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Strategies to Overcome pH-Dependent Solubility of Weakly Basic Drugs by Using Different Types of Alginates

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Weakly basic drugs demonstrate higher solubility at lower pH, thus often leading to faster drug release at lower pH. The objective of this study was to achieve pH-independent release of weakly basic drugs from extended release formulations based on the naturally occurring polymer sodium alginate. Three approaches to overcome the pH-dependent solubility of the weakly basic model drug verapamil hydrochloride were investigated. First, matrix tablets were prepared by direct compression of drug substance with different types of sodium alginate only. Second, pH-modifiers were added to the drug/alginate matrix systems. Third, press-coated tablets consisting of an inner pH-modifier tablet core and an outer drug/sodium alginate coat were prepared. pH-Independent drug release was achieved from matrix tablets consisting of selected alginates and drug substance only. Alginates are better soluble at higher pH. Therefore, they are able to compensate the poor solubility of weakly basic drugs at higher pH as the matrix of the tablets dissolves faster. This approach was successful when using alginates that demonstrated fast hydration and erosion at higher pH. The approach failed for alginates with less-pronounced erosion at higher pH. The addition of fumaric acid to drug/alginate-based matrix systems decreased the microenvironmental pH within the tablets thus increasing the solubility of the weakly basic drug at higher pH. Therefore, pH-independent drug release was achieved irrespective of the type of alginate used. Drug release from press-coated tablets did not provide any further advantages as compound release remained pH-dependent.

Keywords alginates; pH-independent; drug delivery; fumaric acid; weakly basic drug

INTRODUCTION

Many drugs are weak bases or salts thereof, which demonstrate pH-dependent solubility with good solubility at lower pH but poor solubility at higher pH. Hence, drug release of these compounds from controlled release matrices can vary during dissolution at various pH values. These differences in in vitro studies are also crucial in vivo and may lead to inter- and intra-individual variations in plasma profiles and bioavailability (Hoerter & Dressmann, 1997).

Several approaches to overcome pH-dependent solubility of weakly basic drugs have been published. Some authors used blends of enteric and extended release polymers as film-coating materials (Amighi, Timmermans, Puigdevall, Baltes, & Moes, 1998; Dashevsky, Kolter, & Bodmeier, 2004; Munday, 2003). The enteric polymer is insoluble at lower pH whereas rapid dissolution of the polymer is observed at higher pH-values. Because of the dissolution of the enteric polymer at higher pH, the poor solubility of the active ingredient is compensated by the increased porosity of the film coat thus leading to pH-independent drug release.

Another attempt to achieve pH-independent drug release for weakly basic drugs has been described by Takka, Rajbhandari, and Sakr (2001). They incorporated the enteric polymer Eudragit L as pH-dependent soluble filler into hydroxypropyl methylcellulose (HPMC) matrix tablets. At lower pH-values the enteric polymers were part of the core matrix. In contrast, at higher pH-values, the enteric polymers dissolved and formed pores thus increasing drug release rates.

The majority of the approaches to achieve pH-independent release of weakly basic drugs from extended release dosage forms are based on the addition of organic acids (e.g., fumaric or succinic acid) to tablet or pellet matrices in order to create a favorable pH-microenvironment. Drug solubility and consequently dissolution of weakly basic drugs is enhanced at higher pH thus leading to pH-independent drug release profiles. Streubel, Siepmann, Dashevsky, and Bodmeier (2000) achieved pH-independent release of verapamil hydrochloride from matrix tablets consisting of ethylcellulose or HPMC by the addition of fumaric, sorbic, or adipic acid. They demonstrated that the addition of organic acids to both matrix formers

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maintained low pH-values within the tablets during drug release in phosphate buffer pH 6.8 leading to pH-independent drug release. Vinpocetine release from HPMC matrices into phosphate buffer was strongly increased after addition of citric acid (Nie, Pan, Li, & Wu, 2004). Kranz, Guthmann, Wagner, Lipp, and Reinhard (2005) demonstrated pH-independent release of a weakly basic drug, namely ZK 811752, from polyvinylacetate/polyvinylpyrrolidone matrix tablets in the presence of fumaric acid. Guthmann, Lipp, Wagner, and Kranz (2007) showed pH-independent release of a weakly basic drug from polyvinylacetate/polyvinylpyrrolidone-coated pellets after addition of fumaric acid into the pellet core.

