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Research paper

Enteric polymers as acidifiers for the pH-independent sustained delivery of a weakly basic drug salt from coated pellets

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ABSTRACT

Weakly basic drugs and their salts exhibit a decrease in aqueous solubility at higher pH, which can result in pH-dependent or even incomplete release of these drugs from extended release formulations. The objective of this study was to evaluate strategies to set-off the very strong pH-dependent solubility (solubility: 80 mg/ml at pH 2 and 0.02 mg/ml at pH 7.5, factor 4000) of a mesylate salt of weakly basic model drug (pK_a 6.5), in order to obtain pH-independent extended drug release. Three approaches for pH-independent release were investigated: (1) organic acid addition in the core, (2) enteric polymer addition to the extended release coating and (3) an enteric polymer subcoating below the extended release coating. The layering of aspartic acid onto drug cores as well as the coating of drug cores with an ethylcellulose/Eudragit L (enteric polymer) blend were not effective to avoid the formation of the free base at pH 7.5 and thus failed to significantly improve the completeness of the release compared to standard ethylcellulose/hydroxypropyl cellulose (EC/HPC)-coated drug pellets. Interestingly, the incorporation of an enteric polymer layer underneath the EC/HPC coating decreased the free base formation at pH 7.5 and thus resulted in a more complete release of up to 90% of the drug loading over 18 h. The release enhancing effect was attributed to an extended acidification through the enteric polymer layer. Flexible release patterns with approximately pH-independent characteristics were successfully achieved.

1. Introduction

Weakly basic drugs and their corresponding salts often have pH-dependent solubility at the physiological pH-conditions in the gastrointestinal tract. This can result in pH-dependent release or incomplete release due to free base formation with extended release dosage forms such as coated pellets [1,2].

Two main strategies are generally applied to overcome the pH-dependent release of such drugs, namely modifications in the extended release coatings or acidification of the pellet core. One possibility is to increase the permeability of the pellet coating at intestinal pH through the addition of enteric polymers to otherwise pH-independent and water-insoluble film coatings [3]. The enteric polymer, being insoluble at low but soluble at high pH, is expected to leach out and hence increases the coating porosity in order to offset the decreased drug solubility in the pellet core during the intestinal passage. However, more than a 10-fold increase in drug permeability has not been shown yet for pellets coated with non-enteric/enteric blends [4]. According to Fick's first law, the applicability of this approach would therefore be limited to substances with small solubility differences between salt and free base ($\leqslant$ factor 10).

Another way of implementing a pH-dependent drug permeability is an enteric top-coating [2,5], which decreases the drug release at low pH. This approach, however, requires a reasonable solubility of the free base.

The second approach is to maintain the microenvironmental pH inside dosage forms through the addition of acidic buffer substances [6]. The success of this approach is dependent on the amount of the pH-modifier and its acidity (solubility and pK_a) [1]. The solubility should not be too high in order not to leach too rapidly from the formulation and thus maintain a low pH in the formulation throughout extended time periods [7,8].

Besides the traditional use of low molecular weight acids (e.g. fumaric acid), polymeric acids such as enteric polymers facilitated pH-independent release of verapamil hydrochloride [2], which was attributed in part to an acidification of the pellet core. Although the assumed acidification effect of the enteric polymer was confirmed elsewhere [9], addition of Eudragit L did not facilitate pH-independent release from verapamil hydrochloride or

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papaverine hydrochloride matrix tablets, which was attributed to an ionic interaction between the positively charged drug and the negatively charged enteric polymer.

The challenges to successfully deliver a weak base in a pH-independent manner are primarily a large difference between the drug solubility (S) in acidic and neutral medium (as deduced from Fick's first law) as well as a large difference between the pK_a and the pH of the release medium simulating intestinal fluids [10]. Accordingly, pH-independent release approaches for drugs with different challenges (pK_a 4.9–9.4 and solubility differences, $S_{acidic}/S_{neutral}$, 12–3900) have been investigated [3,5,6,8–15]. Difficulties to succeed were apparent in studies with drugs with strongly pH-dependent solubility ($S_{acidic}/S_{neutral} \sim$ 2900–3900) [8,9].

The objective of this study was to explore whether and how a salt of a weakly basic drug (pK_a 6.5) with an exceptional pH-dependent solubility ($S_{acidic}/S_{neutral}$ 4000) could be delivered pH-independently by applying and extending the principles of permeability and solubility modulation discussed above.

