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Development of a Multiple Unit Pellet Formulation for a Weakly Basic Drug

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ABSTRACT SAG/ZK [3-(5-Chloro-2-{2-[(2R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy}phenyl)uronium hydrogen sulfate], a potent candidate for the oral treatment of inflammatory diseases, demonstrated pH-dependent solubility. Drug release from conventional pellet formulations decreased with increasing pH values of the dissolution medium. The aim of this study was to overcome this problem and to achieve pH-independent drug release. Extended release pellets were prepared by extrusion/spheronization followed by film coating with an aqueous polyvinylacetate/polyvinylpyrrolidone dispersion. To overcome the problem of pH-dependent drug release organic acids such as fumaric, tartaric, and adipic acid were incorporated into the core pellets. X-ray diffraction studies were done in order to investigate potential recrystallization and formation of different salts of SAG/ZK. The addition of fumaric acid was found to lower the pH values within the core pellets during the release of SAG/ZK in phosphate buffer pH 6.8. Therefore, increased release rates at higher pH values were observed thus leading to pH-independent drug release. In contrast, drug release remained pH-dependent for pellets containing tartaric and adipic acid, which can be explained with the lower acidic strength and higher aqueous solubility of these acids. X-ray diffraction studies showed no recrystallization and formation of salts of active ingredient and organic acid.

KEYWORDS pH-independent, Controlled release, Organic acid, Matrix pellet

INTRODUCTION

SAG/ZK, a low molecular weight (mol wt 533) antagonist of the human chemokine receptor CCR 1, has been developed for the oral treatment of inflammatory diseases. The weak base SAG/ZK was shown to be selectively active for CCR 1 in pharmacodynamic in vitro models. Based on pharmacodynamic models a certain constant plasma level of SAG/ZK seems to be required in order to demonstrate efficacy of the molecule. However, because of the relatively short half-life of SAG/ZK in humans drug plasma levels dropped rapidly after administration of SAG/ZK. A desired constant plasma level over 24 hr could not be achieved when using immediate release tablets. Therefore, an extended release formulation of the active ingredient has been developed.

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Attributed to the pH gradient along the gastrointestinal tract, there is often a strong variability in drug dissolution from controlled release formulations. This is an important parameter for controlled release formulations that contain active ingredients with pH-dependent solubility such as weak bases or salts thereof. At higher pH values the free base precipitates inside the controlled release formulation which results in incomplete drug release. Hence, therapeutically ineffective drug plasma concentrations and higher intersubject variability in plasma levels are observed (Timmins et al., 1997; Streubel et al., 2000; Varma et al., 2005).

To overcome the problem of pH-dependent drug liberation from extended release formulations containing weak bases some authors used blends of enteric and extended release polymers as film coating materials (Amighi et al., 1998; Dashevsky et al., 2004). The enteric polymer is insoluble at low pH whereas rapid dissolution of the polymer is observed at higher pH values. Therefore, during the stomach passage the enteric polymer acts as diffusion barrier but dissolves within the intestine. Because of the dissolution of the enteric polymer at higher pH values water filled pores are formed thus increasing the diffusion area and leading to pH-independent drug release of weak bases.

Another attempt to achieve pH-independent drug release for weakly basic drugs was to incorporate enteric polymers as pH-dependent soluble fillers into extended release tablets. At lower pH values enteric polymers are part of the core matrix. In contrast, at higher pH values enteric polymers dissolve and form pores thus increasing liberation of the active ingredient. pH-independent drug release of a weakly basic drug from hydroxypropyl methylcellulose (HPMC)/ Eudragit L matrix tablets has been demonstrated by Takka et al. (2001). The release of papaverin hydrochloride from HPMC matrix tablets was increased at higher pH values by the addition of the enteric polymers Carbopol 71G and Eudragit L (Tatavarti et al., 2004). Increasing verapamil hydrochloride release at higher pH values from polyethyleneoxid tablets was achieved by the addition of enteric polymers such as Eudragit L, Carbopol 934 and Eudispers NV (Dimitrov & Lambov, 1999).