In recent years, biomedical and pharmaceutical industries have shown increased interest in the use of biopolymers, particularly alginates (Liew, Chan, Ching, & Heng, 2006; Shilpa, Agrawal, & Ray, 2003; Sriamornsak, Thirawong, & Korkerd, 2007). Alginates are non-toxic polymers that are well established in the food and beverage industry. Hydration of an alginate matrix leads to the formation of a gelatinous layer, which can act as a drug-diffusion barrier. Hence, alginates are also interesting polymers in controlled drug release particularly for weakly basic drugs as they dissolve faster at higher pH. Therefore, they seem to be promising polymers to compensate the poor solubility of weakly basic drugs at higher pH. Commercially available alginates are extracted from marine algae (Gombotz & Wee, 1998). They are linear unbranched polysaccharides containing varying proportions of manuronic (M) and guluronic acid (G) residues. The M and G monomers are 1 and 4 linked by glycosidic bonds, forming homopolymeric MM or GG blocks, which are interspersed with heteropolymeric MG or GM blocks. The composition, sequence of polymer blocks, and molecular weight are important factors when using alginates as controlled release matrices especially for controlled release of weakly basic drugs.

The objective of this study was to achieve pH-independent release of a weakly basic drug from extended release formulations based on the naturally occurring polymer sodium alginate. Three approaches to overcome the pH-dependent solubility of the weakly basic model drug verapamil hydrochloride were investigated. First, matrix tablets were prepared by direct compression of drug substance with different types of sodium alginate only. Second, pH-modifiers were added to the drug/alginate matrix systems. Third, press-coated tablets consisting of an inner pH-modifier tablet core and an outer drug/sodium alginate coat were prepared.

MATERIALS AND METHODS

Materials

The following materials were used as received: verapamil hydrochloride (BASF, Ludwigshafen, Germany), alginate (Protanal® LF 120 M, Protanal® LF 200 M, Protanal® LF 240 D, FMC Biopolymer, Drammen, Norway), calcium phosphate (Fluka, Buchs, Switzerland), colloidal silicon dioxide (Aerosil®, Degussa, Frankfurt, Germany), magnesium stearate (Roquette, Lestrem, France), acetonitrile, fumaric acid, 2-aminoheptane, acetic acid, potassium dihydrogen phosphate, sodium hydroxide, and hydrochloric acid (Merck KGaA, Darmstadt, Germany). All chemicals were reagent grade or higher.

Methods

Preparation of Tablets

Tablets containing 1.5% (wt/wt) magnesium stearate as lubricant and 1% (wt/wt) colloidal silicon dioxide as flow promoter were prepared by direct compression if not otherwise mentioned. The respective powders (drug, polymer and additives, for compositions, see Table 1) were passed through a 0.8-mm sieve (Haver and Böcker, Celle, Germany) and blended with a turbula mixer (W.A. Bachofen AG, Basel, Switzerland). The tablets were prepared by using a single punch tableting machine (EK0, Korsch, Berlin, Germany). The hardness of the tablets was kept constant at 80–100 N if not otherwise mentioned (Schleuniger hardness tester 6D, Schleuniger Pharmatron AG, Solothurn, Switzerland). For wet granulation, the blend (Table 1, formulation no. 10) was granulated in a planetary mixer (MTI, MTI-Mischtechnik Industrieanlagen GmbH, Lage, Germany) by using distilled water.

Preparation of Press-Coated Tablets

Core tablets consisting of only fumaric acid were prepared by using a single punch tableting machine (Table 1, formulation no. 7). The powder for the outer shell was prepared as described above and filled into the die in order to make a powder bed for the fumaric acid core. Afterwards, the core tablet was carefully placed into the die and the equivalent of powder was spread over the core and the base. The hardness of the tablets was kept constant at 80–100 N.

Drug Release Studies

In vitro drug release was determined using the USP rotating paddle method (900 ml 0.1 N HCl or USP phosphate buffer pH 6.8; 37°C; 50 rpm; $n = 3$; Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, NJ, USA). At predetermined time intervals, 10 ml samples were withdrawn (not replaced), filtered, and assayed. The amount of verapamil hydrochloride released was measured by a Waters-HPLC system (600 E Controller, 600 F pump, 717 plus Autosampler, 2487 Dual Absorbance Detector, Waters Corp., Milford, CT, USA) according to the USP 29 (2006) method.

Fumaric Acid Release

Fumaric acid release was determined using the USP rotating paddle method (900 ml 0.1 N HCl or USP phosphate buffer pH 6.8; 37°C; 50 rpm; $n = 3$; Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, NJ, USA). At predetermined time

TABLE 1
Composition of the Investigated Tablets (All Quantities Given in Milligram)

Formulation Number	Protanal LF 120 M	Protanal LF 200 M	Protanal LF 240 D	Verapamil HCl	Fumaric Acid
1	449.2	–	–	233.3	–
2	–	449.2	–	233.3	–
3	379.2	–	–	233.3	70
4	344.2	–	–	233.3	105
5	682.5	–	–	–	–
6	577.5	–	–	–	105
7[a]	379.2	–	–	233.3	70
8	–	–	449.2	233.3	–
9	–	–	682.5	–	–
10[b]	–	–	449.2	233.3	–

In addition, 10.5 mg magnesium stearate and 7.0 mg silica. All tablets manufactured by direct compression if not otherwise mentioned.

[a]Press-coated tablet.

