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Assessment of Tailor-Made HPMC-Based Matrix Minitablets Comprising a Weakly Basic Drug Compound

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Tailor-made, pH-controlled matrix minitablets based on different HPMC types were developed comprising the weakly basic drug dipyridamole. The incorporation of pH modifiers, i.e., fumaric and succinic acid, enhanced the drug release at pH 6.8. Assessing the drug release, acid release, and the microenvironmental pH (pH_M) provided detailed understanding of pH-controlled mini-matrices.

The extent and duration of pH_M alteration was more pronounced in presence of fumaric acid. Minitablets based on the fast dissolving Methocel K100LV (≤ 100 cps) showed simultaneous release rates of dipyridamole and fumaric acid with a constant low average pH_M.

Keywords weakly basic drug; dipyridamole; minitablets; HPMC; molecular weight; pH modifier

INTRODUCTION

Multi-particulate drug delivery systems usually based on subunits such as granules, pellets, or minitablets show numerous advantages over monolithic devices (non-divided forms). Gastric emptying is faster and less dependent on the nutritional state as multi-particulate systems are sufficiently small to be evacuated through the pylorus during the digestive phase (Abrahamsson, Alpsten, Jonsson, Lundberg, Sandberg, Sundgren, Svenheden, & Tolli, 1996; Bechgaard, 1982; Davis, Hardy, Taylor, Whalley, & Wilson, 1984; Davis, Khosla, Wilson, & Washington, 1987). Additionally, owing to the improved reproducibility of transit times and high degree of dispersion in the digestive tract, multi-particulate systems show less variance (Follonier & Doelker, 1992). Advantageously, minitablets mostly having a diameter of 2–3 mm can be manufactured with higher reproducibility compared to pellets, especially, regarding their weight and equal dimension (De Brabander, Vervaet, Fiermans, & Remon, 2000). In pharmaceutical development, formulating weakly basic drugs is a major challenge as the solubility significantly depends upon the pH of the dissolution medium. The changing pH along the GI tract affects the absorption of an orally administered drug compound. The stomach pH varies as the pH is influenced by food, medical conditions (e.g., achlorhydria), or concomitant drug therapies (e.g., H_2-blockers or proton-pump inhibitors). High stomach pH combined with physiologically increasing pH environments along the gastrointestinal tract may lead to low and incomplete drug release. Consequently, high inter- and intra-subject variability in oral absorption is frequently observed (Hörter & Dressman, 1997; Lelawongs, Barone, Colaizzi, & Guarnieri, 1988). The incorporation of organic acids as pH modifiers, such as adipic or succinic acid, is a common strategy to enhance the dissolution rate of weakly basic drugs (Espinoza, Hong, & Villafuerte, 2000; Gabr, 1992; Nie, Pan, Li, & Wu, 2004; Streubel, Siepmann, Dashevsky, & Bodmeier, 2000; Varma, Kaushal, & Garg, 2005). This approach aims at modulating the microenvironmental pH (pH_M) within and in the immediate surrounding of the solid dosage form. Consequently, drug solubility and dissolution of ionizable drugs are enhanced independently of the surrounding pH. Several groups applied this formulation design to enhance drug release from monolithic matrix tablets (Nie et al., 2004; Streubel et al., 2000; Varma et al., 2005) and film-coated pellets (Munday, 2003; Thoma & Ziegler, 1997). Streubel et al.

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(2000) developed conventional matrix tablets based on the polymer hydroxypropyl methylcellulose (HPMC) and ethylcellulose, respectively. Vinpocetine release showed a linear relationship between the incorporated amounts of citric acid and the increase of drug release (Nie et al., 2004). Based on the advantages of multiple unit dosage forms, Munday et al. (2003) developed a promising formulation design by incorporating drug and acid into pellets coated by a blend of Eudragit RS and HMAS (hydroxypropyl methylcellulose acetate, an enteric polymer). In neutral medium, HMAS gradually dissolved by leaving minute pores in the film and, thereby, the drug dissolution was increased. This formulation design achieved pH-independence over a dissolution time of 12 hr. Thoma and Ziegler (1997) investigated the influence of different amounts of succinic acid on fenoldopam mesylate release from pellets coated with Surlease.