The incorporation of organic acids into tablet cores in order to lower the pH inside matrix tablets and therefore to increase the drug solubility at higher pH values has been described to reach pH-independent drug release. Thoma & Zimmer (1990) showed pH-independent release of noscarpin from HPMC matrix tablets by incorporation of succinic, tartaric, and citric acid. Streubel et al. (2000) showed pH-independent verapamil hydrochloride release from HPMC and ethyl cellulose (EC) matrix tablets using fumaric acid as pH-adjuster. In addition, pH-independent verapamil hydrochloride liberation has been demonstrated from Eudragit RS and RL matrix tablets by the addition of blends of succinic acid and KH_2PO_4(Gohel et al., 2003). Gabr (1992) achieved pH-independent papaverin hydrochloride release from cellulose acetate/beeswax matrix tablets by the addition of organic acids.

Despite numerous advantages of multiple unit dosage forms like lower inter- and intraindividual variations in bioavailability caused by food effects and lower risk of dose dumping, few investigations on pH-independent release of weakly basic drugs from pellets have been performed. Thoma & Knott (1991) and Venkatesh (1998) have used acid crystals as pellet cores which were coated with drug substance and finally with a diffusion coating. Further, pH-independent fenoldopam release from matrix pellets has been described by Thoma & Ziegler (1998). However, a fivefold excess of succinic acid relative to the drug was needed to reach pH-independent drug release.

The objective of this study was to develop a multiple unit pellet formulation for SAG/ZK. Because of its weakly basic nature the drug shows lower solubility at higher pH values. Hence, drug release from conventional formulations decreased with increasing pH values. To overcome the pH-dependent drug release from coated extended release matrix pellets, different organic acids like slightly soluble fumaric acid, moderately soluble adipic acid and highly soluble tartaric acid were added to the matrix core to create a low microenvironmental pH within the pellet core to achieve pH-independent release of SAG/ZK.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received:

SAG/ZK (3-(5-Chloro-2-{2-[(2R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy}phenyl)uronium hydrogen sulfate, Schering AG, Berlin, Germany),

polyvinylpyrrolidone 25000, and aqueous dispersion of polyvinylacetate/ polyvinylpyrrolidone (Kollicoat® SR 30 D, BASF, Ludwigshafen, Germany), microcrystalline cellulose (Avicel® PH 101, FMC, Cork, Ireland), dulcitol and triethylammonium acetate buffer (Fluka Chemie GmbH, Buchs, Switzerland), tartaric, adipic, and fumaric acid, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, phosphoric acid, and ammonium dihydrogen phosphate (Merck KGaA, Darmstadt, Germany), hydroxypropyl-β-cyclodextrine (HP- ß –CD, Roquette Services Techniques Laboratories, Lestrem, France), acetonitrile (Sigma-Aldrich-Chemie GmbH, Steinheim, Germany).

Methods

Preparation of Pellets

Pellets were prepared by extrusion/spheronization. Dry powder blending of drug substance and microcrystalline cellulose was done in a Turbula® mixer (W. A. Bachhofen AG, Basel, Switzerland) at 22 rpm for 10 min. Thereafter, remaining excipients were added to the blend and mixed for another 10 min (for compositions of the formulations see Table 1, dry powder blending was done on a 2000 *g* scale). For the discontinuous extrusion/spheronization process the dry powder blend was divided into smaller fractions. Wet granulates were made in a Nica™ high shear mixer (ML 6, Lejus, Mölndal, Sweden) by adding an appropriate amount of purified water. The wet mass (300 g) was then extruded through a ring die with 1 mm holes by using a Nica™ extruder at a feeding speed of 75 rpm. Finally, the extrudate was processed in a Nica™ spheronizer (SP 300, Lejus, Mölndal, Sweden) fitted with a cross hatched friction plate rotated at 400 rpm for 2–6 min. After spheronization the pellets were dried in a fluid bed coater (GPCG-1, Glatt, Binzen, Germany). Pellets in a size range of 800–1250 μm were used for further coating experiments.

Coating of Pellets

Pellets were coated with an aqueous polyvinylacetate/polyvinylpyrrolidone dispersion (Kollicoat® SR 30 D). For coating experiments the total solid content of the dispersion was reduced to 15% (w/w) by addition of an aqueous polyvinylpyrrolidone solution. Thereby, the total polyvinylpyrrolidone content of the coating was increased to 30% (w/w, based on polymer). For the coating process fractions of 500 g of pellets in the desired size range as described above were coated in a fluid bed coater (GPCG-1, Glatt, Binzen, Germany) using bottom spray and Wurster insert until a theoretical coating level of 5% (w/w, based on core pellets) was reached. Coating conditions were inlet temperature 50°C, nozzle diameter 0.8 mm, spray pressure 0.8 bar, spray rate 8.7 g/min and final drying at 50°C for 10 min. Thereafter the pellets were cured for 24 hr at 40°C.

