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Research paper

Development of a novel osmotically driven drug delivery system for weakly basic drugs

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Abstract

The drug substance SAG/ZK has a short biological half-life and because of its weakly basic nature a strong pH-dependent solubility was observed. The aim of this study was to develop a controlled release (cr) multiple unit pellet formulation for SAG/ZK with pH-independent drug release. Pellets with a drug load of 60% were prepared by extrusion/spheronization followed by cr-film coating with an extended release polyvinyl acetate/polyvinyl pyrrolidone dispersion (Kollidon SR 30 D). To overcome the problem of pH-dependent drug release the pellets were then coated with a second layer of an enteric methacrylic acid and ethyl acrylate copolymer (Kollicoat MAE 30 DP). To increase the drug release rates from the double layered cr-pellets different osmotically active ionic (sodium and potassium chloride) and nonionic (sucrose) additives were incorporated into the pellet core. Drug release studies were performed in media of different osmotic pressure to clarify the main release mechanism. Extended release coated pellets of SAG/ZK demonstrated pH-dependent drug release. Applying a second enteric coat on top of the extended release film coat failed in order to achieve pH-independent drug release. Already low enteric polymer levels on top of the extended release coated pellets decreased drug release rates at pH 1 drastically, thus resulting in a reversal of the pH-dependency (faster release at pH 6.8 than in 0.1 N HCl). The addition of osmotically active ingredients (sodium and potassium chloride, and sucrose) increased the imbibing of aqueous fluids into the pellet cores thus providing a saturated drug solution inside the beads and increasing drug concentration gradients. In addition, for these pellets increased formation of pores and cracks in the polymer coating was observed. Hence drug release rates from double layered beads increased significantly. Therefore, pH-independent osmotically driven SAG/ZK release was achieved from pellets containing osmotically active ingredients and coated with an extended and enteric polymer. In contrast, with increasing osmotic pressure of the dissolution medium the in vitro drug release rates decreased significantly.

Keywords: pH-independent; Extended release; Multiparticulates; Enteric coating; Osmotic active

1. Introduction

Effected by the pH-gradient along the gastro intestinal tract the drug release rates from extended release formulations can vary significantly. This is especially critical for dosage forms with active ingredients demonstrating pH-dependent solubility. Weakly basic drugs show pH-dependent solubility characteristics. Based on the pK_a of these compounds, they deprotonate in the intestinal fluids resulting in the formation of the less soluble unionized form. This results in decreasing drug release rates at higher pH-values of the intestine [1,2]. Also a lack of gastric acid production or a comedication with antacids results in an elevation of the gastric pH and therefore may decrease the drug absorption [3].

To overcome the problem of pH-dependent drug release of weakly basic compounds various researchers addressed

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this issue by incorporating low molecular weight acids into pellets or matrix tablets. These additives have been described to lower matrix microenvironmental pH and thus enhance the local solubility of the drug. Therefore, increased drug release rates were observed at higher pH-values. Streubel et al. [4] showed pH-independent verapamil hydrochloride release from hydroxypropyl methylcellulose and ethyl cellulose matrix tablets using fumaric acid as pH-adjuster. Also pH-independent verapamil hydrochloride release was shown from Eudragit RS and RL matrix tablets where succinic acid/potassium dihydrogen phosphate blends were used as pH-adjusters [5].

Kranz et al. [6,7] demonstrated that drug release rates of a weakly basic drug from matrix or mini matrix tablets based on polyvinyl acetate/polyvinyl pyrrolidone, ethylcellulose or hydroxypropyl methylcellulose were increased at higher pH by the addition of organic acids such as fumaric, tartaric, adipic, glutaric, and sorbic acid. However, pH-independent drug release was only achieved for tablets containing fumaric acid. Similar observations were made by Siepe et al. [8]. They incorporated different concentrations of pH modifiers (fumaric, succinic, citric, and ascorbic acid) in matrix tablets based on hydroxypropyl methylcellulose. Owing to its high acidic strength and low aqueous solubility, fumaric acid maintained constant microenvironmental pH within the tablet matrix, thus resulting in pH-independent drug release. In contrast, succinic, citric, and ascorbic acid were less efficient to reach pH-independent drug release. Furthermore, the authors [9] confirmed in an electron paramagnetic resonance imaging study that only fumaric acid is able to maintain constantly reduced microenvironmental pH as it stayed inside the matrix tablets. In contrast, organic acids (e.g. citric acid) with higher aqueous solubility were released from the tablet matrix quickly, thus decreasing the buffer capacity.

