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Research Paper

The Impact of Dose and Solubility of Additives on the Release from HPMC Matrix Tablets—Identifying Critical Conditions

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Purpose. The dissolution of HPMC matrix tablets containing different amounts of highly soluble (mannitol) or poorly soluble (dicalcium phosphate, DCP) was studied to deduce the parameters critical to release robustness.
Methods. The release of HPMC and additives was studied using a modified USP II method at two paddle stirring rates, 50 and 125 rpm, at HPMC content varying from 15% to 100%.
Results. At HPMC contents between 30% and 35% a critical point was identified and found crucial to the release from the HPMC/mannitol tablets. Below this point the matrix rapidly disintegrated in a non robust manner. At higher HPMC contents the mannitol release became increasingly diffusion controlled with maintained matrix integrity. The release robustness was lower for HPMC/DCP than HPMC/mannitol tablets at high HPMC contents, however, lacking critical points. The critical point was interpreted as the percolation threshold for HPMC and differences explained in terms of water transport into the matrix.
Conclusion. The release robustness was lower for formulations with additives of low solubility having an erosion controlled release than for additives with higher solubility and a diffusion controlled release. However, for additives creating a steep osmotic pressure gradient, an HPMC content above the percolation threshold becomes vital for maintaining the release robustness.

KEY WORDS: drug load; HPMC; percolation threshold; release robustness; solubility.

INTRODUCTION

Extended release gelling matrix tablets have been widely used in the pharmaceutical industry as they conform to both regulatory demands, ease of manufacturing and potential for zero-order release kinetics. However in spite of their many advantages, these formulations can sometimes exhibit drawbacks concerning their release functionality. For example, a collapse of the matrix can occur when large shear forces in their release environment are present. In addition, tablet disintegration, rather than controlled erosion as a monolithic unit, can be facilitated by components in the formulation enhancing rapid water transport into the tablets (1,2). *In vivo*, the lack of release robustness has been linked to faster erosion of tablets during fed compared to fast conditions leading to increased amounts of drug absorbed through the gastrointestinal tract (3–5). As these tablets can comply with relatively high dose, this can ultimately imply risk for dose dumping and jeopardize an innocuous pharmaceutical treatment of the patient.

The rate of drug release from gelling matrices is strongly dependent on the gel formation and erosion behavior of the hydrophilic polymers. It is essential that a gelatinous layer is quickly formed around the tablet and that the overall swelling and erosion of the matrix occurs in a controlled manner. The process of gel formation commences as the hydrophilic polymers are hydrated and undergo a progressive phase transition from glassy to rubbery state. This in turn leads to the solvation of the individual chains, originally in an imperturbated state. As the swollen matrix retains more water, the swelling continues until the shear forces in the dissolution medium can disjoint individual polymer chains from the matrix (6,7). The concentration at which this occurs is referred to as the critical disentanglement concentration, which can be linked to the intrinsic viscosity of the polymers in a given dissolution medium (8,9). The concentration at which this occurs is referred to as the critical disentanglement concentration, which can be linked to the intrinsic viscosity of the polymers in the given dissolution medium (8,9). The release profile of the additives during the course of the matrix dissolution is highly dependent on the solubility of the used additives. As the solubility of the additives increases, the release is more determined by a diffusion mechanism. As the solubility of the additives decreases the release will be more governed by the erosion of the matrix (6,10).

The influence of the amount of matrix forming polymer in controlled release formulations has been interpreted by employing the percolation theory. This theory was first applied by Leuenberger in the pharmaceutical field in order to describe the release from extended release hydrophobic

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matrices (11). In a binary tablet composition, this theory concerns the probability of finding one of the tablet components at an arbitrary location in the matrix. This probability can yield a most likely scenario for each component to form an infinite continuous cluster in the matrix. The percolation threshold (P_c) is an important factor in this context and defines the lowest concentration of forming continuous phase of the respective component. The fundamental equation of the percolation theory expresses changes in the studied properties based on the percolation threshold (P_c):

$$X \alpha S(p - p_c)^q \quad (1)$$

where X is the studied property, S is a constant, p is the observed parameter and q is a critical exponent.

The percolation theory has been applied in both binary and multi-component gelling matrices (12–15). The studies have shown that both the release and water retaining properties of hydrophilic extended release matrices can undergo a sudden change below the P_c of the matrix former. As these studies have indicated, many compositional factors can influence the P_c of the matrix former. However, more studies are needed to provide insight to the differences in the expression of the percolation threshold between systems which are governed by diffusion or erosion. In addition, as the Pc expresses a critical point in the release functionality of the tablets, it is also of interest to examine the effect of this point on the different release mechanisms and hydrodynamic conditions.