Drug Release Studies

In vitro drug release was determined using the USP XXV rotating basket method (1000 ml 0.1 N HCl or USP phosphate buffer pH 6.8 containing 5% HP- ß-CD to reach sink conditions, 37°C, 100 rpm, $n = 3$). Using a Distek Premiere 5100 Dissolution System (Distek Inc., North Brunswick) 10 mL samples were withdrawn (not replaced) at predetermined time intervals, filtered and assayed. The amount of released SAG/ZK was measured using a computer connected Waters-HPLC system (2695D Separation Module, Transfer Module, 2487 Dual Absorbance Detector, Waters Corporation,

TABLE 1 Compositions of the Investigated Core Pellets (%)

Formulations	SAG/ZK	MCC	Fumaric acid	Tartaric acid	Adipic acid	Dulcitol
1	60	40	–	–	–	–
2	60	30	10	–	–	–
3	60	25	15	–	–	–
4	60	20	20	–	–	–
5	60	25	–	15	–	–
6	60	25	–	–	15	–
7	60	25	–	–	–	15

Milford). A 20 µL volume was injected onto a Symmetry C-18 column (3.5 µm, 4.6 × 150 mm, Waters, Milford). A mixture of 55 mL 0.05*M* triethylammoniumacetate buffer and 45 mL acetonitrile (flow rate 1.0 mL/min, UV detection at 244 nm) was used as mobile phase. Known concentrations of SAG/ZK were used to calculate the amount of drug released.

Fumaric and Tartaric Acid Release Studies

In vitro release of fumaric and tartaric acid was determined using the USP XXV rotating basket method (1000 ml 0.1 N HCl or USP phosphate buffer pH 6.8 containing 5% HP- ß-CD, 37°C, 100 rpm, $n = 3$). The amount of released fumaric and tartaric acid was measured by using the above-mentioned Distek-Dissolution system connected to a Waters high-performance liquid chromatography (HPLC) system. A 5 µL volume was injected onto a Hydrosphere C-18 column (YMC Europe GmbH, Schermbeck, Germany) using a mixture of ammonium dihydrogen phosphate pH 2.0 (mobile phase A) and acetonitrile (mobile phase B) as the mobile phase (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) at a flow rate of 1.0 mL/min and UV detection at 210 and 226 nm for fumaric and tartaric acid, respectively. Fumaric and tartaric acid solutions of known concentration were used to calculate the amount of fumaric and tartaric acid released. The method was checked with respect to linearity ($r > 0.99$), precision (3% RSD) and accuracy (4% RSD).

Powder X-ray Diffraction Studies

X-ray diffraction studies were performed on an automated STOE powder diffractometer STADI P (Stoe & Cie, Darmstadt, Germany) using CuKα1-radiation. The X-ray tube with copper anode was operated at 40 kV and 30 mA. The samples were enclosed between two polyacetate films that were held together by double-sided adhesive tape.

SEM Photographs

Pellets were coated for 60 s under an argon atmosphere with gold-palladium (MED 020, Bal-tec AG, Liechtenstein) and then observed with a scanning electron microscope (SEM) (DSM 982, Zeiss, Oberkochen, Germany).

RESULTS AND DISCUSSION

Irrespectively of the addition of organic acids SAG/ZK containing core pellets were successfully prepared by extrusion/spheronization (compositions are given in Table 1). Afterwards, pellets in the size range of 800–1250 µm were coated with an extended release polyvinylacetate/polyvinylpyrrolidone shell. In order to obtain the desired in vitro release profile of approximately 60% drug release within 6 hr the content of the water soluble polyvinylpyrrolidone within the commercially available coating suspension was increased to 30% (w/w, based on polymer). Smooth and coherent film coating was reached by application of 5% (w/w, based on core pellets) polymer (Fig. 1). Upon exposure with dissolution medium the water soluble polyvinylpyrrolidone dissolves thereby creating pores for the actives to diffuse out.