2. Materials and methods

2.1. Materials

Mesylate salt of a weakly basic drug with solubilities of 80 mg/ml at pH 2 and 0.02 mg/ml at pH 7.5 (Pfizer Ltd., Sandwich, UK); hydroxypropyl methylcellulose (HPMC, Methocel E5, Colorcon, Orpington, UK); ethylcellulose (Ethocel 10 cP, DOW, Midland, USA); hydroxypropyl cellulose (Klucel JF, Hercules Incorporated, Wilmington, USA); dibutyl sebacate (DBS, Morflex, Greensboro, NC, USA); talc (micronized pharma grade, Luzenac, Toulouse, France); sugar beads (Suglets sugar spheres NF, 425–500 μm, NP pharma S.A., Bazainville, France); aspartic acid (Merck KGaA, Darmstadt, Germany); Eudragit L 100–55 (Evonik Röhm GmbH, Darmstadt, Germany); hydroxypropyl methylcellulose phthalate (HPMCP, HP-50 and 55, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan).

2.2. Methods

2.2.1. Preparation of drug cores

Drug cores were prepared using a fluidized bed coater (Aeromatic Strea-1, Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland) under the following conditions: inlet temperature 60–70 °C; outlet temperature 40 °C; air flow rate 60–80 m^3/h; atomizing air pressure 2.0 bar; spray nozzle diameter 1.2 mm. The drug was layered onto 400 g sugar spheres from an aqueous solution (10% w/w solids) with HPMC as the binder (10% w/w based on drug). The total (drug and HPMC) weight gain was 440%.

After drug layering, the cores were sealed with a HPMC layer of 5% weight gain, sprayed from a 5% (w/w) aqueous solution under the same conditions as the drug layering.

2.2.2. Pellet layering/coating

2.2.2.1. Aspartic acid layering. An aqueous aspartic acid dispersion (30% w/w solids) containing HPMC (10% w/w based on aspartic acid amount) as binder was sprayed onto 400 g HPMC-sealed drug cores to obtain an aspartic acid weight gain of 10% or 20% (w/w). The layering was conducted in a fluidized bed coater (Aeromatic Strea-1, Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland) under the following conditions: inlet temperature 60 °C; outlet temperature 37 °C; air flow rate 80 m^3/h; atomizing air pressure 2.0 bar; spray nozzle diameter 1.2 mm.

2.2.2.2. Ethylcellulose/HPC coating. EC/HPC (70:30) was sprayed onto HPMC-sealed drug cores from an isopropanolic polymer solution of 6.5% (w/w) solids content, which contained the following ingredients: ethylcellulose, HPC JF, dibutyl sebacate, isopropanol and DI-water in a ratio of 63:27:4.5:1190:162 (w/w). A theoretical polymer weight gain of 5%, 10% and 15% (w/w) was applied. Sixty grams of drug cores was coated using a fluidized bed coater (Mini-Glatt, Glatt GmbH, Binzen, Germany) under the following conditions: inlet temperature 46 °C; product temperature 34 °C; fluidization air pressure 0.2 bar; atomizing air pressure 0.9 bar; spray nozzle diameter 0.8 mm.

2.2.2.3. Ethylcellulose/Eudragit L and Eudragit L only coating. The EC/Eudragit L was sprayed onto HPMC-sealed drug cores from an isopropanolic polymer solution of 6.5% (w/w) solids content, which contained the following ingredients: ethylcellulose, Eudragit L 100–55, dibutyl sebacate, isopropanol and DI-water in a ratio of 90:30:6:1588:217 (w/w). A theoretical polymer weight gain of 5% and 10% (w/w) was applied. Four hundred grams of drug cores was coated using a fluidized bed coater (Aeromatic Strea-1, Niro Inc., Aeromatic-Fielder AG, Bubendorf, Switzerland) under the following conditions: inlet temperature 46 °C; outlet temperature 34 °C; air flow rate 60–80 m^3/h; atomizing air pressure 2.0 bar; spray nozzle diameter 1.2 mm.

2.2.2.4. Enteric coating layers. Eudragit L 100–55 30D was sprayed onto HPMC-sealed drug cores from an aqueous dispersion containing the following ingredients: Eudragit L 100–55 30D, DI-water, talc and TEC in a ratio of 450:332.5:67.5:13.5 (w/w) to obtain a polymer weight gain of 10%, 20% or 40% (w/w). Sixty grams of drug cores was coated using a fluidized bed coater (Mini-Glatt, Glatt GmbH, Binzen, Germany) under the following conditions: inlet temperature 34 °C; product temperature 30 °C; fluidization air pressure 0.2 bar; atomizing air pressure 0.9 bar; spray nozzle diameter 0.8 mm.