The objective of the present study was to study the release robustness from tablets containing different amounts of hydroxypropyl methylcellulose (HPMC) and a highly or poorly soluble additive, mannitol and dicalcium phosphate. The influence of shear forces on the tablet was studied by changing the hydrodynamic conditions during the release. The results were interpreted in the light of the theory of percolation.

MATERIALS AND METHODS

Materials

Hydroxypropyl methylcellulose of grade 90SH-100 SR (Hypromellose, Shin-Etsu Chemical Co., LTD. Tokyo, Japan) and mannitol (Pearlitol 50, Roquette, France) or calcium phosphate dihydrate (DCP; Merck, Germany) were used in the tablet compositions.

Characterisation of the Starting Materials

The solubility of the additives was determined in the used dissolution media at 37°C. The concentration of a saturated solution of mannitol was measured by chromatography according to the method described in "HPMC/mannitol assays". The solubility of DCP was estimated by mixing 120 mg of model substance in 500 ml dissolution media for approximately 1 h (three replicates), followed by centrifuging the suspension and carefully withdrawing the supernatant. The remaining media containing the DCP sediments were dried in an oven until no more water was evaporated. The weights of the sediments were measured and the mass of the dissolved DCP was calculated.

The size of the primary particles of additives was determined by laser diffraction method (Malvern, Mastersizer 2000, Scirocco dispersion unit, England). The apparent density of the starting materials was determined by He-pycnometry (Micromeritics, Accupyc 1330, USA), using 1.5 bar pressure and ten consecutive runs and purges.

Tablet Preparation

Binary tablet compositions containing different amounts of HPMC and additives were prepared using HPMC amounts ranging from 15% to 100% in the compositions. The remaining part of the compositions was consisted of mannitol or DCP. The compositions were named accordingly: (HPMC content)/(additive content) with M and D as postfixes for mannitol and DCP, respectively. Prior to compaction, the starting materials for each composition were mixed in a small diffusion mixer (Turbula, Willy A. Bachhofen AG Maschinenfabrik, Switzerland) at medium speed for 2 min. Tablets were produced by direct compaction using 10 mm flat faced punches and mean weight of 311±5 mg. The compaction forces varied between the different formulation series (0.8–1.4 MPa). The resultant tablet heights were 3.0±0.3 mm. Tablet hardness, expressed as the radial tensile strength (σ) was derived from the force (F) needed to fracture the tablets (C50 Holland Tablet Hardness Tester Engineering Systems, England) and was calculated according to:

$$\sigma = \frac{(2F)}{(\pi D h)} \quad (2)$$

where D is the tablet diameter and h is the tablet height.

The theoretical porosity E (%) of the tablets was calculated according to Eq. 3:

$$E = \frac{\left(\pi r^2 h - \left(\frac{X m_{tot}}{\rho_{(HPMC)}}\right) + \left(\frac{(1-X) m_{tot}}{\rho_{(additive)}}\right)\right)}{\pi r^2 h} \times 100 \quad (3)$$

where r is the radius of the tablet (cm); ρ is the apparent density (g/cm^3), X is the ratio HPMC and m_{tot} is the total weight of the tablet (g).

Release and Assay of the Tablet Content

The release of both HPMC and additives was determined from the tablets (two replicates). Tablet dissolution was carried out using a USP dissolution apparatus (Varian 705 DS, Weston Parkway Cary, NC, USA) equipped with PEAK vessels. A modified USP II method was used and the paddle rotation speeds at 50 and 125 rpm were applied. The modification compared to the standard methods was that the tablets were fixed in baskets (2.5×2.5×1 cm with mesh size of 2.5×2.5 mm), which were positioned 2.5 cm from the shaft and 4 cm from the blades of the paddle. The blade of the paddle was placed about 1 cm above the bottom of the vessel. The release medium consisted of 700 ml phosphate buffer (37°C, I=0.1, pH=6.8).

HPMC/mannitol assays

A sample of 1 ml was collected at predefined time intervals for the HPMC and mannitol assays. The polymer concentration in the release medium was determined by size exclusion chromatography with refractive index detector (SEC-RI). The mobile phase consisted of 0.1 M phosphate

buffer (I=0.1, pH 6.8) with 0.02% w/w NaN_3. The analyses were performed at a flow rate of 0.8 ml/min, injecting 100 μl samples into the SEC column. The column, a TSK gel $GMPW_{XL}$, 7.8 mm ID×30.0 cm L with a pore size 13 μm (TOSOH corporation, Japan) was placed in a column oven at 30°C. The temperature of the RI-detector (Varian, RI-4, Japan) was fixed at 35°C and the range at 1/8. The software CSW32 Chromatography Station was used to evaluate the raw data.