Because of its weakly basic nature SAG/ZK showed pH-dependent solubility. The solubility in 0.1 N HCl was found to be 3.24 mg/mL whereas the solubility in phosphate buffer pH 6.8 was only 0.01 mg/mL. To reach sink conditions and primarily control the drug release by the dosage form, 5% (w/v) HP-ß-CD were added to the buffer medium at pH 6.8 (solubility of SAG/ZK after addition of 5% HP-ß-CD was 2.40 mg/mL). This indicates that sink conditions were reached after the addition of 5% HP-ß-CD. Detailed investigations on the selection of the in vitro release medium are given elsewhere (Kranz et al., 2005). However, even after the addition of HP-ß-CD to the buffer medium pH 6.8, the release of SAG/ZK from coated matrix pellets consisting of microcrystalline cellulose and drug (Table 1, formulation 1) was slower compared to the drug release at pH 1.0 (Fig. 2). After 6 hr 67.0% active ingredient was released in 0.1 N HCl whereas only 32.8% was released at pH 6.8. This might be explained as follows: HP-ß-CD is known to increase the solubility of compounds by the formation of inclusion complexes. It is well known that the drug release is mainly driven by concentration gradients of dissolved compound within the dosage, between dosage form and release medium, and within the release medium. The solubility of SAG/ZK in the release medium was increased by the addition of HP-ß-CD to buffer medium (pH 6.8). However, much lower quantities of HP-ß-CD can be expected within the pellets (at least at early time points), compared to the release

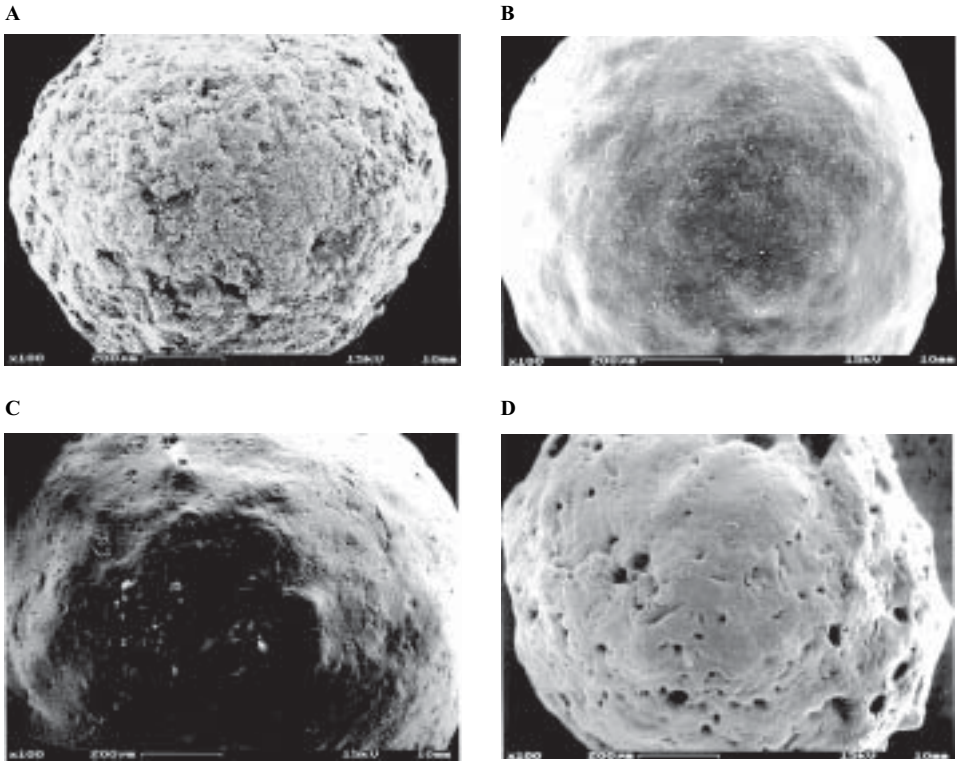

FIGURE 1 **SEM-Photographs of Matrix Pellets Before Film Coating (A), After Film Coating (B), After Dissolution in Phosphate Buffer at pH 6.8 (C) and After Dissolution in 0.1*N* HCl (D).**

