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Research paper

The influence of crystallization inhibition of HPMC and HPMCAS on model substance dissolution and release in swellable matrix tablets

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ABSTRACT

One of the drawbacks with solid solution systems is their thermodynamic instability in solution. Considering the release of these systems from extended-release formulations, in particular swellable matrix tablets, a successful tablet formulation can be regarded as a composition able to maintain the molecular state of the poorly soluble crystalline drug through diffusion in the matrix. This may in turn provide molecular rather than particulate delivery of the substance from the matrix. In this study, the solid state and dissolution behavior of amorphous solid dispersions of a model crystalline substance, butyl paraben in HPMC and HPMCAS, was investigated. In addition, the suitability of HPMCAS as both effective solid solution carrier and as extended-release matrix forming polymer was examined. The release from all systems investigated showed extended-release capacity with a release rate similar to the rate of matrix erosion. However, a detailed study of the factors affecting the release mechanism revealed that upon hydration, the model substance crystallized in the gel layer of the HPMC-based formulation, whereas it remained in amorphous form in the HPMCAS tablets. In the case of HPMCAS formulation, this effect was attributed to (i) the ability of this polymer to keep the model substance in a supersaturated state and (ii) the very slow matrix hydration, resulting in a steep concentration gradient of the drug substance and a short diffusion path through the matrix into the dissolution bulk.

1. Introduction

In 2000, the FDA adapted a Biopharmaceutical Classification System (BCS) devised by Amidon and co-workers, which categorized active pharmaceutical agents into four groups. Among these, scientists have devoted most attention to BCS II and BCS IV drugs, which have poor solubility in common [1]. Today, about 35–40% of lead substances are known to have an aqueous solubility of less than 5 mg/ml at pH 7 (termed as "slightly soluble" according to the United State Pharmacopoeia, USP) [2], and this figure is not expected to decrease in the future. On this basis, tablet formulators can at times find themselves not only dealing with finding the optimum release profile from the tablet but also improving the dissolution properties of the drug substance for optimum drug absorption. An optimum formulation approach for improving bioavailability can be to deliver the drug substance from the matrix in a form that is already dissolved or readily dissolvable in the gastrointestinal tract. The consequence of this can not only be a faster drug uptake through the epithelial cells but also a higher fraction of drug absorbed as drug absorption can occur even at the distal regions of the intestine containing lower amount of free water.

One approach to overcome poor dissolution properties is to employ solid dispersion technology. Fundamental characterizations of the physical state of these systems have been under study for over 50 years. Recent review articles have summarized the proposed mechanisms, by which the drug is kept dispersed in the solid carrier [3,4]. One of the most commonly encountered types of solid dispersions is amorphous solid solutions. In these systems, the drug substance is molecularly distributed within the amorphous carrier. One type of amorphous carrier, which have recently grown in popularity, is cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetyl succinate (HPMCAS) [5–8]. For example, Taylor and co-workers found that both HPMC and HPMCAS were more effective than polyvinylpyrrolidone (PVP) for inhibiting crystallization growth of felodipine in amorphous dispersions [9]. In this regard, most studies hitherto have focused on stabilizing the molecular drug in the solid form during storage, and few have focused on stabilizing the drug during tablet dissolution. Even though many studies have shown the importance of selecting the appropriate polymer for stabilizing supersaturated solutions, more studies are needed to put this wisdom in a context of tablet dissolution and release behavior.

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Historically, the majority of publications dealing with the effect of solid dispersions on the drug release have focused on the impact on immediate release formulations. However, it is well known that for some products, controlled drug release is a prerequisite for desired clinical outcome. Therefore, solid dispersions in different types of extended-release formulations have recently been under investigation [10–12]. In this respect, the number of studies focusing on the release mechanism of the most common extended-release platform, namely swellable matrix tablets, is scarce.

The release and dissolution functionality of swellable matrices have been extensively described in the literature [13,14]. In some studies, hydrophilic polymers have been used to serve both the purpose of being carriers in amorphous solid solutions and constructing the backbone of swellable matrix tablets [15–19]. In this respect, one interesting issue is the drug substance can withstand precipitation within the time interval between hydration and release from the matrix. If the substance due to poor solubility exhibits non-Fickian release mechanism, converting the drug to a readily dissolvable form may tune the release mechanism towards one with higher influence of diffusion. In a recent study, we examined the substance dissolution rate and release of a homologous series of parabens in a polyethylene glycol (PEG) 4000 solid solution system, imbedded in a polyethylene oxide (PEO) swellable matrix [16]. The influence of the crystalline solubility and release mechanism, swelling and erosion of the matrix, and crystallization on the release rate of the substances was studied. It was found that the rate of crystallization of the parabens in the gel layer was the governing factor for their release behavior. Therefore, the question of whether a more effective solid dispersion carrier could maintain the substance in the amorphous form in the gel until release arose.

The objective of the present work was to characterize binary extended-release matrix tablets comprising HPMC or HPMCAS and the model substance, butyl paraben (Fig. 1), in solid and wet state. By comparing the behavior of solid dispersions with that of physical mixtures, an explanation model was developed regarding the ongoing mechanisms of molecular bonding between the substance and the carrier.

2. Material and methods

Butyl paraben (BP) with purity >99% (Sigma–Aldrich, Japan) was used as a model drug. Hydroxypropyl methylcellulose (HPMC: Shin-Etsu Chemical Co., Ltd., Tokyo, Japan, grade 90SH100 SR) and hydroxypropyl methylcellulose acetate succinate (HPMCAS: ShinEtsu AQOAT®, Type AS-MF) were used as solid dispersion carrier and matrix former in the extended-release swellable tablets. Some physicochemical properties of the two polymers are presented in Table 1.

