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Influence of ionic strength and HPMC viscosity grade on drug release and swelling behavior of HPMC matrix tablets

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This work is dedicated to the late Prof. Saša Baumgartner who did a great piece of research on HPMC-based formulations and their biopharmaceutical characterization.

ABSTRACT: Matrix tablets containing paracetamol and hydroxypropyl methylcellulose (HPMC 2906) of different viscosity grades (50, 400, 1500, and 4000 mPa·s) were evaluated for drug release and change in matrix tablet mass [ΔM (%)] after exposure to 0.09, 0.15, 0.31, and 0.52*M* ionic strengths of dissolution media. At 0.09 and 0.15*M* ionic strength, drug-release profiles reflected the extended release characteristic; in addition the increase in ΔM was slow and continuous within first few hours. At 0.31*M* the higher viscosity grade matrices showed extensive initial swelling and the loss of extended release whereas at 0.52*M* a similar tablet performance is observed for the matrices of all viscosity grades. Notably, when extensive increase in ΔM occurs in the very beginning of exposure to medium the loss of extended release from the matrix is expected. © 2016 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43604.

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INTRODUCTION

Hypromellose (hydroxypropyl methylcellulose, HPMC) is widely used as a matrix polymer in oral controlled-release dosage forms.[1] When in contact with aqueous fluid, hydration of the matrix occurs[2–4] and the polymer changes from a glassy to a rubbery state, forming a gel layer structure. The gel acts as diffusion barrier and slows further intake of water into the core of the matrix tablet, thus, controlling drug release. Rapid hydration and formation of a coherent gel layer with sufficient mechanical integrity is crucial for controlled release from the matrix.[5,6] The mechanism of drug release is diffusion through the gel layer (mainly highly soluble drugs) and/or by matrix erosion (mainly poorly soluble drugs).[1]

A variety of matrix parameters can interfere with hydration of the HPMC tablet; for example, HPMC substitution type and viscosity grade, HPMC content and particle size, manufacturing characteristics, mechanical properties of the tablet, and other compounds present in the matrix.[1,7] In particular, the formation of the gel layer may be significantly influenced by the hydrophilic/hydrophobic character of HPMC[8]: a higher content of methoxy substituents promotes hydrophobic interactions and decreases hydrogen bonding within and between particles in close proximity.[1] Depending on the level of methoxy and hydroxypropoxy substituents, there are three types of HPMC listed in the United States Pharmacopeia (USP): 2910, 2906, and 2208. The percentage limits for methoxy/hydroxypropoxy content are 28–30/7–12%, 27–30/4.0–7.5%, and 19–24/7–12% for HPMC 2910, 2906, and 2208, respectively.[9]

Water uptake into the matrix is also affected by the HPMC viscosity grade and this might be reflected in the swelling and drug-diffusion rates from the HPMC matrix.[10–15] The degree of HPMC polymerization is related to the average number of monomers in the chain and determines the polymer viscosity grade.[16] In commonly used dissolution media, it is usually observed that an increase in viscosity grade of the polymer promotes water entry and increases the rate of swelling of the matrix tablet.[10–12,17] Furthermore, a trend toward lower dissolution rates from HPMC matrices of higher viscosity grades has been reported.[3,10,18,19] The proposed mechanism is that if the matrix is of a higher viscosity grade the viscosity of the gel layer will be greater, because of the degree of polymer-chain entanglement.[20] Thus, the gel layer becomes more resistant to diffusion and drug release is slowed.[4,10] Faster disentanglement and dissolution of the polymer is expected when lower viscosity grades are used.[21]

The process of swelling and formation of a gel layer can also be affected by solutes present in the medium surrounding the

HPMC matrix, with subsequent differences in drug release. The influences of electrolytes, dietary sugars or their combination, and other substances such as sodium lauryl sulfate and ethanol have been investigated.[22–27] Increasing the concentration of electrolytes/sugars, within lower concentration range, results in progressively slower drug release[27]; however, high concentrations may result in decreased polymer hydration if the affinity of the ions toward the water molecules is greater than the affinity of the polymer. Thus, the amount of water available for polymer hydration is reduced since the electrolytes[27–32] are competing for water molecules in the polymer hydration layer and causing the polymer to precipitate or "salt-out." This results in compromised formation of the active gel diffusion barrier and water penetration into the matrix is enhanced. Consequently, drug release is increased.[24,29,33] Moreover, the extent of hydrophobic interaction is increased primarily between methoxy substituents of the HPMC polymer chains,[33] which is a possible explanation for suppression of polymer swelling and coalescing of the hydrophobic parts of HPMC. Accordingly, the methoxy content is important factor affecting the precipitation of cellulose ethers.[31,34] Additionally, due to the dissolved solutes in dissolution medium osmotic pressure may be considered as a factor affecting matrix erosion process.[35]

