug (Bonferoni *et al.* 1995).
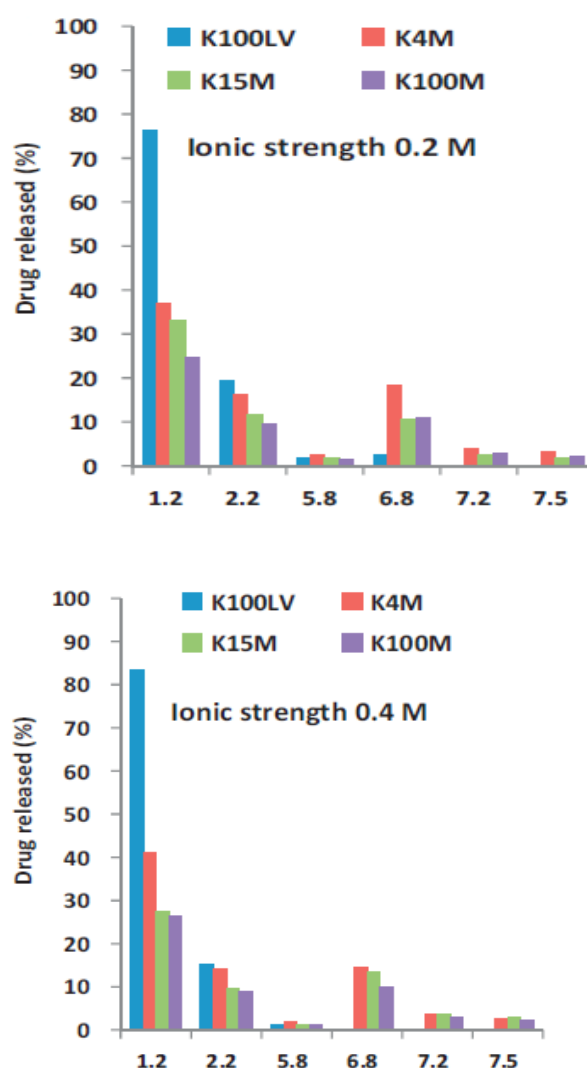

Fig. 10. Graph showing the drug release contribution from matrices made from different HPMC grades in ionic strength of 0.2 M and 0.4 M (taken from Asare-Addo *et al.* 2011).

Alginate

Alginates are found in brown marine algae and are natural polymers that are used in various areas such as the food industry used them as thickeners and in the pharmaceutical industry they are used in tablet manufacture as binders and tablet disintegration. Alginates have been used controlled release formulations due its ability to form a gel upon hydration. Liew and co-workers (2006) evaluated sodium alginate (NaAlg) as a drug release modifier in matrix tablets by using 17 different grades with differing particle size, viscosities and chemical compositions. They concluded that sodium alginate has a unique feature which enables gel-formation in acidic media as well as neutral media and these features need to be utilised when designing a controlled release formulation. A study conducted by Giunchedi and co-workers (2000) focused on evaluating alginate compressed matrices as prolonged release systems. They found that sodium alginate (NaAlg) can be used successfully as a drug release modifier in matrix tablets alongside another polymer. In all studies mentioned, the contribution of a cation (mainly calcium) has also given varying results which suggests that this interaction is a vital determinant of drug release.

Effect of cations

Polyvalent cations such as Al^{3+}, Ca^{2+}, Zn^{2+} and Mg^{2+} have been used to form cross-links with alginate molecules (Al-Musa *et al.* 1999, Nokhodchi and Tailor 2004). The presence of cations within a matrix

containing alginate allows for bridges to be formed between the anionic polymer chains (Braccini 1999, Ching *et al.* 2008) forming a network known as a hydrogel. The link can also be described as the 'egg-box model' (Fig. 11), describing the bonding between alginate and a divalent cations (such as Ca^{2+} and Zn^{2+}) in a two dimensional manner (Grant *et al.* 1973).
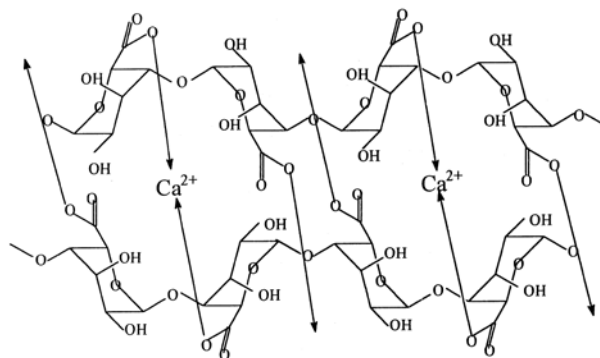

Fig. 11. Egg box model of calcium and alginate in a two dimesional planar manner network (Al-Musa *et al.* 1999).