2.1. Preparation of solid dispersions

Solid dispersions (SD) were prepared using a solvent evaporation method. BP was dissolved in a 1:1 solution of ethanol and dichloromethane followed by the addition of HPMC or HPMCAS. The amount of BP in the solid dispersions was 10%. The solvents were evaporated by a rotary evaporator at relatively high vacuum pressure (500 mm Hg) to ensure a slow and effective process for polymers and BP interaction. The aggregates were further dried in a vacuum oven at 35 °C for at least 8 h. The solid dispersions were subsequently milled by a rotar mill (Fritsch, Pulverisette 14, Germany), equipped with a 500-μm sieve, set at 10 000 rpm. The size and distribution of the resultant particles was examined by laser diffraction method, dry mode and 1 bar pressure to disperse the particles (Malvern, Mastersizer 2000, Scirocco dispersion unit, Worcestershire, England).

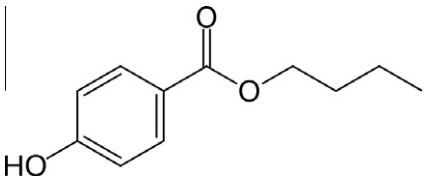

Fig. 1. Schematic figure of the molecular structure of butyl paraben.

2.2. Preparation of tablets for release studies

Tablets comprising either a physical mixture (PM) of polymer and crystalline BP or SD particles were prepared. The composition of the PM formulations was the same as that of the SDs, i.e. 90% polymer and 10% BP. BP used in the PM tablets was sieved and particle size fraction 40–200 μm was used in the tablet compositions. The polymers used in the PM formulations were first dissolved in the solvent used for preparation of the SDs and solvent evaporated according to Section 2.1. This was done in order for the PM tablets to undergo the same history as for the SDs. Tablets weighed 200 ± 3 mg and were produced using 10-mm punches. The powder was compacted using a hydraulic press and compaction force of 25 kN with dwell time of approximately 10 s. Due to the high degree of deformation of the particles, strong tablets were produced. However, the high degree of deformability also implied deformation of the tablets during hardness measurements, which in turn did not allow an accurate determination of the tensile strength.

2.3. Contact angle measurements

Contact angle measurements were carried out on tablet compacts similar to those described in Section 2.2. The apparatus (DAT 1100, FIBRO system AB, Sweden) was equipped with a magnifying video camera which automatically captured images of a 4-μl water droplet during 60 s upon initiation of the measurements.

2.4. Differential scanning calorimetry (DSC)

The DSC analysis was performed with a Perkin Elmer DSC 7 equipped with an Intracooler 1P add-on. Calibration of temperature and enthalpy of fusion was performed using Indium (temperature of fusion 156.60 °C and enthalpy of fusion 28.51 Jg^{-1}) and Zinc (419.53 °C) in a standardized two-point method. Samples were weighed into 25-μl aluminum pans and heated from room temperature to 100 °C at 10 °C/min.

2.5. X-ray diffraction (XRD)

XRD analysis of crystalline BP, PM, and SD formulations was carried out on the tablets prior to release studies and on hydrated tablets, approximately 2.5 h after the initiation of the release. In addition, XRDs were recorded on test solutions of BP according to Section 2.10. The measurements were performed using a Bruker AXS D8 Advance Diffractometer (Karlsruhe, Germany) equipped with rotating sample holders. The radiation was generated by Cu at 30 kV and 50 mA with 12-μm K_β filter. Scanning was performed over the angular range of 1–40° 2θ.

2.6. Raman spectroscopy

The Raman spectra of the crystalline and amorphous BP, SD tablets prior release, and approximately 2.5 h after the initiation of the release were recorded. Melted BP was used as reference for the amorphous form. The paraben was melted using a hot-stage (Linkam TMS 93, Tadworth, England) kept at 85 °C, which was

Table 1
Some physicochemical properties of HPMC 90SH100 SR and HPMCAS MF.

R	M_w ($\times 10^4$ g/mol)	T_g (°C)	Methoxy subst. (%)	Hydr.prop. sub. (%)	Succinyl. sub. (%)	Acetyl sub. (%)	Dissolution thresh. pH
90SH100 SR	12.3[a]	190[b]	23.3[a]	11[a]	–	–	–
AS-MF	1.71[c]	130[d]	23.5[c]	7.3[c]	10.9[c]	9.0[c]	6[d]

[a] Data acquired from Ref. [20].
[b] Data acquired from Ref. [21].
[c] Data acquired from Ref. [22].
[d] Data acquired from Ref. [23].

above the melting temperature of BP (T_m = 73 °C). Spectra were recorded with a Renishaw inVia Raman microscope (Gloucestershire, UK) using a 785-nm laser. The spectrometer is equipped with a CCD, a notch filter, and a 1200 l/mm grating. The spectral resolution was better than 2 cm^{-1}. The laser excitation was focused using 50x LWD objective. Each spectrum was an average of three accumulations of at least 20-s exposure time. Several spectra at different sample positions were measured to ensure representative sampling.

2.7. Plane polarized microscopy

Plane polarized microscopy (Laborlux Pol 12; Leica, Germany) was used as an additional tool to detect crystals in test solutions and in the gel of the hydrated tablets. The test solutions were prepared according to Section 2.10, and the gel layer of the tablets was collected, approximately 2.5 h after the initiation of the release. This was done by carefully scraping off the very outer layer of the gel and immediately examining the samples on a microscopy slide at 10–40× magnifications.

2.8. Solubility determination of crystalline BP in phosphate buffer

The equilibrium solubility of crystalline BP in phosphate buffer (pH 6.5) was determined at 37 °C in the presence and absence of 10 mg/ml (1%, w/w) polymers. To 200 ml of the test solutions was added 500 mg BP . The solutions were stirred for 24 h, after which samples were taken out, centrifuged at 4000 rpm for 10 min and the concentration of BP in the supernatant was determined by UV-spectrophotometer (Cary 50 Bio; Vairan, Victoria, Australia) at 256 nm. The polymer test solutions were prepared by dissolving appropriate amount of polymer in the phosphate buffer and stirring for 24 h. The HPMCAS solution was slightly pH adjusted in order to allow the polymer to fully dissolve in the solutions. The measurements were carried out with two replicates.