During development of controlled-release dosage forms, relevant physicochemical conditions in the gastrointestinal (GI) tract must be taken into account. For HPMC matrix tablets, the ionic strength of the dissolution medium could be the parameter of great importance, as it interferes with the process of controlled release from the matrix. The information regarding the measurement and calculation of physiological ionic strengths are rare, probably due to the possible complexity of medium composition in the GI tract. Lindahl *et al.*[36] determined the ionic strengths of fasted gastric and jejunal fluids as $0.100 \pm 0.025M$ and $0.139 \pm 0.014M$, respectively. The ionic strength of gastric fluid can increase after intake of food or beverage, because of the variety of consumed ionic compounds. However, the ionic strength of intestinal fluids is not easily raised for external reasons, because electrolytes concentrations in the GI tract are regulated unless there is a pathophysiological condition.[37,38]

In the scope of the present study, tablets containing paracetamol and HPMC of different viscosity grades were investigated for drug release and swelling behavior at ionic strengths 0.09–0.52*M*. The simple composition of the matrix tablets (70% HPMC, 30% paracetamol) enabled avoidance of the effects of other compounds commonly present in the tablets. The ionic strengths that were selected are within reported physiological values and up to almost four times higher. The intent of this work was to observe whether significant changes in the dissolution or swelling process of the matrix tablet might occur in the studied ionic strengths range.

MATERIALS AND METHODS

Materials

Paracetamol (99.0%) was purchased from Sigma-Aldrich, The United States, and hypromellose (HPMC 2906; 27–30% methoxy and 4.0–7.5% hydroxypropoxy content) of different viscosity grades was produced by Shin Etsu Chemical Co., Ltd, Tokyo and obtained from Harke Pharma, Mülheim an der Ruhr. HPMC Metolose® 65SH-50, 65SH-400, 65SH-1500, and 65SH-4000 were used with declared viscosities as 50, 400, 1500, and 4000 mPa·s of a 2% w/w aqueous solution at 20 °C, respectively. Monobasic potassium phosphate, Titrisol® for the preparation of 1.0*M* sodium hydroxide solution, and sodium chloride were of analytical grade (Merck, Darmstadt, Germany).

Preparation of HPMC Matrix Tablets

Tablets (175 ± 4 mg) containing $30 \pm 0.5\%$ paracetamol and $70 \pm 0.5\%$ HPMC were compressed from a physical mixture of the two components using an instrumented single-punch tablet press (Kilian SP300, IMA Kilian, Germany) with 12 mm flat-faced punches and a compaction force of 6.0 ± 0.5 kN.

Drug-Release Studies

A USP apparatus 2 (paddle apparatus)[9] was used for dissolution testing (USP Vankel 7000 dissolution tester, Vankel Technology Group, The United States) in 1000 mL medium at 37 ± 0.5 °C and rotation speed 100 rpm. Dissolution media were 50 m*M* phosphate buffers pH 6.8 at four ionic strengths (0.09, 0.15, 0.31, and 0.52*M*) adjusted using sodium chloride.

The tablets were placed in dissolution sinkers made of stainless-steel wire. Samples were taken after 10, 20, 30, and 45 min, and after 1, 2, 3, 4, 5, 6, 8, 12, and 24 h. Drug release was tested at least in triplicate for all experimental conditions. Samples were analyzed at 243 nm in a UV–Vis spectrophotometer (Agilent 8453, Agilent Technologies Deutschland GmbH, Germany).

The time to achieve 50% of cumulative drug release ($t_{50\%}$) was estimated from the dissolution profiles by linear interpolation between the two nearest time points.

Swelling Studies

A USP apparatus 1 (basket apparatus)[9] was used for swelling studies in 500 mL medium at 37 ± 0.5 °C and rotation speed 100 rpm with two tablets in each basket. Media were the same as those used in the drug-release tests described above. Dry mass was determined by weighing two tablets in a basket; wet mass was determined at chosen time points by weighing the basket with the two swollen tablets after draining and blotting excess dissolution medium. The change in tablet mass (ΔM) was calculated as a percentage increase/decrease in mass of a wet tablet at chosen time points in relation to the initial mass of a dry tablet. The swelling tests were performed in triplicates.

