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Strategies for the design of hydrophilic matrix tablets with controlled microenvironmental pH

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Abstract

Incorporation of weak acids as pH modifiers enhances the release of weakly basic drugs in higher pH environments by reducing the microenvironmental pH (pH_M). The objectives of this study were: (a) to investigate the relationship between pH_M, drug release, and pH modifier release and (b) to achieve simultaneous release of the drug and the pH modifier over the entire dissolution time (6 h, phosphate buffer, pH 6.8). Using dipyridamole as a model drug, we investigated drug and acid release and determined the average pH_M potentiometrically using tablet cryosections. The first approach was based on incorporating different concentrations of pH modifiers in conventional matrix tablets based on hydroxypropylmethylcellulose. Owing to its high acidic strength and low aqueous solubility, fumaric acid resulted in simultaneous release and maintained a constant acidic pH_M. Secondly, press-coated matrix tablets, comprising an acidic reservoir, were found to be a valuable approach for retarding the diffusion of more water-soluble acids. Using the power law expression ($M_t/M_\infty = kt^n$) it became evident that the inclusion of acids increased drug release. Higher acid concentrations tended to decrease n standing for the slope, whereas the release constant k increased. Furthermore, the medial check term parameters depended on the type of pH modifier used.

Keywords: Weakly basic drug; Dipyridamole; Microenvironmental pH; pH modifier; HPMC

1. Introduction

The oral absorption of drug compounds is influenced by drug dissolution and permeation through the intestinal mucosa. The dissolution of active compounds from solid dosage forms is sometimes more rate limiting to the overall oral absorption than its ability to cross the intestinal mucosa (Hörter and Dressman, 1997). Many drugs are weak bases or salts thereof showing distinct pH-dependent solubility with good solubility at low pH, however poor solubility in higher pH environments. As the pH increases along the gastrointestinal tract (GI-tract), the solubility of weakly basic drugs decreases as the fraction of the unionized form is enhanced. Food, age, pathophysiology, or concomitant drug therapies, such as H_2-receptor antagonists or proton pump inhibitors influence the physiological pH conditions of the GI-tract. Consequently, inter- and intrasubject variability in drug bioavailability due to incomplete drug absorption is frequently observed (Hörter and Dressman, 1997). Several groups have demonstrated that the elevated gastric pH leads to incomplete absorption of the basic drugs ketoconazole, dipyridamole, and rifampicin (Lelawongs et al., 1988; Russell et al., 1994). Chin et al. (Chin et al., 1995) investigated the effect of Coca-Cola on the absorption of ketoconazole in patients with drug-induced achlorhydria. Administration of this acidic beverage led to an approximately seven-fold increase in $AUC_{0-\infty}$. Although the ketoconazole absorption can be increased by Coca-Cola, patients with severe odynophagia or active peptic ulcer diseases are no candidates for this approach (Chin et al., 1995). Therefore, it is essential to develop formulation designs for weakly basic drug substances to enhance the bioavailability and reduce the variability.

The incorporation of pH modifiers such as citric, fumaric, or sorbic acid is a common approach employed with matrix and coated systems (Thoma and Ziegler, 1998; Streubel et al.,

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2000; Espinoza et al., 2000; Nie et al., 2004). Nevertheless, the selection of an adequate pH modifier for a specific drug is not as straightforward as it may appear. The majority of the frequently used pH modifiers are more soluble at higher pH as compared to most basic drug compounds. Since we assume that the pH modifiers diffuse out more rapidly as compared to the drug, the pH-modifying effect within and in the interface of the dosage form will be decreased. The microenvironmental pH (pH_M) can be described as the pH of the saturated solution in the immediate vicinity surrounding the drug particles. Consequently, maintaining the desired pH over the entire period of drug dissolution is a challenging task. The principal goals of our study were: (a) to investigate the relationship between the pH_M, the drug release, and the pH modifier release and (b) to design matrix tablets based on hydroxypropylmethylcellulose (HPMC) which enable simultaneous release rates of the weakly basic drug dipyridamole and different pH modifiers. We employed two different formulation designs and systematically investigated different types and concentrations of acids as potential pH modifiers. They were selected on the basis of their acidic strength and aqueous solubility. This study provides an in-depth understanding of the interplay of drug release, acid release, and the microenvironmental pH with regard to pH-controlled solid dosage forms. Dipyridamole was chosen as the model compound due to its distinct pH-dependent solubility.