The incorporation of pH-dependent soluble enteric polymers into single unit solid dosage forms was another attempt to reach pH-independent drug release of weakly basic compounds. At low pH the enteric polymer works as part of the matrix. Whereas, with increasing pH-values of the dissolution medium or intestinal fluids the enteric polymer dissolves thus resulting in the formation of porous networks with increased drug release rates. The release of propranolol hydrochloride from hydroxypropyl methylcellulose matrix tablets containing anionic polymers was investigated by Takka et al. [10]. They achieved pH-independent drug release from matrix tablets containing the enteric polymer Eudragit L. Furthermore, the addition of sodium alginate resulted in pH-independent release of verapamil HCl from hydroxypropyl methylcellulose matrix tablets [1].

Several authors used layers or blends of extended release and enteric polymers as coating membranes to modify the drug release of compounds with pH-dependent solubility from coated pellets. Blends of the extended release polymer ethyl cellulose and the enteric polymer Eudragit L resulted in a broad range of propranolol HCl release patterns from coated pellets [11]. pH-Independent drug release was reached from pellets coated with blends of the extended release polymer Eudragit NE 30 D with the enteric polymer Eudragit L [12]. Furthermore, verapamil HCl was released pH-independently from drug layered pellet formulations coated with mixtures or layers of the extended release polymer Kollicoat SR 30 D and the enteric polymer Kollicoat MAE 30 DP [13].

The objective of this study was to develop a controlled release multiple unit pellet formulation for SAG/ZK with pH-independent drug release. The drug substance SAG/ZK has a short biological half-life and because of its weakly basic nature a strong pH-dependent solubility was observed. Therefore, to overcome the problem of pH-dependent solubility layers of the extended release polymer polyvinyl acetate/polyvinyl pyrrolidone (Kollicoat SR 30 D) and the enteric methacrylic acid and ethyl acrylate copolymer (Kollicoat MAE 30 DP) were applied on matrix pellet cores. To increase the drug release rates from the double layered cr-pellet formulations different osmotically active ionic (sodium and potassium chloride) and nonionic additives (sucrose) were incorporated into the pellet core.

2. Materials and methods

2.1. Materials

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

SAG/ZK (3-(5-chloro-2-{2-[(2*R*)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy}phenyl)uronium hydrogen sulfate, Schering AG, Berlin, Germany), acetonitrile, ammonium dihydrogen phosphate, hydrochloric acid, phosphoric acid, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sodium hydroxide (Merck KGa, Darmstadt, Germany), sucrose (Nordzucker GmbH, Braunschweig, Germany), hydroxypropyl-β-cyclodextrine (HP-β-CD, Roquette Services Techniques Laboratories, Lestrem, France), microcrystalline cellulose (Avicel PH 101, FMC, Cork, Ireland), aqueous dispersion of polyvinyl acetate/polyvinyl pyrrolidone (Kollicoat SR 30 D), aqueous dispersion of methacrylic acid and ethyl acrylate copolymer (Kollicoat MAE 30 DP), polyvinyl pyrrolidone 25000 (PVP, BASF, Ludwigshafen, Germany), triethylammonium acetate buffer (Fluka Chemie GmbH, Buchs, Switzerland), and purified water. All chemicals were of reagent grade or higher.

2.2. 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 (Lejus, Mölndal, Sweden) 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.

2.3. Coating of pellets

Pellets were coated with an aqueous polyvinyl acetate/polyvinyl pyrrolidone 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 polyvinyl pyrrolidone solution. Thereby, the total polyvinyl pyrrolidone 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: 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. A second layer of the enteric methacrylic acid and ethyl acrylate copolymer dispersion (Kollicoat MAE 30 DP) was applied on top of the extended release coated pellets. Coating conditions were similar than described above. Finally, the pellets were cured for 24 h at 40 °C.