The concentrations of mannitol in the samples were analysed using liquid chromatography equipped with a mass spectrometry (MS) detector (Waters, Micromass ZQ 2000, USA). The mobile phase consisted of acetonitrile/water in 45:55 volume proportions and 0.2 vol.% formic acid. The analyses were performed at a flow rate of 0.15 ml/min. Five-microliter sample was injected into the column [Genesis NH_2, 250×2.1 mm, with pore size 3 μm and 120 Å (USA)]. The MS detector used a cone voltage of 15 kV with the mass number (m/z) set at 183. The source and desolvation temperatures used were 120°C and 350°C, respectively.

HPMC/DCP Assays

The release of HPMC from HPMC/DCP tablets was determined according to the method described in "HPMC/mannitol assays". The release of DCP for tablets containing the ratio 70:30 was studied at 50 rpm. Owing to the low solubility of DCP, focused beam reflectance measurement (FBRM®) was used to determine the release of DCP in particulate form. The use of this technique for the purpose of studying release kinetics from tablets has been previously reported (16,17). In brief, the FBRM technique allows particle registration as a continuous beam of monochromatic laser light is launched down a probe (Lasentec®, model S400Q, Mettler Toledo, USA) with the focal point positioned at the interface between the probe window and the actual process. As the scanning beam sweeps across the face of the probe window, individual particles or aggregates of particles backscatter the laser light back into the probe, which are translated into chord lengths. Hence, a measure of particle count and size is obtained.

The FBRM measurements were performed by placing the probe in the dissolution medium. It was found that the most optimal performance of the FBRM probe was obtained when sufficient particle flow was present in the dissolution medium. The flow dynamics in the dissolution medium was sufficient for the release studies performed at 125 rpm. Therefore, due to the low flow dynamics at 50 rpm, the FBRM measurements were performed at predefined time intervals, at which the paddle flow was increased to 125 rpm. At these time intervals the basket containing the tablet was carefully removed and the rotation speed was increased. In the case of continuous particle counts, 5 s scanning duration was applied. The registered particle size range was 1–100 μm.

RESULTS

Raw Materials and Tablet Properties

The measured solubility of mannitol and DCP in phosphate buffer was 240 and 0.05 mg/ml, respectively. Apparent densities of HPMC, mannitol and DCP were 1.34, 1.49 and 2.14 g/cm^3, respectively (standard deviations less than 0.01 g/cm^3). The median of the primary particle size distribution for the additives was between 25 and 56 μm.

Compaction was conducted in such way that all tablets featured similar relative surface area exposed to the dissolution medium. This implied compaction with different forces for each composition and hence differences in tablet porosities ranging from approximately 13% to 15% for HPMC/mannitol and 14% to 28% for HPMC/DCP tablets. Both HPMC/mannitol and HPMC/DCP tablets exhibited the same lowest radial tensile strength (1.5 MPa) in the respective formulation series.

The Influence of Solubility and Dose Effect on the Release

The relative release of HPMC/mannitol tablets at 50 rpm paddle speed is illustrated in Fig. 1a and Table I.

With increased amount of polymer in the compositions the release of both mannitol and HPMC was prolonged. At HPMC concentrations of 30% and above the release of mannitol was faster than that of HPMC, indicating that diffusion contributed largely to the release mechanism of mannitol. However, for the tablets containing less than 30% polymer the release of HPMC and mannitol occurred at approximately the same rate, indicating the erosion of the