[b]Manufactured after wet granulation.

intervals 10 ml samples were withdrawn, filtered, and assayed. Afterwards the tablets were removed from the dissolution medium for water uptake and mass loss studies. The amount of fumaric acid released was measured with the above-mentioned Waters-HPLC system. A 5-µl volume was injected onto a Hydrosphere C 18 column (YMC Europe GmbH, Schermbeck, Germany) using as the mobile phase a mixture of ammonium dihydrogen phosphate pH 2.0 (mobile phase A) and acetonitrile (mobile phase B) (gradient program: 100% mobile phase A at time 0–6 min; 20% mobile phase A at time >6–13 min; 100% mobile phase A at time >13–20 min); flow rate: 1.0 ml/min; UV-detection at 210 nm. Fumaric acid solutions of known concentration were used to calculate the amount of fumaric acid released.

Solubility Studies

Excess amount of verapamil hydrochloride was placed in water, and the pH was adjusted to various values by adding HCl or NaOH (n = 3). After equilibrium, the final pH of the medium was measured and the drug solubility in the supernatant was determined by HPLC as described above.

Water Uptake and Alginate Mass Loss Studies

The water uptake and alginate mass loss of the tablets was determined gravimetrically with a microbalance. Tablets were placed in 900 ml 0.1 N HCl or USP phosphate buffer pH 6.8 at 37°C. At predetermined times, the drug and fumaric acid release was determined as described above. At each sampling point the tablets were removed from the medium, blotted to remove surface medium, immediately weighed and then dried until constant weight was reached. Three different tablets were measured for each sampling point and fresh tablets were used for each individual time point. The percentage of water uptake of the tablets was calculated according to the following equation:

$$\text{Percentage of water uptake} = 100\ (W_w - W_d)/W_d$$

where W_w and W_d are the weights of wet and dry tablets measured at different time periods.

The percentage of alginate mass loss was calculated according to the following equation:

$$\text{Percentage of alginate loss} = 100\ [M_0 - (M_d + M_f)]/M_0$$

where M_0 and M_d are the initial and the final dry mass after incubation in buffer medium at predetermined time periods and M_f the mass of fumaric acid released at predetermined time periods.

Determination of the Microenvironmental pH

After specific time intervals, the tablets were removed from the dissolution medium and immediately frozen. Subsequently, the height of each tablet was measured separately in the frozen state using a caliper (Helios Messtechnik, Niedernhall, Germany). The tablets were fixed and cut into individual cryosections by using a microtome in a cryostat at −10°C. The microenvironmental pH (pH_M) of the cryosections was determined potentiometrically using a surface pH electrode (Methrom AG, Switzerland) and plotted against the fractional distance f/f_0 where f_0 is the initial distance from the edge to the center of the tablet and f the distance at the respective cryosection ($f/f_0 = 1$ represents the center of the tablet, whereas $f/f_0 = 0$ indicates the edge of tablet).

RESULTS AND DISCUSSION

Alginates are known to have a pH-dependent solubility. They dissolve slower at lower pH as alginate precipitates in the form of poorly soluble alginic acid (Liew et al., 2006). Hence, they seem to be a promising matrix former for tablets to overcome pH-dependent solubility of weakly basic drugs that demonstrate good solubility at lower pH but poor solubility at higher pH (solubility differences of the drug should be compensated by the inverse solubility of the polymer).

To investigate the release of the weakly basic model drug verapamil hydrochloride from alginate matrix tablets two grades of sodium alginate namely Protanal® LF 120 M and Protanal® LF 200 M were studied first (Table 1, formulation nos. 1 and 2). Both polymers have similar manuronic to guluronic acid ratios but varying molecular weights (Table 2). Verapamil hydrochloride release from alginate-based matrix tablets consisting of Protanal® LF 120 M and Protanal® LF 200 M showed significant differences when measured in 0.1 N HCl and phosphate buffer pH 6.8 (Figure 1). Drug release at pH 6.8 was significantly slower compared with drug release at pH 1, which can be explained by the weakly basic nature of the compound. At pH < 6.4, the solubility of verapamil hydrochloride was higher than 100 mg/ml. The solubility decreased to approximately 50 mg/ml at pH 6.5 and dropped even to 3 mg/ml at pH 6.8. Therefore, drug release profiles are in good agreement to the solubility of the weakly basic drug. Both alginates (Protanal® LF 120 M and Protanal® LF 200 M) were not able to compensate the pH-dependent solubility of the drug. Interestingly, at pH 1 no differences in the release profiles of tablets prepared with alginates of different molecular weights were observed. In contrast, at pH 6.8 the drug release was faster from tablets prepared with alginates of lower molecular weight. These differences might be explained with the different release mechanism at pH 1 versus pH 6.8. It is well known that for alginates at pH 6.8, erosion is an important factor influencing drug release (Timmins, Delargy, & Howard, 1997). As higher molecular weight fractions dissolve slower, drug release at pH 6.8 was slower from the higher molecular weight Protanal LF 200 M. In contrast, at pH 1, diffusion of dissolved active agent through the polymer and water-filled pores into the release medium is the release-limiting factor. Here, differences in the molecular weights seem to be negligible.