2.9. Crystallization study of BP from supersaturated solutions

The inhibitory effect of polymers on BP crystallization was measured in plain phosphate buffer and polymer test solutions as described in Section 2.8. First, a concentrated solution of BP in ethanol (100 mg/ml) was prepared, after which appropriate amount of the BP solution was added to the test solutions to generate a BP concentration of up to 0.6 mg/ml. This concentration was hypothetical and assumed that all added amount of BP was dissolved. The solutions were mixed on a vibration table at 100 rpm for 72 h, after which samples were taken out, centrifuged and the concentration of BP in the supernatant was determined by UV-spectrophotometer.

2.10. Cloud point measurements

The phase behavior of polymers in SDs and plain polymer solutions was studied by turbidimetric measurements. Appropriate amount of SD particles and plain polymers was dissolved in 50 mg phosphate buffer to yield a 0.25% (w/w) polymer concentration and approximately 0.2 mg/ml BP. Light transmission was measured by a Mettler Toledo FP90 Central Processor, Mettler FB81C MBC combined with the IPClab software (Switzerland). The temperature during the measurements was raised by 1 °C/min. The measuring interval was 30–80 °C. The light transmittance through the polymer solutions was normalized to 100% at the starting temperature. The cloud point for the samples was identified at the temperature corresponding to 96% transmittance. The measurements were performed as three sets.

2.11. Release and assay of the tablet contents

Tablet dissolution (two replicates) was carried out using a modified USP II method as previously reported [24] and 50 rpm paddle rotation speed. The vessels in the dissolution apparatus (Prolabo, France) consisted of 900 ml phosphate buffer (37 °C, pH 6.5), which provided sink condition for the dissolution of BP. Samples (1.5 mL) were collected at predefined time intervals for concentration determinations of BP and polymers. The paraben concentrations in the release medium were measured by a spectrophotometer according to the above description. The polymer concentration in the release medium was determined by size-exclusion chromatography (SEC) with refractive index detector (Optilab rEX; Wyatt Technology, Santa Barbara, CA). The mobile phase was the same as the phosphate buffer used as dissolution medium. The analyses were performed at a flow rate of 0.5 mL/min, injecting 200 μL samples into the SEC column (TSK gel GMPWXL, 7.8 mm ID × 30.0 cm L with a pore size 13 μm, TOSOH Corporation, Japan). The temperature of the RI detector was fixed at 35 °C.

3. Results and discussion

3.1. Physical state of butyl paraben in solid dispersions

The presence of crystalline BP in the tablets prior to release studies was investigated by XRD (Fig. 2).

XRD patterns of the SDs of BP in both HPMC and HPMCAS showed no peaks in the diffractograms, indicating that both systems were in amorphous form. This result was confirmed by DSC, which showed no endothermic peak at the melting point of BP (data not shown). The XRD patterns for crystalline BP showed sharp and intense crystalline peaks, which was to a large extent also observed in the PM tablets. This observation indicates that the chosen XRD method was sensitive enough to detect crystalline BP in the amounts used in tablet formulations. Based on the heights of the observed peaks and their relation to the noise level, we estimate that the detection limit for crystals in the sample is at least 1% of the total tablet content. Raman spectra for individual components and SDs were recorded in order to examine the nature of the bonds between BP and the polymers in the dispersions (Fig. 3).

The crystalline and amorphous forms of BP (as melted form) showed clear differences in their spectra. In general, the majority

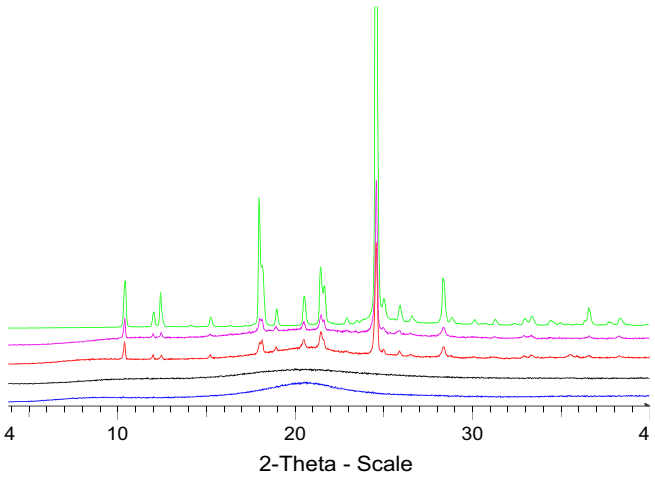

Fig. 2. X-ray diffraction pattern for tablets of crystalline BP (top), physical mixture of crystalline BP in HPMC (second from top), physical mixture of crystalline BP in HPMCAS (third from top), solid dispersion of BP in HPMC (forth from top) and solid dispersion of BP in HPMCAS (bottom). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