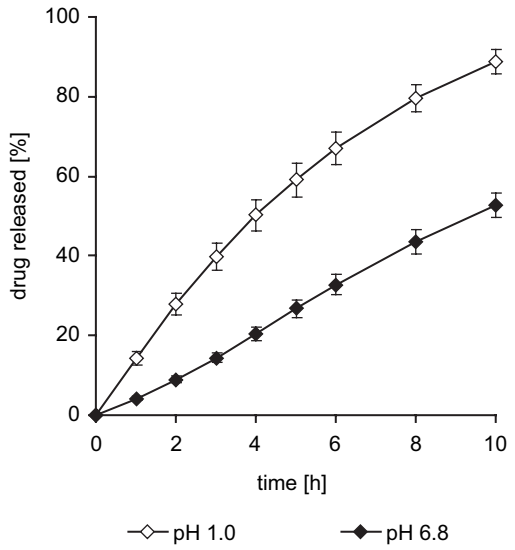

FIGURE 2 **pH-Dependent Drug Release From Coated Matrix Pellets at pH 6.8 and pH 1.0 (*n* = 3).**

medium, resulting in less pronounced increases in drug solubility. Therefore, even after addition of 5% HP-ß-CD to buffer medium (pH 6.8), the release of SAG/ZK was slower compared to the drug release at pH 1.0.

To overcome the problem of the pH-dependent drug release different levels of organic acid were incorporated into the pellet core. Independent of the pH of the dissolution medium, the pH inside the matrix tablet was expected to be acidic and thus the solubility of the weakly basic drug to be high. Therefore, drug release should be pH-independent. Fumaric acid was chosen because of its high acid strength ($pK_{a1} = 3.03$ and $pK_{a2} = 4.54$) and relatively low aqueous solubility (4.9 mg/mL water, 20°C) (all values taken from Merck & Co., 2001).

The addition of fumaric acid (Table 1, formulations 2–4) significantly increased the drug release in phosphate buffer (pH 6.8) for polyvinylacetate/polyvinylpyrrolidone film coated pellets compared to pellets without fumaric acid (Fig. 3). The higher the amount of fumaric acid added the faster the drug dissolution rates. In vitro dissolution rates of pellet formulations containing 15% fumaric acid (w/w, based on core pellet) almost overlapped with release profiles of pellets without fumaric acid in 0.1 N HCl. Due to the addition of 15 or 20% (w/w, based on core pellets) fumaric acid (Table 1, formulations 3 and 4) the drug release

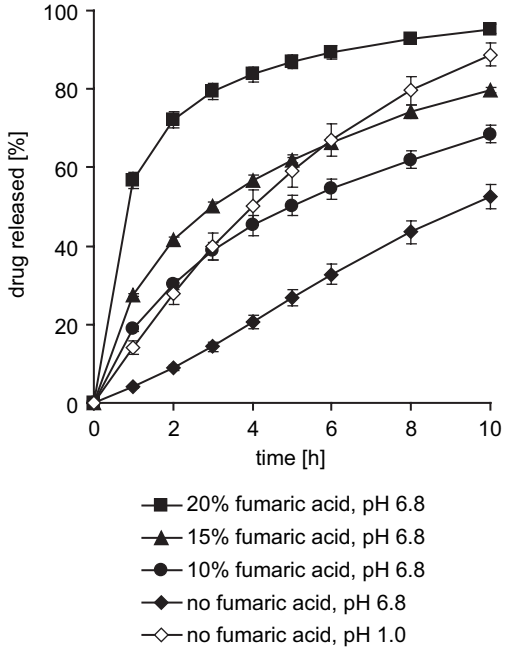

FIGURE 3 **Effect of the Addition of Fumaric Acid on the In Vitro Drug Release From Coated Matrix Pellets (*n* = 3).**

