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Modulation of drug release kinetics from hydroxypropyl methyl cellulose matrix tablets using polyvinyl pyrrolidone

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Abstract

Hydrophilic matrix tablets are widely used to extend the release of a broad range of pharmaceutically active materials. The mechanism and kinetics of drug release are dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer, with water soluble compounds released predominantly by diffusion. The swelling and erosion properties of hydroxypropyl methyl cellulose (HPMC), typically lead to a first order release rate for water soluble compounds as opposed to the more desirable zero-order kinetics. In addition, for compounds with differences in regional absorption within the gastrointestinal tract a dosage form with a bi-modal release profile may be required, which is difficult to achieve with a simple dosage form. The following paper presents a simple, cost effective and elegant solution for achieving a range of predictable release profiles from linear to bi-modal for a water soluble drug (caffeine) from HPMC matrices, through the inclusion of polyvinyl pyrrolidone (PVP). Mechanistic studies using gel rheology, excipient dissolution and near-infrared microscopy (NIR) microscopy are presented which show that the modulation of drug release kinetics is mediated through a reduction in HPMC viscosity in the presence of a critical concentration of PVP, which leads to a break-up of the extended release tablet. A validated mathematical model is also presented which allows drug release profiles to be reliably predicted based on the initial HPMC and PVP content in the tablet.

Keywords: Zero-order release; Bi-modal release; HPMC; Matrix tablet; PVP; NIR imaging

1. Introduction

Hydroxypropyl methyl cellulose (HPMC) is widely established as a release rate control polymer for hydrophilic extended release matrix tablets (Alderman, 1984), as a result of its regulatory acceptability, the variety of viscosity and substitution types available and the ability to be formulated into simple, robust and easily fabricated dosage forms.

Upon contact with water or biological fluids, the outer layers of the polymer matrix hydrate, leading to transformation of the polymer from the glassy to the rubbery state causing the polymer to swell. A pseudo-gel layer is formed surrounding the core of the tablet, which controls the rate of drug release from the matrix and the rate of water diffusion into the matrix. The mechanism and kinetics of drug release are dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer, with water soluble drugs being released predominantly by diffusion with a limited contribution from matrix erosion and anomalous diffusion resulting from the relaxation of the macromolecular polymer chains (Melia, 1990). The release of water soluble moieties will typically follow first order release kinetics. Water insoluble drugs are released predominantly through matrix erosion and therefore exhibit time independent or zero-order release kinetics (Lapidus and Lordi, 1968; Ranga Rao et al., 1990; Ford et al., 1987; Vazquez et al., 1992; Colombo et al., 1996, 1999). In certain instances drug release kinetics may deviate from first order for water soluble drugs dependent on the other components within the matrix tablet.

Typically, zero-order release kinetics are desirable for extended release dosage forms in order to match the drug input rate with the rate of elimination thereby maintaining steady state

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plasma profiles (Shah, 1988). Occasionally bi-modal release profiles are desirable to accommodate variations in absorption rate throughout the gastrointestinal tract (Shah, 1988). The relative inflexibility in release rate kinetics for water soluble drugs from HPMC matrices can lead to sub-optimal pharmacokinetic profiles in vivo. Several strategies have been reported to achieve zero-order or bi-modal release profiles for water soluble drugs from solid dosage forms. These include the Geomatrix® system, whereby barrier layers are compressed onto the face(s) of a tablet in order to reduce the surface area available for release (Conte and Maggi, 1996). In addition, the use of core in cup technologies has been widely reported where swelling of the hydrophilic matrix tablet is controlled by surrounding three faces of the tablet with a hydrophobic coating (Shenouda et al., 1990; Dankwerts, 1994; Zoglio et al., 1996). Bi-modal release has been achieved using a mixture of controlled and immediate release beads in a single capsule (Wang et al., 2004), through the use of multi-layer tablets (Streubel et al., 2000) and through the action of pectinolytic enzymes in the colon on controlled release tablets with film coatings containing pectin (Macleod et al., 1999). However, many of these systems are relatively complex compared with the simplicity and benefits gained from using a single hydrophilic matrix tablet.

The following paper describes a simple, cost effective and elegant solution for achieving a range of predictable release profiles from linear to bi-modal for a water soluble drug from HPMC matrices containing polyvinyl pyrrolidone (PVP). A mechanistic understanding of the influence of PVP on drug release profiles from HPMC matrices is also presented.

2. Materials and methods

2.1. Materials

Anhydrous caffeine was purchased from Fluka Chemie GmbH, Methocel® E10 M premium CR (hydroxypropyl methylcellulose, HPMC) was provided by Colorcon, Dartford, UK. Plasdone K-90 (Povidone® USP K-90, polyvinyl pyrrolidone) was obtained from ISP Technologies, Inc., Wayne, NJ, USA. Stearic acid was sourced from Oleotec Ltd., Ellesmere Port, Cheshire, UK.