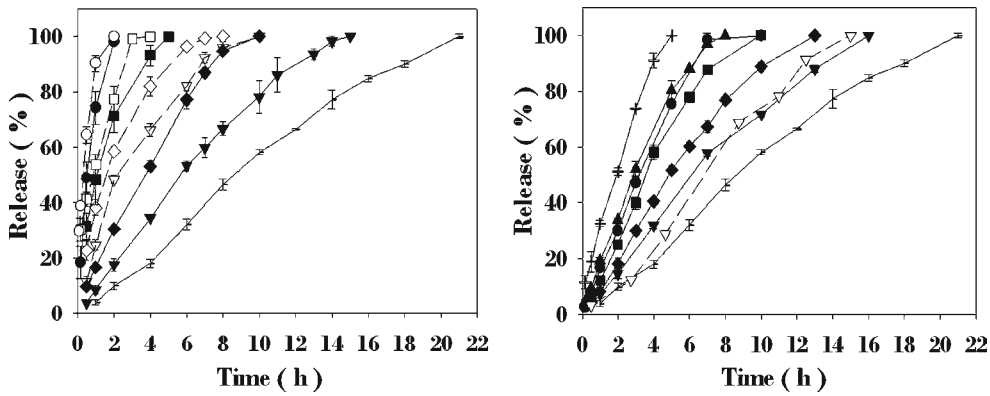

Fig. 1. Release of HPMC and additive at 50 rpm stirring rate for (*left*) HPMC/mannitol and (*right*) HPMC/DCP tablets. HPMC release is indicated as *solid lines* (*filled symbols*) and additive release as *dashed lines* (*open symbols*). According to the HPMC content, the formulations are denoted as: 100% (*solid line*), 70% (*inverted triangle*), 50% (*diamond*), 35% (*square*), 30% (*circle*), 25% (*triangle*)and 15% (*plus symbol*).

Table I. *T*-Values for HPMC/Mannitol and HPMC/DCP Compositions, Released at 50 rpm

Formul.	T_{20} HPMC (h)[a]	T_{50} HPMC (h)[b]	T_{80} HPMC (h)[c]	T_{20} man. (h)[d]	T_{50} man. (h)[e]	T_{80} man. (h)[f]
15/85M	0.02	0.06	0.18	0.02	0.05	0.14
25/75M	0.11	0.38	0.86	0.07	0.26	0.64
30/70M	0.18	0.52	1.2	0.08	0.32	0.81
35/75M	0.45	1.6	3.7	0.27	1.1	2.8
50/50M	1.3	3.7	6.3	0.48	1.6	3.8
70/30M	2.3	5.6	10.2	0.82	2.18	5.73
15/85D	0.53	1.9	3.4	–	–	–
25/75D	1.1	2.9	5.0	–	–	–
30/70D	1.2	3.2	5.4	–	–	–
35/75D	1.6	3.6	6.2	–	–	–
50/50D	2.2	4.8	8.5	–	–	–
70/30D	2.8	6.2	12	–	–	–
HPMC	4.3	8.6	15	–	–	–

[a] Time when 20% of the HPMC is released
[b] Time when 50% of the HPMC is released
[c] Time when 80% of the HPMC is released
[d] Time when 20% of the mannitol is released
[e] Time when 50%, 80% of the mannitol is released

matrix as the rate limiting factor for the release of mannitol. With T_{80} at approximately 10 min, the 15/85 M tablets showed high initial release burst. Increasing the HPMC content from 15% to 30% extended the release of the tablet content with roughly 1.5 h. Further increase of polymer in the formulations by merely 5% to 35% HPMC content increased the T_{80} value of HPMC considerably (T_{80}=3.7 h). The influence of polymer content on prolonging the release from tablets was found to be more pronounced as the HPMC content increased in the tablets. As seen in the T_{80} values, this effect had a higher impact on HPMC compared to the mannitol release.

The release of HPMC from HPMC/DCP tablets containing various amounts of HPMC is illustrated in Fig. 1b. Similar to the HPMC/mannitol tablets the HPMC release rate decreased as the HPMC content increased. In addition, the relative amount of detected DCP from the formulation containing 70% HPMC at 50 rpm paddle speed is lower than that of HPMC. This has been previously observed and was assigned to the analytical feature of the FBRM technique (10,16). In brief, FBRM measures only particulate DCP and given the solubility of DCP and the amount used in the 70/30 D tablets, certain dissolution can be expected before the steady increase of particulate DCP can be measured in the dissolution medium. The influence of the DCP dissolution was investigated by calculating the total particle count per milligram DCP and subtracting the potential amount dissolved from the time, where the steady increase of DCP was seen in the plot. The result suggested the same release kinetics of DCP as for HPMC. In contrast to mannitol, the presence of DCP in the tablets did not cause in initial burst of the tablets. In addition to an overall slower release from the HPMC/DCP tablets, a more steady increase of *T*-values can be seen with increasing HPMC concentrations in the tablets (Table I).

The Influence of Hydrodynamic Conditions on the Release

The influence of shear forces in the dissolution media on the release from the two formulation series was studied by increasing the stirring rate from 50 to 125 rpm.

The rate of polymer dissolution from both HPMC/mannitol and HPMC/DCP tablets was increased at 125 rpm (Fig. 2). The 15/85, 25/75 and 30/70 M formulations exhibited a very high initial release, as the first two mentioned tablets were disintegrated within minutes (graphs not shown) and the latter exhibited T_{80} value of 25 min (Table II). The simultaneous release of HPMC and mannitol for these tablets indicated that the release of mannitol was mainly governed by erosion. After this point, the release by diffusion was increasingly promoted as the concentration of mannitol was increased in the compositions. Similar to the release behaviour at 50 rpm, the HPMC/mannitol formulations exhibited a considerable increase of HPMC and mannitol *T*-values as the polymer content increased from 30% to 35%. As no abrupt changes in the release profiles could be detected, the HPMC/DCP formulations showed a steady increase of release profile at 125 rpm with increasing amount of HPMC in the composition.