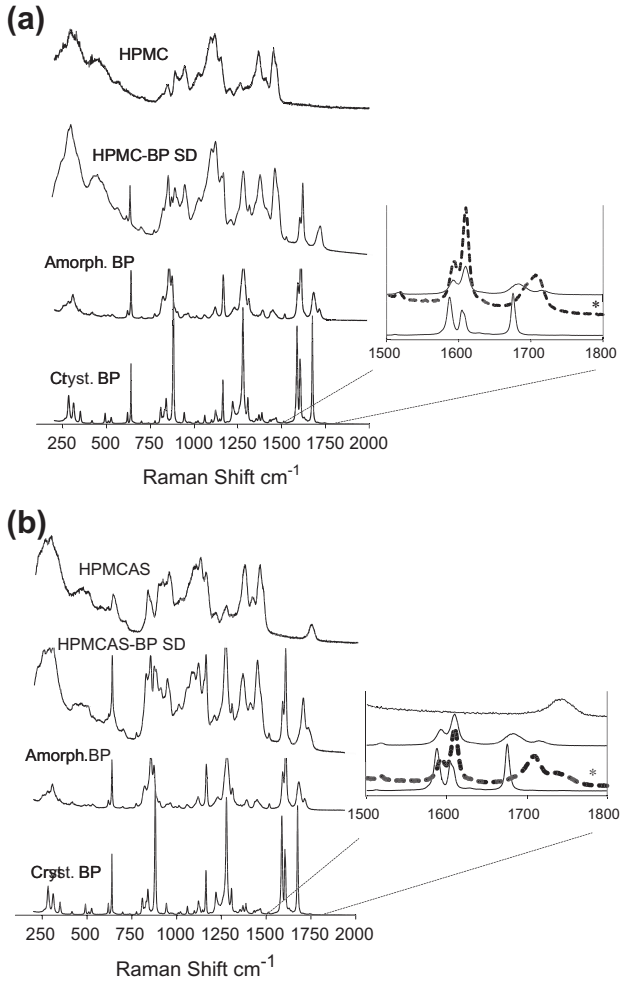

Fig. 3. (a) Raman spectra of crystalline and amorphous BP, HPMC–BP solid dispersion and plain HPMC, (b) Raman spectra of crystalline and amorphous BP, HPMCAS–BP solid dispersion and plain HPMCAS. The inserted figures illustrate a close-up of the wave numbers between 1500 and 1800 cm^{-1}. The lowest spectrum is the crystalline form, the dotted spectrum* is the SD form, and the third spectrum from below is the melted BP. The inserted figure to the right also contains the spectra of HPMCAS.

of the peaks associated with amorphous BP were broader than those of crystalline BP, indicating a lower degree of order around the bonds. In addition, some peaks associated with the amorphous form had shifted compared to that of the crystalline spectrum, indicating that the coordination of the bond had changed as it experienced a different chemical environment. This was seen for the two peaks at 1580 and 1600 cm^{-1} and the peak at 1680 cm^{-1}. The first two peaks showed a shift towards higher wave numbers for the amorphous compared to that of the crystalline form (inserted figures). In addition, the peak at 1580 cm^{-1} exhibited lower intensity in relation to the peak at 1600 cm^{-1} for the amorphous BP. These peaks are likely attributed to aromatic C–C bonds [25,26]. Moreover, the peak at 1680 cm^{-1} for the amorphous BP was not only broadened, but a small shoulder (~1715 cm^{-1}) was also developed towards higher Raman shift compared to that of the crystalline spectrum. Shifts at these wave numbers are likely attributed to C=O (carbonyl groups) bonds [25,26]. Hence, the Raman spectrum of the amorphous form of BP (taken as the melted form) showed variations in bond coordination related to the aromatic C–C and carbonyl groups, compared to the crystalline form.

The Raman spectra of the SD formulations showed a combination of the vibrational modes that can be associated with the polymers and with BP. As seen in the inserted figures in Fig. 3a and b, no differences in terms of Raman shift could be seen between the amorphous BP in melted form and as present in the SD formulations for the aromatic C–C groups. However, evident differences could be seen between the two amorphous forms of BP with regard to the peaks associated with the carbonyl groups, as the main peak at 1680 cm^{-1} was slightly shifted towards higher wave numbers in the SD spectra. In summary, results from DSC, XRPD, and Raman showed the amorphous nature of BP in the dispersions. The exact nature of all bonds between BP and polymers is at this point difficult to deduce. However, the shift patterns attributed to the carbonyl groups suggest involvement of hydrogen bonds between BP and polymers. The ability of BP to form hydrogen bonds has been previously discussed in the literature [27].

3.2. Solubility of crystalline butyl paraben

The crystalline solubility of BP in test solutions of plain phosphate buffer and 10 mg/ml polymers was measured. The solubility of BP in both plain phosphate buffer and HPMC solution was 0.21 ± 0.01 mg/ml, whereas the solubility in HPMCAS solution was 0.24 ± 0.02 mg/ml.

3.3. Inhibitory effect of polymers on recrystallization from supersaturated solutions

The inhibitory effect of the polymers on recrystallization of BP from supersaturated solutions were evaluated by adding a concentrated solution of BP in ethanol (100 mg/ml) to the test solutions containing plain phosphate buffer, 1.0 mg/ml and 10 mg/ml polymer. Fig. 4 illustrates the measured concentration of BP in test solutions after 72 h, as the function of total concentration of BP. The concentration on the x-axis is a theoretical concentration, assuming that all BP was dissolved in the solution. Due to the solubility limit of BP, this was not always the case.

Linear correlation was obtained between the added amount of BP and the concentrations in plain phosphate buffer for concentrations less than 0.2 mg/ml (e.g. just below the crystalline solubility). Increasing the added amount to 0.6 mg/ml showed non-linearity, which coupled with observed precipitation in the test solutions implied solution saturation and crystallization of BP. The dashed trend line for the first three measuring points is extended beyond the respective actual coordinates to illustrate the line of equal

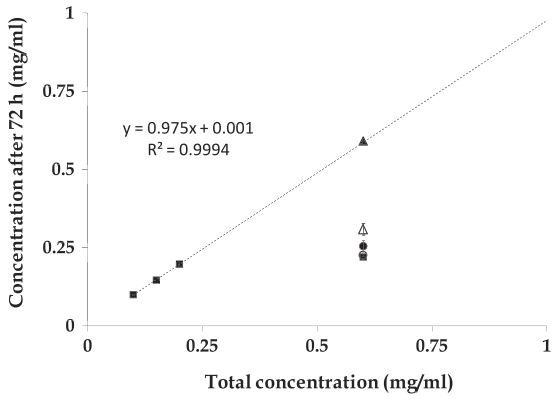

Fig. 4. Inhibitory effects of polymers on the recrystallization of BP in plain phosphate buffer (squares), 1 mg/ml HPMC (open circle), 10 mg/ml HPMC (filled circle), 1 mg/ml HPMCAS (open triangle), and 10 mg/ml HPMCAS (filled triangle).