To our best knowledge, all these investigated formulations aimed at sustaining drug release over 8 hr. However, during pharmaceutical processing, we frequently face different requirements for the target drug release time. Therefore, the aim of the present study is to manufacture tailor-made, pH-controlled minitablets ranging from short-duration modified release (≤ 2 hr) to more extended release over several hours. We assume, that these short duration modified release formulations are advantageous over immediate release solid dosage forms to reduce the inter- and intra-patient variability in absorption resulting from incomplete dissolution of the drug compound. The pH modifier should be present inside the formulation over the entire dissolution time of the drug compound or at least as long as possible. This should be achieved by a careful selection of polymer, the type of pH modifier, and the concentration of the pH modifier. Formulations exhibiting pH independent drug release and simultaneous release rates of the drug and the pH modifier are desirable.

We used hydroxypropyl methylcellulose (HPMC) with different molecular weights (MW) as polymer and different types and concentrations of pH modifiers. By investigating the relationship between drug release, acid release, the microenvironmental pH (pH_M), and different MW HPMC grades, we gained further understanding of pH-controlled multi-unit dosage forms. Dipyridamole (DP) was used as model compound, based on its distinct pH-dependent solubility.

MATERIALS AND METHODS

Materials

Different types of Methocel (Methocel K100LV, Methocel K4M, and Methocel K100M) were purchased from Dow Chemical Company (Michigan). Methocel is the trademark of the Dow Chemical Company or an affiliated company of Dow for methylcellulose and hypromellose products. Methocel K100LV, Methocel K4M, and Methocel K100M are hydroxypropyl methylcellulose (Hypromellose 2208), differing in their molecular weights. Methocel K100LV has an apparent viscosity of 80–120, Methocel K4M of 3000–5600 and Methocel K100M of 80000–120000 cp (all measured by Ubbelhode).

The following materials were used as received. Dipyridamole (DP) (Chemgo Organica AG, Basel, Switzerland), fumaric (FA), and succinic acid (SA) (Fluka, Switzerland), lactose monohydrate 200 mesh (Meggle J.A., Reitmehring, Germany), magnesium stearate (FACI SRL, Carasco, Italy), Aerosil 200 (Cabot Rheinfelden GmbH, Germany).

Preparation of Minitablets

For this study, pH-controlled matrix minitablets based on different HPMC viscosity grades (Methocel K100LV, K4M, and K100M) were manufactured. DP, lactose q.s., HPMC, and the pH modifier were homogeneously blended (Turbula, Willy A. Bachenhoffen-WAB, Maschienenfabrik, Basel, Switzerland). Granules were manufactured manually in a mortar by wet granulation (granulation fluid: ethanol 90%, distilled water 10%). Afterwards the granules were dried at 40°C, and passed through a 400-mesh sieve. The outer phase consisted of 1.0% magnesium stearate as lubricant and 1.5% Aerosil as glidant. Minitablets (2 mm in diameter) were compressed by using an eccentric tableting machine (Korsch Type, EKO, Berlin, Germany). The minitablet weighed 9.1 ± 0.2 mg. The hardness of the minitablets ranged from 16 to 24 N. Minitablets (n = 27), equivalent to approx. 250 mg, were filled in a hard gelatin capsule. We summarized the compositions of the investigated formulations in Table 1.

TABLE 1
Investigated Compositions, Drug Loading: 10% [w/w]

Formulation	DP	Methocel K100LV	Methocel K4M	Methocel K100M	FA	SA
	[%] w/w					
1	10	30	–	–	10	–
2	10	30	–	–	20	–
3	10	30	–	–	40	–
4	10	30	–	–	–	20
5	10	30	–	–	–	–
6	10	–	30	–	20	–
7	10	–	30	–	–	20
8	10	–	30	–	–	–
9	10	–	–	30	20	–
10	10	–	–	30	–	20
11	10	–	–	30	–	–

Lactose q.s.

Dissolution Studies

The dissolution behavior of DP from the various formulations was carried out on USP paddle apparatus (Sotax A7). The media were 500 mL of pH 6.8 (phosphate buffer) or pH 2 (0.01N HCl) maintained at 37 ± 0.5°C. We used a stirring speed of 100 rpm to prevent sticking of the minitablets at the bottom of the dissolution vessel. The hard gelatin capsules containing the minitablets were opened and the minitablets were put into the vessel. The addition of SDS 0.1% w/V to the dissolution medium of pH 6.8 (phosphate buffer) was necessary to prevent the precipitation of the drug compound. 0.1% w/V SDS was a compromise between having an adequate discrimination of the investigated formulations and a suitable solubility of DP. Thereby a solubility of DP of 0.16 mg/mL was achieved. At predetermined time intervals, samples were withdrawn from the dissolution medium and filtered through 0.45 μm membrane filters. We analyzed the DP content spectrophotometrically at a wavelength of 410 nm (Perkin Elmer 5L4-SP1, Lambda 20). The release of the pH modifiers was analyzed by HPLC. Dissolution medium was added to maintain a constant volume. All experiments, assessing the drug and acid release, were performed in triplicate.