RESULTS AND DISCUSSION

For the purpose of the study, a matrix tablet with a simple composition was chosen (70% HPMC, 30% paracetamol). Influences from other compounds that are usually present in dosage forms were thus avoided. The 2906 substitution type of HPMC with different viscosity grades was used for testing as it has higher methoxy content and lower sol–gel transition temperature than the frequently researched 2208 HPMC.[2,5,10–12,14,16–18] Consequently, due to the hydrophobic character of 2906 HPMC, the susceptibility to salting out by electrolytes may be enhanced.[30] Both matrix compounds are uncharged at physiologically relevant pH values, thus ionic interactions are minimized. Sodium chloride was used to regulate the ionic strengths of the buffered solutions used in the

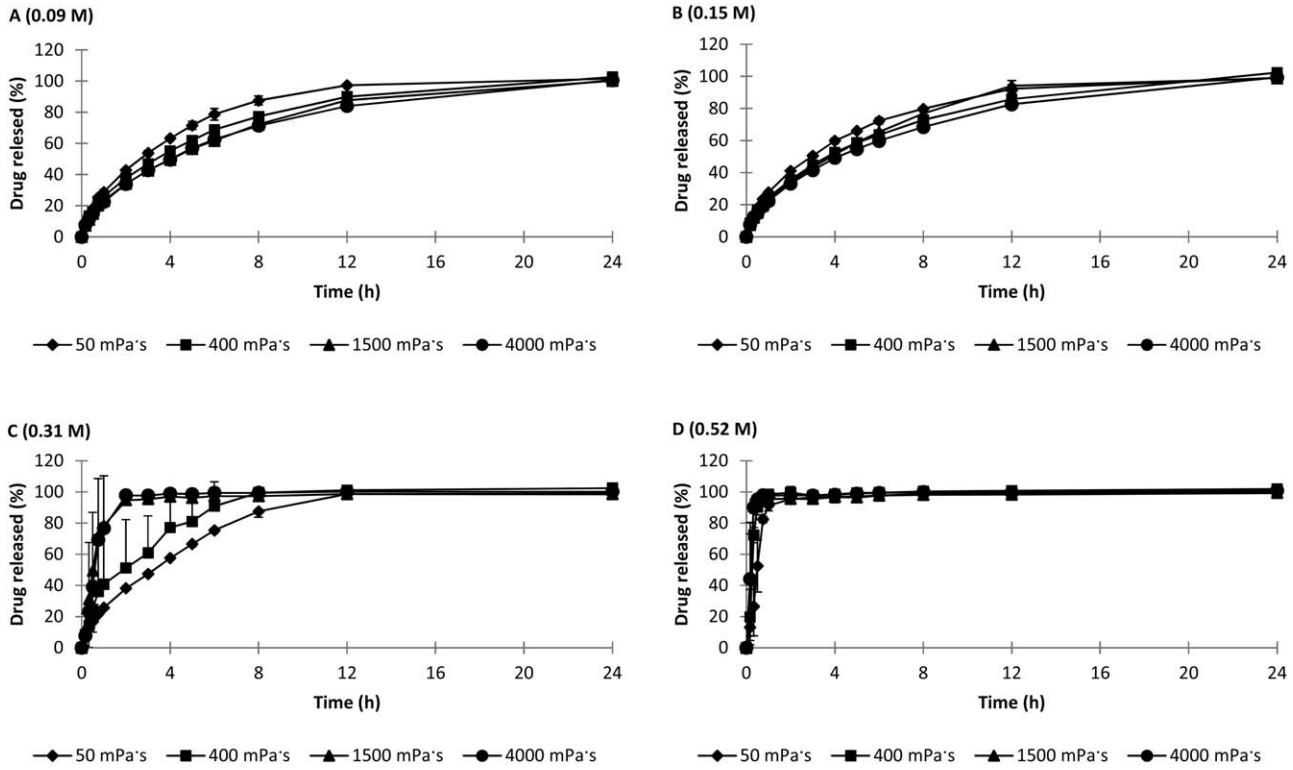

Figure 1. Drug release profiles from HPMC matrices of different viscosity grades (50, 400, 1500, and 4000 mPa·s) in dissolution media at ionic strengths 0.09, 0.15, 0.31, and 0.52*M*. Mean ± SD.

dissolution tests, because of its ability to salt out polymers in the midrange of the lyotropic series.[27]