concentrations in both the initial and the test solution, illustrating that all BP added to the solution was solubilized. As encountered in the literature, in some cases supersaturated solutions may show a metastable zone (giving an apparent higher solubility), within which spontaneous nucleation is not likely to occur until the metastable limit. At this point, a sudden spontaneous nucleation, seen as a drop in monomer concentration, occurs [28,29]. Depending on the type of polymer used in the test solutions containing 0.6 mg/ml BP (i.e. threefold higher concentrations than the solubility level), different degrees of supersaturation could be observed. Solutions containing 1 mg/ml (0.1%, w/w) HPMC and HPMCAS were able to maintain 0.22 and 0.31 mg/ml BP in non-crystallized form, respectively. Compared to the concentration of BP in plain phosphate buffer (0.22 mg/ml), this showed that HPMCAS had a notable influence on the crystallization of BP, whereas HPMC had virtually no effect for the stated polymer concentration. Increasing the polymer concentration to 10 mg/ml showed higher discrimination between the crystallization inhibitory effect of HPMCAS and HPMC. By using HPMCAS, the entire amount of added BP (in line with the hypothetical total concentration and the equal concentration trend line) was obtained, indicating that this polymer concentration could maintain at least 0.6 mg/ml BP in the supersaturated condition during 72 h. In this polymer concentration, HPMC also showed the ability to increase the level of supersaturation ([BP] = 0.31 mg/ml); however, the results were modest compared to that of HPMCAS.

In order to gain an understanding of the physical state of the BP in precipitated solutions, XRD measurements and plane polarized microscopy was conducted on the solutions containing plain phosphate buffer and 10 mg/ml polymer. Microscopic images revealed that in plain phosphate buffer without polymers, extensive crystalline growth of BP was observed (Fig. 5a). The size of the crystal aggregates varied from few micrometers to about 3 mm. In the solution containing HPMCAS, no crystalline structures could be observed (visual detection limit of approximately 1–2 μm). This finding was confirmed by XRD measurements of the solution (data not shown). In the case of HPMC solution, crystalline structures were observed. However, the size of the crystals was approximately 2–60 μm, which was clearly smaller, compared to those of plain phosphate buffer (Fig. 5b). Based on these observations, it is not possible to at this point surely conclude that the ability of HPMCAS to maintain BP in supersaturated condition is only due to inhibition of nucleation. It is also possible that the observed effect is due to inhibition of crystalline growth by polymer adsorption on very small crystals in primary growth state [9,28]. This statement is based on that both XRD and microscopy have a certain level of detection, which cannot identify small amounts of crystals in primary growth states.

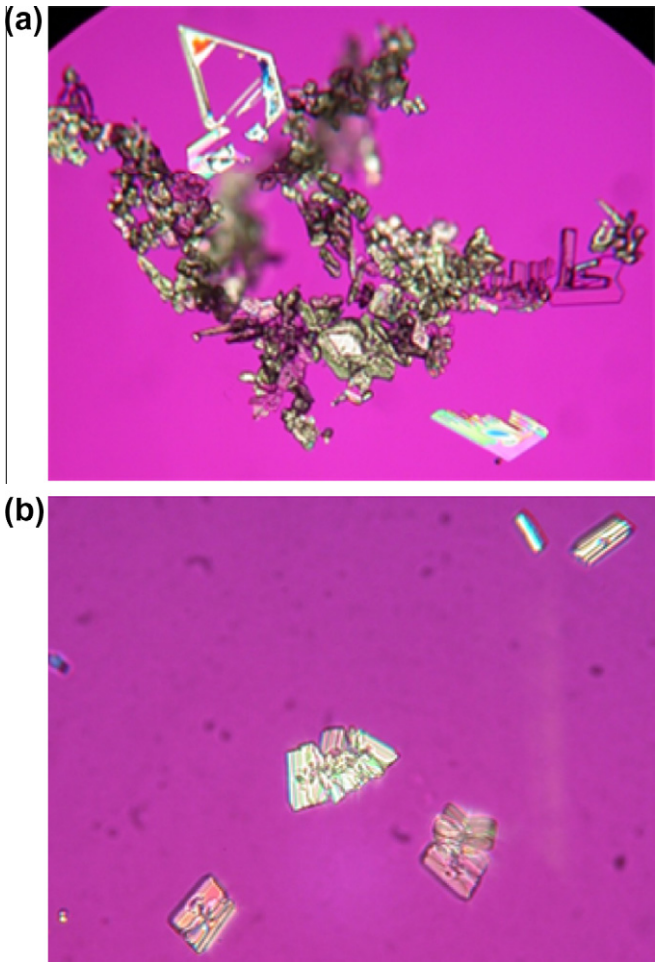

Fig. 5. Appearance of the BP crystals in (a) phosphate buffer and (b) 10 mg/ml HPMC solution. The size of the crystals is not comparable from the photographs as they are taken with different magnifications. However, as seen with scales in visual field of the microscope, the approximate size of the crystalline agglomerate was assessed based on markings on the microscope objective to 1 mm and 50 μm for (a) and (b), respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Tablet dissolution studies

The release pattern of BP and polymers from the SD and PM tablets is illustrated in Fig. 6a and b. Regardless of the polymer type, the PM formulations showed similar release rates for BP and polymers, indicating matrix erosion as the main release mechanism. However, the tablets based on HPMCAS eroded at a considerably faster rate (~7 h) compared to HPMC-based formulation (~12 h) (Table 2). During visual observation of the HPMCAS-based PM formulation, it was seen that the tablets were rapidly disintegrated in a manner not according to the slow dissolution of polymer from the outer gel layer of the tablets. The HPMC-based PM formulation did form a gel layer and slowly dissolved as a coherent matrix.