2.2. Tablet preparation

The formulations consisted of caffeine, HPMC, PVP and stearic acid. Caffeine, HPMC and PVP were blended in a Turbula T2C mixer (Willy Bachofen UK, Welwyn Garden City, UK) for 10 min at a speed of 42 rpm. The stearic acid was sieved using a 250 μm stainless steel laboratory test sieve and added to the formulation, which was then blended in the Turbula T2C mixer for a further 1 min.

Tablets were compressed using a Lloyds LR50K Plus instrumented press. 10.5 mm (diameter) by 12 mm (radius) round convex tablets were compressed at a speed of 10 mm/min using a load of 20 kN. All tablets contained 300 mg caffeine, so the total tablet weight varied for different formulations.

2.3. Tablet dissolution

Dissolutions studies were performed using USP I Apparatus (XXVIII edition, 2005) in a Vankel VK 7025 dissolution tester equipped with a VK8000 autosampler (Varian Inc., Palo Alto, USA). The dissolution medium was 900 mL of de-aerated de-ionised water, which was kept at a constant temperature of 37 °C, with the baskets rotating at 100 rpm.

Ten samples were taken at timed intervals and the caffeine dissolution profile was obtained by performing a UV analysis (λ_{max} 273 nm) using HP 8453 UV/Vis Spectrophotometer with ChemStation Dissolution Testing Software (Agilent Technologies, Stockport, UK).

The combined analysis of HPMC and PVP from dissolution samples was performed by size exclusion chromatography (SEC) with refractive index (RI) detection using a Waters Ultrahydrogel 250, 6 μm, 300 mm × 7.8 mm i.d. column and de-ionised water as mobile phase (0.7 mL/min flow rate, room temperature, 900 μL injection volume). The separate analysis of PVP was performed by size exclusion chromatography with UV detection at 217 nm using a Waters Ultrahydrogel 250, 6 μm, 7.8 mm i.d. × 300 mm column and 0.025 M NaCl in water as mobile phase (0.7 mL/min flow rate, room temperature, 100 μL injection volume). Agilent 1100 Series high performance liquid chromatographs (HPLC) systems were employed for both analyses.

2.4. Effect of PVP on the rheology of HPMC

Gels containing 4% (w/w) HPMC in de-ionised water with 0, 0.5, 1, 2, 4 and 8% (w/w) PVP were prepared to study their rheological properties. The required amounts of water, PVP and HPMC were weighed, and the water was heated to 37 °C with continuous stirring. The PVP and HPMC were slowly added to the stirred solution, whilst maintaining the temperature at 37 °C. Upon addition of all the PVP and HPMC, the gels were weighed, and water lost due to evaporation was replaced. The HPMC and PVP gels were then stored in a refrigerator to complete the hydration. Prior to testing, the samples were allowed a 16 h equilibration period at room temperature and centrifuged at 2000 rpm for 10 min to remove entrapped air (Eppendorf Centrifuge 5810R, Eppendorf UK, Cambridge, UK).

For the measurement of the rheological properties a TA instruments AR 1000 (TA Instruments, Crawley, UK) rheometer was used. The rheometer was fitted with a 40 mm aluminium plate, and all tests were carried out with a gap of 0.5 mm and a solvent trap filled with de-ionised water. To determine the linear viscoelastic region (LVR), an oscillatory sweep test was performed, where an oscillatory torque is applied ranging from 1–10,000 μNm at a frequency of 1 Hz. The test was performed at a constant temperature of 37 °C, using an equilibration time of 10 s, and a conditioning and sampling time of 3 s. The storage modulus (G') which is the ratio of in-phase stress to strain (elastic response) and the loss modulus (G'') which is the out of phase stress to strain ratio (viscous response) were then determined as the average of the measured G' and G'' values over the linear viscoelastic region, where G' and G'' are constant.

Table 1a
Formulation composition of caffeine extended release tablets containing 10% Methocel E10MCR with varying levels of PVP

10% HPMC system	Formulation 1 (%, w/w)	Formulation 2 (%, w/w)	Formulation 3 (%, w/w)	Formulation 4 (%, w/w)	Formulation 5 (%, w/w)
Caffeine	89	87	86.3	85.6	84
Methocel® E10MCR	10	10	10	10	10
Povidone K90	0	2	2.7	3.4	5
Stearic acid	1	1	1	1	1

Table 1b
Formulation composition of caffeine extended release tablets containing 20% Methocel E10MCR with varying levels of PVP

20% HPMC system	Formulation 6 (%, w/w)	Formulation 7 (%, w/w)	Formulation 8 (%, w/w)	Formulation 9 (%, w/w)	Formulation 10 (%, w/w)	Formulation 11 (%, w/w)
Caffeine	79	74	69	66.5	64	59
Methocel® E10MCR	20	20	20	20	20	20
Povidone K90	0	5	10	12.5	15	20
Stearic acid	1	1	1	1	1	1