To achieve pH-independent verapamil hydrochloride release, the addition of fumaric acid to the matrix of the tablets was investigated next (Table 1, formulation nos. 1, 3, and 4). Fumaric acid was chosen because it has high acidic strength (pK_{a1} 3.03 and pK_{a2} 4.54, from Merck & Co. Inc., 2001) and relatively low solubility in 0.1 N HCl (7.79 mg/ml, from Streubel et al., 2000). Independent of the pH of the dissolution medium, the pH inside the matrix tablet was expected to be acidic and thus the solubility of verapamil hydrochloride should be high. These studies were carried out on Protanal® LF 120 M formulations only as similar results were expected for the higher molecular weight Protanal® LF 200 M. Addition of 10 or 15% (wt/wt) fumaric acid resulted in pH-independent drug release when measured in 0.1 N HCl and phosphate buffer pH 6.8 (Figure 2). Irrespective of the amount of fumaric acid added, the drug release from Protanal® LF 120 M matrix tablets decreased at pH 1 when compared with alginate tablets without fumaric acid (Figure 1). Surprisingly, almost identically release profiles were observed for tablets with and without fumaric acid at pH 6.8. The explanation for these observations might be as follows: Addition of fumaric acid to the matrix of the tablets resulted in an acidic microenviron-

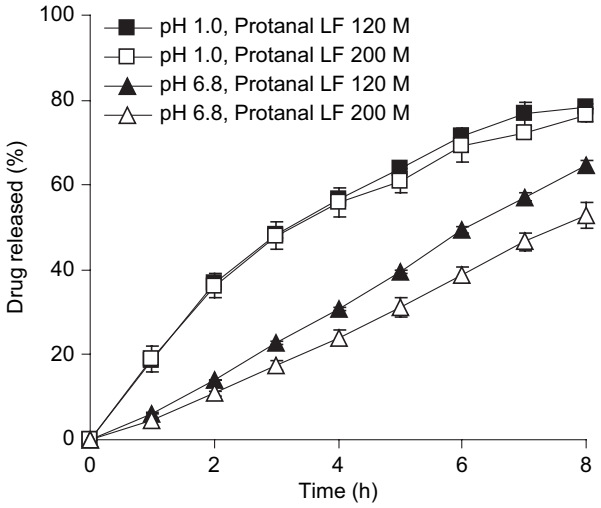

FIGURE 1. pH-dependent release of verapamil hydrochloride from alginate matrix tablets (Table 1, formulation nos. 1 and 2).

TABLE 2
Physical-Chemical Properties of the Investigated Alginates

Alginate	Viscosity (mP)[a]	M/G (%)[a]	Molecular weight (g/mol)[a]
Protanal LF 120 M	70–150	55–65/35–45	230,000–280,000
Protanal LF 200 M	200–400	55–65/35–45	290,000–360,000
Protanal LF 240 D	70–150	65–70/30–35	230,000–280,000

M: manuronic acid; G: guluronic acid.
[a]from FMC BioPolymer (2003).

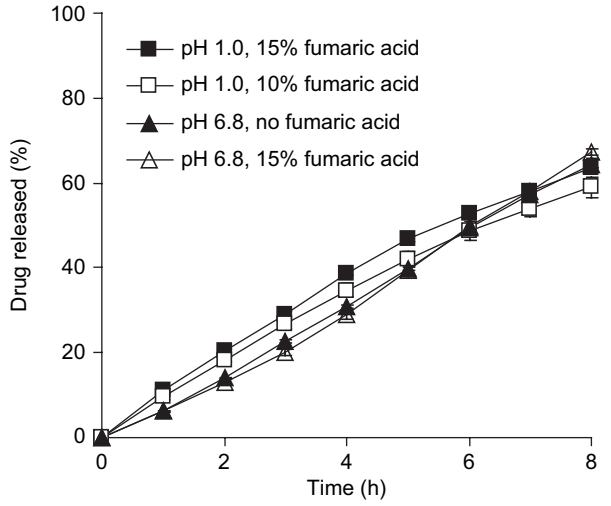

FIGURE 2. Effect of the addition of fumaric acid on the release of verapamil hydrochloride from alginate (Protanal LF 120 M) matrix tablets (Table 1, formulation nos. 1, 3, and 4).