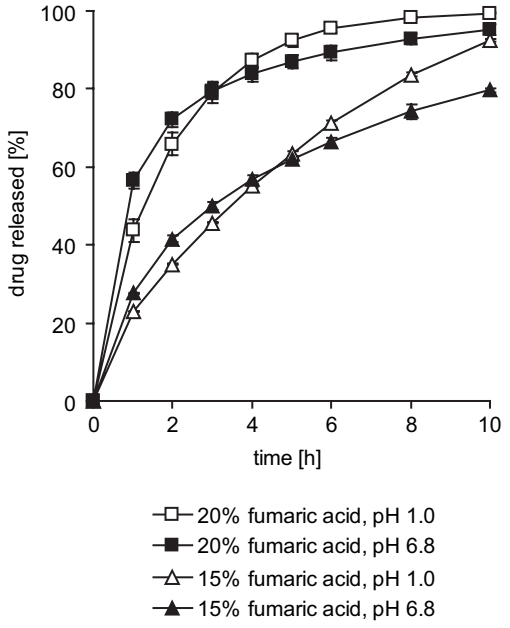

FIGURE 4 **pH-Independent Drug Release From Coated Matrix Pellets Containing Fumaric Acid (% Based on Core Pellet) (*n* = 3).**

was independent of the pH of the bulk fluid in the range of pH 1.0–6.8 (Fig. 4). This is in agreement with the above mentioned hypothesis of a constant microenvironmental pH within the dosage form. Irrespective of the dissolution medium, the drug release from formulations containing 20% (w/w, based on core pellets) fumaric acid was fast. This can be explained with the reduced amount of the matrix former microcrystalline cellulose within the core pellets, leading to fast pellet disintegration.

To prove the hypothesis of low microenvironmental pH values for pellets containing fumaric acid the surface pH of the pellet formulations was measured by using pH test paper at predetermined time intervals. Kohri et al. (1991) have described this method to investigate the effect of pH-adjusters on the surface pH of tablets. Incorporation of pH indicator into the dosage form to monitor the pH during drug release has been described elsewhere (Streubel et al. 2000; Kranz et al. 2005). However, as similar results can be expected for both methods only the method described by Kohri et al. was used. In addition, the hypothesis of the low microenvironmental pH within the dosage form was further investigated by release studies of the organic acids (see below). In contrast to matrix pellets without organic acid, the surface pH of pellets containing 15% and 20% (w/w, based on core pellets) fumaric acid remains low (< pH 2.0) during dissolution testing in pH 6.8.

Next the effect of the type of organic acid (tartaric and adipic acid) was investigated on pellets containing 15% (w/w, based on core pellets) organic acid (Table 1, formulations 5 and 6). Similar trends were also observed for formulations containing 10% and 20% (w/w, based on core pellet) tartaric and adipic acid (data not shown). The drug release was determined in 0.1 N HCl and buffer medium at pH 6.8 (Fig. 5). In all cases, the addition of the organic acids increased the drug release rates at pH 6.8 when compared to pellets without organic acid (Fig. 1). However, the increase in the drug release rates at pH 6.8 was less pronounced compared to pellets containing fumaric acid (Fig. 4). This might be explained with the lower pK_a value, therefore, higher acidic strength of fumaric acid (pK_1 3.03 and pK_2 4.54) when compared to adipic acid (pK_1 4.41 and pK_2 5.28). The aqueous solubility of tartaric (1390 mg/mL) and adipic acid (31 mg/mL) is higher than the aqueous solubility of fumaric acid (4.9 mg/mL) (all values taken from Merck & Co., 2001). Compared to fumaric acid a faster leaching of adipic and tartaric acid from the pellet matrix is expected. This results in higher microenvironmental pH values and thus leading to slower drug release rates at pH 6.8. Therefore, drug release rates from formulations

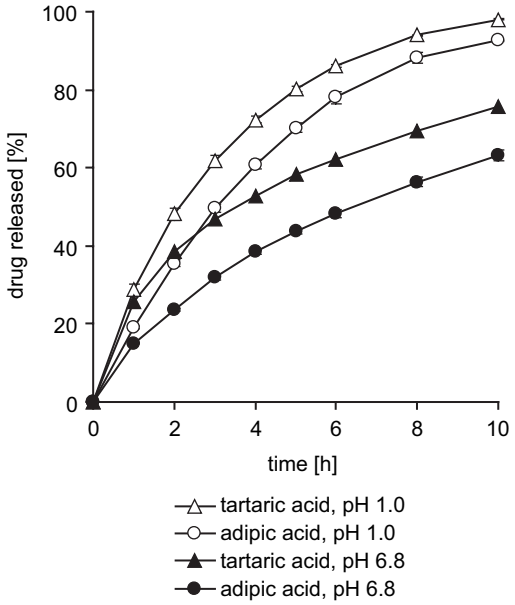

FIGURE 5 **Effect of the Addition of Different Organic Acids on the Drug Release From Coated Matrix Pellets (*n* = 3).**

containing adipic and tartaric acid remained pH-dependent.