2.5. Chemical imaging of component distribution

Samples were hydrated using USP apparatus I (XXVIII edition, 2005) in a Distek Evolution 6100 dissolution tester (Omicron Research Ltd., Wilts, UK). The dissolution medium was 900 mL of de-aerated de-ionised water, which was kept at a constant temperature of 37 °C, with the baskets rotating at 100 rpm. The hydrated sample was removed from the dissolution bath, whilst retained in the basket, and deposited in a freeze dryer tube, which was immediately put into a carbon dioxide ice and methanol bath to freeze the sample. Once the condenser temperature was below −50 °C and the pressure below 13 Pa vacuum, the freeze dryer tube containing the sample was attached to the Freezone 1 L (Labconco, Kansas City, USA) freeze drier. Water was then removed by sublimation (As sublimation can occur at room temperature for pressures below approximately 700 Pa, the pressure in the freeze-dryer was always kept below 130 Pa.). Once a pressure of 130 Pa or below had been re-established, the sample was removed from the ice bath and dried over night.

The dried tablets were subsequently microtomed across the horizontal plane at the mid-point using a Leica EM Trim, to enable the imaging of the core and gel layer of the tablet. A Perkin-Elmer Spectrum One NTS FT-NIR spectrometer and Spectrum Spotlight FT-IR Imaging system were utilized to image the samples. The depth of imaging is in the order of 1–5 μm. Images of the formulations were compared to the spectra of compressed tablets of the constituent materials—caffeine, HPMC and PVP to allow detection and hence spatial mapping of the individual components. Images were obtained for dry tablets, as well as tablets that had been hydrated for 2, 4 and 7 h.

3. Results and discussion

3.1. The effect of PVP on caffeine release rate modulation

To understand the effect of PVP on caffeine release profiles at two fixed HPMC loadings (10 and 20%), 11 formulations with a range of PVP levels were prepared (Tables 1a and 1b). Fig. 1a and b show that at both 10 and 20% HPMC loadings, formulations with 0% PVP exhibit a typical first order release profile. As the PVP level in the formulation increases, the release profile becomes increasingly linear (between 2 and 20 h), until eventually becoming bi-modal at higher PVP loadings. The increased linearity is evidenced by the R^2 value of the linear regression

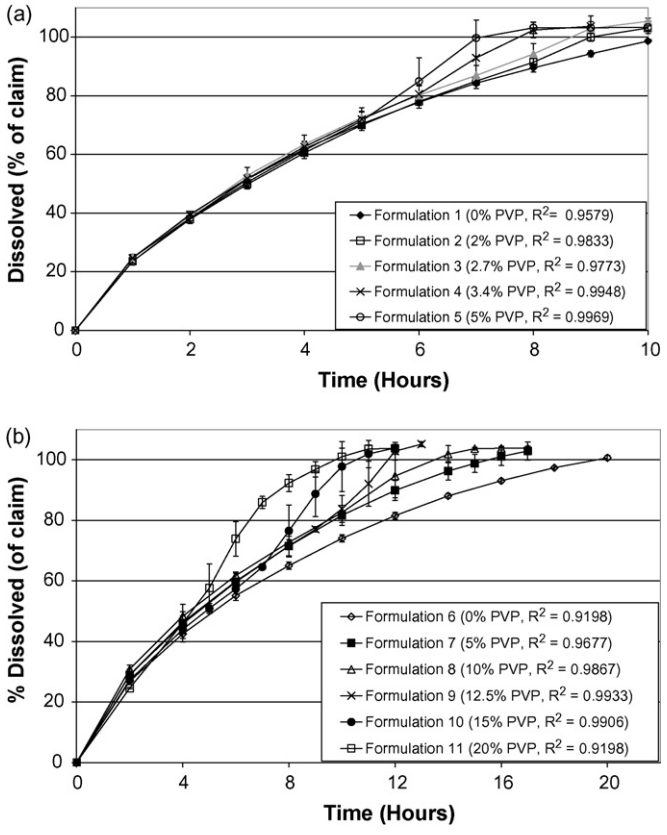

Fig. 1. (a) In vitro caffeine dissolution profiles for extended release caffeine tablets containing 10% Methocel E10MCR with varying levels of PVP (900 mL water at 37 °C, baskets at 100 rpm). (b) In vitro caffeine dissolution profiles for extended release caffeine tablets containing 20% Methocel E10MCR with varying levels of PVP (900 mL water at 37 °C, baskets at 100 rpm).