The release from the HPMC-based PM tablets was somewhat faster than that of the SD tablets (T50-values of 5 and 6 h and T80-values of 7.5 and 8.2 h for the PMs and SDs, respectively). This difference was more pronounced in the case of HPMCAS tablets, where the PM formulation eroded at much higher rate than that for the SD formulation (T50-values of 2.5 and 6 h and T80-values

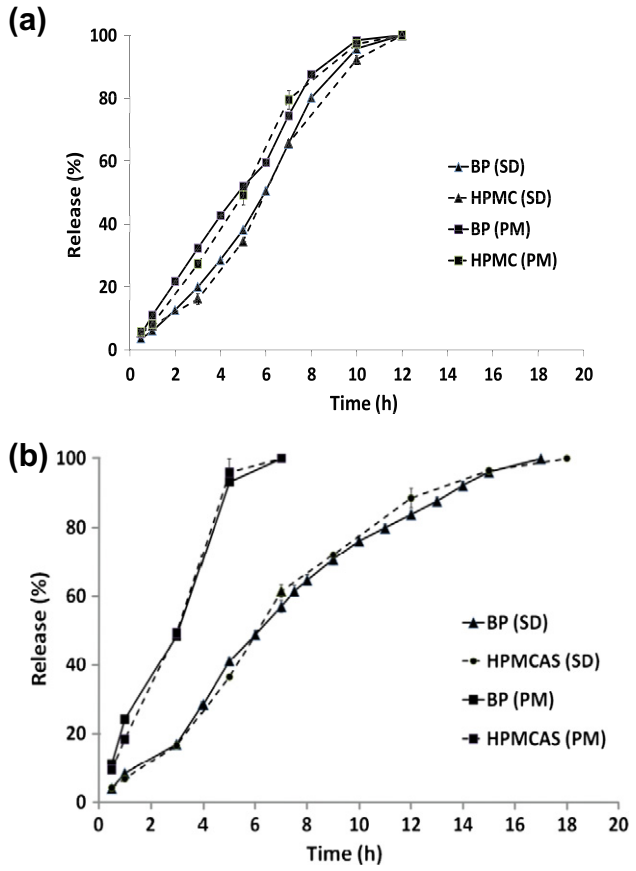

Fig. 6. The release profiles for tablets comprising (a) solid dispersions and physical mixture of BP and HPMC and (b) solid dispersion and physical mixture of BP and HPMCAS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
T-values for the physical mixture and solid dispersion tablets.

	T_{50}	T_{80}	T_{100}
HPMCAS–BP PM	2.5	4.2	7
HPMC–BP PM	5	7.3	12
HPMCAS–BP SD	6	10.8	18
HPMC–BP SD	6	8.2	12

of 4.2 and 10.8 h for the PMs and SDs, respectively). Similar to the PM tablets, the release of BP and polymers occurred at the same rate. This showed that in spite of initial molecular dispersion of BP in the polymers and their ability to keep BP in supersaturated condition, the release mechanism was still mainly governed by matrix erosion. This result suggests that BP is either rapidly precipitated in the gel upon hydration of the matrix or do not readily leave the tablet. The slow release of HPMCAS-based SD tablets was most evident in the time interval approximately after the T_{50}-points, where this formulation showed a notable decelerated release kinetic compared to that of the HPMC-based formulation (Table 2). In this regard, comparing the SD formulations of HPMC and HPMCAS, it can be seen that both formulations exhibited the same T_{50}-values for the release of BP and polymer, whereas their T_{80} and total erosion time values differed more.

In addition, visual differences could be seen between the two SD formulations during the release. The HPMC-based formulation constructed a thick gel, whereas the HPMCAS matrix virtually formed no or a very thin gel layer around the tablet. Moreover, the gel layer of the HPMC-based SD formulation was opaque (Fig. 7).

3.5. Explanations for the dissolution differences between HPMCAS and HPMC tablets

In spite of the much lower molecular weight of HPMCAS (Table 1), the SD formulation of this matrix released at a considerably lower rate compared to that of HPMC. Moreover, the erosion rate difference between the SD and PM tablets was much larger for HPMCAS compared to that of HPMC. Below, possible explanations for these behaviors are discussed.

3.5.1. The influence of matrix wettability

The lower dissolution rate of the HPMCAS–BP SD tablets compared to that based on HPMC may be due to lower hydrophilicity, hence wettability of the matrices. This hypothesis was tested by measuring the contact angle of the dissolution medium at the surface of the tablets. If the HPMCAS-based SD formulation possessed lower wettability compared to that of the HPMC formulation, the

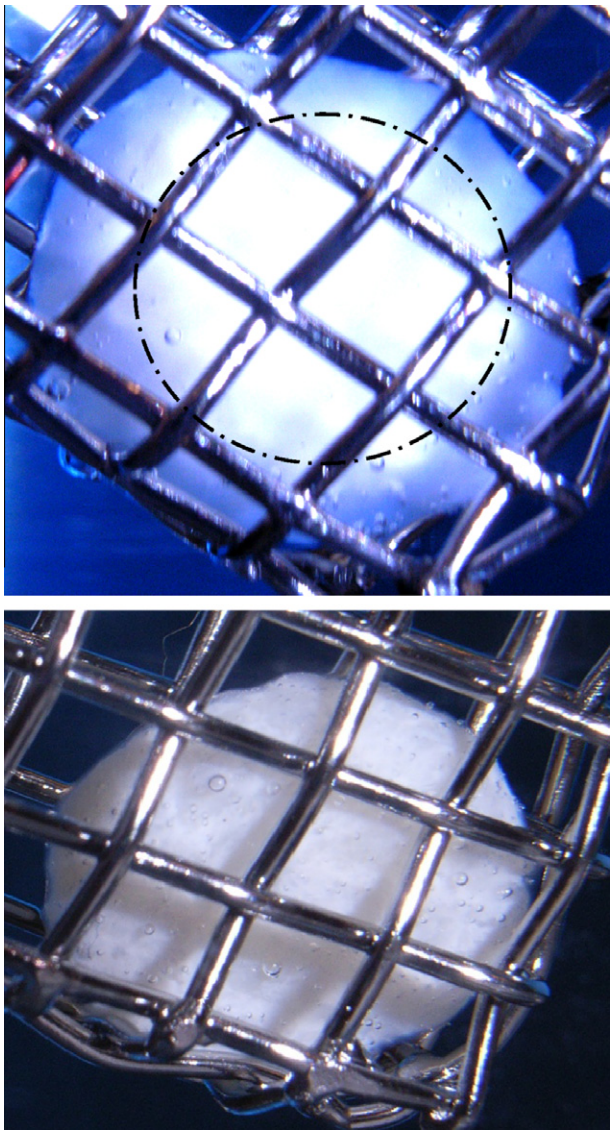

Fig. 7. Digital photographs representing solid dispersion tablets of HPMC–BP (top) and HPMCAS–BP (bottom). The photographs are taken with same magnification and same distance to the tablets, meaning that the sizes are comparable. The dashed line in HPMC solid dispersion represents a rough estimation of the position of the swelling front as seen by mere visual inspection. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

contact angle of the dissolution medium on HPMCAS should be higher, implying lower liquid distribution and wettability. However, the measurements showed contrary results as the obtained contact angles were in the order: HPMCAS–BP SD (46.6°), Plain BP (53.9°), HPMC–BP SD (63.6°) and plain HPMC (74.5°). This result is not strange as both the acetyl and the double carboxylic acid sites on the succinate groups of HPMCAS render the polymer more hydrophilic. Nonetheless, this finding indicates that the slower dissolution of the HPMCAS SD tablets is not due to decreased wetting properties of this matrix.