2.4. Drug release studies

In vitro drug release was determined using the USP XXV rotating basket method (1000 ml of 0.1 N HCl or USP phosphate buffer, pH 6.8, 37 °C, 100 rpm, $n = 3$). Five percent HP-β-CD was added to the buffer medium, pH 6.8, in order to reach sink conditions. HP-β-CD increases the solubility of the active ingredient by formation of an inclusion complex independently of the ionic strength or pH of the dissolution medium. Using a Distek Premiere 5100 Dissolution System (Distek Inc., North Brunswick, USA) 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 Corp., Milford, USA). A 20 μL volume was injected onto a Symmetry C 18 column (3.5 μm, 4.6 × 150 mm, Waters, Milford, USA). A mixture of 55 ml 0.05 M triethylammonium acetate buffer and 45 ml acetonitrile (flow rate 1.0 ml/min, UV-detection at 244 nm) was used as mobile phase. An external calibration curve of SAG/ZK was used to calculate the amount of drug released. The method was checked with respect to linearity ($r > 0.99$), precision (2% RSD) and accuracy (3% RSD). In order to study the influence of the osmotic pressure of the dissolution medium on the drug release 1 or 2 mol sodium chloride was added to one liter buffer medium, pH 6.8. The resulting osmotic pressure of the release medium was measured with a vapor pressure osmometer type 5520 (Schlag GmbH, Bergisch Gladbach, Germany).

2.5. 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 (DSM 982, Zeiss, Oberkochen, Germany).

Table 1
Compositions of the investigated pellets (%, w/w)

Formulation No.	SAG/ZK	MCC	Sodium chloride	Potassium chloride	Sucrose	ER sub coating	Enteric top coating
1	60	40	–	–	–	5	–
2	60	40	–	–	–	5	2.5
3	60	40	–	–	–	5	5
4	60	32.5	7.5	–	–	5	2.5
5	60	25	15	–	–	5	–
6	60	25	15	–	–	5	2.5
7	60	25	15	–	–	5	4
8	60	25	15	–	–	5	5
9	60	25	–	15	–	5	–
10	60	25	–	15	–	5	2.5
11	60	25	–	15	–	5	5
12	60	25	–	–	15	5	–
13	60	25	–	–	15	5	2.5
14	60	25	–	–	15	5	5

MCC, microcrystalline cellulose.
ER, extended release.

3. Results and discussion

3.1. pH-dependent release of SAG/ZK from single coated pellets

SAG/ZK, a low molecular weight (Mw 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 these models a constant plasma level of the compound seems to be required to demonstrate efficiency of the molecule. Immediate release tablets developed for the compound failed in clinical studies phase I to achieve the desired constant plasma level. Therefore, an extended release dosage form for SAG/ZK has been developed.

Because of its weakly basic nature the active ingredient showed pH-dependent solubility. The solubility in 0.1 N HCl and phosphate buffer, pH 6.8, was 3.24 mg/ml and 0.01 mg/ml, respectively. Pellets manufactured by extrusion/spheronization and coated with the extended release polymer polyvinyl acetate/polyvinyl pyrrolidone (Kollicoat SR 30 D) only (Table 1, formulation 1) showed due to the remarkable difference in drug solubility pH-dependent dissolution profiles (Fig. 1). After 6 h 67% and 32% of the active ingredient was released in 0.1 N HCl and phosphate buffer, pH 6.8, respectively. The observed differences in the drug release profiles were in good agreement to the solubility of the compound in both media.

3.2. Effect of an enteric top coating on the drug release

In order to overcome the problem of the pH-dependent drug release a second layer of the enteric methacrylic acid and ethyl acrylate copolymer (Kollicoat MAE 30 DP) was coated on top of the extended release coated pellets (Table 1, formulations 2 and 3). Enteric polymers show an opposite solubility to the weakly basic drug. At low pH-values where the solubility of the drug is high, the enteric polymer remains insoluble and works as a part of the diffusion barrier. At higher pH-values, where the solubility of the active ingredient is low, the enteric coating dissolves and thus increases the permeability of the dosage form. SEM cross-sections of pellets before and after dissolution testing in 0.1 N HCl showed two polymer layers (enteric and extended release layer) (Fig. 2A and B). In contrast, after dissolution testing in phosphate buffer, pH 6.8, only the extended release layer was still present (Fig. 2C). As indicated by the SEM pictures the SAG/ZK release at pH 1 is controlled by diffusion through the intact extended and enteric polymer membrane whereas dissolution at pH 6.8 is mainly controlled by diffusion through the extended release polymer only. Unfortunately, already the addition of 2.5% and 5% (w/w) enteric polymer on top of the extended release coated pellets resulted in a strong decrease in drug release rates at pH 1 (Fig. 3). After 10 h, only 16.6% and 1.3% of the active ingredient have been released at pH 1 from pellets coated with 2.5 and 5% Kollicoat MAE 30 D, respectively. As