Drug Release from HPMC Matrices

Figure 1 shows the effect of ionic strength on drug release from HPMC matrices of different viscosity grades. Experimental ionic strengths (0.09–0.52*M*) were in the physiological range or higher. In media with ionic strengths within or close to physiological values (0.09 and 0.15*M*) the matrices provided extended drug release over a 24 h period [Figure 1(A,B)]. The trend for a slightly faster drug release at lower viscosity grades of HPMC is shown in Figure 1(A,B) and is reflected in the calculated $t_{50\%}$ values in Figure 2. A small increase of $t_{50\%}$, that is, a decrease in dissolution rates, was observed with increasing viscosity of HPMC at ionic strengths 0.09 and 0.15*M*. Similar observations have been made by other authors: in media with low ionic strengths, the use of a higher viscosity grade resulted in lower rates of dissolution from the HPMC matrices.[18,19] The rationale behind is in the greater degree of chain entanglement, that is, more tortuous gel layer, that reduces drug permeation across the matrix what results in slower drug release.[4,39]

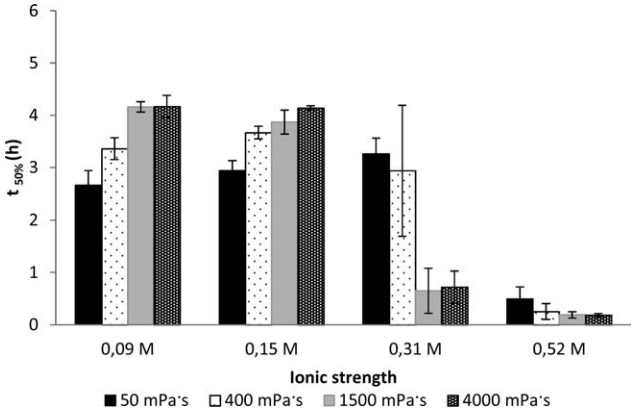

Figure 2. Calculated $t_{50\%}$ values of drug release at different ionic strengths of medium for HPMC viscosity grades 50, 400, 1500, and 4000 mPa·s.

A notable change in dissolution profiles and $t_{50\%}$ values was observed in medium with 0.31*M* ionic strength [Figures 1(C) and 2]. Higher dissolution rates were observed from matrices of higher viscosity grade (1500, 4000 mPa·s), whereas dissolution rates at lower viscosities (50, 400 mPa·s) were similar to those at lower ionic strengths. Significant differences in $t_{50\%}$ values were determined in matrices with low and high viscosities: between 50 and 1500/4000 mPa·s and between 400 and 1500/4000 mPa·s ($p \leq 0.001$, one-way ANOVA, Bonferroni *post hoc* test).

The underlying mechanism for acceleration of drug release at higher viscosities is difficult to specify. On the basis of the drug-release profile, we assumed that a functional diffusion barrier was weak or absent when longer polymer chains (i.e., higher viscosity grade of HPMC) were present in the matrices. We assume that the greater degree of polymer chains entanglement presents important factor for the comprehension of the effect. The influence of ionic strength on the rate of hydration and alteration in formation of the gel layer, due to the clustering of hydrophobic methoxy groups of HPMC, has been