2. Materials and methods

2.1. Materials

The following materials were used as received. Dipyridamole (DP) (Chemgo Organica AG, Basel, Switzerland), Methocel K100LV (Dow Chemical Company, Michigan, USA), fumaric (FA) and succinic (SA) acid (Fluka, Switzerland), citric acid (CA) (Roche, Vitamines, Basel, Switzerland), ascorbic acid (AA) (Merck, Darmstadt, Germany) (Table 1), lactose monohydrate 200 mesh (Meggle J.A., Reitmehring, Germany), magnesium stearate (FACI SRL, Carasco, Italy), Aerosil 200 (Cabot Rheinfelden GmbH, Germany). All other reagents were analytical grade and were used without further purification.

2.2. Methods

2.2.1. Preparation of tablets

After blending DP, lactose q.s., Methocel K100LV, and the pH modifier, the powder mixture was manually wet granulated (granulation fluid: ethanol 90%, distilled water 10%) in a mortar. After drying at 40 °C, granules were passed through an 800 μm sieve. The outer phase consisted of 1.0% magnesium stearate and 1.5% w/w Aerosil as lubricant and glidant. During tablet manufacture on a single punch press (EK0, Korsch, Germany), the compression force was adjusted to the corresponding tablet hardness of 70 ± 5 N. We used flat-faced punches with a diameter of 10 mm. Table 2 summarizes the investigated tablet compositions.

Table 1
Physicochemical properties of the selected pH modifiers

Acid type	pKa_1 (Stahl and Wermuth, 2002)	Solubility (pH = 6.8) (mg/ml)	Solubility (0.1N HCl) (mg/ml)
Fumaric acid	3.0	10.0	4.5
Citric acid	3.1	651.9	608.8
Succinic acid	4.2	72.5	66.6
Ascorbic acid	4.2	301.5	296.1

Table 2
Investigated compositions

Formulation no.	FA (% w/w)	SA (% w/w)	CA (% w/w)	AA (% w/w)
F1[a]	10	–	–	–
F2[a]	20	–	–	–
F3[a]	40	–	–	–
F4[a]	–	10	–	–
F5[a]	–	20	–	–
F6[a]	–	40	–	–
F7[a]	–	–	10	–
F8[a]	–	–	20	–
F9[a]	–	–	40	–
F10[a]	–	–	–	10
F11[a]	–	–	–	20
F12[a]	–	–	–	40
F13[b]	–	40	–	–

All formulations comprised 10% w/w dipyridamole and 30% w/w methocel K100LV; lactose q.s.
[a] Conventional matrix tablet.
[b] Press-coated tablet.

2.2.2. Press-coated tablets

For the preparation of core tablets (8 mm in diameter), 20% w/w SA was fed manually into the die of a single-punch tabletting machine (EK0, Korsch, Germany). The granules for the outer shell were prepared according to the method described above. Granules for the shell were filled into the die to make a powder bed on the center of which a core tablet was carefully placed. Afterwards, the equivalent amount of granules was spread over the core and the base. Flat-faced punches with a diameter of 10 mm were used and the final hardness of the tablets was 70 ± 5 N.

2.2.3. In vitro drug release

We conducted dissolution studies using USP 1 apparatus (A7 Sotax, Switzerland) (100 rpm, 37 °C, and 500 ml dissolution medium). Tablets were exposed to medium with a constant pH (phosphate buffer, pH 6.8) for a period of 6 h. A 0.1% w/v SDS was added to the buffer to create sink conditions. At predetermined intervals samples were withdrawn from the dissolution medium and filtered through 0.45 μm membrane filters. An equivalent amount of fresh buffer was added to maintain a constant dissolution volume. We analyzed DP spectrophotometrically at a wavelength of 410 nm (5L4-SP1 Lambda 20, Perkin-Elmer), whereas acid release was quantified by HPLC. All experiments were performed in triplicate.