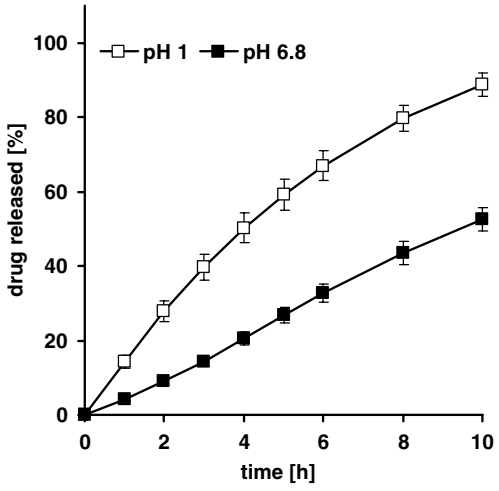

Fig. 1. pH-dependent drug release from pellets coated with an extended release polymer only into 0.1 N HCl and buffer medium, pH 6.8 (Table 1, formulation 1).

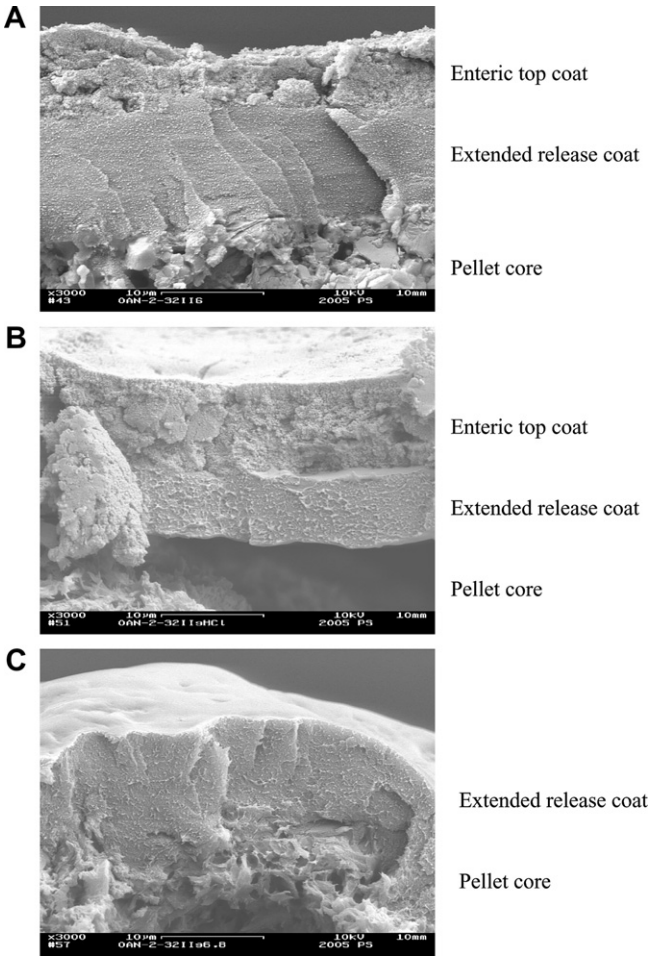

Fig. 2. Scanning electron micrographs of pellets coated with an extended and enteric polymer (A) before dissolution testing, (B) after dissolution testing into 0.1 N HCl, and (C) after dissolution testing into buffer medium, pH 6.8 (Table 1, formulations 2 and 3).

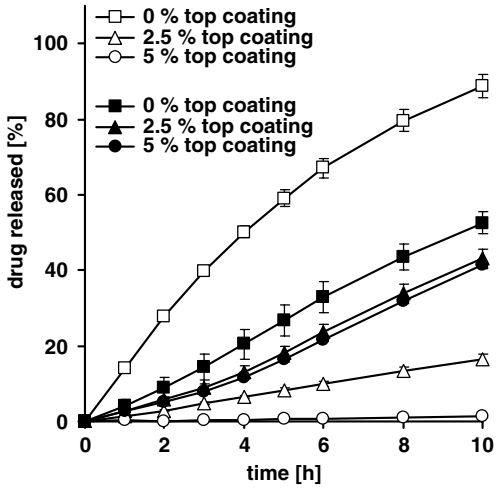

Fig. 3. Effect of the addition of an enteric top coating on the drug release into 0.1 N HCl (open symbols) and buffer medium, pH 6.8 (solid symbols) from extended release coated pellets (Table 1, formulations 2 and 3).