Aluminium ions on the other hand (Fig. 12) would have a different interaction with alginate molecules due them having an extra valence available for bonding (Al-Musa *et al.* 1999).
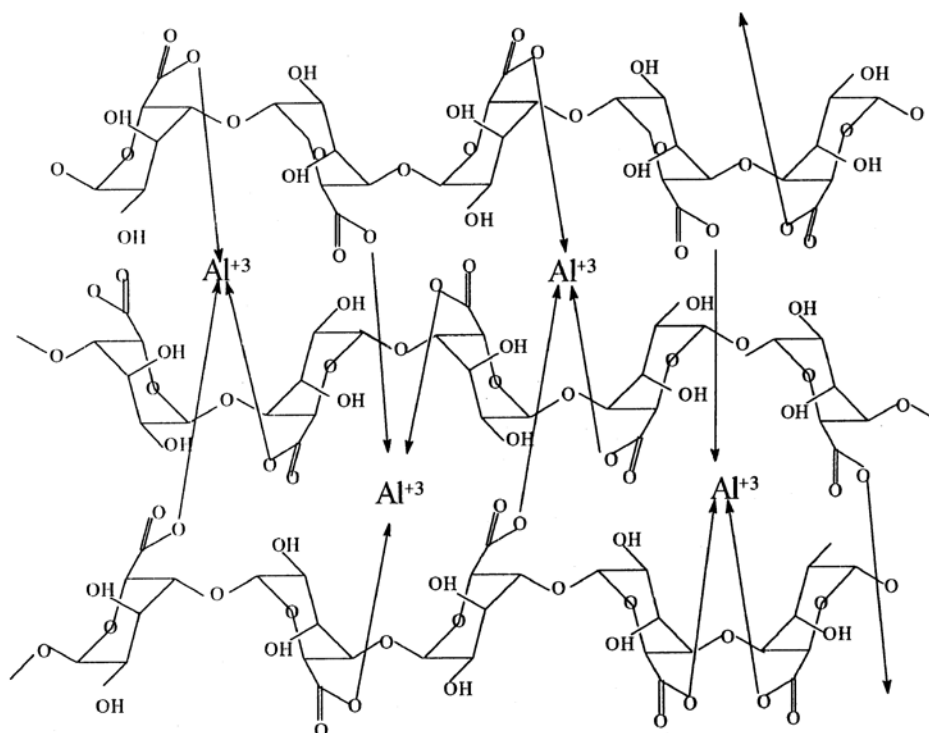

Fig. 12. Diagrammatic representation of possible cross-linking of Aluminium ions with alginate (Al-Musa *et al.* 1999).

This allows cross-linking to a greater extent than divalent cations as aluminium ions have an extra positive charge per unit of surface (Mohammadi 2009). The formation of hydrogels modulates drug release from sustained release formulations and has been used in microspheres, beads and film coating (Chan *et al.* 2006, Lee *et al.* 2005). They are also used extensively in matrix tablets to preserve the matrix structure and avoid early disintegration of the matrix (Ching *et al.* 2007). However, the concentration of cation plays an important role in how quickly or slowly drug is released (Nokhodchi and Tailor 2004, Ching *et al.* 2007, Mohammadi *et al.* 2009).

Kinetics of drug release

The release behaviour of drugs from hydrophilic matrices can be mathematically expressed by the following equation which is known as Higuchi equation:

$$M = k.t^{0.5}$$

Where k is a constant and M is the amount of drug released at time t.

Higuchi's equation initially was valid only for planar matrix systems, and later it was modified to consider different geometrical shapes and matrix characteristics including porous structures (Lapidus and Lordi 1966, 1968, Higuchi 1963, Desai *et al.* 1965, 1966). It should be kept in mind that the classical equation was derived under pseudo-steady state assumptions and cannot be applied to real controlled release systems (Peppas 1984). The final equation shows that if a system is predominantly diffusion-controlled, then it is expected that a plot of the drug release against square root of time will result in a straight line.

The mechanism of drug release from hydrophilic matrix tablets after ingestion is complex but it is based on diffusion of the drug through, and erosion of, the outer hydrated polymer on the surface of the matrix. In the case of a highly soluble drug, this phenomenon may lead to an initial burst release due to the presence of the drug on the surface of the matrix tablet. The gel layer (rubbery state) grows with time as more water permeates into the core of the matrix, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release (Rajabi-Siahboomi *et al.* 1996). The gel layer thickness behaviour is crucial in describing the release kinetics of swellable matrices. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, thereby leading to disentanglement and erosion (dissolution) of the surface of the matrix. Water

continues to penetrate towards the core of the tablet, through the gel layer, until it has been completely eroded (Lee and Peppas 1987, Narasimhan and Peppas 1997). At the point of disentanglement an abrupt change occurs in the rheological properties of the gel layer (Caramella *et al.* 1989). This indicates that the interactions between polymer-polymer and polymer-solvent are important in controlling the gel network structure and erosion. In addition, the strength of gel can play major role in controlling the drug release from this type of matrices.

A large number of mathematical models have been developed to describe drug release profiles from matrices (Siepmann and Siepmann 2008, Siepmann and Peppas 2000, 2001a,b, Siepmann *et al.* 1999, 2002). The simple and more widely used model is the one derived by Korsmeyer *et al.* (Siepmann *et al.* 1999) and is as follows:

$$M_t/M_\alpha = k\,t^{\,n}$$

where M_t/M_α is the fraction of drug release, k is the diffusion rate constant, t is the release time and n is the release exponent indicative of the mechanism of drug release.

It is clear from equations 6 and 7 that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). Here, the polymer relaxation and erosion (Bajwa *et al.* 2006) are the rate-controlling steps. When $n = 0.5$, Fickian diffusion is the rate-controlling step (case I transport). Values of n between 0.5 and 1 indicate the contribution of both the diffusion process as well as polymer relaxation in controlling the release kinetics (non-Fickian, anomalous or first-order release). It should be noted that the two extreme values of $n = 0.5$ and 1 are only valid for slab geometry. For cylindrical tablets, these values range from $0.45 < n < 0.89$ for Fickian, anomalous or case II transport respectively (Siepmann and Peppas 2001b).

Competing interests

Authors declared no competing interests.

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