HPMCP was sprayed onto HPMC-sealed drug cores from an isopropanolic polymer solution of 8.8% (w/w) solids content, which contained the following ingredients: HPMCP (HP-50 or HP-55), isopropanol, DI-water, talc and TEC in a ratio of 60:796:199:30:6 (w/w). A theoretical polymer weight gain of 10% (w/w) was applied. Sixty grams of drug cores was coated using a fluidized bed

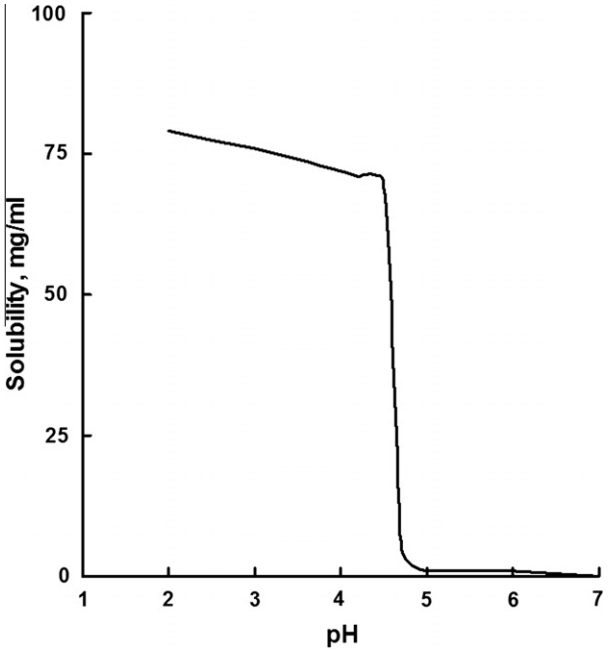

Fig. 1. Solubility–pH plot of the drug.

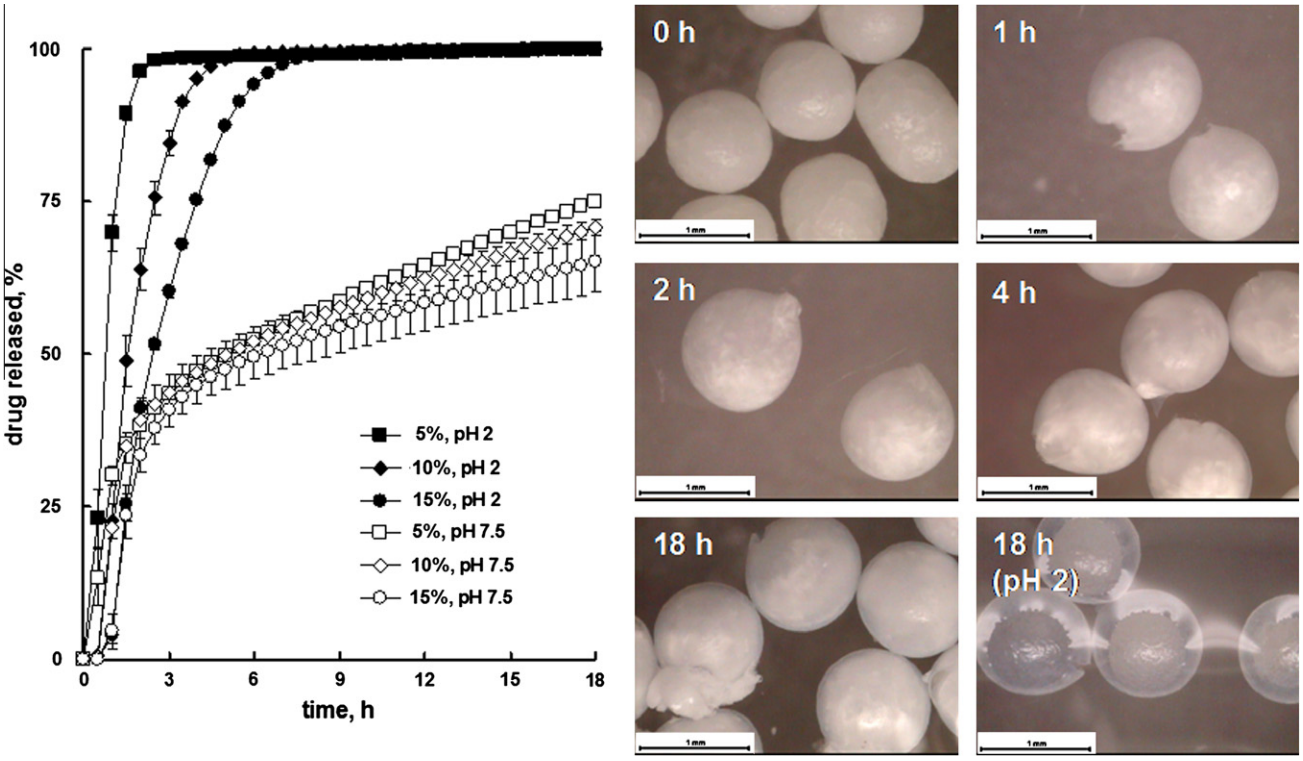

Fig. 2. Drug release profiles of pellets coated with 5%, 10% and 15% ethylcellulose/hydroxypropyl cellulose 70:30 (left) and macroscopic appearance of the 5% coated pellets during release (right) as function of the medium pH. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

coater (Mini-Glatt, Glatt GmbH, Binzen, Germany) under the following conditions: inlet temperature 42 °C; product temperature 30 °C; fluidization air pressure 0.2 bar; atomizing air pressure 0.9 bar; spray nozzle diameter 0.8 mm.