expected drug release rates at pH 6.8 were only slightly affected by the addition of the enteric polymer coat. The slight decrease in the release rates at pH 6.8 for enteric coated pellets can be explained with the additional polymer layer that needs to be dissolved prior to dissolution. Hence, the application of only 2.5% and 5% enteric polymer on top of the extended release coated pellets already resulted in a reversal of the pH-dependency (faster release of SAG/ZK at pH 6.8 than in 0.1 N HCl). According to these findings an enteric top coating level lower than 2.5% should be applied to achieve pH-independent drug release from double layer coated pellets. However, coating levels lower than 2.5% have been described to result in incomplete and incoherent film coating, thus leading to irreproducible drug dissolution patterns [14]. This is especially critical for the above-described dosage form where only slight differences of the enteric film coating level strongly affected the in vitro dissolution profiles.

3.3. Effect of osmagents on the drug release

In order to increase the drug release from the double layered coated pellets, the osmotically active sodium chloride was incorporated into the pellet cores by decreasing the amount of microcrystalline cellulose. Drug release rates of pellets containing 7.5% and 15% sodium chloride were compared to drug release of pellets without sodium chloride (Fig. 4A and B, formulation Nos. 2, 4, and 6). The extended release sub coating layer and the enteric top coating layer were kept constant at 5% and 2.5%, respectively. The addition of sodium chloride increased SAG/ZK release rates irrespective of the pH of the dissolution medium. This can be explained as follows. The addition of the osmotically active ingredient increased the imbibing of aqueous fluids into the pellet cores thus providing a saturated drug solution inside the beads and increasing drug concentration gradients (being the driving force for dissolution). Hence drug

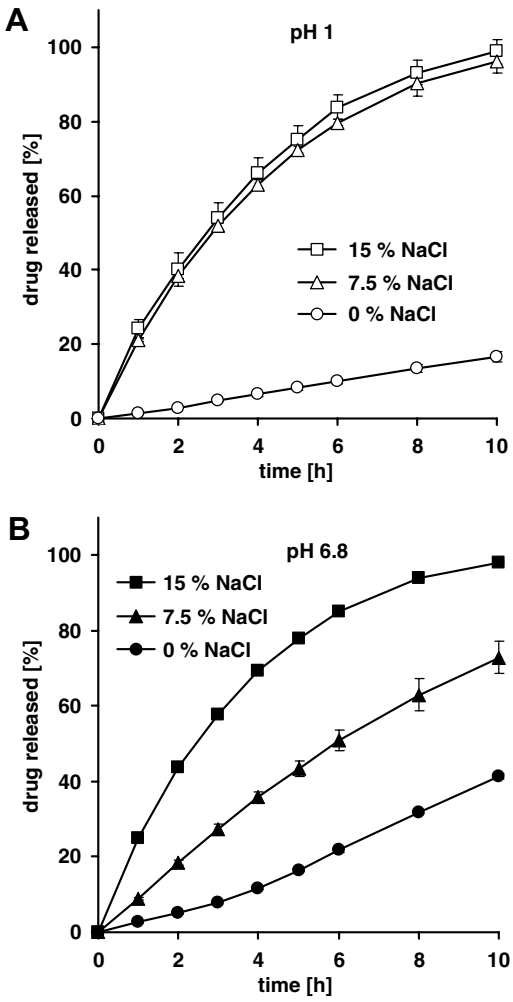

Fig. 4. Effect of the incorporation of sodium chloride into pellet cores on the drug release into (A) 0.1 N HCl and (B) buffer medium, pH 6.8, from pellets coated with an extended and enteric polymer (Table 1, formulations 2, 4, and 6).

release rates in both media increased significantly and indicating that release rates were strongly driven by osmotic effects. Increased and faster hydration of pellets containing sodium chloride was also confirmed visually. Whereas swelling of beads without an osmotically active additive was minor, significant hydration as indicated by swelling was observed for beads prepared with 7.5% and 15% sodium chloride. Interestingly, during dissolution in 0.1 N HCl drug release rates for pellets containing 7.5% and 15% sodium chloride almost overlapped. In contrast, drug release rates of pellets with 7.5% sodium chloride were slower compared to release rates of pellets with 15% sodium chloride upon release in phosphate buffer, pH 6.8. This might be explained as follows. For drug dissolution not only the osmotic pressure inside the beads but also the pressure gradient is important. As the osmotic pressure of the buffer medium, pH 6.8, is higher compared to 0.1 N HCl lower pressure gradients can be expected upon release in phosphate buffer. This is especially critical for beads with lower sodium chloride levels where the osmotic pressure

inside the beads is lower thus leading to lower pressure gradients and hence slower drug release rates.