To confirm this hypothesis, the amount of fumaric and tartaric acid released into the dissolution medium was determined experimentally (Table 1, formulations 3 and 5) . The amount of tartaric and fumaric acid remaining within the pellets was calculated by subtracting the amount of acids released from the total amount of organic acids (Fig. 6a and 6b). Irrespective of the pH of the bulk fluid (pH 1.0 or 6.8) tartaric acid was completely released after 1 h. In contrast, dissolution of fumaric acid from polyvinylacetate/polyvinylpyrrolidone coated pellets was slower. These findings are in agreement with dissolution studies of organic acids from matrix tablets (Kranz et al., 2005). They confirm the hypothesis of a constant microenvironmental pH within fumaric acid containing matrix pellets being the main factor for pH-independent drug release. For tartaric acid containing formulations it can be assumed that increased drug release rates at pH 6.8 compared to formulations without organic acid are mainly influenced by the good water solubility of tartaric acid. Upon contact with the release medium, tartaric acid diffuses from the pellets, thereby increasing the porosity of the matrix pellets thus increasing drug release rates.

To check the hypothesis that the pH-independent drug release from fumaric acid containing pellets is

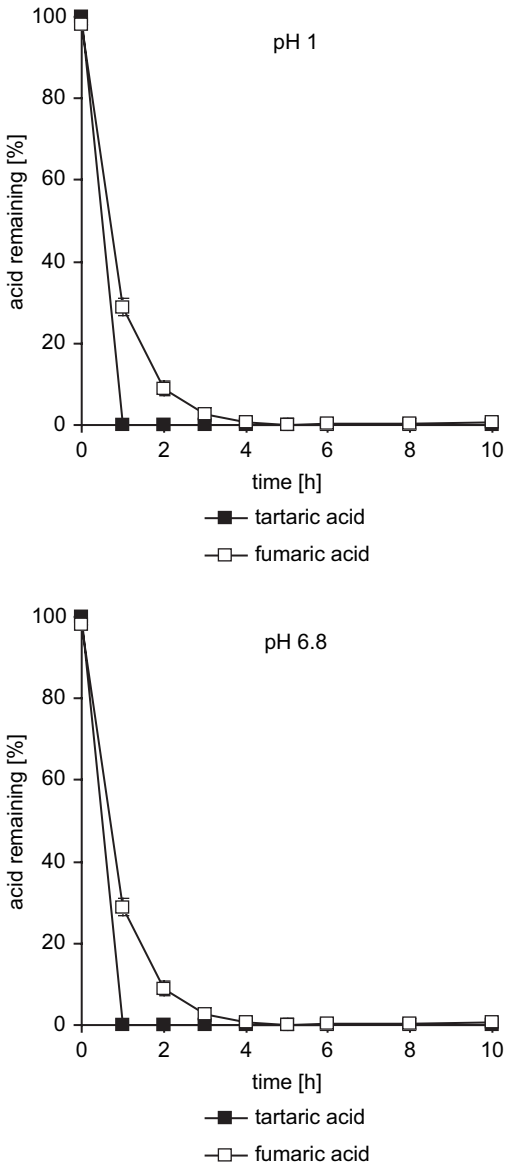

FIGURE 6 **Organic Acids Remaining Inside Core Pellets During Dissolution in (a) 0.1*N* HCl and (b) Phosphate Buffer at pH 6.8 (*n* = 3).**

mainly triggered by the microenvironmental pH values within the pellets, fumaric acid was replaced by an excipient that does not influence the pH within the pellets but has similar aqueous solubility. Therefore, the sugar alcohol of galactose, namely dulcitol was used as model substance for the preparation of polyvinylacetate/polyvinylpyrrolidone coated pellets. The aqueous solubility of dulcitol and fumaric acid is 5.6 mg/mL and 4.9 mg/mL water, respectively.