2.2.3. Drug release

Release was tested at pH 2 (0.01 M HCl with NaCl, 0.2 Osm/kg) and at pH 7.5 (6.4 mM phosphate buffer with NaCl; 0.2 Osm/kg) at 100 rpm, 37 °C for two or more replicates using a USP XXVI paddle apparatus equipped with an online UV to quantify drug release at 293 nm (Vankel 7000/8000 with Cary 50, Varian Inc., Palo Alto, USA).

2.2.4. Solubility–pH-profile

The equilibrium drug solubility was determined in water, aqueous hydrochloric acid solution (0.01 M hydrochloric acid) and in

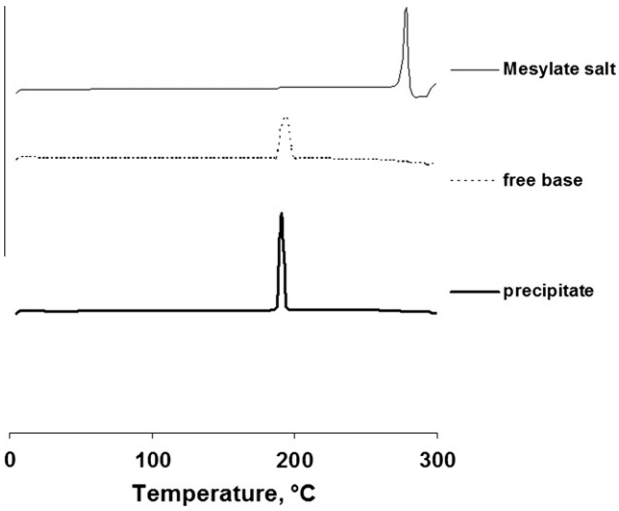

Fig. 3. DSC thermograms of the precipitate formed in pH 7.5 in comparison with the free base and the mesylate salt of the drug.

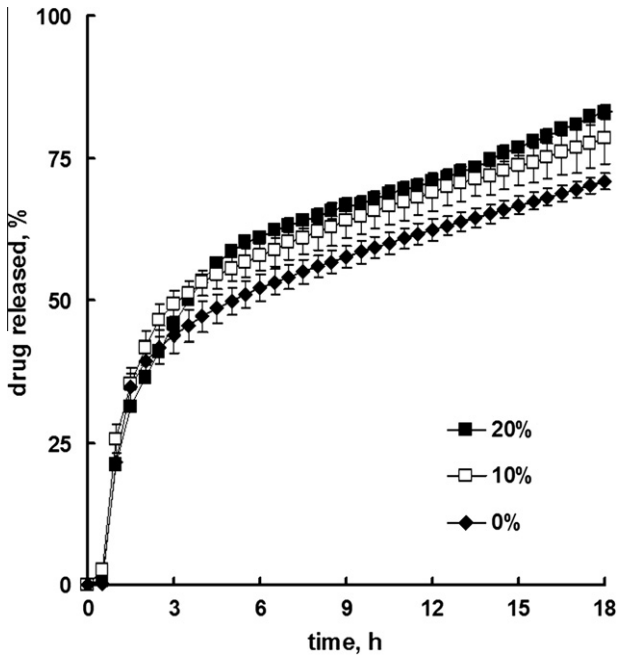

Fig. 4. Drug release of pellets layered with aspartic acid and top-coated with 10% ethylcellulose/hydroxypropyl cellulose 70:30 as a function of the aspartic acid level.

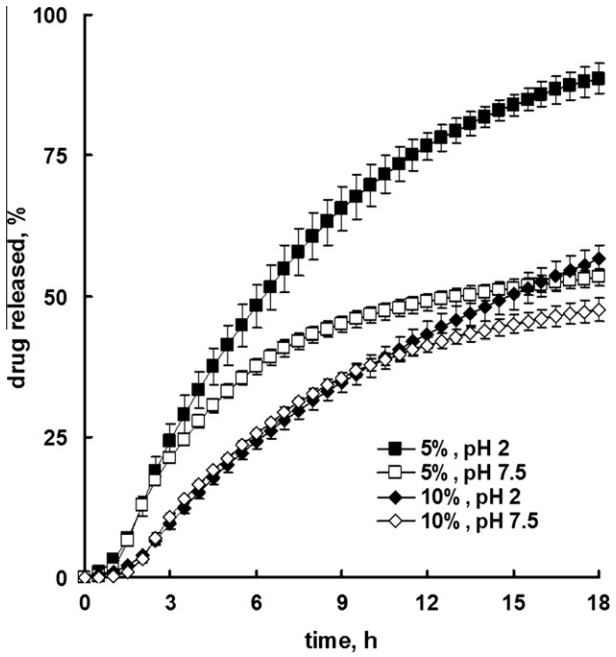

Fig. 5. Drug release of 5% and 10% ethylcellulose/Eudragit L 60:40-coated drug pellets as a function of medium pH.