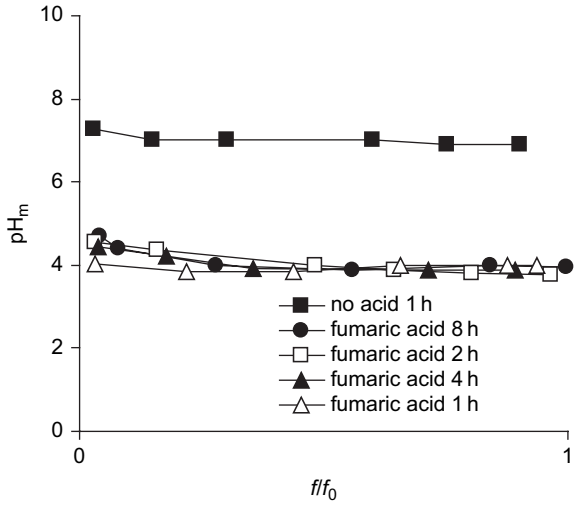

FIGURE 3. The influence of fumaric acid on the microenvironment pH (pH_M) of alginate matrix tablets after exposure to pH 6.8 buffer for 1, 2, 4, or 8 h (Table 1, formulation nos. 1 and 3).

mental matrix pH (pH_m) irrespective of the pH of the bulk medium. Therefore, at pH 6.8, the solubility of the drug within the matrix of the tablets was increased. However, as dissolution/erosion of alginate decreases with decreasing pH of the matrices, the increased solubility of verapamil hydrochloride was compensated by the decreased dissolution/erosion of the tablet. Hence, similar release profiles of tablets prepared with and without fumaric acid were observed at pH 6.8. At pH 1, drug release from alginate-based tablets is mainly driven by diffusion of water in the tablet followed by diffusion of dissolved active agent through the polymer and water-filled pores into the release medium. As fumaric acid is poorly soluble at pH 1, a less porous matrix tablet could be expected at low pH thus decreasing drug release from tablets containing fumaric acid.

To proof the assumption of different pH values of the matrices, the pH_m of tablets with and without fumaric acid was measured by a micro pH electrode (Figure 3). Tablets (Table 1, formulation nos. 1 and 3) were exposed to buffer medium pH 6.8 for up to 8 h. For alginate-based matrix tablets without fumaric acid, a pH_m of approximately 7 was measured throughout the entire tablet. In contrast, the pH_m of tablets containing 10% (wt/wt) fumaric acid was in the range of 4–5 for up to 8 h. The pH_m of these tablets slightly increased from the centre to the edge and with increasing exposure time to the buffer medium pH 6.8. However, the data clearly demonstrate that pH_m of tablets containing fumaric acid was acidic throughout the entire dissolution period.

To explain the release phenomena the water uptake and alginate mass loss of the tablets (Table 1, formulation nos. 5 and 6) were investigated gravimetrically (Figures 4 and 5). As expected for alginate-based matrix tablets without fumaric acid at pH 6.8 the water uptake and alginate mass loss was significantly

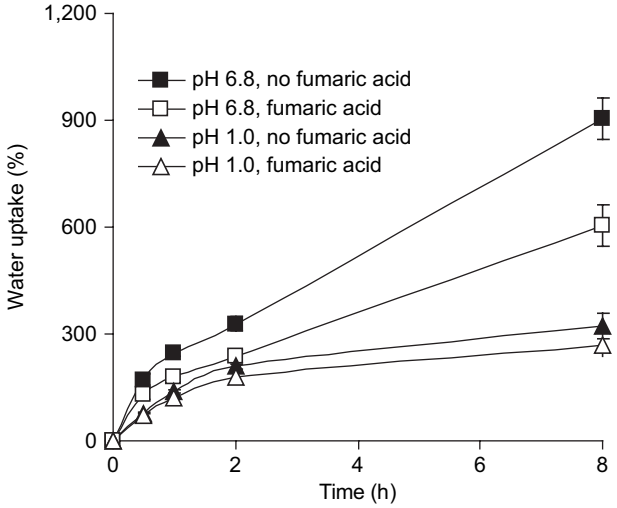

FIGURE 4. Effect of the addition of 15% (wt/wt) fumaric acid on the water uptake of alginate (Protanal LF 120 M) matrix tablets stored up to 8 h in pH 6.8 buffer or 0.1 N HC (Table 1, formulation nos. 5 and 6).

faster compared with pH 1. These findings are in good agreement to the above-mentioned hypothesis that drug release at higher pH is mainly driven by erosion/degradation whereas at low pH drug release is mainly driven by diffusion through the matrix and water-filled pores. Furthermore, at pH 6.8, the addition of fumaric acid decreased water uptake and alginate mass loss thus also being in good agreement to the drug-release studies. Lowering of pH_m increases the solubility of verapamil hydrochloride but also decreases water uptake and alginate erosion at pH 6.8. Hence, almost identically drug release profiles from tablets prepared with and without fumaric acid were observed during dissolution studies in pH 6.8 buffer as shown