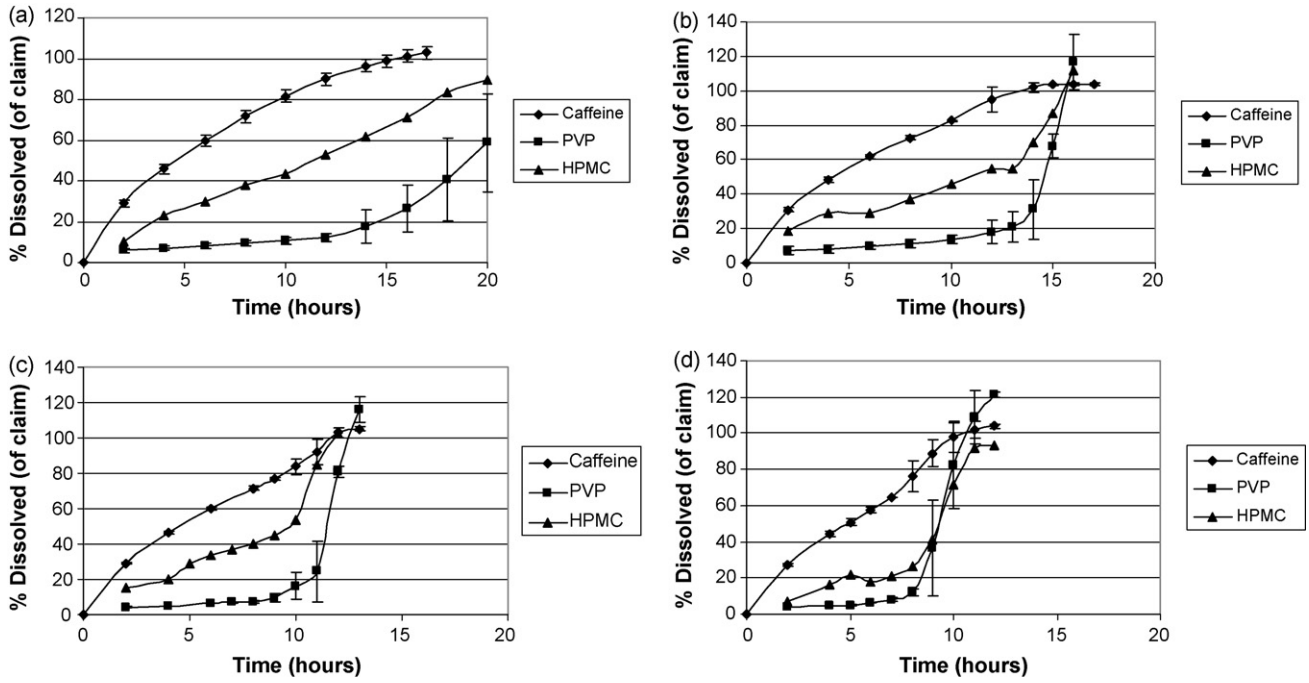

Fig. 2. (a) In vitro caffeine, PVP and HPMC dissolution profiles for extended release caffeine tablets containing 74% caffeine, 20% Methocel E10MCR, 5% PVP and 1% stearic acid (900 mL water at 37 °C, baskets at 100 rpm). (b) In vitro caffeine, PVP and HPMC dissolution profiles for extended release caffeine tablets containing 69% caffeine, 20% Methocel E10MCR, 10% PVP and 1% stearic acid (900 mL water at 37 °C, baskets at 100 rpm). (c) In vitro caffeine, PVP and HPMC dissolution profiles for extended release caffeine tablets containing 66.5% caffeine, 20% Methocel E10MCR, 12.5% PVP and 1% stearic acid (900 mL water at 37 °C, baskets at 100 rpm). (d) In vitro caffeine, PVP and HPMC dissolution profiles for extended release caffeine tablets containing 64% caffeine, 20% Methocel E10MCR, 15% PVP and 1% stearic acid (900 mL water at 37 °C, baskets at 100 rpm).

line being closer to 1 as the level of PVP is increased in formulations 1–5 (Fig. 1a) and formulations 6–9 (Fig. 1b), before decreasing as the release profile becomes bi-modal in formulations 10 and 11 (Fig. 1b). Evidence suggests that the underlying caffeine release profile is similar at each constant HPMC loading, however a point exists where the release rate is 'modulated' which is dependent on the level of PVP in the formulation. As the PVP level increases, the point (or time) of release rate modulation occurs earlier leading to a greater deviation from the underlying release profile determined by the HPMC loading in the formulation.

To understand the effect of formulation composition on the release kinetics of all three major components in the formulation, the dissolution profiles of HPMC and PVP were measured from a selection of the 20% HPMC formulations (Table 1b, formulations 7–10). Fig. 2a–d show that the majority of both PVP and HPMC are released in a sudden burst, which coincides with the point of caffeine release rate modulation. From the dissolution profiles for HPMC, caffeine and PVP and from the initial mass of components per tablet it was possible to calculate the approximate mass of PVP, HPMC and caffeine in the tablet (excluding water) at the point of modulation, along with the ratio of HPMC to PVP at the point of modulation (Table 2). Whilst this technique provides an approximation of tablet composition close to the point of modulation, it can be seen that the ratio of HPMC to PVP in the formulation at the point of modulation is largely constant, irrespective of the initial formulation composition. Higher absolute amounts of PVP in the formulation lead to an earlier modulation point before the majority of caffeine has been released, resulting in the observed bi-modal release profiles. The constant ratio of PVP to HPMC in the tablet at the point of modulation also suggests that the properties of the HPMC matrix are modified at a critical PVP concentration. It could be argued that the level of caffeine in the formulation is also influencing the break-up of the tablet and modulation of drug release kinetics. However, this appears unlikely as the