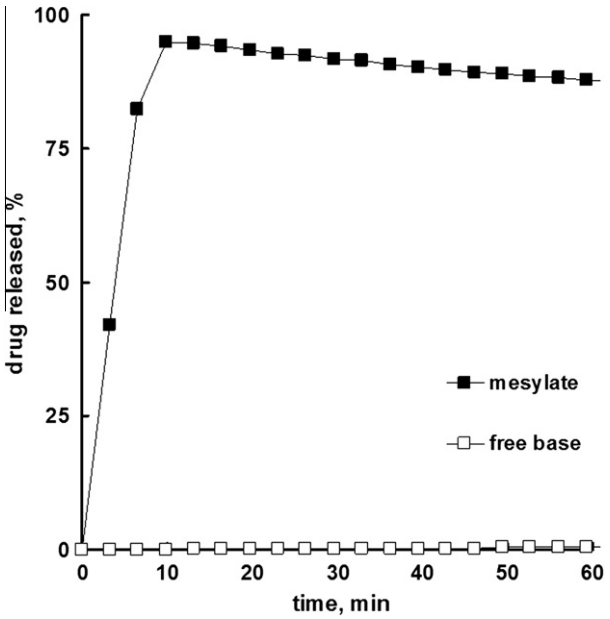

Fig. 7. Drug release at pH 7.5 of 50 mg tablets containing 25 mg free base or the corresponding mesylate salt.

citrate and phosphate buffer solutions ranging in pH between pH 2.5 and 7. The equilibrium solubilities were determined by adding drug to the aqueous media, subjecting the solutions to ultrasonication for 1 h followed by stirring for approximately 13 h at 23 °C. After achieving equilibrium, the undissolved solids were separated by filtration and the concentration in the remaining solution was determined.

2.2.5. Pellet pictures

Pictures of single pellets during or after dissolution were taken with an optical light macroscope (Axioscope, Carl Zeiss Jena GmbH, Jena, Germany) and analysed with image analysis software (Easy-Measure, Inteq Informationstechnik GmbH, Berlin, Germany).

2.2.6. Differential scanning calorimetry (DSC)

Melting points were derived from DSC thermograms (DSC821e, Mettler Toledo GmbH, Giessen, Germany) of samples obtained upon heating from 5 to 300 °C (one cycle only) at a scanning rate of 10 K/min.

3. Results and discussion

A mesylate salt of a weak base (tertiary amine; pK_a 6.5) with a strong pH-dependent solubility was used as model compound in

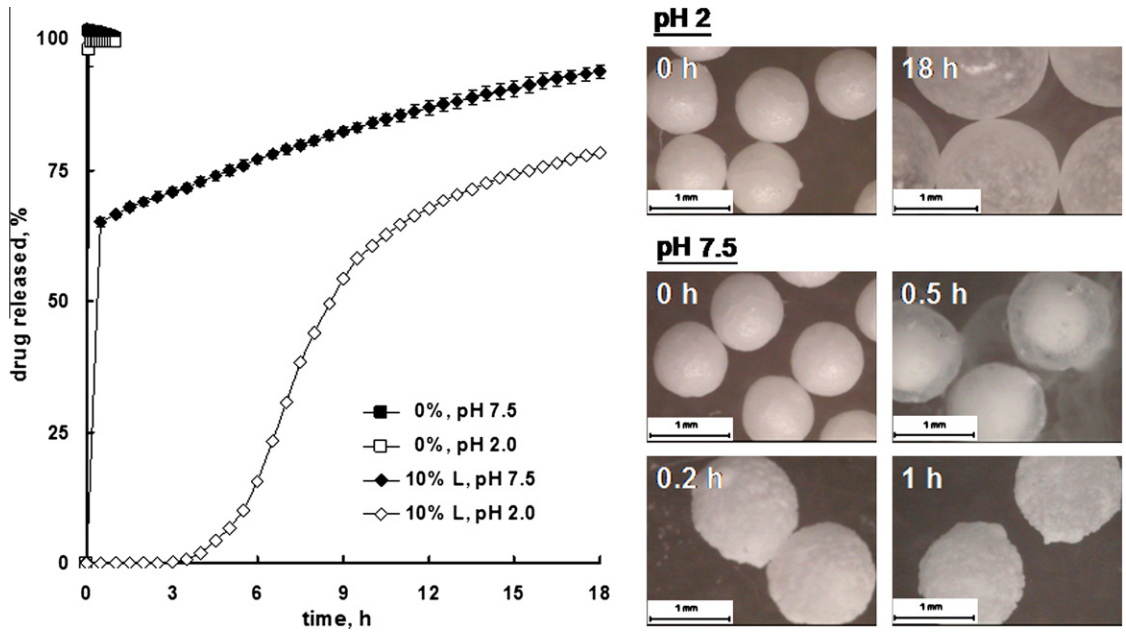

Fig. 6. Drug release of 0%, 10% and 20% Eudragit L-coated drug pellets as a function of medium pH (left) and appearance of drug pellets coated with 10% Eudragit L as a function of incubation time in pH 7.5 and pH 2.0 (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