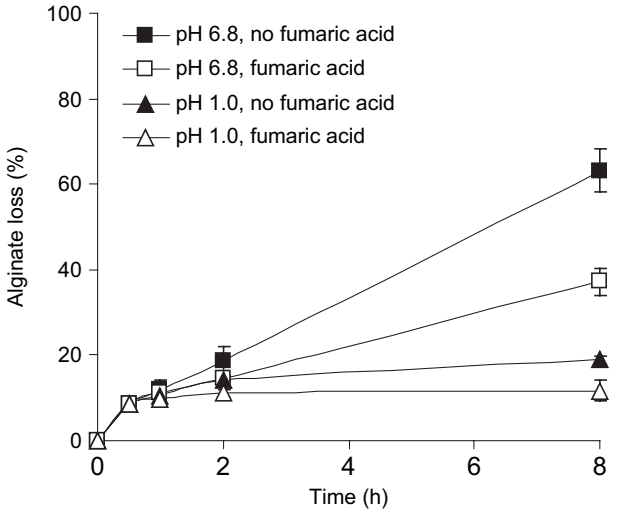

FIGURE 5. Effect of the addition of 15% (wt/wt) fumaric acid on the alginate loss of alginate (Protanal LF 120 M) matrix tablets stored up to 8 h in pH 6.8 buffer or 0.1 N HCl (Table 1, formulation nos. 5 and 6).

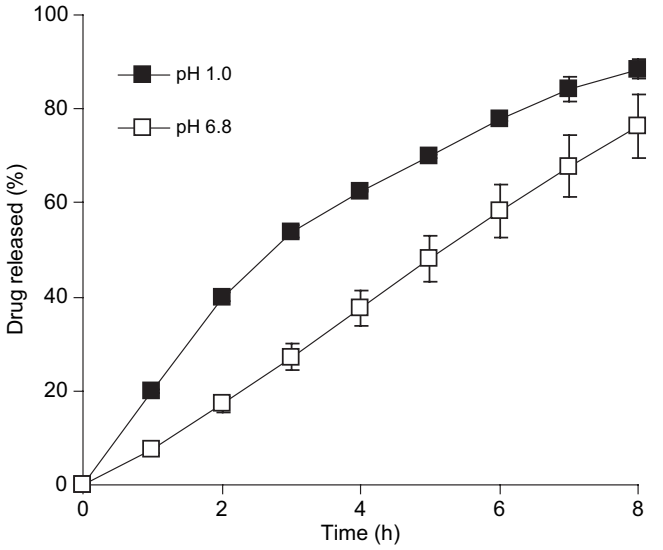

FIGURE 6. pH-dependent release of verapamil hydrochloride from press-coated tablets based on an inner fumaric acid core and an outer alginate : drug shell (Table 1, formulation no. 7).

in Figures 1 and 2. At pH 1, the mass erosion was reduced for tablets containing fumaric acid. This can be explained as follows: the pH_m of tablets containing fumaric acid was reduced throughout the entire tablet and not only on the tablet shell through imbibing dissolution medium. Therefore, the formation of less soluble alginic acid was accelerated throughout the tablet, thus decreasing mass loss and consequently formation of water-filled pores. Hence, diffusion-controlled drug release through water-filled pores was reduced for tablets containing fumaric acid during release studies in 0.1 N HCl as shown in Figures 1 and 2. In addition, the low solubility of fumaric acid at pH 1 also contributes to a less porous tablet and decreased release rate.

It has been reported in the literature that organic acids tend to leach from pellets and matrix tablets upon release testing (Siepe, Lueckel, Kramer, Ries, & Gurny, 2006). Hence, drug release became pH-dependent in later stages of dissolution testing. As fumaric acid primarily leaches from the outer regions of the matrices, press-coated tablets with an inner core of fumaric acid and an outer shell of alginate were prepared (Table 1, formulation no. 7). However, drug release from these tablets was faster at pH 1 when compared with buffer medium pH 6.8 (Figure 6). Obviously, before wetting of the inner fumaric acid layer with dissolution medium, the verapamil hydrochloride release was controlled by the alginate layer only. This results in pH-dependent drug-release profiles that were almost identical to drug release from tablets prepared without fumaric acid (Figure 1). Further optimization of the press-coated tablets (e.g., addition of fumaric acid into the outer shell) was beyond the scope of the article as it was intended to separate both (fumaric acid and drug) layers to minimize potential incompatibilities between active ingredient and fumaric acid when using the press-coating technology. It has to be pointed out that fumaric acid did not change the pH of the dissolution medium upon dissolution testing.

To achieve pH-independent drug release irrespectively from the addition of an organic acid an other type of alginate was investigated. Protanal LF 240 D was chosen as this type of alginate has a similar viscosity compared with Protanal LF 120 M but at a different ratio of manuronic to guluronic acid (Table 2). For Protanal LF 240 D, the ratio of manuronic to guluronic acid is increased when compared with Protanal LF 120 M. Verapamil hydrochloride release from Protanal LF 240 D matrix tablets (Table 1, formulation no. 8) was almost pH-independent in a range of 1–6.8 (Figure 7). When compared with the drug release from guluronic rich Protanal LF 120 M (Figure 1), the drug release from the manuronic rich alginate was almost identical at pH 1 (after 8 h 78.4 and 74.1% for Protanal LF 120 M and Protanal 240 D, respectively) but higher at pH 6.8 (after 8 h 64.5 and 78.8% for Protanal LF 120 M and Protanal 240 D, respectively). Hence, drug-release profiles at different pH almost overlapped when using the manuronic rich alginate.