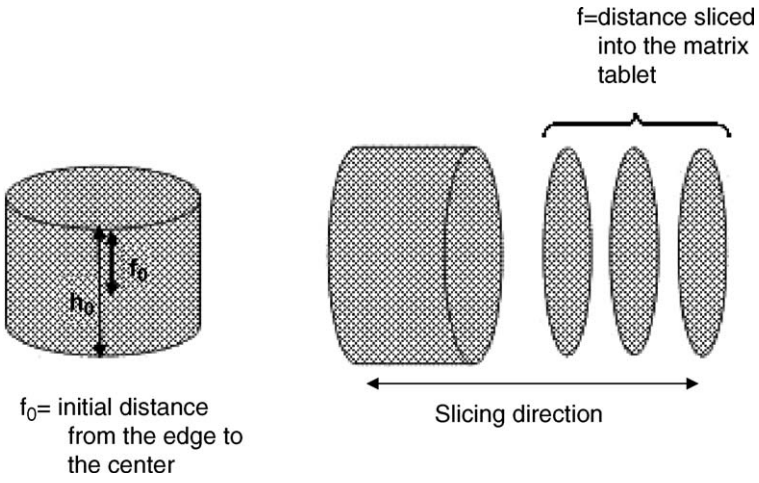

Fig. 1. Illustration of the pH_M determination.

2.2.4. HPLC-assay

The chromatography was carried out on an Agilent HP1100, equipped with the multi-wavelength detector (MWD detector) G1365A and Chromeleon™ software for data analysis. During the first 8 min, the mobile phase consisted of 0.1 M $NH_4H_2PO_4$ buffer adjusted with phosphoric acid to pH 2.7. Subsequently, a gradient (acetonitrile/$NH_4H_2PO_4$ buffer (pH 2.7)) was used to remove any remaining drug compound completely. Separation was achieved by using an Inertsil C8-3.5 μm, 4.6 mm × 150 mm column (Erchatech AG, Switzerland). A flow rate of 1 ml/min, an injection volume of 5 μl (FA) and 10 μl (CA and SA), and run times of 15 min were employed. Chromatograms were recorded at 210 nm.

2.2.5. Solubility determination

We performed solubility measurements of DP over a pH range of 2.5–7.0 at 25 °C. Following buffer systems were used: glycinate buffer (pH 1–3), citrate buffer (pH 3.7–4.7), and phosphate buffer (pH 6–7). Excess of DP was added to the buffer solutions. After equilibrium the final pH and the drug solubility in the supernatant were determined spectrophotometrically at a wavelength of 284 nm using the spectrometer mentioned above.

We determined the solubility of the weak acids used as pH modifiers at pH 1 (0.1 M HCl) and pH 6.8 (phosphate buffer). The solubility of SA and CA were analyzed by HPLC, while AA and FA were determined by UV spectroscopy.

2.2.6. Determination of pH_M

After specific time intervals, tablets were removed from the dissolution medium and immediately frozen using dry ice. We measured the height of each tablet separately in the frozen state using a caliper (Digit-Call II, Tesa, Switzerland). After fixing the tablets with embedding materials, tablets were sliced (slice thickness 50 μm) with a microtome in a cryostat (−23 °C). Three cryosections were positioned over each other, thus the final slice thickness was 150 μm. The average pH_M (pH_{Mav}) over the surface of each slide was determined potentiometrically using a surface pH electrode (Methrom AG, Switzerland) and plotted against the fractional distance f/f_0. We assumed that the pH gradients from the center of the tablet to both edges are similar. $f/f_0 = 1$ represents the center, whereas $f/f_0 = 0$ indicates the edge of the gel layer (Fig. 1). The fractional distance was calculated for each point.

3. Results and discussion

DP with significant solubility properties over the physiological pH is an excellent candidate to investigate formulation strategies to overcome the pH-dependency. The measured solubility of DP at 25 °C was 18.2 mg/ml at pH 2.9, 8.63 mg/ml at pH 3.0, and only 0.003 mg/ml at pH 6.2 (Fig. 2). These data are consistent with previously reported work (Kohri et al., 1992). In general drug release from HPMC-based matrix tablets is distinctly dependent on the molecular weight of the polymer (Gao et al., 1996). We chose the low molecular weight HPMC, Methocel K100LV, as we aimed to achieve at least approximately 80% drug release after a maximum dissolution time of 6 h. As expected, the dissolution medium strongly influenced DP release from Methocel K100LV matrix tablets. At pH 2 (0.01 M HCl) drug release was completed after a dissolution period of 6 h, whereas at pH 6.8 (phosphate buffer, SDS 0.1% v/w) only 24.8%

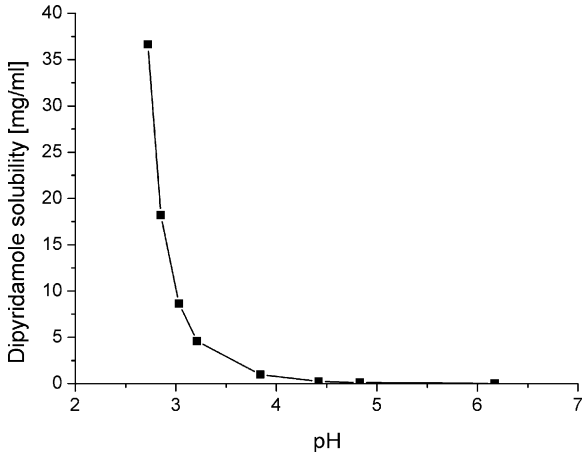

Fig. 2. pH-solubility profile of dipyridamole at 25 °C.