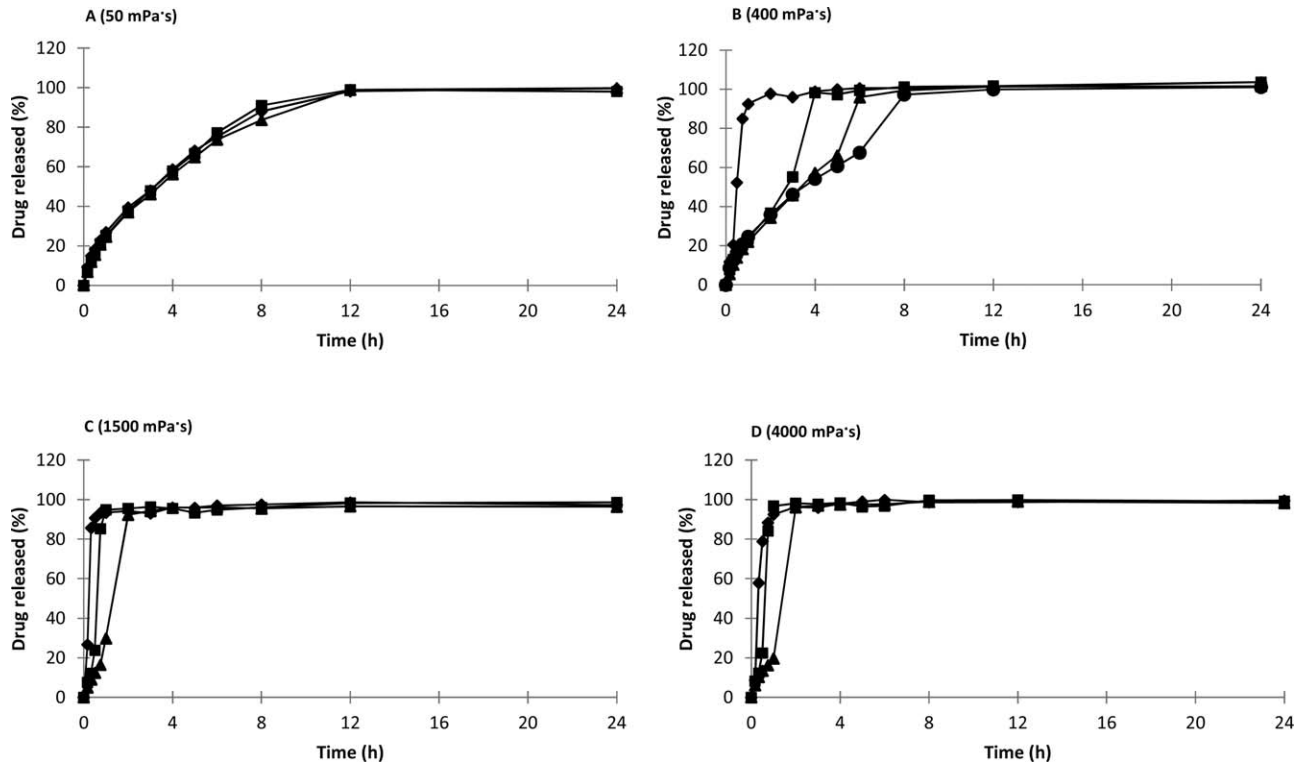

Figure 3. Parallel drug-release profiles at each viscosity grade of HPMC matrices (50, 400, 1500, and 4000 mPa·s) in 0.31*M* ionic-strength medium.

demonstrated.[30,31,40] These mechanisms may also be relevant in explanation of the present results, where different HPMC viscosities were investigated.

Standard deviations in the drug-release profiles [Figure 1(C)] were high at ionic strength 0.31*M*, especially for HPMC matrices of viscosity grade 400 mPa·s. The individual release profiles for all HPMC matrices are shown in Figure 3. In the case of matrices of viscosity grade 400 mPa·s, either the dissolution rate was high already in the first hours, or dissolution rates were low in the first few hours followed by sharp increase at a certain time point. Presumably, the concentration of electrolytes in medium with ionic strength 0.31*M* is near the critical concentration for the tested matrices, causing a discontinuity in the structure of the gel layer.[7] Thus, either sufficient suppression of polymer hydration and loss of the diffusion-barrier function of the gel layer occurs, causing faster drug release from the beginning, or the gel layer is formed and slows release for only certain period of time. The matrices of higher viscosity grades of HPMC 2906 were more prone to show loss of extended drug-release properties at 0.31*M*.

Asare-Addo *et al.*,[28] when testing HPMC 2208, demonstrated that only HPMC matrices with the lowest grade of viscosity showed high rates of drug release when media of higher ionic strength were used; matrices with high viscosity grade remained unaffected in a wide range of ionic strengths (0–0.4*M*) of dissolution media. The difference from our results, regarding susceptibility of various viscosity grade matrices to media of higher ionic strength, may be due partly to the substitution type of HPMC: type 2906 has a higher content of methoxy substitution than type 2208 and is consequently more hydrophobic in character. Moreover, the lower methoxy substitution makes the 2208 type less susceptible to "salting-out."[34] Furthermore, Asare-Addo *et al.* showed that, when medium with increased ionic strength was used, rates of drug release were higher from matrices with higher methoxy content than from those with lower methoxy content.[41] Pygall *et al.* reported higher release rates from the matrices with incorporated sodium citrate in the HPMC matrix when substitution type of higher methoxy content was used.[30] Nevertheless, direct comparison of the studies cannot be made because also the differences in composition of the matrix tablets may influence drug-release behavior.

A high rate of drug release or "burst" release[42] for matrices of all viscosity grades at 0.52*M* ionic strength is shown in Figure 1(D). It is assumed that there was no formation of coherent gel and that a limiting diffusion barrier was absent. The tested ionic strength is higher than reported fasted *in vivo* values.[36] However, after intake of solid meal with high salts content relatively high values of ionic strength might occur in the stomach fluid for a certain period of time. Nevertheless, with buffer pH 6.8 intestinal fluid is simulated and the ionic strength of intestinal fluids is not expected to be raised to this extent. However, we suspect that due to the variety of components in GI fluids and diversity in matrix composition similar effects can be expressed *in vivo* at lower ionic strength of the medium. Additionally, in the case when different salts or ionizable drugs are incorporated in the matrix, these components might also contribute to local and transient increase of ionic strength inside the tablet matrix.[35]