To better understand these phenomena, water uptake and mass loss of Protanal LF 240 D formulations was compared to Protanal LF 120 M formulations (Table 1, formulation nos. 5 and 9). No significant differences in water uptake and mass loss were observed for all formulations at pH 1 (data not shown) thus being in good agreement to the almost identical drug-release profiles at lower pH. Distinct differences were observed at pH 6.8 (Figures 8 and 9). Water uptake and consequently mass loss was faster for the manuronic rich alginate Protanal LF 240 D

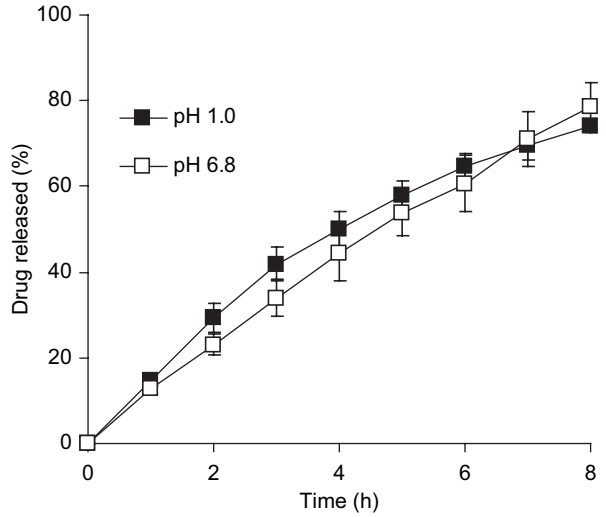

FIGURE 7. pH-independent release of verapamil hydrochloride from alginate (Protanal LF 240 D) matrix tablets (Table 1, formulation no. 8).

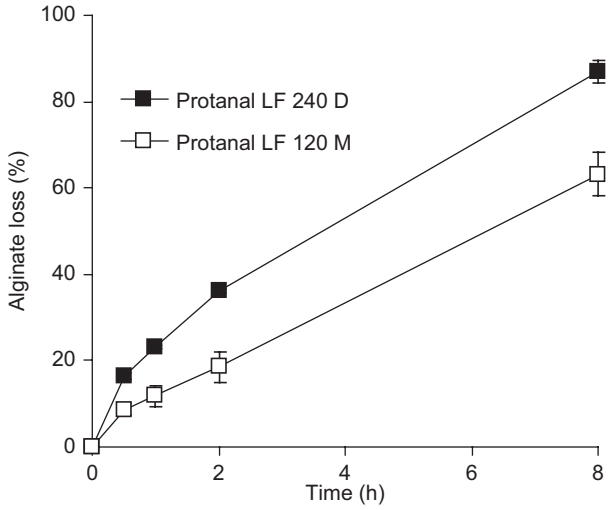

FIGURE 9. Effect of the type of alginate on the alginate mass loss of matrix tablets stored up to 8 h in pH 6.8 buffer (Table 1, formulation nos. 5 and 9).

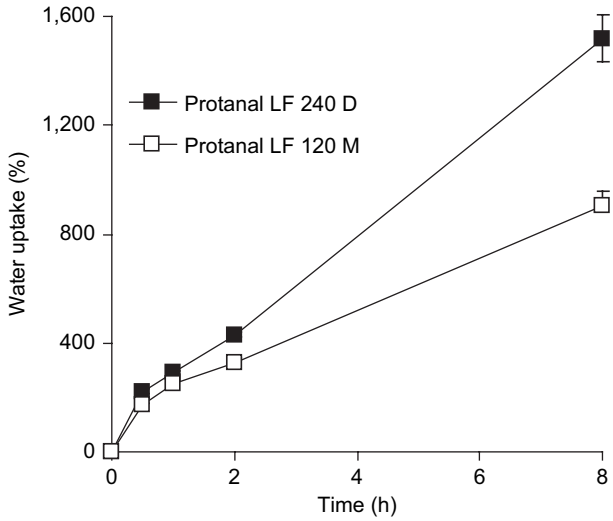

FIGURE 8. Effect of the type of alginate on the water uptake of matrix tablets stored up to 8 h in pH 6.8 buffer (Table 1, formulation nos. 5 and 9).

when compared with guluronic rich Protanal LF 120 M. As erosion of manuronic rich alginates was faster at higher pH, the poor solubility of verapamil hydrochloride was compensated by the dissolution of the polymer matrix. Hence, the drug release from Protanal LF 240 D was faster compared with Protanal LF 120 M when investigated at pH 6.8. These findings are in good agreement to other studies (Liew et al., 2006). Also, release of chlorpheniramine maleate from manuronic rich alginates was faster compared with guluronic rich alginates when investigated in phosphate buffer medium pH 6.8.