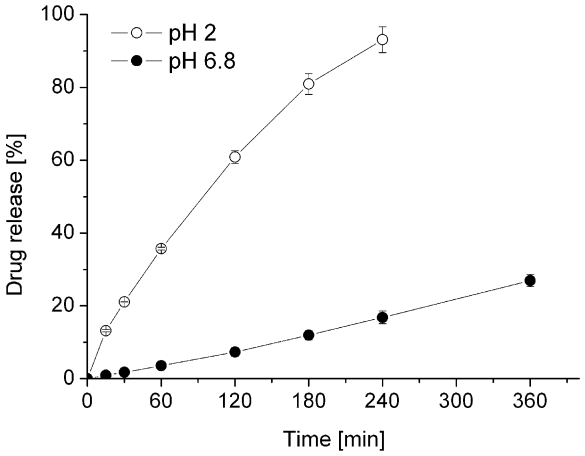

Fig. 3. Drug release in different pH media (pH 2, 6.8).

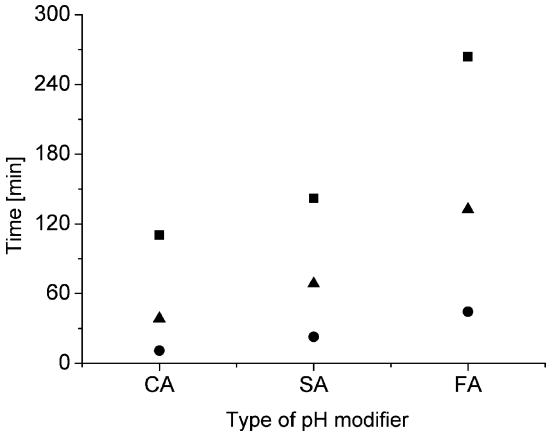

Fig. 5. Release parameters of pH modifiers, Time to (●) 25%, (▲) 50%, and (■) 75% release.

was released (Fig. 3). This significant effect was attributed to the reduced drug solubility at higher pH values. Based on the results, we assume that drug release leads to high inter-and intrasubject variability caused by incomplete and unsatisfactory dissolution in elevated pH environments.

3.1. Conventional matrix tablets

3.1.1. Effect of different pH modifiers

We selected the pH modifiers on the basis of their physicochemical properties, explicitly their acidic strength and aqueous solubility (Table 1). The influence of various pH modifiers on the time-dependent release of DP is illustrated in Fig. 4. All tablets contained 20% w/w pH modifying agents and the drug loading was 10% w/w. In all cases, the incorporation of pH modifiers significantly enhanced the drug release rate at pH 6.8, but the extent of release enhancement was dependent on the type of pH modifier. The addition of FA led to the highest drug release (86.8%), followed by CA (65.6%), SA (51.7%) and AA (41.8%) after a dissolution time of 6 h. These findings support our assumptions that the acidic strength and aqueous solubility of the incorporated acids impact on the drug release. Included pH modifiers

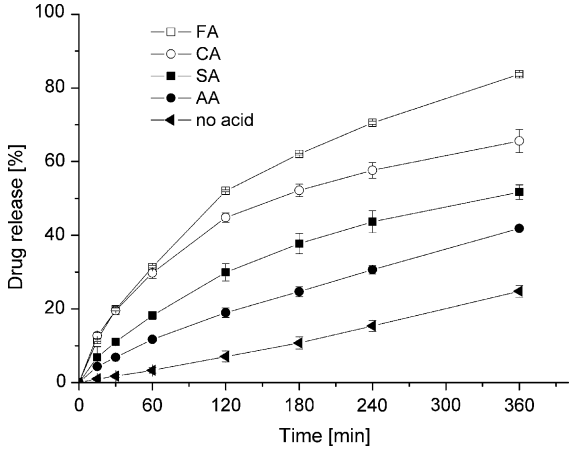

Fig. 4. Effect of different pH modifiers (20% w/w) on dipyridamole release rate (phosphate buffer pH 6.8, SDS 0.1%).