Assessing the Acid Release by HPLC

We determined the acid concentration by HPLC (Agilent, HP1100, MWD Detector G1365A). During the first 8 min the mobile phase consisted of 0.1 M ammonium dihydrogenphosphate buffer adjusted to a pH of 2.7 with phosphoric acid. Subsequently, a gradient (acetonitrile/ammonium dihydrogenphosphate buffer (pH 2.7) was used to remove remaining drug compound completely. Separation was achieved by using the column Inertsil C8-3, 5 μm, 4.6*150 mm (Erchatech AG, Switzerland). We applied a flow rate of 1 mL/min, an injection volume of 5 (FA) and 10 μL (SA), and run times of 15 min. The chromatograms were recorded at 210 nm. In each sequence, a five-point calibration was performed using reference solutions ranging from 10 μg/mL to 200 μg/mL depending on the investigated acid concentration.

Potentiometric Determination of the Average Microenvironmental pH

At different incubation times, the matrix minitablets were withdrawn from the dissolution medium and manually placed on a glass slide without damage. The average microenvironmental pH (pH_{Mav}) of the hydrated minitablets was quantified potentiometrically using a surface pH electrode (Methrom, Switzerland). All experiments were performed in triplicate.

RESULTS AND DISCUSSION

pH-Dependent Release of DP

DP release from HPMC based matrix minitablets significantly depended on the pH of the surrounding medium. Drug release from Methocel K100M based minitablets was completed after 2 hr at pH 2, whereas at pH 6.8 only 31.2 ± 0.9% of the total drug amount were released (Figure 1c). DP is a weakly basic drug compound with a pK_a of 6.1 (Terhaag, Donath, Le Pitt, & Feller, 1986). The protonation and deprotonation has a significant effect on the solubility of DP. 29.9 mg/mL of DP are soluble at pH 2.5. The solubility drops sharply to 0.54 mg/mL at pH 4, to 0.013 mg/mL at pH 6 and to 0.005 mg/mL at pH 7 (Kohri, Miyata, Takahashi, Endo, Iseki, Miyazaki, Takechi, & Nomura, 1992). This means that DP displays an approximately 6000-fold solubility difference within this pH range.

The polymer molecular chains of HPMC hydrate in contact with water, entangle, and form a gel matrix. The diffusional spaces inside the gelling system are controlled by the molecular weight of the polymer. Diffusion is the predominant drug release mechanism from high MW HPMC matrices. At acidic pH the drug is well soluble, therefore resulting in higher drug concentration gradient and higher driving force for diffusion (Streubel et al., 2000). At elevated pH values, the solubility of DP is very low and drug release is mostly incomplete. Consequently, we assume highly variable drug absorption rates resulting in poor bioavailability in vivo. Recently, Zhou et al. (Zhou, Moench, Heran, Lu, Mathias, Faria, Wall, Hussain, Smith, & Sun, 2005) demonstrated the pH-dependent bioavailability of DP using a canine model. The administration of famotidine and pentagastrin showed a marked effect on the DP exposure with a significantly increased concentration-time curve in the presence of pentagastrin. Based on the strong pH-dependent solubility, DP seems to be an ideal model compound for formulation approaches, which aim at overcoming the pH-dependent dissolution of weakly basic drugs.

Drug Release of DP from Minitablets in Presence of pH Modifiers

The incorporation of SA and FA as pH modifiers enhanced the drug release at pH 6.8 from matrix minitablets in case of all HPMC viscosity grades (Figure 1a–c) using a drug to acid ratio of 1:2 (based on wt. %). The increased drug release in presence of pH modifiers can be attributed to the modulation of the pH_M inside the matrix minitablets independently of the pH of the dissolution medium. Immediately after water infiltration, the organic acids dissolve and create an acidic microenvironment in the direct vicinity of the drug compound. Consequently, the solubility and the release rate of weakly basic drug compounds are increased.