DISCUSSION

The Influence of Tablet Porosity on the Release

In general, it is believed that tablet porosity does not have a considerable impact on the release behaviour of gelling matrices (18,19). However, in compositions containing low amounts of polymer and highly soluble additives, capillary forces may partially be involved in faster transport of water into the matrix at the initial stages of tablet dissolution (20). As shown in Tables I and II, the T_{20}-values increased with the amount of HPMC in the tablets. However, no systematic trend between the increase of T_{20} and tablet porosity could be seen within and between the formulation series, hence the porosity has a minor effect on the matrix dissolution process in the investigated systems.

Estimation of the Percolation Thresholds

The faster matrix erosion and release of additive from the HPMC/mannitol compared to the HPMC/DCP tablets has

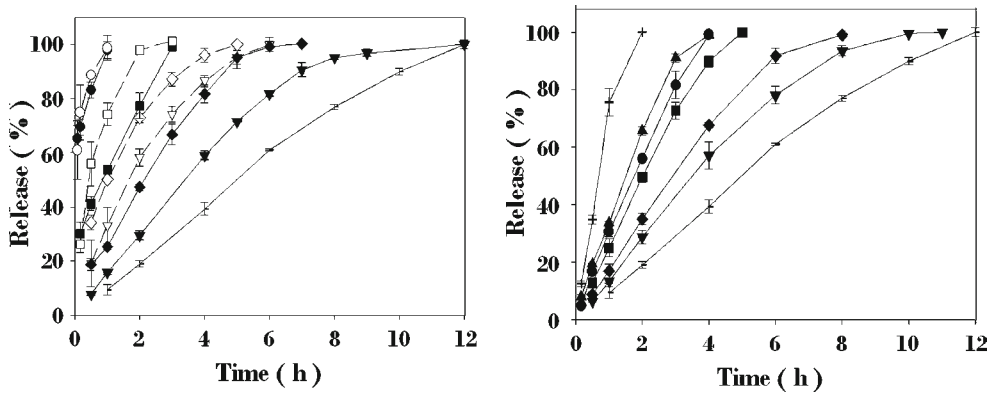

Fig. 2. Release of HPMC and additive at 125 rpm stirring rate for (*left*) HPMC/mannitol and (*right*) HPMC/DCP tablets. HPMC release is indicated as *solid lines* (*filled symbols*)and additive release as *dashed lines* (*open symbols*). According to the HPMC content, the formulations are denoted as: 100% (*solid line*), 70% (*inverted triangle*), 50% (*diamond*), 35% (*square*), 30% (*circle*), 25% (*triangle*)and 15% (*plus symbol*).

been attributed to the higher rate of water transport into the HPMC/mannitol tablets. This was proposed to be an effect of increased osmotic pressure gradient, which can be explained by:

$$J_{H_2O} \propto D_{eff} \times \frac{d\prod}{dz} \quad (4)$$

where J_{H2O} is the flux of water, D_{eff} the effective diffusion coefficient and $d\Pi/dz$ the gradient in osmotic pressure (ref. submitted article). In addition, the D_{eff} of water into the HPMC/DCP tablets is likely to decrease due to the presence of particulate DCP extending the diffusion path of water.

In the present study, the release from the two formulation series not only showed dependency on the solubility, but also on the amount of additives used in the compositions. However, the effect of dose appeared differently in the two formulation series. The increase of T_{50}-values for HPMC and mannitol from the HPMC/mannitol tablets showed a distinct discontinuity above 30% HPMC at both 50 and 125 rpm (Fig. 3). However, this release behavior was not seen for the HPMC/DCP tablets.