To better understand these phenomena, to be able to explain the dramatically increased drug release rates at low pH SEM pictures of pellets prepared with sodium chloride were taken before and after dissolution testing in 0.1 N HCl (Fig. 5A–D). Double layered beads prepared with 15% sodium chloride showed a smooth and nonporous surface before dissolution testing. Cross-sections of the pellets before dissolution testing are indicating a relatively homogeneous and dense matrix. In contrast, after dissolution testing small pores and cracks were distributed all over the surface of the pellets. Consequently, for pellets prepared with sodium chloride drug diffusion at low pH not only occurred through the two polymer layers but also through water-filled pores and cracks. As expected from the observed drug release profiles (Fig. 4), beads prepared with 15% sodium chloride showed a highly porous network after dissolution testing in 0.1 N HCl. Similar observations have been made after dissolution testing in phosphate buffer, pH 6.8 (data not shown). These findings further emphasize that drug release rates of pellets containing sodium chloride were strongly influenced by osmotic effects.

3.4. Effect of enteric top coating level on the in vitro release of pellets containing sodium chloride

Next, the influence of the enteric top coating level on the release of SAG/ZK from pellets containing 15% sodium chloride was investigated in 0.1 N HCl and phosphate buffer, pH 6.8 (Fig. 6, formulation Nos. 5–8). The extended release polymer level was kept constant at 5% throughout these investigations. For all formulations containing sodium chloride drug release rates increased drastically when compared to pellets without osmotically active agent (Fig. 3) irrespective of the pH of the dissolution medium. However, for extended release coated formulations only (denoted 0% top coating in the Figure) drug release rates at pH 6.8 were still slower compared to release rates at pH 1 which is in good agreement to the lower solubility of SAG/ZK at higher pH-values. This indicates that in order to achieve pH-independent drug release profiles not only the addition of an osmotically active agent which is important to increase drug release rates at low and high pH but also the addition of an enteric top coating layer is important. Differences in drug release rates at pH 1 and 6.8 from double layer coated pellets with 2.5% Kollicoat MAE were less pronounced compared to pellets without an additional enteric polymer coat. However, drug release from these pellets was still pH-dependent. In contrast, for double layer coated pellets with an enteric coating level of 4% drug release profiles in both media almost overlapped. These results demonstrate that pH-independent drug release profiles from double layered pellets can be obtained by careful balance of extended and enteric coating level in combination with the addition of an osmotically active agent. The application of higher enteric polymer levels (e.g. 5%) on top of the extended release coat resulted in a reversal of the pH-dependency (faster release of SAG/ZK at pH 6.8 than in 0.1 N HCl) (data not shown).