As compared to SA, FA exhibited a more pronounced effect on enhancing the drug release from HPMC based minitablets irrespective of the HPMC MW. FA reduced the pH_M inside the minitablets to a higher magnitude based on the more favorable physicochemical properties (Table 2), i.e., the high acidic strength and the low aqueous solubility. Therefore, the remaining pH modifier inside the matrix tablets could replenish the

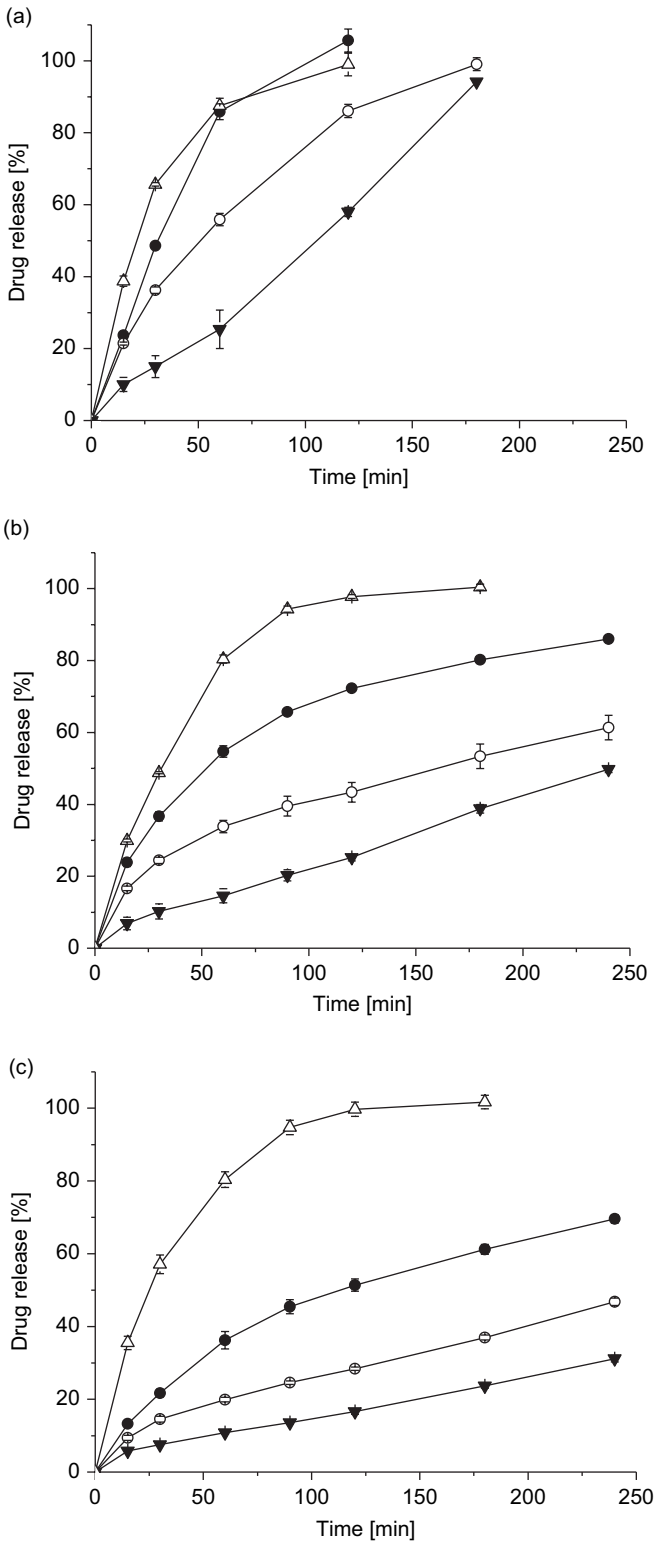

FIGURE 1. Effect of pH modifiers on DP release (drug to acid ratio of 1:2) from minitablets based on (a) Methocel K100LV (formulations 2, 4, 5), (b) Methocel K4M (formulations 6, 7, 8), (c) Methocel K100M (formulations 9, 10, 11) (●) FA, (○) SA, (▼) without acid (pH 6.8), (Δ) without acid (pH 2).

TABLE 2
Physicochemical Properties of the Selected pH Modifiers

Acid Type	Acidic Strength (Stahl, 2002)	Solubility (pH = 6.8) [mg/mL (25°C)]	Solubility (0.1 M HCl) [mg/mL (25°C)]
FA	pK_{a1} 3.0 pK_{a2} 4.4	10.0	4.5
SA	pK_{a1} 4.2 pK_{a2} 5.6	72.5	66.6

released acid by diffusion over a longer period of time. A low pH_M was maintained resulting in increased drug release.