3.5.2. The influence of the butyl paraben as cloud point decreasing component in the matrices

During the release process of the HPMC-based SD tablets, it was observed that the gel layer around the tablets was opaque (Fig. 8). This observation can be a result of two factors: one being the presence of particulate BP in the gel and the other being that the phase behavior of HPMC was altered due to the presence of intimately close BP in the SD matrices. These two explanations do not exclude each other, and they both may be present factors in the gel layer.

Factors affecting the phase behavior of HPMC are known to ultimately affect the performance of swellable matrix tablets [30–32]. In the present study, in spite of higher molecular weight, the HPMC-based SD formulation showed faster release and dissolution behavior compared to that of HPMCAS-based formulation. Therefore, it is possible that BP may have decreased the cloud point of HPMC at the relevant concentrations in the gel layer to a point below the temperature of the release measurements, e.g. 37 °C. In order to check this hypothesis, turbidimetric measurements were conducted on dissolved SD powder in phosphate buffer in proportions corresponding to 0.25% polymer solution (giving a calculated concentration of BP, below its solubility limit). It was found that the cloud point of HPMC from the SD system had decreased compared to plain HPMC solution from 63.8 to 60.6 °C. For the HPMCAS SD or plain polymer solution, no cloud point was observed during the measuring interval, an indication of the higher hydrophilicity of this polymer compared to that of HPMC, which was in accordance with the contact angle measurements.

The clouding temperatures, which have been observed for HPMC, are far from the temperatures valid during release. As previously reported, the clouding behavior of HPMC is a concentration-dependent phenomenon [33]. Assuming that the polymer concentration at the erosion front of the dissolving matrix is approximately 10% [14,34], the implication of the presence of BP may affect the functionality of the tablet at 37 °C. In recent work, it was found that with the presence of BP, the cloud point of 10% HPMC (the same grade and batch used in this study) was decreased to values as low as 55 °C. This is a marginal concentration effect compared to the obtained results in this study. This indicates that the influence of BP on the clouding of HPMC was not decisive for the rate of tablet dissolution. Hence, the observation of opaque gel layer should rather be a consequence of precipitated BP in the gel layer.

The presence of crystalline BP in SD matrices of both HPMC and HPMCAS was examined by XRD measurements, conducted directly on both HPMC- and HPMCAS-based SD tablets, approximately 2.5 h after the initiation of the release process. The XRDs showed traces of crystalline BP in only the HPMC-based SD tablet (Fig. 8). These results were further supported by plane polarized microscopy, where the presence of crystals in the gel layer of HPMC-based SD was clearly seen. Therefore, it can be concluded that BP crystallized in the HPMC-based SD matrices upon hydration without being able to diffuse to the erosion front. No evidence was found for this behavior in the HPMCAS matrix.

3.5.3. The influence of the internal pH of the gel

One underlying factor for the slower dissolution of the HPMCAS SD tablets compared to that of HPMC may be that the carboxyl acid groups substituted on HPMCAS may decrease the local pH in the matrix, to a point affecting the swelling and dissolution of this polymer. In order to check for this hypothesis, a series of polymer solutions of various concentrations were made in phosphate buffer and their pH and appearance were studied.

A decrease in the solution pH was observed already at 0.5%, where the pH dropped from 6.5 to 6.12 (Fig. 9, Table 1). At higher concentrations, the pH of the solution dropped below the solubility threshold for HPMCAS, which was noted as partial dissolution of the polymer. As the concentration increased, the amount of dissolved polymer drastically decreased and the pH was also decreased to an almost steady state. Hence, the concentration of HPMCAS affected the pH and the amount of undissolved polymer in the solutions.

Based on the approximation that the polymer concentration at the erosion front is roughly 10%, this indicates that during the tablet-release trials, the internal pH of the HPMCAS matrix had dropped well below the threshold necessary for the swelling and dissolution of this polymer. This in turn affected the rate of water transport into the matrix, an outcome which decreased the rate of total drug and matrix hydration.

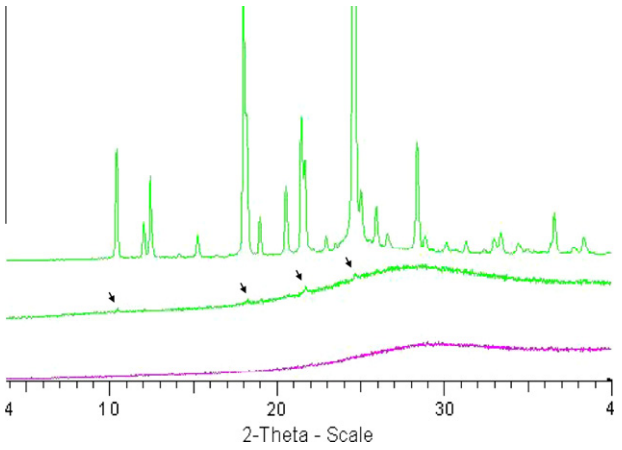

Fig. 8. X-ray diffraction pattern for tablets of crystalline BP (top), hydrated solid dispersion HPMC–BP tablet (middle plot) and hydrated solid dispersion HPMCAS–BP tablet (bottom). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

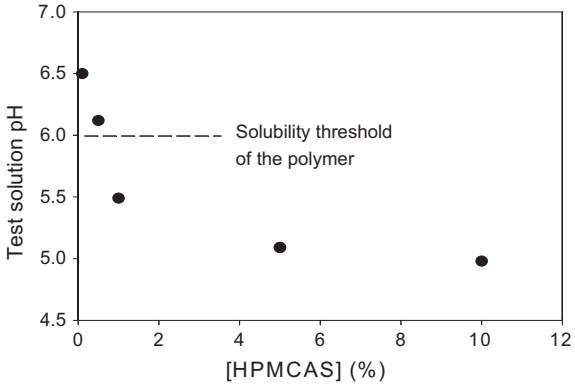

Fig. 9. The influence of HPMCAS concentration in phosphate buffer on the solution pH.