the present study. The solubility below pH 4.5 (70–80 mg/ml) was significantly higher than the solubility of the free base (0.02 mg/ml) above pH 4.5 (Fig. 1). The large solubility decrease of more than three orders of magnitude made it an interesting compound to study different strategies to overcome pH-dependent or incomplete release.

3.1. pH-dependent release with standard EC/HPC-coated pellets

Continuous and complete drug release over 2–7 h was obtained at pH 2 with pellets coated with a 70:30 blend of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) (Fig. 2, left). In contrast to pH 2, a biphasic and incomplete release was obtained at pH 7.5. Drug release commenced after an osmotically triggered rupturing of the external coating (Fig. 2, right). The release incompleteness in pH 7.5 medium correlated with the formation of a precipitate at the rupture of the coating. The precipitate had a similar melting point as the free drug base (Fig. 3). Continuous ingress of pH 7.5 buffer obviously caused an elevation of the initially acidic pH in the core resulting in free base precipitation. Saturated solutions of the mesylate salt in water had a pH of 3.7. The biphasic drug release was therefore attributed to a first more rapid release phase dominated by the self-buffering effect of the mesylate salt and to a second slower release phase, where the dissolution of precipitated free base occurred.

3.2. Acid incorporation into the core of EC/HPC-coated pellets

The adjustment of a low microenvironmental pH inside the dosage forms with low molecular weight acids is a conventional approach towards pH-independent delivery of weakly basic drugs [11,12,16] with limitations for drugs with highly pH-dependent solubilities [8].

The amino acid aspartic acid was chosen due to its acidity (pK_a 3.6, pH_{sat} 2.7) and its relatively low solubility (4.5 mg/ml), which was expected to provide a prolonged acidification in the pellet core [7]. However, the incorporation of 10% and 20% aspartic acid led only to a slight improvement of the release completeness in pH 7.5 (Fig. 4) and was therefore inappropriate to sufficiently acidify the microenvironmental pH to avoid free base formation.

3.3. Coating with ethylcellulose/Eudragit L and Eudragit L only

Coatings with blends of water-insoluble and enteric polymers were previously studied in order to set-off the pH-dependent solubility of weak bases [3] or salts thereof [2]. In this study, it