Since drug release strongly depends on the viscosity grade of the polymer (Gao, Skoug, Nixon, Ju, Stemm, & Sung, 1996; Campos-Aldrete & Villafuerte-Robles, 1997), we confirmed that higher MW HPMC polymers significantly retarded the drug release from minitablets. After incubation for 2 hr at pH 6.8, the drug release from Methocel K100LV based minitablets containing FA was completed, whereas only 72.3 and 51.4% were released from Methocel K4M and Methocel K100M mini-matrices, respectively. Minitablets based on higher MW HPMC polymers such as Methocel K4M or Methocel K100M swell to a higher extent, therefore, resulting in stronger retardation of the drug release. According to previously reported work (Gao et al., 1996; Tahara, Yamamoto, & Nishihata, 1995), drug release from Methocel K100LV is markedly faster, attributed to the increased overall polymer erosion. Gao et al. (1996) investigated different HPMC viscosity grades and demonstrated that Methocel K100LV matrix tablets showed a thin gel layer and slow growth rate due to its fast matrix dissolution. DP release from low MW HPMC was predominantly influenced by the interconnected mechanism of drug diffusion and polymer erosion.

Release of the pH Modifiers from Minitablets

In pharmaceutical processing, detailed understanding of pH-controlled systems is essential to optimize sustained release solid dosage forms containing weakly basic drugs. To maintain acidification inside the drug delivery system during the entire dissolution process, pH modifiers should be present during the whole lifetime of the system. However, due to the higher solubility at neutral pH, weak acids are supposed to be washed out more rapidly compared to the poorly soluble basic drug. Consequently, the pH_M may rise and drug release will decrease. Therefore, we evaluated the duration and extent of the pH modulating effect by assessing the acid release from different HPMC-based minitablets.

In contrast to the drug release, which notably depended on the HPMC type, the FA and SA were rapidly washed out from minitablets regardless of the HPMC viscosity grades (Figure 2a). SA completely dissolved after 60 min, whereas FA remained

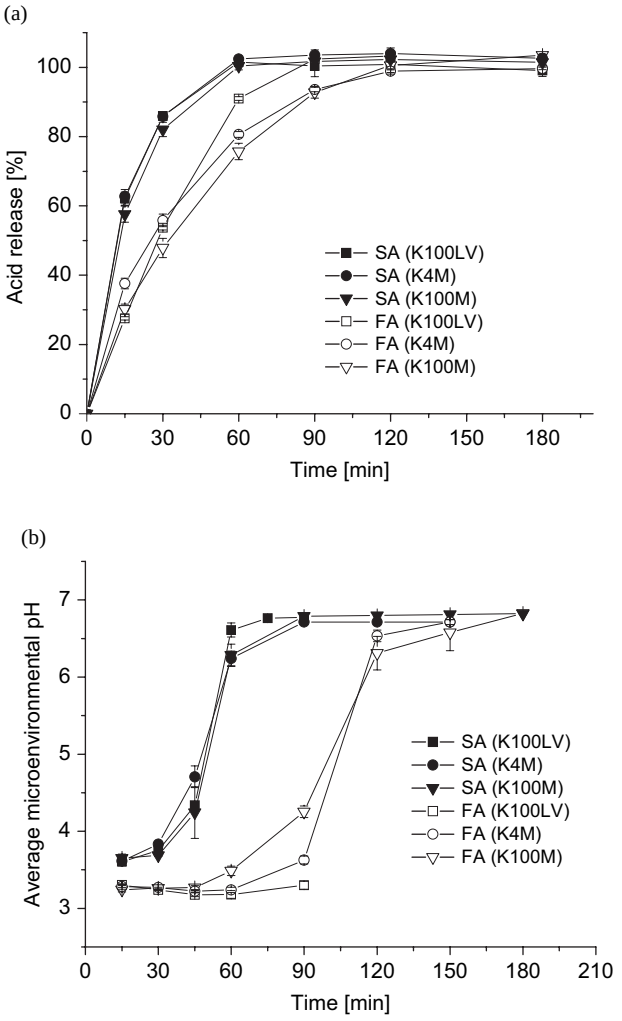

FIGURE 2. (a) FA and SA release from matrix minitablets comprising different MW HPMC at pH 6.8 (formulations 2, 4, 6, 7, 9, 10) (b) average pH_M inside matrix minitablets (phosphate buffer, pH 6.8).

for 2 hr inside the minitablets based on Methocel K4M and Methocel K100M. With regard to the low viscous Methocel K100LV, the release of both FA and DP was completed after 90 min. The faster release of SA can be attributed to the higher aqueous solubility (Table 1).