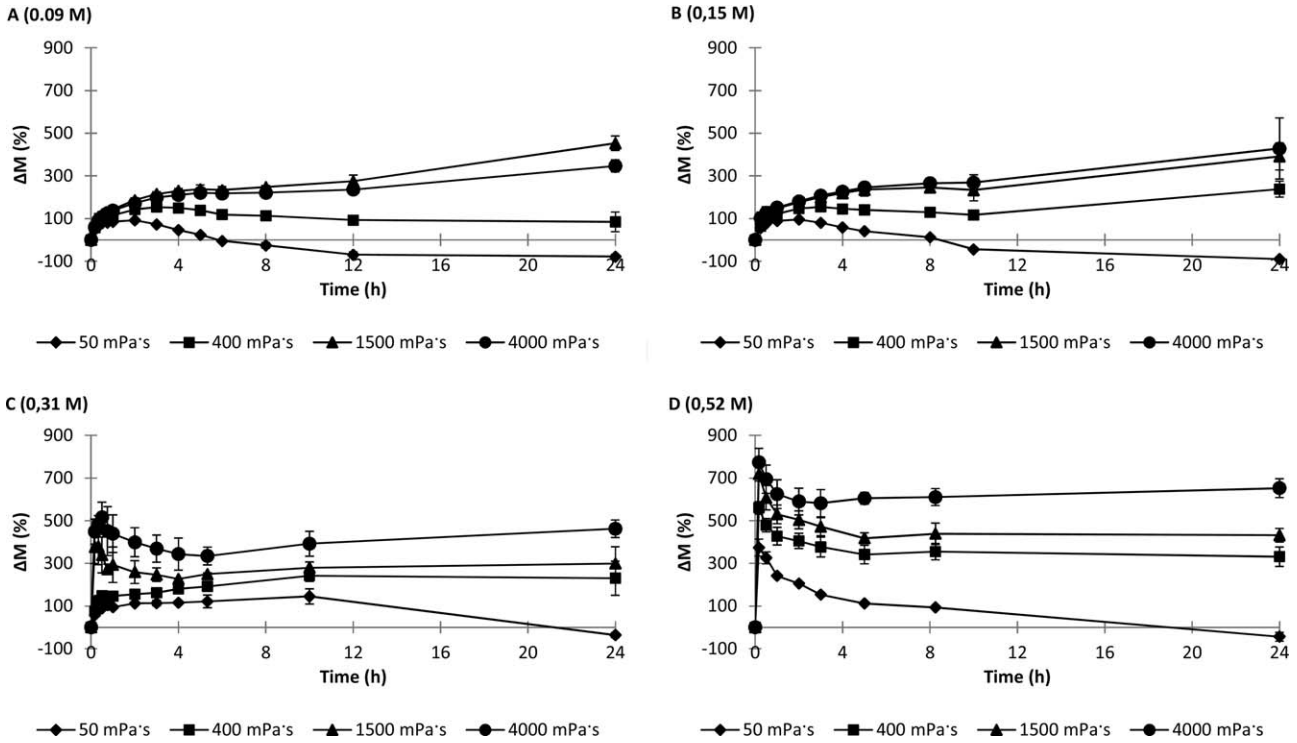

Figure 4. Change in mass [Δ*M* (%)] of matrix tablets at each HPMC viscosity grade (50, 400, 1500, and 4000 mPa·s) as a function of time after exposure to the media with ionic strengths: 0.09, 0.15, 0.31, and 0.52*M*. Mean ±SD.

Swelling Behavior of HPMC Matrices

The increase or decrease in tablet mass (Δ*M*) was determined by weighing dry and wet tablets at determined time points. Increase in tablet mass was due to water uptake into the matrix, whereas decrease in tablet mass was due to drug dissolution and diffusion out of the matrix, and also to polymer chain disentanglement with consequent dissolution. Figure 4 shows the time dependence of Δ*M* for matrices of different HPMC viscosity grades exposed to a range of ionic strengths. The profiles demonstrate the trend for greater swelling at higher viscosity grades irrespective to the ionic strength. These observations are in accordance with others,[11,12,17,43] where rate and extent of swelling was greater at higher viscosity grades of HPMC. Higher intrinsic water holding capacity is provided by longer polymer chains.[12] Therefore, larger amount of water is required for disentanglement concentration to be reached, that is, polymer concentration below which the polymer chain disentangle and detach from a gelled matrix.[3] Additionally, after 24 h, the lowest Δ*M* values are achieved by matrices with the lowest viscosity grade probably due to the rapid disentanglement process.