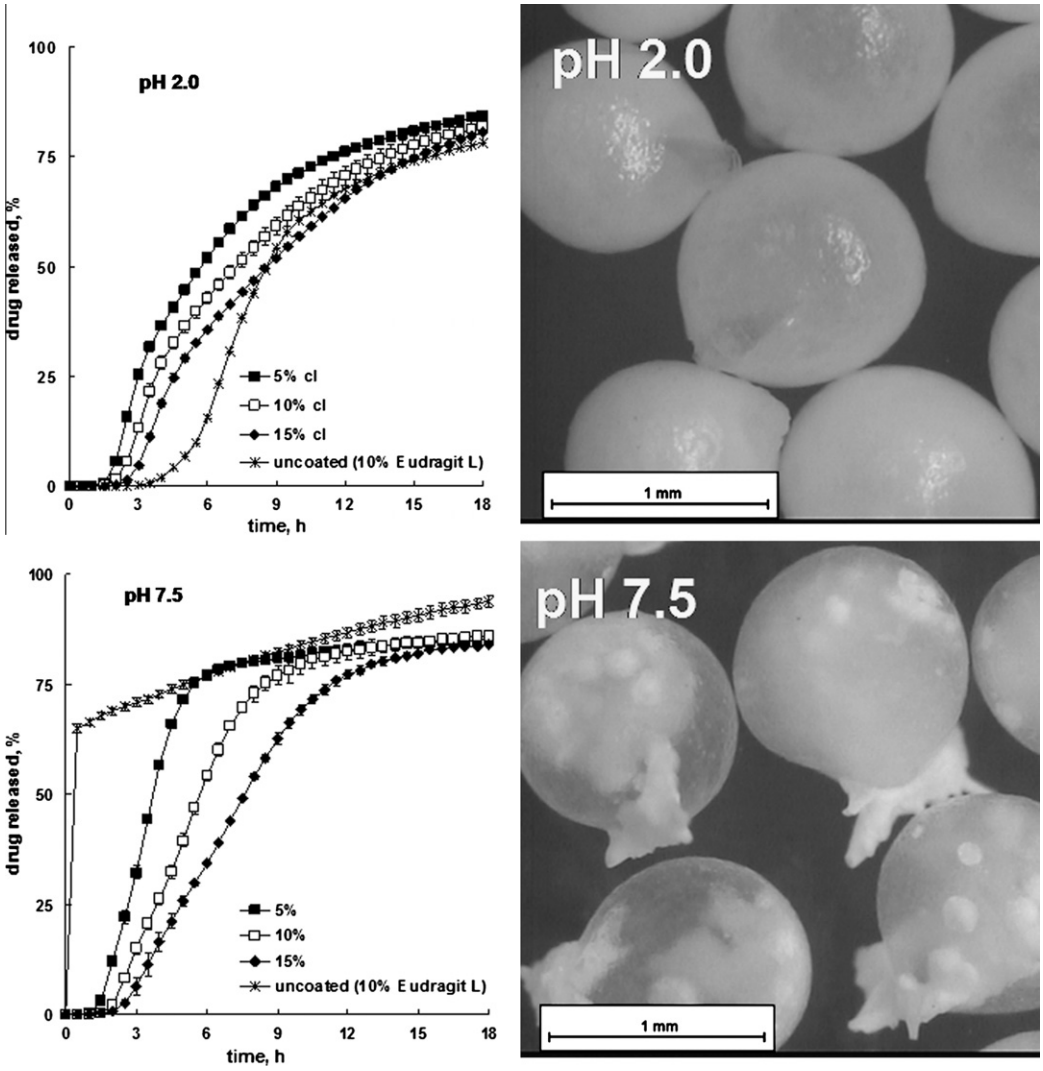

Fig. 8. Drug release at pH 2.0 and 7.5 of pellets coated with 10% Eudragit L ("uncoated") followed by 5%, 10% and 15% ethylcellulose/hydroxypropyl cellulose 70:30 (left) and appearance of 10% ethylcellulose/hydroxypropyl cellulose-coated drug pellets with a 10% Eudragit L subcoating after 18 h in pH 2.0 or pH 7.5 release medium (right).

was anticipated that high amounts of the enteric polymer would be necessary to account for the large solubility difference between low and neutral pH (factor 4000 vs. factor 20 [3] or 50 [2]).

Accordingly, a blend of ethylcellulose and Eudragit L (60:40) was applied onto the drug cores. Despite a prolongation of the pH-independent release phase to about 10 h compared to 2 h in case of EC/HPC, the completeness of the release in pH 7.5 medium was not improved (Fig. 5). Not more than 53% drug was released within 18 h.

A coating with Eudragit L only (10%) decreased the release at pH 2 drastically and resulted in a sigmoidal pattern (Fig. 6, left), which is typical for drug release through osmotic pumping [2]. Accordingly, pellets coated with the enteric polymer swelled extensively from initially 0.9 mm to about 1.5 mm during dissolution at pH 2 without an obvious rupturing of the coating (Fig. 6, right), which indicated a high flexibility of the polymer layer in the acidic release medium. A biphasic release pattern was obtained at pH 7.5 (Fig. 6, left). This was surprising because a rapid release as seen for the uncoated pellets was expected after the dissolution of Eudragit L above pH 5.5. However, the biphasic release was accompanied by precipitation of the free base, which occurred prior to dissolution of the Eudragit L layer. Accordingly, the formation of a free base precipitate layer around the pellets was observed during release (Fig. 6, right). Once the almost insoluble free base was formed, its dissolution rate was too slow to achieve completion of the release within 18 h. The very low dissolution rate of the free base was in agreement with dissolution results of immediate release tablets of the drug (50 mg; drug/lactose 25/25). Tablets containing the mesylate salt dissolved within 10 min, while only 0.44% drug dissolved from the free base tablets within 60 min (Fig. 7). Although complete tablet dissolution would result in non-sink conditions (25 mg/900 ml vs. S_{mesylate} of 23 mg/900 ml and $S_{\text{free base}}$ of 19 mg/900 ml), it was unlikely that saturation effects affected the free base dissolution, since 0.44% dissolved drug corresponded to only 0.58% of its solubility. It was therefore concluded that complete release of the drug could only be achieved when the precipitation of the free base was avoided.

3.4. Incorporation of an enteric polymer layer into EC/HPC-coated pellets

A modulation of the microenvironmental pH inside dosage forms with enteric polymers was previously suggested for the delivery of salts of weakly basic drugs to increase the completeness of the release and to achieve pH-independent drug release [2,9].