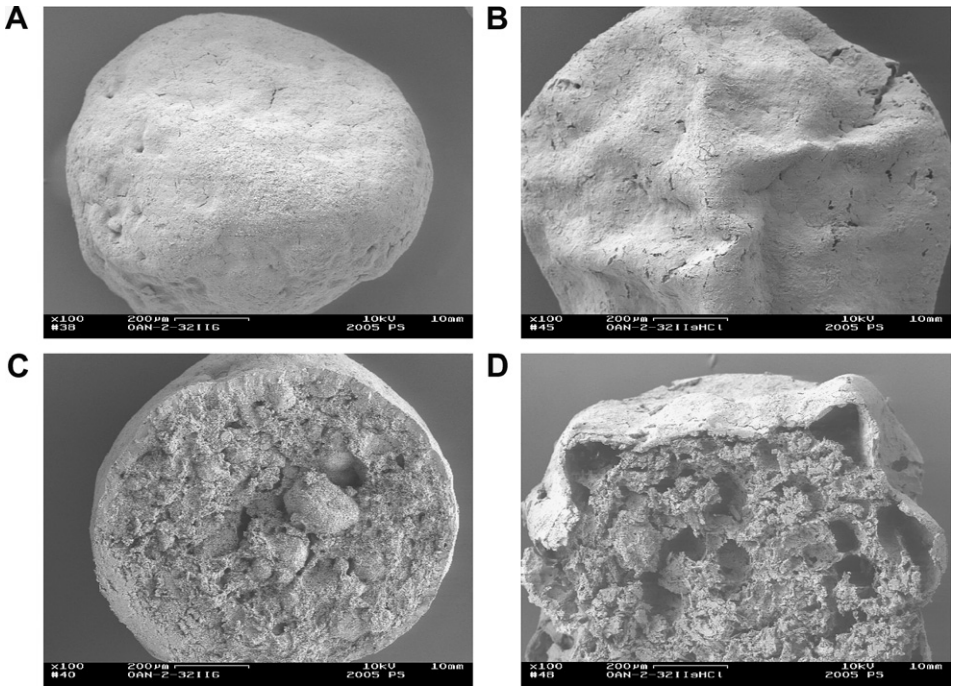

Fig. 5. Scanning electron micrographs of surface properties of pellets containing 15% sodium chloride and coated with an extended and enteric polymer (A) before and (B) after dissolution testing. Scanning electron micrographs of cross-sections of these pellets (C) before and (D) after dissolution testing (Table 1, formulation 6).

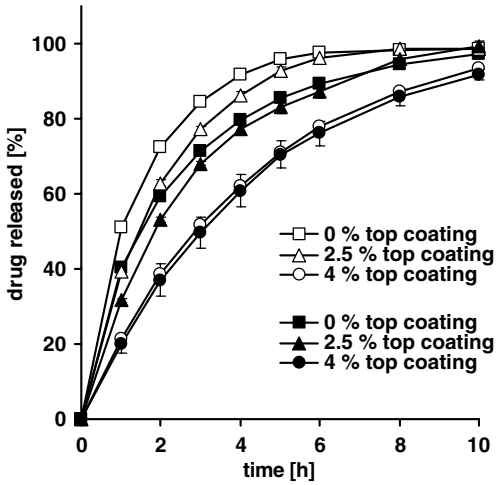

Fig. 6. Effect of the addition of an enteric top coating on the drug release into 0.1 N HCl (open symbols) and buffer medium, pH 6.8 (solid symbols) from extended release coated pellets containing 15% sodium chloride (Table 1, formulations 5–7).

3.5. Effect of the osmotic pressure of the dissolution medium on in vitro drug release rates

To further prove the hypothesis of an osmotically driven drug release, dissolution studies at pH 6.8 from double layered pellets containing 15% sodium chloride were carried out in media of different osmotic pressures (Fig. 7, formulation No. 7). The extended and enteric coating level was kept constant at 5% and 4%, respectively. The incorporation of an osmotically active agent into the beads was expected to increase the imbibing of aqueous fluids into the pellet cores thus providing a saturated drug solution inside the beads and increasing drug concentration gradients (being the driving force for dissolution). However, by decreasing the osmotic pressure difference between beads and dissolution medium the imbibing of water into the beads should be less pronounced thus leading to decreased dissolution rates. Good agreement between theory and in vitro dissolution was observed. With increasing osmotic pressure of the dissolution medium the in vitro drug release rates decreased significantly. Again these findings emphasize that drug release from the double layer coated beads containing sodium chloride was strongly driven by osmotic effects.

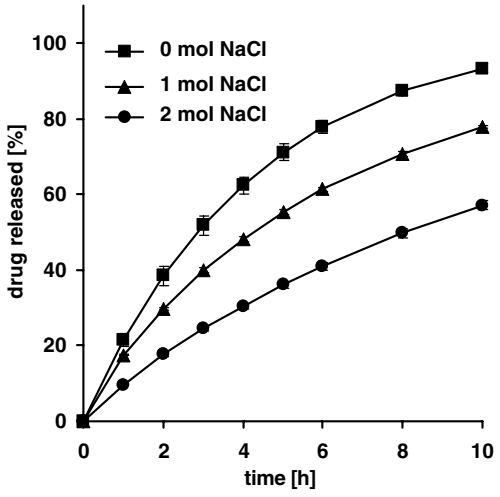

Fig. 7. Effect of the addition of sodium chloride into the dissolution medium, pH 6.8, on the drug release from extended and enteric coated pellets containing 15% sodium chloride (Table 1, formulation 7).