At lower ionic strengths (0.09*M*, 0.15*M*) the increase in Δ*M* due to water uptake was slow in the first few hours increasing up to 200% [Figure 4(A,B)]. Water uptake within the first 10 min was similar in all matrices (Figure 5). In profiles of the HPMC matrices with lower viscosity grades, matrix mass decreased after the initial increase since the chain entanglement is lower than in high-viscosity grades.[3,17] Nevertheless, as described earlier, extended drug release was established for all viscosity grades [Figure 1(A, B)].

A change in the shape of the swelling profiles at 0.31*M* [Figure 4(C)] was more profound in matrices with high viscosity grades HPMC (1500, 4000 mPa·s), where rapid swelling occurred within the first hour, with values of Δ*M* increasing above 350% within the first 10 min. The same effect can also be seen from Figure 5. The rationale for these results, in analogy with drug-release profiles, presumably lies in affected integrity of gel and, thus, water uptake is less restricted. In addition, Δ*M* partly decreased after the initial rapid increase, because of drug release and matrix erosion. The swelling profiles of low viscosity grade matrices (50, 400 mPa·s) indicated slower increase in matrix mass, with Δ*M* below 100% within the first 10 min. Notably, a slow decrease was observed at later time points (after 10 h), but

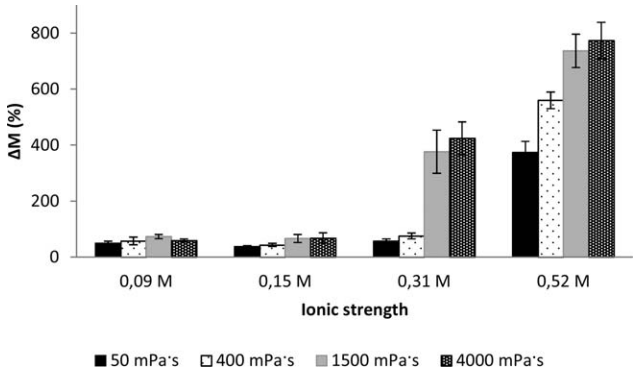

Figure 5. Change in mass [Δ*M* (%)] of matrix tablets after 10 min of exposure to the media with different ionic strengths (0.09, 0.15, 0.31, and 0.52*M*) for each HPMC viscosity grade (50, 400, 1500, and 4000 mPa·s).

the profile shape resembled the results at 0.09 and 0.15*M* ionic strength.

At 0.52*M*, all matrix tablets underwent extensive initial swelling, with increase of Δ*M* for 350–800% within 10 min, followed by a decrease that was more profound in the first 1–2 h [Figure 4(D)]. The trend of greater swelling of higher HPMC viscosity grades is clearly indicated. Extensive early swelling is probably a consequence of no gel barrier being formed and water penetrating freely into the tablet core. This interpretation is supported by the study of Bajwa *et al.*,[33] where at high ionic strength the HPMC (2910) particles of the matrix swelled but could not form a gel layer, and enhanced liquid penetration and surface disintegration of the matrix was observed using an imaging method.

Relation between Drug Release and Swelling Behavior

Drug release controlling parameters from hydrophilic matrices are drug diffusion, swelling of matrix, and its erosion. The processes can occur simultaneously however one of them may dominate.[4,44] Interestingly, drug release profiles are similar for all viscosity grades at 0.09 and 0.15*M* [Figure 1(A,B)] though the differences in Δ*M* are clearly indicated [Figure 4(A,B)]. At 24 h the drug was completely released (Figure 1); however, the evident trend for the larger matrix mass of higher viscosity grade matrices was observed (Figure 4) in each of the ionic strength media.

When swelling was slow and continuous, with Δ*M* below 100% within the first 10 min, the drug release was extended, probably because the gel layer barrier had sufficient integrity. However, massive swelling, with Δ*M* greater than 350% within the first 10 min, followed by immediate decrease in Δ*M*, corresponds to rapid drug release, and formation of a non-coherent gel layer and rapid penetration of water is assumed (Table I, Figures 1 and 4). Information regarding drug release and change in matrix mass cooperatively contributed to the understanding of the matrix tablet behavior. At similar percentage of drug release the difference in Δ*M* values could be observed from HPMC matrices of 4000 mPa·s in 0.09–0.31*M* ionic strength media (Table I). Combination of low drug release (8%) and high Δ*M* value (420%) at 10 min has resulted in total drug release and partial decrease in Δ*M* (370%) at 180 min in 0.31*M* medium. However, low drug release (8%) in combination with moderate increase in Δ*M* (60%) at 10 min provides 40% drug release and increase in Δ*M* to 200% at 180 min in 0.09 and 0.15*M* media.