Owing to the minitablets' high surface area, the dissolution medium quickly penetrated to the center and thoroughly hydrated the minitablets. Since SA and FA are sufficiently water soluble, they dissolved in the infiltrated dissolution medium, leached out, and the pH modulating effect was minimized. The minor diffusional pathway, high driving forces to diffusion, and the small molecular size contributed to the fast dissolution of the incorporated pH modifiers. The depletion of acidic compounds was significantly faster compared to the drug release, particularly regarding the high viscous HPMC polymers such as Methocel K4M and Methocel K100M. In correlation to the washing out of pH modifiers, the pH_{Mav} profile inside the minitablets was elevated towards the pH of the dissolution medium (pH 6.8) (Figure 2b). Drug solubility and drug release were reduced. FA lowered the pH_M to a higher magnitude based on the higher acidic strength. The pH_M inside the minitablets containing SA significantly increased after the incubation of 45 min as the acid rapidly diffused out from the minitablets. In contrast to that, the less-water soluble FA remained inside the minitablets over a longer period of time and an acidic microenvironment was maintained.

Moreover, for visual assessment of the pH_M gradient, we incorporated the pH-sensitive indicator bromophenol blue into Methocel K100M based minitablets comprising FA (drug to acid ratio of 1:2-based on wt. %). The indicator exhibits a yellow color at pH < 3 and a blue color at pH > 4.6. The concentration of bromophenol blue within the minitablets was 0.15% w/w adapted from Streubel et al. (2000) who used methyl red as pH sensitive indicator in the same concentration. By performing dissolution studies, we observed that the inner core of the minitablets remained acidic for more than 90 min (yellow), whereas the outer hydrogel layer rapidly turned to blue. These observations were consistent with the FA release and pH_M determination. The blue layers moved steadily towards the center and after 2 hr the minitablets thoroughly exhibited increased pH values.

Summarizing, the acidic strength and the aqueous solubility of the acid modifiers significantly influenced the duration of pH control inside HPMC-based matrix minitablets. Therefore, incorporating pH modifiers such as FA with low pK_a value and poor solubility seems to be a valuable approach to optimize pH control.

In particular, minitablets based on high MW HPMC grades displayed biphasic drug release. Initially, the included acid created a favorable microclimate, and thereby drug release was enhanced. After the acids diffused out from the gelling system, the pH_M was increased and drug release was decreased.

Incorporation of FA into Methocel K100LV based minitablets (drug to acid ratio of 1:2-based on wt. %) enabled simultaneous release rates of the drug and the pH modifier during the entire drug dissolution (Figure 1a). A constant low pH was maintained (Figure 2b). This formulation design achieved pH-independence from the dissolution medium. This means, drug release at pH 6.8 in presence of FA was comparable to the acid-free release profile at pH 2 (Figure 1a). The included pH modifier did not affect the DP release at low pH where drug solubility is high itself. Moreover, as the dissolution for DP was completed within 90 min, the combination of Methocel K100LV as polymer and FA as acidifier is an adequate approach for a short duration modified release formulation.

Impact of Varying Concentrations of Fumaric Acid on DP Release

We investigated the effect of different FA concentrations on the release behavior of DP from Methocel K100LV minitablets

while keeping the polymer and the drug loading constant (Figure 3). Increasing the FA contents enhanced drug release significantly at pH 6.8 (SDS 0.1% w/V). Compared to the control minitablets without pH modifiers, even small amounts of FA (drug to acid ratio of 1:1-based on wt. %) showed a notable impact on the drug release. After incubation for 4 hr, DP release was completed from Methocel K100LV-based minitablets with and without pH modifiers. Since the low viscous Methocel K100LV is characterized by high overall polymer erosion, minitablets were entirely eroded after this dissolution period, and drug release was completed.