Table 2
Modulation time and the absolute amounts of caffeine, PVP and HPMC at the point of modulation

Formulation	Modulation time (h)	Quantity of caffeine at modulation (mg)	Quantity of PVP at modulation (mg)	Quantity of HPMC at modulation (mg)	Ratio of PVP:HPMC at modulation
Formulation 7 (20% HPMC and 5% PVP)	18	0	12.0	13.4	0.90
Formulation 8 (20% HPMC and 10% PVP)	12	16	35.7	39.3	0.91
Formulation 9 (20% HPMC and 12.5% PVP)	10	48.6	47.3	49.7	0.95
Formulation 10 (20% HPMC and 15% PVP)	8	70.4	61.7	69.2	0.89

Quantities based on the dissolution profile and the initial tablet composition.

amount of caffeine in the tablet at the point of matrix break-up ranges from 0 mg (Fig. 2a) to 13 mg (20% of initial, Fig. 2d). It should also be noted that the modulation point for formulation 11 in Fig. 1b is after only 60% caffeine release, which equates to a caffeine concentration of 23 mg in the tablet at the point of modulation.

3.2. Mechanism of release rate modulation in HPMC/PVP matrices

Whilst the in vitro dissolution profiles (Fig. 1a and b) show that the presence of PVP in the formulation leads to a modulation of the drug release kinetics, the mechanism behind the change in kinetics is unclear. It was hypothesized that this may have resulted from a change in the properties of the 'pseudo-gel layer' surrounding the tablet, which controls the drug release rate. To study this hypothesis further, 4% HPMC solutions with a range of PVP contents (0–8%) were prepared and the storage (G') and loss (G'') modulus measured using a parallel plate rheometer (Fig. 3). It can be seen both the loss (G'') and storage (G') modulus of HPMC gels is dramatically reduced between 0.5 and 2%, beyond which further decreases in gel modulus are minimal. The change in modulus is indicative of a reduction in the strength and structure of the HPMC gel in the presence of PVP. HPMC and PVP are highly miscible through hydrogen bonding between the free hydroxyl groups of HPMC and the carbonyl group of PVP (Hiremath et al., 2002). Through intimate mixing during hydration of the dosage form and through the formation of strong hydrogen bonds between PVP and HPMC, the strength of the HPMC gel is reduced at a critical PVP concentration.

In order to correlate the deleterious effect of PVP on HPMC gel structure with the modulation of drug release kinetics, an understanding of the spatial distribution of caffeine, HPMC and PVP within a tablet following hydration was required. Near-infrared microscopy (NIR) allows the spatial distribution of components in a sample to be mapped based on the unique spectroscopic signature of each component (Clarke, 2004). Fig. 4 shows a series chemical images of dried microtomed tablets (Tables 1a and 1b, formulation 10) following 0, 2, 4 and 7 h hydration in the in vitro dissolution apparatus. The point of modulation for this particular formulation was approximately 7 h. The absorbance scale on each image is fixed (absorbance range 0.3–0.9 au) with areas of high absorbance (concentration) colored red and areas of low absorbance (concentration) colored blue. It can be seen that at 0 h the PVP, HPMC and caffeine are dispersed throughout the matrix, with the largest spectral response from caffeine as a result of its higher concentration in the formulation (64%, w/w). There is a slight clustering of PVP as evidenced by regions of high absorbance in the PVP image, and from the HPMC and caffeine images, these domains of high PVP absorbance appear to be deficient in both HPMC and caffeine. At 2 h, the gel layer surrounding the tablet is clearly visible by the high HPMC absorbance on the outer edge of the tablet. The tablet is also becoming progressively PVP and HPMC rich as the caffeine diffuses out of the matrix. PVP has a high molecular weight of approximately 1,000,000 Da (Rowe et al., 2003) and it is hypothesized that diffusion of the PVP within the tablet is inhibited by its high molecular weight. In addition, there is evidence for a band of PVP forming close to the gel layer at the 4 and 7 h timepoint. At the 7 h timepoint around the time of release rate modulation, a large proportion of the caffeine has diffused from the matrix and the tablet is PVP and HPMC rich, with the PVP concentrating close to the gel layer. The change in component proportions from the NIR images is supported by both the caffeine, HPMC and PVP dissolution profiles (Figs. 1b and 2c). The dissolution profiles also show that the matrix is becoming progressively PVP rich as a result of the relative lack of PVP diffusion compared to HPMC. Therefore, with an increasing relative concentration of PVP with time, the gel structure within the matrix becomes progressively weak leading to a catastrophic break-up of the gel structure and a modulation in drug release kinetics.