Most of the research reported in the literature utilizes alginates as a directly compressible excipient for extended release matrices (Efentakis & Buckton, 2002; Hodsdon, Mitchell, Davies, & Melia, 1995). The aim of this study was also to investigate the drug release from manuronic rich alginate tablets (Table 1, formulation nos. 8 and 10) that have been manufactured after wet granulation to improve the flow properties of drug and matrix former during tableting thus minimizing potential issues during scale-up of the manufacturing process. The in vitro release of verapamil hydrochloride from tablets prepared by direct compression or after wet granulation was almost similar when investigated in buffer medium pH 6.8 (Figure 10). The formation of a gel layer around the alginate tablets was observed visually immediately after exposure of the tablets into buffer medium. Hence, drug release is primarily controlled by the hydrated gel layer and erosion of this layer,

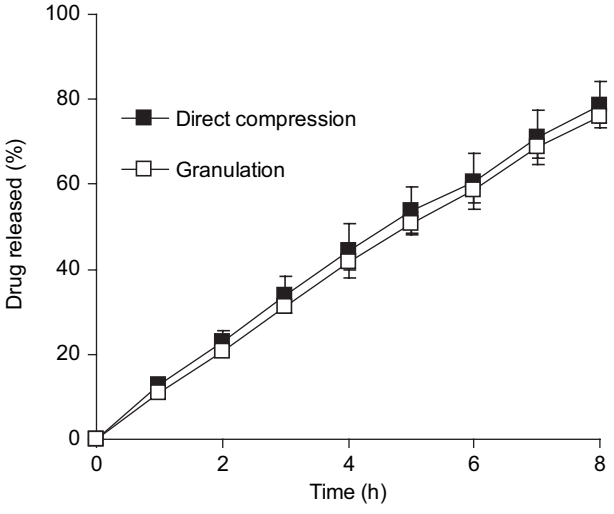

FIGURE 10. Effect of the manufacturing method (direct compression versus granulation) on the release of verapamil hydrochloride from alginate (Protanal LF 240 D) matrix tablets in pH 6.8 buffer (Table 1, formulation nos. 8 and 10).

which is independent of the dry alginate matrix. Therefore, different alginate particle sizes as obtained by direct compression or granulation technique do not have an influence on the drug-release profiles.

To establish a robust tableting process, the drug release from tablets should be relatively independent of the compression force and thus of the hardness of the tablets. The compression force during tableting of alginate matrix tablets was varied in a range of 10–15 kN leading to a tablet hardness of 80 and 125 N. The drug release from matrix tablets (Table 1, formulation no. 8) was independent of the tablet hardness within the investigated range when investigated in buffer pH 6.8 (Figure 11). Similar considerations as mentioned above can be held. Varying compression forces lead to different tablet hardness and different porosity of the matrices. Again the formation of a gel layer around the alginate tablets was observed visually immediately after exposure of the tablets into buffer medium. Hence, the drug release from alginate-based matrix tablets at pH 6.8 was mainly driven by the hydrated gel layer and erosion of this layer and independent of the porosity of the matrices in the dry state.

In conclusion, pH-independent drug release of weakly basic drugs was achieved from drug/alginate-based formulations when using selected alginates that demonstrate pronounced erosion at higher pH. For other alginates, pH-independent drug release was achieved by the addition of pH modifiers to the matrices.

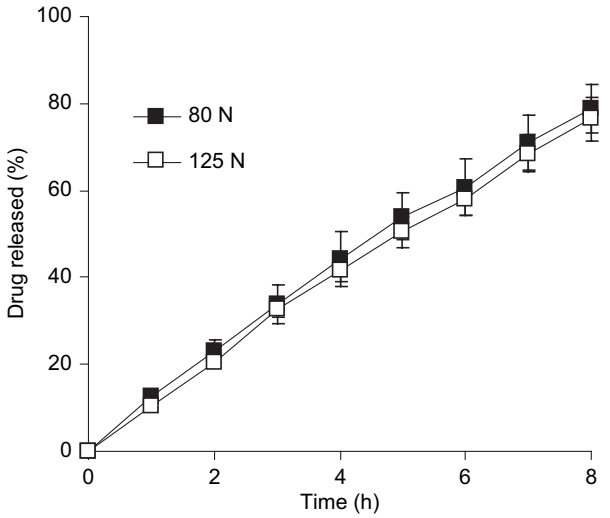

FIGURE 11. Effect of the tablet hardness on the release of verapamil hydrochloride from alginate (Protanal LF 240 D) matrix tablets in pH 6.8 buffer (Table 1, formulation no. 8).

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