The release of SAG/ZK from formulations containing 15% (w/w, based on core pellet) fumaric acid or dulcitol compared to formulations without additional

excipient was investigated in phosphate buffer pH 6.8 (Fig. 7) (Table 1, formulations 1, 3, and 7). Drug release from formulations containing dulcitol was slightly faster compared to formulations without additional excipient. This can be attributed to the slightly water solubility of dulcitol. Upon contact with the release medium, dulcitol partly dissolves thus increasing the porosity of the pellet matrix leading to increasing drug release rates. In contrast, the drug release from formulations containing fumaric acid was significantly increased thus demonstrating that drug release rates from polyvinylacetate/polyvinylpyrrolidone coated pellets are strongly influenced by the microenvironmental pH within the pellets.

Solubility is strongly influenced by polymorphic and salt form of active compounds. Therefore, X-ray diffraction studies were done in order to investigate potential formation of different polymorphic forms and salts of SAG/ZK with organic acids during extrusion/spheronization. X-ray studies were done on MCC, organic acid and drug substance individually. The diffractograms of the individual components of the pellet formulation were graphically combined and compared to the diffractogram of pellets that were manufactured by extrusion spheronization (Fig. 8) (Table 1, formulation 3). No difference between the graphically combined diffractograms of the individual components and the pellet formulation was observed. This indicates that extrusion spheronization does not lead to the formation of new salts (e.g., fumaric acid salt of SAG/ZK).

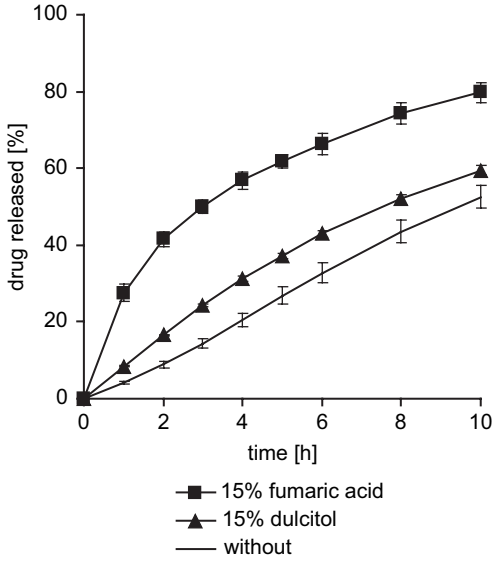

FIGURE 7 **Drug Release From Formulations Containing 15% (Based on Core Pellet) Fumaric Acid or Dulcitol Compared to Formulations Without Additional Excipient Into Phosphate Buffer at pH 6.8 (*n* = 3).**

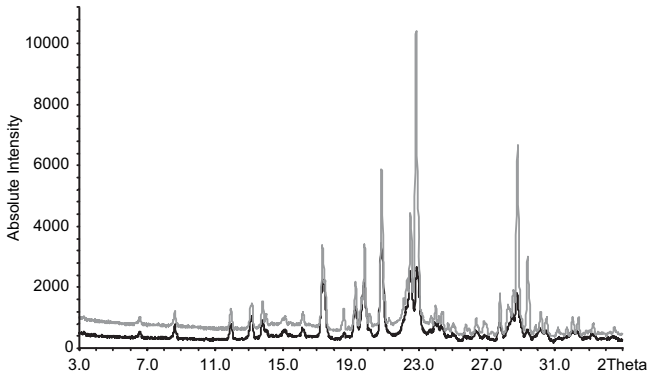

FIGURE 8 **Graphically Combined X-ray Diffractograms of the Individual Components (Gray Line) in Comparison to the Diffractogram of Pellets Containing Fumaric Acid (Black Line) (*n* = 3).**

CONCLUSIONS

Pellets containing 60% (w/w, based on core pellet) of the weakly basic drug SAG/ZK were prepared by extrusion/spheronization. Because of the pH-dependent solubility of the drug substance formulations without organic acids showed pH-dependent drug release. Addition of fumaric acid resulted in increasing drug release rates in phosphate buffer at pH 6.8 thus leading to pH-independent drug release. In contrast, the in vitro release of formulations with adipic and tartaric acid remained pH-dependent. The drug release patterns of formulations containing fumaric acid were mainly influenced by the pH-adjusting properties of the organic acid. In contrast, increasing porosity of the core pellets mainly influenced the dissolution behavior of formulations with adipic and tartaric acid. X-ray diffraction studies showed no recrystallization and formation of salts of active ingredient and organic acid.

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