The sudden increase of T_{50}-values for the HPMC/mannitol tablets indicates a mechanistic shift in regards to the release of additive and tablet dissolution. This finding can be explained in view of the percolation threshold of HPMC (Eq. 1). Below this compositional point, the HPMC showed the least probability to percolate the geometrical figure of the tablet during the course of hydration and dissolution of the matrix. Therefore, the tablets below this critical point quickly disintegrated as the polymer molecules were unable to form a coherent gel with sufficient mechanical integrity. This was likely to occur in the presence of high concentrations of mannitol, which rapidly dissolved upon contact with water. Consequently, a faster water transport into the matrix and rapid wetting of the glassy tablet core was obtained. As the polymer amount in the compositions exceeded the HPMC percolation threshold (e.g. greater than approximately 30%), the tablets were able to build a coherent gel layer allowing the matrix to erode according to a gradual disentanglement of

Table II. *T*-Values for HPMC/Mannitol and HPMC/DCP Formulations, Released at 125 rpm

Formul.	T_{20} HPMC (h)[a]	T_{50} HPMC (h)[b]	T_{80} HPMC (h)[c]	T_{20} man. (h)[d]	T_{50} man. (h)[e]	T_{80} man. (h)[f]
15/85M	0.02	0.03	0.05	<0.01	0.03	0.01
25/75M	0.02	0.04	0.07	<0.01	0.02	0.04
30/70M	0.03	0.06	0.42	0.02	0.05	0.29
35/75M	0.09	0.85	2.20	0.08	0.43	1.2
50/50M	0.60	2.15	3.90	0.25	1.0	2.5
70/30M	1.30	3.40	5.83	0.60	1.7	3.5
15/85D	0.28	0.68	1.2	–	–	–
25/75D	0.52	1.63	2.6	–	–	–
30/70D	0.62	1.77	2.9	–	–	–
35/75D	0.79	2.11	3.4	–	–	–
50/50D	1.17	2.92	5.1	–	–	–
70/30D	1.43	3.58	6.25	–	–	–
HPMC	2.10	5.00	8.5	–	–	–

[a] Time when 20% of the HPMC is released
[b] Time when 50% of the HPMC is released
[c] Time when 80% of the HPMC is released
[d] Time when 20% of the mannitol is released
[e] Time when 50%, 80% of the mannitol is released

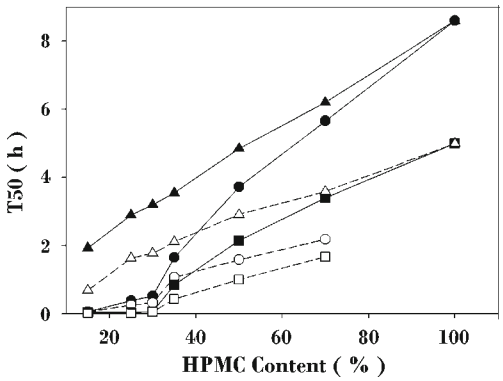

Fig. 3. T_{50}-values of HPMC from HPMC/DCP (*filled triangle*) and HPMC/mannitol (*filled circle*), and mannitol (*open circle*) at 50 rpm, and HPMC from HPMC/DCP (*open triangle*) and HPMC/mannitol, (*filled square*) and mannitol (*open square*) at 125 rpm.

the polymer chains at the erosion front of the matrix. This ultimately reduced the rate of wetting of the dry tablet core.

The alteration of the release and dissociation mechanism for the HPMC/mannitol tablets can be seen in the associated change of the rate of polymer dissolution. As seen in Fig. 4a, the tablets containing 100%, 70%, 50% and 35% HPMC were found to have approximately the same polymer release rate (mg/h). This implies that these tablets had the same critical disentanglement concentration and thereby displayed the same release mechanism of HPMC. However, with polymer contents below 30% of the composition, the absolute release of HPMC became notably faster, showing relatively fast dissolution of the tablets. These observations support a sudden shift of release mechanism from a controlled erosion and release above the polymer percolation threshold to a rapid uncontrolled release below the threshold.

In contrast to the HPMC/mannitol formulations, the HPMC/DCP tablets showed a linear increase of the T_{50}-values at 50 rpm stirring rate as a function of HPMC content (Fig. 3). This result shows that the erosion and release rate of these tablets are insensitive to the percolation threshold of HPMC in the matrix. Studies conducted on multi component HPMC matrices containing 30% DCP have suggested increased gel strength compared to formulations containing the highly soluble sprayed dried lactose (10). Consistently, the presence of DCP in the presented formulations can aid to maintain the mechanical integrity of the matrix, even at concentrations below the HPMC percolation threshold.

A further mechanistic view of the dissolution pattern of the HPMC/DCP tablets is shown in Fig. 4b. Interestingly, a gradual decrease of polymer release rate was seen as the amount of DCP in relation to that of HPMC was increased in the tablets. On one hand, as discussed earlier the increased amount of DCP in the tablets can reduce the rate of wetting of the glassy tablet core. On the other hand, as the swelling of the polymer chains proceeds, the gel retains more water to the point where critical disentanglement concentration is reached. However, increased amount of DCP in the tablets, imply incrementally higher volume fraction of particulate DCP present at the erosion front of the matrix. Consequently, DCP particles can contribute to the viscosity of the erosion front and lower polymer amount disjoint via the erosion process of the tablet. In summary, the contribution of DCP to increased mechanical strength of the hydrated matrix; slower wetting of the glassy tablet core, and the eventual contribution to the viscosity at the erosion front are likely the main factors regulating the dissolution of the HPMC/DCP tablets.