are assumed to modulate the pH_M independently from the bulk pH thus enhancing drug solubility and drug dissolution. The pH modifying effect is maintained as long as the pH modifier is present inside the solid dosage form. However, the solubility of the incorporated acids is more soluble at elevated pH values compared to DP. It follows that a formulation designed to provide matching release profiles of drug and pH modifier during the entire dissolution period is expected to offer optimal pH control. For evaluation of this approach, the release of the pH modifiers, i.e., CA, FA, and SA, from the matrix tablets into the bulk medium was monitored and quantified.

The dissolution of the acids from the matrix tablets significantly increased with higher aqueous solubility (Fig. 5). CA (0.65 g/ml) was already released to 60% after one hour due to its high solubility. However, even though the difference in solubility between CA and SA is nine-fold, their release profiles were almost identical. pH modifiers, showing good aqueous solubility, dissolved immediately in the infiltrated medium in the matrix and, afterwards rapidly diffused out. In contrast, as a result of its low saturation solubility, a large amount of the initially incorporated FA remained undissolved in the matrix tablet and was able to replenish the released acid over time. This phenomenon is illustrated by the respective release. After 4 h CA and SA were almost completely released (CA 95.6%, SA 93.9%), whereas significant amounts of the initial FA dose (28.4%) were still present. In the presence of either CA or FA an acidic and favorable environment was created initially, thus resulting in rapid and similar drug release profiles with both pH modifiers. However, as CA diffused out rapidly, pH_M was increased, and drug release slowed down dramatically during dissolution. In contrast, fair amounts of FA remained within the tablet and, consequently prolonged acidification led to further enhancement of drug release. Moreover, Fig. 6 reveals that both DP and FA were released at simultaneous release rates over the entire dissolution period, whereas CA release was completed much faster than the drug release. Contrary to the work of Espinoza et al. (Espinoza et al., 2000), we claim that pH_M modulation is the main contribution to enhance drug release. Loosening the matrix structure and pore formation have only a secondary effect on the drug release. Additionally, we could successfully demonstrate that

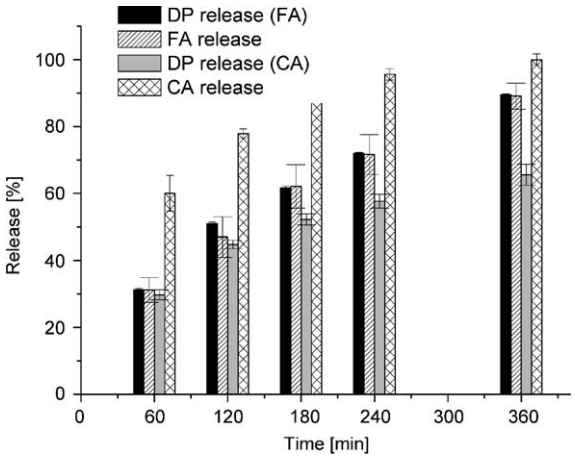

Fig. 6. Comparison of dipyridamole and pH modifier release (phosphate buffer pH 6.8, SDS 0.1%).

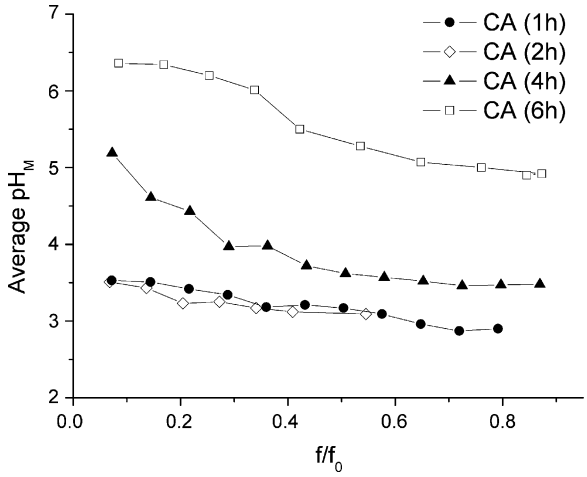

Fig. 8. The influence of CA on pH_M within HPMC matrix tablets incubation time 1, 2, 4, and 6 h (phosphate buffer pH 6.8, SDS 0.1%).

drug release significantly decreased as soon as the pH modifying agent was diffused out from the matrix system. Espinoza et al. (Espinoza et al., 2000) assumed that CA acts more as a hydrosoluble excipient than an acidic one. That means, that the rapid release of CA from the tablet increases the porosity and thereby the drug release.