3.6. Effect of the type of osmotically active agent on the in vitro drug release

Next, the influence of the type of osmotically active agent on the in vitro drug release was investigated (Fig. 8A and B, formulation Nos. 9–14). The amount of

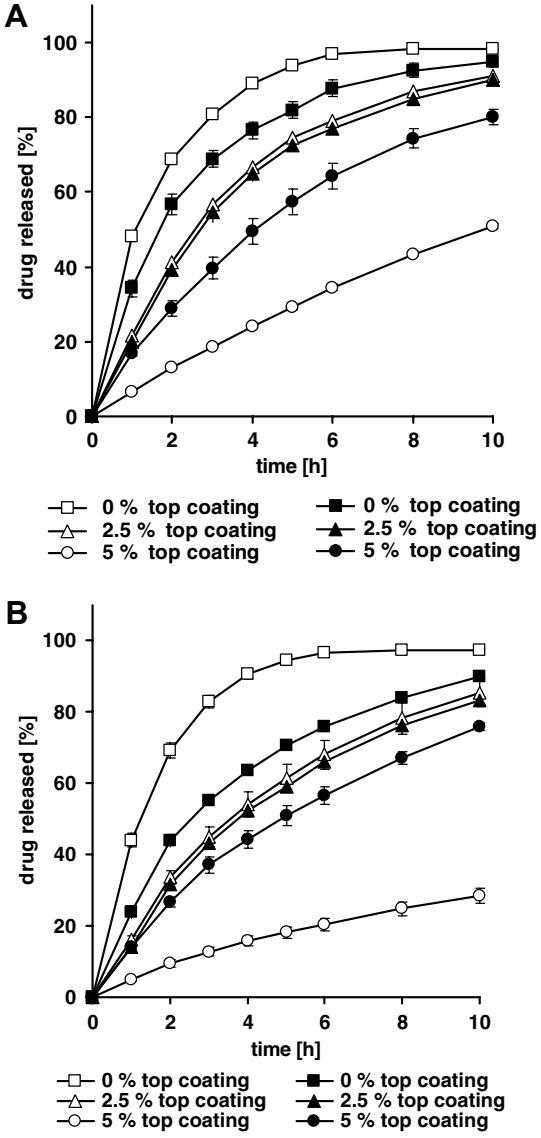

Fig. 8. Effect of the addition of an enteric top coating on the drug release into 0.1 N HCl (open symbols) and buffer medium, pH 6.8 (solid symbols) from extended release coated pellets containing (A) 15% potassium chloride and (B) 15% sucrose (Table 1, formulations 9–14).

the osmatically active agent within the beads was kept constant at 15%. The extended release coating level was kept constant at 5% whereas the amount of enteric polymer level was varied between 0% and 5%. In principle, the osmotically agent used should not alter the pH inside the pellet formulation as this might influence the solubility of the drug substance or affect the properties of the enteric coating. Therefore, two substances that also (comparable to sodium chloride) do not affect the pH-values within the pellets were investigated, namely ionic potassium chloride and nonionic sucrose. The drug release rates from beads containing potassium chloride indicate that pH-independent SAG/ZK release was achieved for pellets coated with 2.5% Kollicoat MAE (Fig. 8A). At lower enteric coating levels the drug release at pH 1 was faster when compared to release rates at pH 6.8 whereas at an enteric coating level of 5% a reversal of the pH dependency was observed (faster release at pH 6.8). Again these findings are explained by the solubility of the drug substance and the properties of the enteric polymer which acts as an additional barrier during release at pH 1. Similar observations have been made for beads containing 15% sucrose (Fig. 8B). Faster release rates at pH 1 for pellets without enteric film coat, almost overlapping drug release rates for pellets coated with 2.5% Kollicoat MAE and a reversal of the pH-dependency at an enteric coating level of 5%.

4. Conclusion

Extended release pellets containing SAG/ZK showed pH-dependent drug release profiles. Addition of a second enteric coat resulted in slow drug release rates at pH 1 thus leading to a reversal of the release profiles (faster release at pH 6.8 than in 0.1 N HCl). The addition of osmotically active ingredients (sodium and potassium chloride, and sucrose) increased the imbibing of aqueous fluids into the pellet cores thus providing a saturated drug solution inside the beads and increasing drug concentration gradients. In addition, for these pellets increased formation of pores and cracks in the polymer coating was observed. Hence drug release rates from double layered beads increased significantly and pH-independent osmotically driven SAG/ZK release was achieved from pellets containing osmotically active ingredients and coated with the extended release polymer polyvinyl acetate/polyvinyl pyrrolidone and the enteric polymer methacrylic acid and ethyl acrylate copolymer.

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