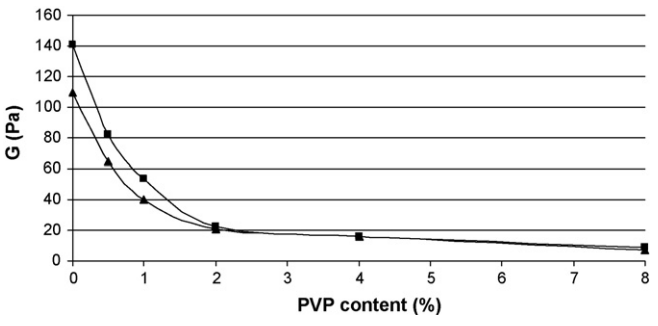

Fig. 3. Effect of PVP concentration on the loss (G'', ■) and storage (G', ▲) modulus of 4% (w/w) Methocel E10MCR gels in water.

It is hypothesized that when this occurs relatively early during the drug release profile where the actual amounts of HPMC and PVP in the matrix are high (e.g. Table 1a formulation 6), the tablet breaks into smaller sub-units which still possess extended release properties leading to a bi-modal release profile.

For systems with lower PVP levels, an understanding of the linearization of the drug release profile can be gained through examining the interplay between drug diffusion and gel layer growth. Previous research has suggested that three distinct fronts exist within the gel layer surrounding a matrix tablet: (i) erosion front (matrix-external media), (ii) swelling front (gel layer–core boundary) and diffusion front (solid drug–drug solution boundary) (Colombo et al., 1996, 1999). The rate of drug release is controlled by movement of the diffusion front and the kinetics of drug release are controlled by movement of the erosion front. Initially on hydration, there is a rapid increase in gel layer thickness as swelling of the dosage form predominates. A portion of water soluble compound within the matrix is rapidly released as a result of an incomplete gel layer being formed around the tablet. This is followed by a period of constant gel layer thickness as swelling and dissolution of the gel are synchronized (Harland et al., 1988). The release of water soluble drugs is controlled by movement of the diffusion front, resulting in a period of zero-order release kinetics as the surface area available for release remains constant (synchronization of erosion and swelling fronts). Eventually erosion of the dosage form predominates resulting in a reduction in the surface area available for drug release and a reduction in drug release rate, leading to a first