The incorporation of 10% FA (drug to acid ratio of 1:1-based on wt. %) increased the drug release especially at the beginning of the dissolution due to the acidification of the gelling system (Figure 4). In the course of incubation time, dissolution medium penetrated into the minitablets, the pH modifier leached out, and the overall pH_M was increased. The low FA content was not sufficient to maintain an acidic pH over an adequate time, and consequently the drug release was just enhanced at the initial dissolution period. Increasing the FA quantity (drug to acid ratio of 1:2-based on wt. %), the drug release was significantly faster. However, additional increase of the FA loading to 40% (drug to acid ratio of 1:4-based on wt. %) did not show any further effect on the DP release. Acid levels of 20 and 40% resulted in overlapping drug release profiles and the overall dissolution time was decreased to 90 min. These findings are in good agreement with the work of Nie et al. (2004) who demonstrated that citric acid levels above 45 mg/tablet did not further increase the vinpoectine release from conventional matrix tablets. The ideal acid concentration is evidently drug specific. In our study the incorporation of 20 and 40% FA resulted in a constant and similar reduction of the pH_M during the entire dissolution time. Therefore, the drug release was enhanced to a comparable degree.

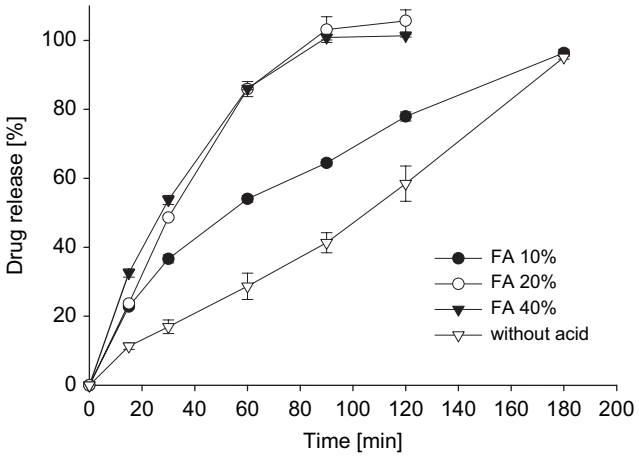

FIGURE 3. Dissolution of DP from Methocel K100LV minitablets with different FA loadings at pH 6.8 (formulations 1, 2, 3, 5).

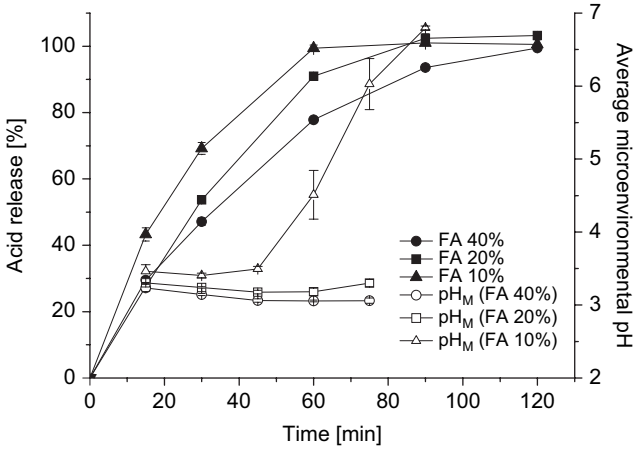

FIGURE 4. Investigation of Methocel K100LV based minitablets with different FA loadings, the acid release and the average microenvironmental pH at pH 6.8 (formulations 1, 2, 3).

CONCLUSIONS

We prepared pH-controlled, tailor-made matrix minitablets based on hydroxypropyl methylcellulose with different molecular weights (MW). Incorporation of two pH modifiers, i.e., succinic and fumaric acid, enhanced the release of the weakly basic drug dipyridamole (DP). Drug release significantly depended on the viscosity grade of the HPMC, whereas pH modifiers were rapidly washed out nearly independently of the HPMC type. FA showed a stronger effect on reducing the microenvironmental pH and maintained an acidic pH_M inside the minitablets over a longer period of time as compared to SA. Minitablets based on the low viscous HPMC Methocel K100LV showed pH independent drug release. Additionally, DP and FA were simultaneously released during the entire dissolution time at the specific acid:drug ratio of 2:1 (based on wt. %). On the contrary, pH independence was not achieved with minitablets based on high MW HPMC grades, i.e., Methocel K4M and Methocel K100M. As the dissolution of the pH modifiers from these minitablets was significantly faster as compared to the drug compound, the pH_M inside the minitablets was enhanced and drug release decreased.

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