To further understand the effect of the pH modifiers on the acidification and duration of pH control, we quantified the pH_{Mav} inside the matrix tablets comprising the pH modifiers in question. The pH_{Mav} refers to the mean pH_M of each cryosections. Within the first hour of dissolution at pH 6.8 the pH_{Mav} was mainly influenced by the acidic strength (Fig. 7). Due to the washing out of pH modifiers, pH_{Mav} was slightly increased at the edges of the tablet. The pH_M of the control matrix tablets, without acid, matched the bulk pH (pH 6.8). In the course of time, the more soluble acids could not maintain an acidic microenvironment adequately, particularly at the margins, as highlighted in Fig. 6. After 4 h, we observed a distinctive pH gradient from the edges to the center inside CA containing tablets, after 6 h the pH_{Mav} of the entire tablet nearly approached the pH of the dissolution medium (Figs. 8 and 9). Summarizing, the low pH environment dissipated more rapidly in presence of highly soluble acids. In contrast, the less soluble FA acidified the microenvironment throughout the entire dissolution period of 6 h. The pH_{Mav} gradient from the margins to the center of the tablets in this case was almost negligible. For that reason, the maintenance of a low pH_{Mav} was the principal explanation for the higher drug release in the presence of FA. The conclusions drawn from the pH_M measurements and release profiles of the pH modifiers could accurately explain the ranking of DP release in the presence of different pH modifiers (Fig. 4). FA with a high acidic strength and the lowest aqueous solubility resulted in the most pronounced enhancement of the drug release.

3.1.2. Impact of pH modifier's concentration

The inclusion of 10–40% pH modifiers was examined, while keeping drug and polymer concentration constant. In general, increasing levels of pH modifiers progressively enhanced drug release (Fig. 10). Fig. 10 shows the effect of different con-

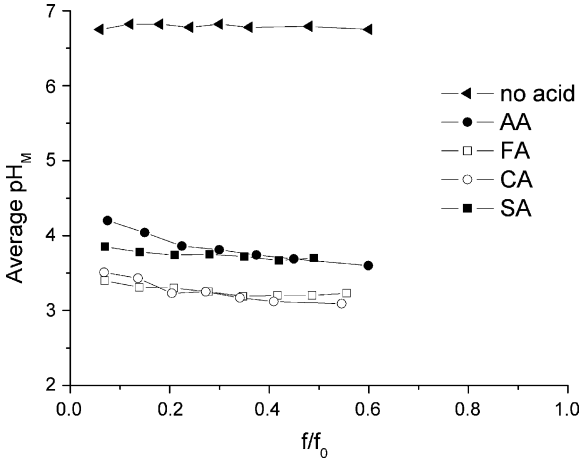

Fig. 7. The influence of various pH modifiers on pH_M within HPMC matrix tablets, incubation time 1 h (phosphate buffer pH 6.8, SDS 0.1%).

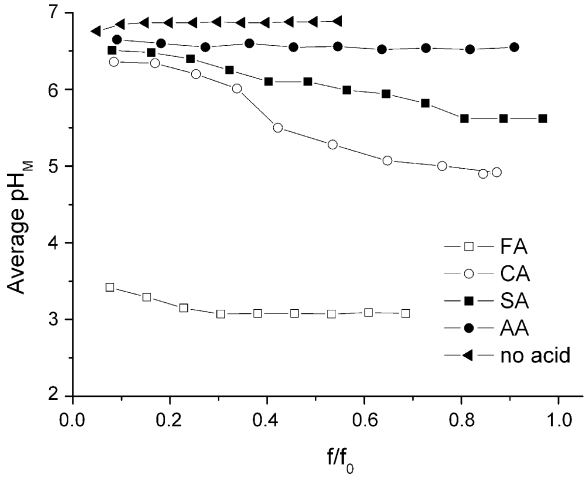

Fig. 9. The influence of various pH modifiers on pH_M within HPMC matrix tablets, incubation time 6 h (phosphate buffer pH 6.8, SDS 0.1%).