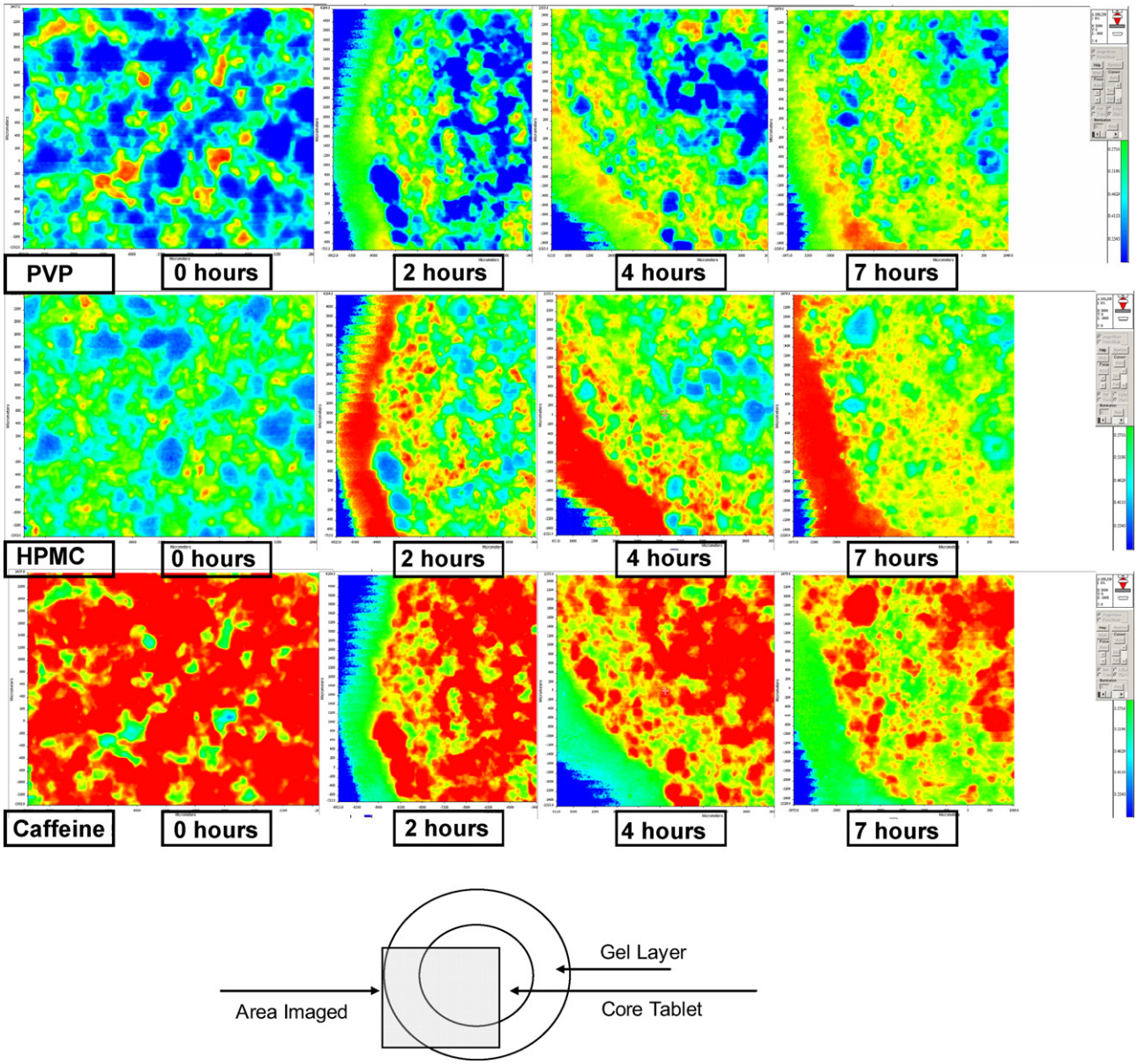

Fig. 4. Spatial distribution of caffeine, PVP and HPMC in caffeine extended release matrix tablets following 0, 2, 4 and 7 h hydration (900 mL water at 37 °C, baskets at 100 rpm) determined using near-infrared microscopy.

order release profile. For systems containing PVP which produce a zero-order profile following the initial 'burst', it is hypothesized that the matrix tablet breaks up during the phase when swelling and dissolution of the gel are synchronized and before erosion of the gel predominates leading to constant zero-order drug release kinetics.

3.3. Mathematical modeling of caffeine release from HPMC/PVP matrices

The relatively controlled manner in which PVP modulates caffeine release kinetics, led to the possibility of modeling and predicting the dissolution profiles of caffeine from HPMC tablets containing PVP. From the caffeine dissolution profiles (Fig. 1a and b) it can be seen that the release curve can be divided into two parts; the dissolution profile prior to and following the modulation in release kinetics.

For a given HPMC concentration, the dissolution profile was independent of PVP content until the modulation in release kinetics was observed. This was termed the underlying release profile for the system and could be modeled by fitting a third order polynomial to the averaged data for formulations with 10 and 20% HPMC up to the point of modulation. The second portion of the release curve following the point of modulation which was dependent on the PVP content, resembled a normal cumulative distribution function. In order to model the second part of the release curve as a *y*-axis scaled normal cumulative distribution function, three points were required: (i) the time at which the change in release kinetics occurs (the modulation point), (ii) the time at which the cumulative distribution function

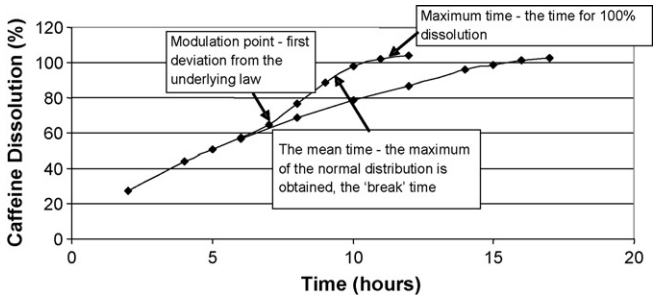

Fig. 5. Modeling of caffeine release from a formulation containing 59% caffeine, 20% Methocel E10MCR, 20% PVP and 1% stearic acid showing the modulation point, mean time and maximum time.

reaches its mean value (the mean time, which is the point where the *y*-scaled cumulative distribution reaches its peak), and (iii) the time where 100% caffeine has been released (the maximum time) (Fig. 5). Linear relationships between PVP content and the modulation point, mean time and maximum time of the cumulative distribution function were obtained (Fig. 6a–c) from the dissolution data presented previously (Fig. 1b).