3.5.4. Summary on the dissolution differences between HPMCAS and HPMC tablets

The results from the release studies have shown that the PM tablets dissolved faster than that of SD matrices, an observation valid for the formulations of both polymer types. In this respect, the PM of HPMCAS formulation was clearly distinguished from the SD tablets. Finally, the HPMCAS-based SD formulation exhibited a considerably slower overall erosion than that of HPMC. In addition, both SD formulations exhibited erosion-based release mechanism in spite of the increased dissolution rate of BP.

As Ju and co-workers showed, the molecular weight of polymers is an important factor for their release from erosion front of swellable matrix tablets [35,36]. In these studies, it was found that a system containing a lower molecular weight polymer exhibits higher critical disentanglement concentration (polymer concentration at which individual or small clusters of the matrix is dissociated from the gel). This will in turn lead to faster matrix erosion. Due to the lower molecular weight of HPMCAS, this effect can be one of the contributing factors for the higher dissolution rate of the PM matrix comprising this polymer compared to that of HPMC. However, this factor cannot alone contribute to the rapid disintegration of the PM formulation of HPMCAS. An additional factor influencing the swelling and gel formation of the polymer is likely at play in the erosion mechanism of this matrix. This factor is plausibly the pH-dependent dissolution of this polymer as described earlier, leading to inability of this polymer to quickly construct a retardative gel layer, leading to the disintegration rather than slow dissolution of the matrix by mechanisms valid for swellable matrix tablets.

In the case of SD tablets, a series of circumstances resulted in a slower erosion of the HPMCAS tablet compared to that of HPMC and a non-discriminating release of BP from both HPMCAS and HPMC tablet formulations. The mechanism by which this occurred was different for the two polymer formulations. The characterization work showed that both polymers, presumably by hydrogen bonds, were able to sustain BP in molecularly amorphous form in dry state. However, upon hydration, HPMCAS proved to be able to maintain BP in supersaturated state much more efficiently than HPMC. Now, looking at the tablet-dissolution process, a thicker gel layer was observed for the HPMC tablets compared to that of HPMCAS, which showed no or a very thin gel layer. This was attributed to the low local pH of the tablet, inhibiting free dissolution and swelling of this polymer. Although similar to the first-order release kinetics of hydrophobic matrices, the substance release and erosion behavior of HPMCAS matrix was very much in accordance with the mechanism of hydrophilic matrix tablets. This statement is based on the fact that both BP and polymer were released at the same rate, which is a typical erosion-based release mechanism. Therefore, concerning the dissolution and release behavior of this formulation, two mechanistic scenarios are possible. In one case, assuming that the release and tablet dissolution is controlled by a gel layer, this implies that tablet dissolution follows the mechanism of a swellable matrix tablet, with a very thin gel layer containing a steep concentration gradient of BP. In this case, where the release can be discussed in terms of front movements, the diffusion front of BP is plausibly very close to the swelling front and the diffusion path is very short. In the other case, assuming that no gel layer is constructed around the tablet, the mechanism of matrix erosion is likely governed by surface erosion of thin hydrated films of HPMCAS–BP complex, which upon dissociation from the matrix separate into free monomers of BP and HPMCAS in the dissolution medium bulk. Hence, the erosion-based release mechanism of BP (in spite of exhibiting better dissolution properties) was likely due to i) the strong ability of this polymer to keep BP in supersaturated solution and ii) the matrix providing a short diffusion path to the outer layer of the gel. In the case of HPMC tablets, the release mechanism of BP was mainly governed by typical erosion mechanism determined by the polymer dissolution rate as this substance crystallized in the matrix upon hydration and the matrix followed a slow dissolution typical for swellable matrix tablets.

4. Conclusions

We have investigated the solid state and dissolution behavior of amorphous solid dispersions of a model crystalline substance, BP in HPMC and HPMCAS. On the basis of these characterizations, the release behavior of the drug substance was investigated from binary tablet compositions containing the SD and PM of the components. In a concentration-dependent manner, HPMCAS was found to keep the solution in highest extent of supersaturation compared to that of HPMC. In spite of its lower molecular weight, HPMCAS tablets gave considerably lower erosion rate than that of HPMC, a phenomenon which was associated with the lowering of the internal pH of these matrices, leading to decreasing solubility of the polymer and water transport into the matrix. This in turn prolonged the dissolution and swelling of the polymer chains, resulting in a very slow hydration of the matrix. The release mechanism was clearly governed by polymer dissolution and matrix erosion. No discrimination was found between the release mechanism of SD and PM formulation of BP. The underlying mechanism for this common behavior was proposed to be different for the two polymer formulations. In the case of HPMC, BP was evidently recrystallized during its residence in the gel, hence negating release of molecular state of this compound. In the case of HPMCAS, both the ability of this polymer to keep BP in a metastable solubility zone and a very short diffusion path through the matrix were discussed as reasons for maintaining BP in a molecular state during the release process. A specific molecular interaction between HPMCAS and BP may have resulted in a complex formation between the two compounds, resulting in a higher apparent molecular weight of the polymer. This in turn gave lower disentanglement concentration and lower release and dissolution rate of the tablet.

In spite of the non-discriminating release from the SD tablet formulations compared to that of PM, these results suggest other advantages SD technology may bring to extended-release formulations of this type, namely that upon release from the tablet, the drug can more easily dissolve in the dissolution bulk, negating the issues of dissolution in the BSC II and IV drugs.

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