The Influence of Polymer Percolation Threshold and Hydrodynamic Conditions on the Tablet Release

The release sensitivity from the two formulation series to increasing shear forces in the dissolution medium was expressed as the ratio of the T_{50}-values at 50 and 125 rpm (Fig. 5). The T_{50}-ratios of the formulations became more alike as the HPMC content of the tablets increase above 35%. This shows that as the polymer amount increased above the percolation threshold, the influence of additives on the release decreases. In this respect, the erosion rate of the tablet became more dependent on the dissolution of HPMC.

In contrast, the T_{50}-ratios of both HPMC and mannitol from the HPMC/mannitol compositions below the HPMC percolation threshold showed higher dependency on the agitation rate with decreasing polymer amount in the tablets. The highest ratio was observed for the 25/75 M, followed by a decrease of this parameter for 30/70 and 35/65 M formulations indicated decreasing sensitivity to the agitation rate. The very fast release of the 15/85 M tablets at both stirring rates and the associated difficulties in determining the T_{50} value

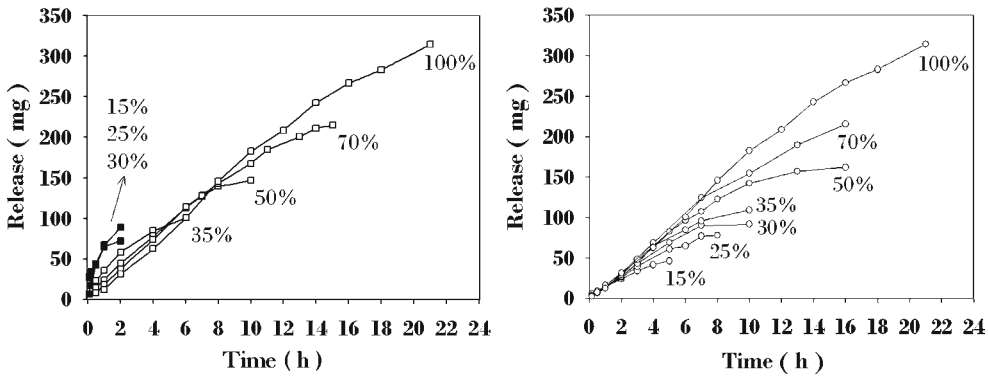

Fig. 4. The amount of released HPMC (mg) at 50 rpm stirring rate expressed as a function of time for **a** HPMC/mannitol and **b** HPMC/DCP tablets 50 rpm.

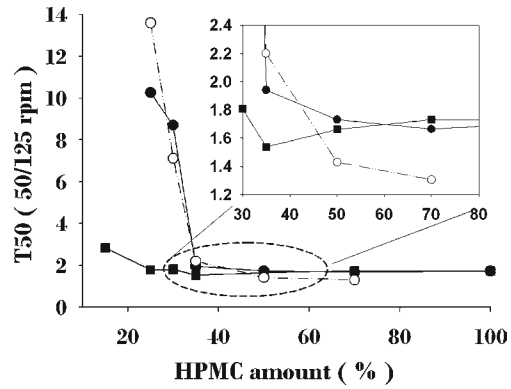

Fig. 5. The ratio between T_{50}-values at 50 and 125 rpm stirring rate for HPMC from HPMC/mannitol and HPMC/DCP tablets and mannitol. HPMC from HPMC/DCP is denoted as (*square*), HPMC and mannitol from HPMC/mannitol is denoted (*filled circle*) and (*open circle*), respectively. The inserted graph magnifies the ratios between approximately 35% to 70% HPMC content in the tablets.

implied some uncertainty in their ratios. Therefore, this composition is not included in Fig. 5. The results imply that tablets containing HPMC below the matrix percolation threshold exhibited up to five times higher sensitivity to increasing shear forces in the dissolution medium. This extremely large sensitivity in the variation of stirring rates was not seen in the HPMC/DCP tablets, not even at low fractions HPMC in the matrix.