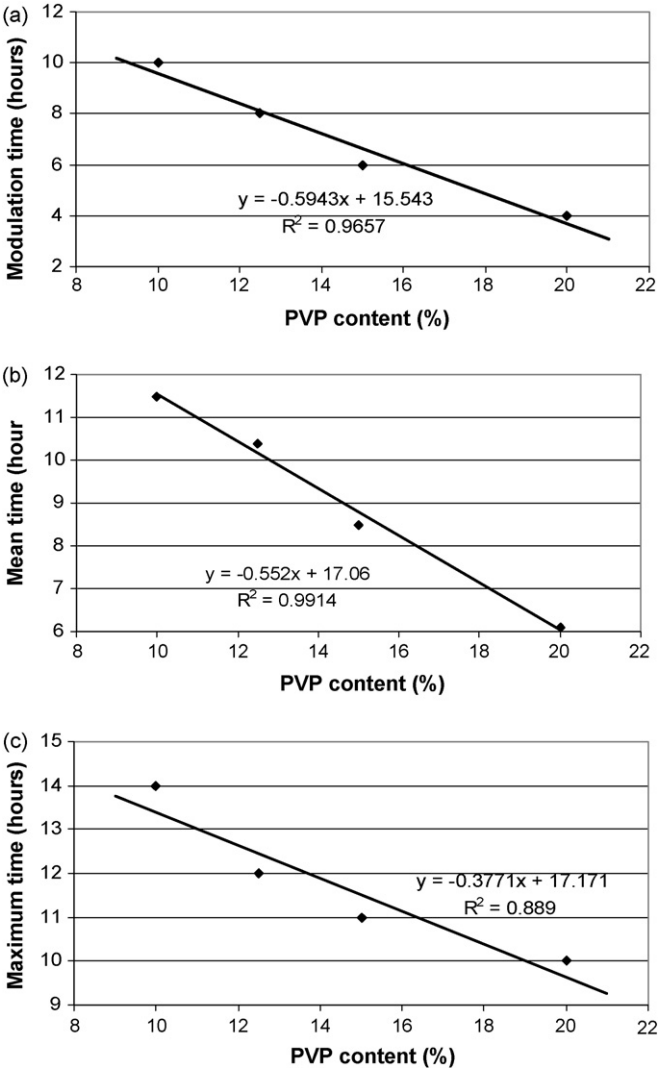

Fig. 6. (a) Effect of PVP content on the modulation point for caffeine release from formulation containing 20% Methocel E10MCR. (b) Effect of PVP content on the mean time for caffeine release from formulation containing 20% Methocel E10MCR. (c) Effect of PVP content on the maximum time for caffeine release from formulation containing 20% Methocel E10MCR.

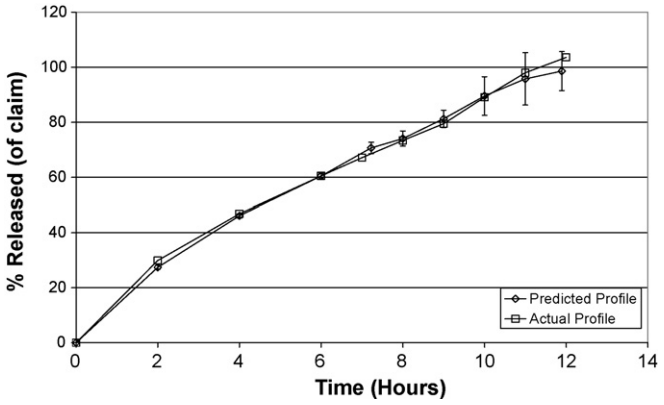

Fig. 7. Predicted and observed in vitro caffeine dissolution profiles for extended release caffeine tablets containing 65% caffeine, 20% Methocel E10MCR, 14% PVP and 1% stearic acid (900 mL water at 37 °C, baskets at 100 rpm).

Using a spreadsheet (Microsoft Excel, Microsoft Inc., USA) it was possible to model the underlying dissolution profile for both 10 and 20% HPMC using the third order polynomial and then to combine this with the modulation point, mean time and time for 100% caffeine release (maximum time) from the cumulative distribution function for a given PVP content. The validity and predictability of the model was assessed by using the model to identify a formulation which gave a zero-order caffeine release profile (between 2 and 12 h). Fig. 7 shows the predicted and observed dissolution profile for a formulation containing 65% caffeine, 20% HPMC, 14% PVP and 1% stearic acid. It can be seen that the observed and predicted dissolution profiles are in close agreement, providing a useful tool for predicting the role of PVP in modulating caffeine release kinetics from HPMC matrices.

4. Conclusion

This study has shown that the addition of PVP to HPMC matrices can produce a range of drug release profiles from bimodal to zero-order for a water soluble compound, in a simple single-unit dosage form. From the rheology, component dissolution data and NIR microscopy images we propose the following mechanism for the role of PVP in modulating release kinetics of caffeine from HPMC matrices.

(1) In the initial stages of hydration, the release properties of caffeine are governed by the HPMC content in the tablet, regardless of the amount of PVP as this is dispersed throughout the matrix.
(2) As caffeine diffuses out of the tablet, the matrix becomes progressively rich in both PVP and HPMC.
(3) HPMC diffuses from the matrix at a faster rate compared with PVP, leading to the matrix becoming progressively PVP rich. At a critical concentration, PVP sufficiently reduces the strength of the HPMC gel leading to a catastrophic break-up of the matrix.

(4) For matrices with high levels of PVP this occurs early in the drug release process leading to a bi-modal release profile which may result from the formation of smaller extended release sub-units. For lower levels of PVP this may occur when swelling and erosion of the gel are synchronized leading to a linearization of the drug release profile.

It has also been possible to develop a mathematical model consisting of a third order polynomial and a cumulative distribution function to predict the effect of changes in PVP concentration on the modulation of drug release kinetics. However, it should be recognized that the modulation in release kinetics has been demonstrated using a single compound and further work is required to demonstrate the applicability of this system across a wider range of compounds.

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