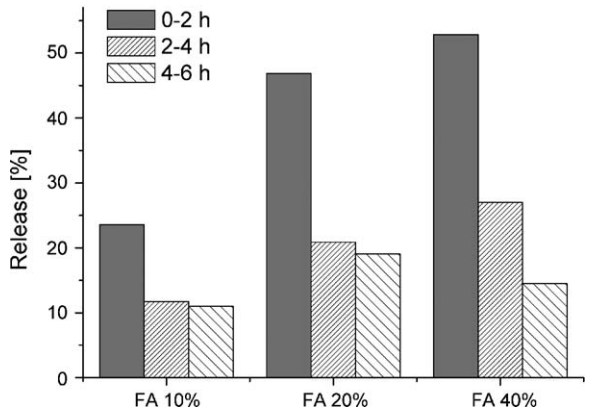

Fig. 10. Effect of type and concentration of pH modifiers on dipyridamole release (phosphate buffer pH 6.8, SDS 0.1%).

Table 3
Regression parameters of dipyridamole dissolution curves from HPMC-based matrices in presence of various pH modifies (phosphate buffer pH 6.8)

Acid type	Acid concentration	Slope (n)	k	R^2
FA	10	0.6063	1.3060	0.9567
FA	20	0.5998	2.5706	0.9735
FA	40	0.5793	3.1232	0.9950
CA	10	0.5317	1.8643	0.9730
CA	20	0.4650	4.4492	0.9737
CA	40	0.5979	2.9559	0.9684
SA	10	0.7105	0.8603	0.9944
SA	20	0.6617	1.2838	0.9818
SA	40	0.6026	2.4801	0.9635
AA	10	1.0175	0.0848	0.9868
AA	20	0.7219	0.5922	0.9955
AA	40	0.5996	2.3476	0.9573
Without acid	0	1.0957	0.0439	0.9912

centration of fumaric acid only, but similar trends have been observed for the other investigated acids, namely citric acid, ascorbic acid and succinic acid. Even 10% acid, the lowest concentration analyzed, showed a notable increase in DP release as compared to the acid-free tablets. However, at this low concentration drug release was improved insufficiently. After 6 h the incorporation of 10% FA achieved a double increase of drug release as compared to the control matrix tablet (46.3% (10% FA); 24.8% (no acid)). In the presence of higher quantities of FA, 86.8% (20% FA) and 94.3% (40% FA) of the initial drug amount were released. We assume that the addition of low levels of FA (10% w/w) is insufficient to achieve and maintain a favorable acidic microenvironment. As demonstrated previously, the addition of higher FA amounts resulted in matching release rates of drug and pH modifier and a constant and low pH_M over the entire dissolution period. A further increase of the FA concentration to 40% did not result in additionally enhanced DP release. Based on our experience, inclusion of 20% FA appears to be optimal with regard to enhanced drug release and also technical feasibility, since high acid amounts tend to cause adhesion during the tablet manufacturing process.

At the high acid concentration of 40% w/w secondary phenomena besides of pH_M reduction may also occur, pH modifiers may additionally influence the osmotic pressure, alter swelling dynamics, gel properties, or hydration behavior. It is well known that electrolytes compete for water of hydration, and thereby, dehydrate the hydrophilic polymer, and suppress the initial swelling; hence, changed swelling dynamics can be observed (Pillay and Fassihi, 1999; Durig and Fassihi, 2002; Varma et al., 2005). These aspects may also influence drug release.

At all acid concentrations tested the same ranking order as described in Fig. 4 between the acids was observed (not all data shown). The incorporation of FA resulted in the fastest drug release, followed by CA, SA, and AA. The maximal effect on DP release was observed within the first 2 h for all pH modifiers investigated. However, the effect diminished with time due to outward diffusion of the pH modifier from the tablet. As compared to the more soluble pH modifiers, FA containing matrix tablets showed a markedly improved drug release over the whole release period of dissolution at all acid concentrations.

3.1.3. Data analysis

The semi-empirical power law expression can be used to model transport and reveal the mechanism of drug release (Eq. (1)) (Ritgers and Peppas, 1987a; Ritgers and Peppas, 1987b):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

M_t is the amount released at time t, M_∞ the quantity of drug released at infinite time, n the diffusional exponent indicative of the release mechanism, and k is the kinetic constant. In the case of a cylinder, $0.45 < n < 0.89$ is indicative of Fickian release, anomalous release, or case II transport kinetics, respectively. The incorporation of pH modifiers resulted in an anomalous release, which corresponds to coupled diffusion and polymer relaxation. The control formulation produced a n-value of 1.0175, corresponding to a zero-order release mechanism (purely relaxation controlled). Table 3 summarizes the release parameters. In the case of fumaric, succinic and ascorbic acid, with increasing pH modifier concentrations the slope (n) tended to decrease, whereas constant (k) increased, suggesting that higher acid concentrations increased drug diffusivity. Furthermore, the slope (n) and the release constant (k) depended on the type of pH modifier (Fig. 11). The incorporation of 10% and 20% AA resulted in the highest n value indicative of reduced diffusivity, which confirmed previous results obtained by pH_M determination and drug release studies.