As commonly known, the erosive nature of gelling matrices leads to a high dependency of their release on the hydrodynamic conditions. However, the results in Fig. 3 reveal that the appearance of the critical point in respect to the HPMC amount in the tablets was independent on the stirring rates of the dissolution medium but instead depend dramatically on the solubility of the used additive. As seen earlier the release of mannitol from the tablets containing 30% or less HPMC was mainly governed by the rate of matrix erosion. As the polymer concentration increased above 35%, the T_{50} ratio for mannitol release decreased more than the corresponding values for polymer release from the same tablets. More importantly, the T_{50} ratio of mannitol was significantly lower than that of HPMC from both HPMC/mannitol and HPMC/DCP tablets (Fig. 5, inserted graph). This indicates that above the polymer percolation threshold substances with diffusion controlled release are less sensitive to agitation rate variations than those with release mechanism determined by erosion.

Release Robustness Map

The results from the present study can be illustrated schematically by Fig. 6 defining regions of release robustness as a function of variations of shear forces in the dissolution medium. For the release of easily and freely soluble substances two regions can be clearly distinguished. At matrix former (HPMC in the present study) contents higher than the percolation threshold the sensitivity of the release to varying shear forces in the environment is quite low (region 2). In the ideal case, when the rate of polymer release is much slower than that of the easily soluble compound, the ratio of the T_{50} values determined at a low and a high stirring rate approaches one. However, as the rate of matrix erosion increases, due to for example the use of a lower viscosity grade matrix former, the release of the soluble compound becomes increasingly sensitive to shear forces. In this case the T_{50} ratio may also increase as the amount of matrix former decreases and approaches the percolation threshold. Even under such circumstances, the release from matrices belonging to this group should be considered to have controllable release robustness. Most hydrophilic ER matrix tablets on the market should belong to region 2. Below the percolation threshold, though, a situation of uncontrollable and non robust release is observed (region 1). These matrices rapidly fall apart and disintegrate and are thus not suitable as controlled release formulations. For poorly soluble compounds, however, no region of uncontrollable release is observed in the investigated range of shear forces (region 3). Formulations of this type are quite sensitive to shear force variations but this sensitivity does not vary dramatically with changes of the amount of matrix former and should therefore be considered controlled. In summary, this study implies that when developing hydrophilic matrix formulations they should preferable belong to region 2 to be the least sensitive to variations of shear forces or at least belong to region 3 were the release robustness is lower but often acceptable.

CONCLUSION

Critical conditions for release robustness of binary HPMC matrix tablets in respect to the solubility and dose of additives at two hydrodynamic conditions have been studied. It was found that matrices containing the highly soluble mannitol erode in a controlled manner only if a percolating cluster of polymer can be formed upon contact with the dissolution media. As the polymer content decreases to and below the percolation threshold, the tablets undergo rapid

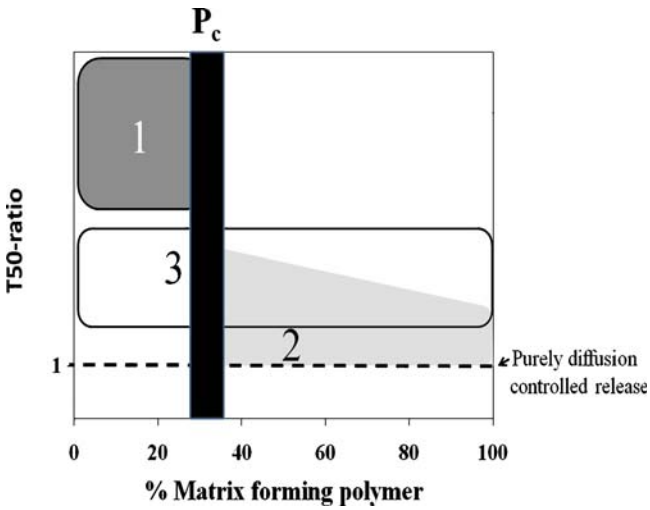

Fig. 6. Schematic sketch of the shear robustness displaced as the ratio between the T_{50} values at 50 and 125 rpm against the amount of matrix polymer in the formulation. The *dark grey* region corresponds to formulation with additives with high solubility and low amounts of matrix polymer that disintegrates, light grey region corresponds to formulations with additives with high solubility that have diffusion controlled release. Transparent region corresponds to formulations with additives with low solubility and erosion controlled release.

disintegration. However, increased release robustness of the highly soluble additive can be expected in the compositional regimes above the polymer percolation threshold. In contrast to mannitol, the practically insoluble DCP stabilizes the erosion of the tablets compared to the effect of mannitol in a given hydrodynamic release condition. This in turn, permits a controlled dissolution of the matrix even below the polymer percolation threshold. However, as the release of the additive in this case is governed by the dissolution rate of the matrix, a higher dependency on the hydrodynamic conditions can be seen at large fraction of HPMC.

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