Interestingly, Williams *et al.*[45] demonstrated the difference in early gel layer formation in water and sucrose medium with respect to HPMC (2208) viscosity grade. In medium with relatively high concentration of sucrose (0.7*M*) at low viscosity grade HPMC rapid hydration and significant particle coalescence is observed with a small increase in gel layer thickness thereafter. By contrast, at higher viscosity grades irregular hydration and swelling was exhibited with some evidence of poorly hydrated particles within the gel. The gel layer was thicker than that in water due to incomplete or slower particle hydration and coalescence therefore the more liquid penetrated in the matrix. However, these observations were not

Table I. Amount of Drug Released (%) and Change in Matrix Mass [Δ*M* (%)] of Formulation Containing HPMC with Cited Viscosity Grade after 10 and 180 min of Exposure to Media of Varying Ionic Strengths

Time (min)	Ionic strength (M)	Formulation									
		Drug released (%)				Δ*M* (%)					
		65SH-50	65SH-400	65SH-1500	65SH-4000	65SH-50	65SH-400	65SH-1500	65SH-4000
10	0.09	7.9 ± 1.2	7.2 ± 2.1	7.1 ± 1.1	7.6 ± 2.5	49.8 ± 6.7	57.7 ± 14.0	73.3 ± 8.0	59.1 ± 5.8
10	0.15	9.2 ± 1.2	8.6 ± 0.9	7.5 ± 0.4	7.7 ± 0.8	37.3 ± 3.4	43.3 ± 5.7	66.2 ± 14.4	68.1 ± 18.8
10	0.31	7.9 ± 1.2	8.4 ± 2.6	12.0 ± 9.9	7.7 ± 1.1	57.2 ± 7.9	75.6 ± 10.5	376.1 ± 76.9	424.1 ± 58.6
10	0.52	13.0 ± 8.2	19.7 ± 17.7	45.0 ± 28.2	44.0 ± 36.5	373.7 ± 39.2	560.4 ± 30.0	718.3 ± 33.4	773.6 ± 65.4
180	0.09	53.8 ± 1.5	46.9 ± 1.5	42.6 ± 0.9	42.8 ± 1.7	73.0 ± 8.0	153.7 ± 13.3	214.9 ± 10.5	198.2 ± 4.7
180	0.15	50.5 ± 1.1	44.8 ± 0.2	43.2 ± 0.5	41.5 ± 1.3	80.1 ± 3.8	154.9 ± 4.9	200.4 ± 13.7	207.8 ± 3.3
180	0.31	47.3 ± 1.1	60.8 ± 23.9	95.4 ± 2.2	97.7 ± 1.8	113.5 ± 13.1	162.7 ± 14.5	247.1 ± 30.9	369.3 ± 63.6
180	0.52	96.8 ± 3.3	97.7 ± 2.7	95.6 ± 2.1	97.7 ± 0.9	153.7 ± 9.1	376.7 ± 46.9	472.3 ± 42.4	582.1 ± 63.3

manifested in dissolution profiles since the high viscosity matrices still maintained extended release more effectively than low viscosity matrices. The importance of other matrix properties such as gel layer strength was suggested.[45] Contrary, in our study extended release properties in dissolution profile were not obtained at the higher viscosity grades of 2906 HPMC in the case of 0.31*M* medium. However, the mentioned alterations in gel formation[45] between high and low viscosity grade might attribute to the explanation of present study results. Since the responses in drug release between both studies are not in accordance we assume this could be due to the substitution type of HPMC as it has been already indicated that differences exist between gel characteristics of the various substitution types-the 2208 HPMC offers the highest gel strength[34] and greater diffusional resistance to water within the inner gel region.[46]

CONCLUSION

Hypromellose (HPMC 2906) matrix tablets of different viscosity grades were evaluated in media of ionic strengths 0.09, 0.15, 0.31, and 0.52*M* to determine the effects on drug release and change in mass (ΔM) of the swelled tablets. In 0.31*M* ionic strength medium a loss of extended release properties and rapid release rate was demonstrated from matrices of higher viscosity grade (1500 and 4000 mPa·s) in accordance with massive initial swelling, that is, increase in ΔM. Lower viscosity grade matrices (50 and 400 mPa·s) exhibit extended release characteristics and slow and continuous increase in ΔM within first few hours. Similar response as in the latter case was observed from all tested matrices in 0.09 and 0.15*M* ionic strength media. In contrast, burst release and extensive initial swelling was provoked at 0.52*M*. In addition, in the cases when evident escalation in ΔM occurred in first minutes after exposure to the medium the loss of extended release from the matrix was observed.

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