3.2. Press-coated tablets

3.2.1. Assessment of press-coated tablets containing SA

We demonstrated so far that more soluble pH modifiers, such as CA or SA, rapidly diffuse out of the system. Therefore, acid release was completed much faster than the drug release. To overcome this, we applied the approach of press-coated tablets to prolong the release of the pH modifier. The inner core contained the pH modifier, in our case SA, functioning as an acidic reservoir. SA was additionally incorporated into the outer shell, otherwise, drug release was too slow in the initial phase until enough water penetrated into the system to dissolve the SA in the inner core. The outer phase consisted of HPMC, drug, pH

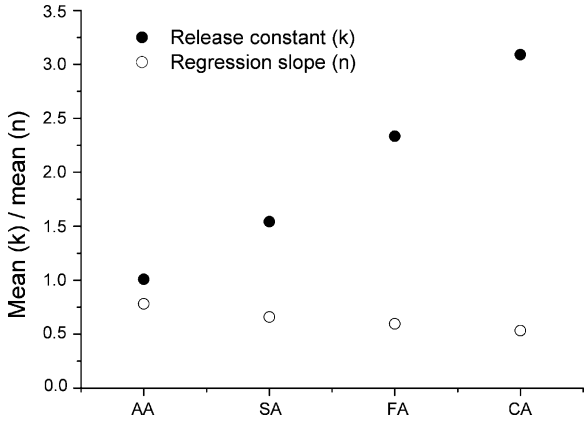

Fig. 11. Relationship between the medial slope (n) and release constant (k) of dipyridamole release curves from HPMC matrices containing various types of pH modifiers.

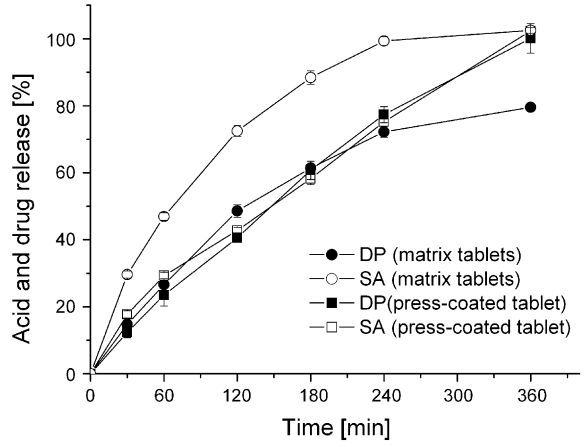

Fig. 12. Comparison of drug and SA release from conventional matrix tablets and press-coated tablets (phosphate buffer pH 6.8, SDS 0.1%).

modifier, and lactose. Fig. 12 illustrates that DP and SA were released at linear and simultaneous release rates at pH 6.8. The acid and drug release was completed after a dissolution time of 6 h. On the contrary to conventionally prepared matrix tablets, formulating press-coated tablets prolonged the DP release. In particular after a dissolution time of 3 h SA entirely diffused out from conventionally prepared matrix tablets and thereby drug release decreased significantly. That means that drug release was enhanced as long as the pH modifier was present inside the matrix tablet. The rapid diffusion of the pH modifier was markedly slowed down in press-coated tablets.

4. Conclusions

The assessment of drug release alone is not sufficient to understand pH controlled systems in detail. Release profiles of the incorporated pH modifiers in addition to the microenvironmental pH (pH_M) should also be investigated. We have demonstrated that the choice of an ideal pH modifying agent is crucial since the effect and duration of acidification strongly depends on the type of the incorporated pH modifier. Using conventional matrix tablets, we achieved simultaneous release rates of DP and fumaric acid, thus allowing maximal drug release as compared to the other acids after the investigated dissolution time. Fumaric acid was the selected best candidate to maintain a favorable low pH_M for drug release over the lifetime of the system. In addition, we demonstrated that press-coated tablets were a novel approach to sustain release of more water-soluble pH modifiers. Drug release was controlled over a longer time interval as compared to conventional matrix tablets using the same acid.

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