Accordingly, Eudragit L was coated on the drug cores prior to the EC/HPC top-coating. Drug release in pH 2 was accelerated compared to corresponding enterically coated pellets without the EC/HPC top-coating (Fig. 8). The top-coating with the inflexible ethylcellulose-based film appeared to limit the swelling of the enteric core, which forced the pellets to rupture comparable to pellets coated with EC/HPC only. Rupturing of the pellets was also observed at pH 7.5. The release after the rupturing was faster in pH 7.5 compared to pH 2, which was attributed to an increasing permeability of the coating due to the dissolution of the enteric subcoating. Incorporation of the enteric polymer increased the completeness of drug release at pH 7.5 from ~70% without the Eudragit L layer (Fig. 2) to 80% at 18 h, which suggested a lower degree of free base formation in the presence of the enteric polymer. However, the release was still incomplete. The improved completeness was attributed to an acidification effect of Eudragit L, as shown previously [9]. Although dissolution of Eudragit L occurs not below pH 5.5, an excess of the enteric polymer put into pH 7.5 release medium (m/m ~ 1:1) led to an acidification to pH 4.3, which would be low enough to avoid the precipitation of the drug inside the core (Fig. 1).

According to a balance between acidification and free base formation, an increase in the buffer strength of the release medium through an increase in the phosphate ion concentration from 6 mM to 50 mM (both adjusted to 0.2 Osm/kg with NaCl) decreased the release from 80% to 64%, which was attributed to an increased precipitation of the free base as indicated by a rapid completion of the dissolution upon acidification (HCl addition) to pH 2 after 18 h (Fig. 9). Noteworthy, the buffer capacity of the 6 mM phosphate buffer (3.3 mM/pH) can be expected to be closer

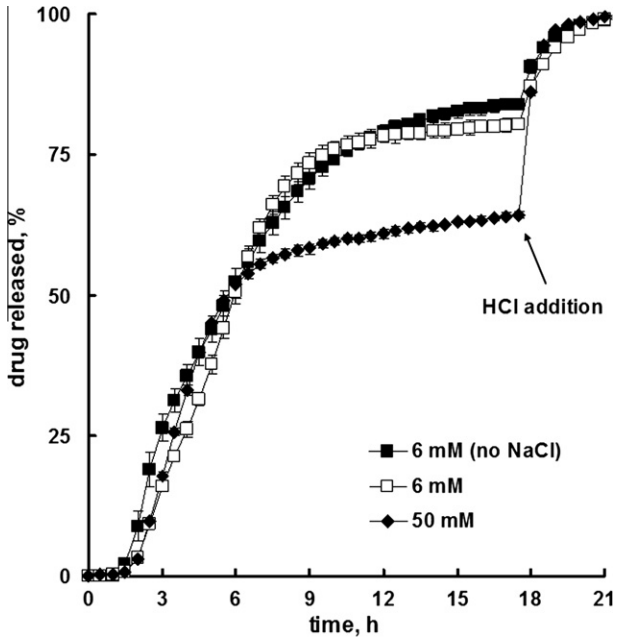

Fig. 9. Drug release of pellets coated with 10% Eudragit L and top-coated with 15 ethylcellulose/hydroxypropyl cellulose 70:30 as a function of the release medium composition.

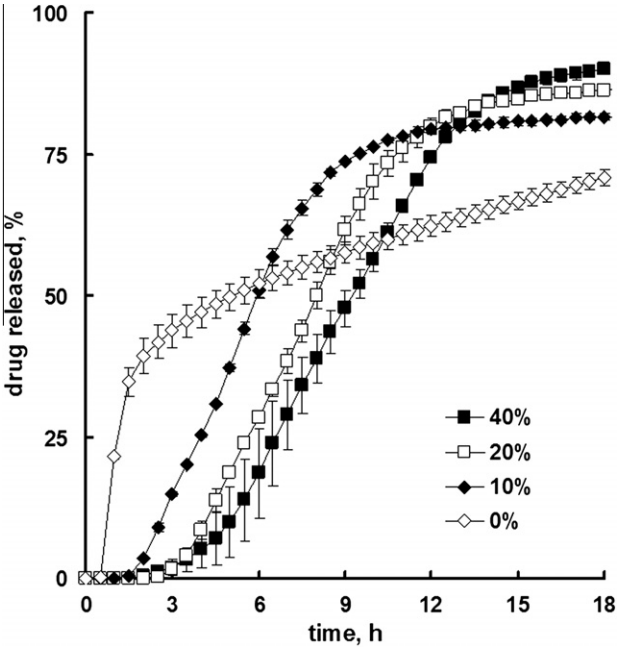

Fig. 10. Drug release of pellets coated with Eudragit L and top-coated with 10% ethylcellulose/hydroxypropyl cellulose 70:30 as a function of the Eudragit L level.

to the physiological conditions in the intestine (5 mM/pH [17]) than the 50 mM buffer (25.8 mM/pH).

An exclusion of sodium chloride from the release buffer showed no marked effect, which indicated that ionic interactions between drug and Eudragit L, which were observed elsewhere [9], were probably not responsible for the still incomplete release. This was further supported upon an increase of the Eudragit L level from 10% over 20% to 40%, which resulted in a slight increase of the total drug release from 80% over 86% to 90% within 18 h (Fig. 10), indicating an improved acidification.

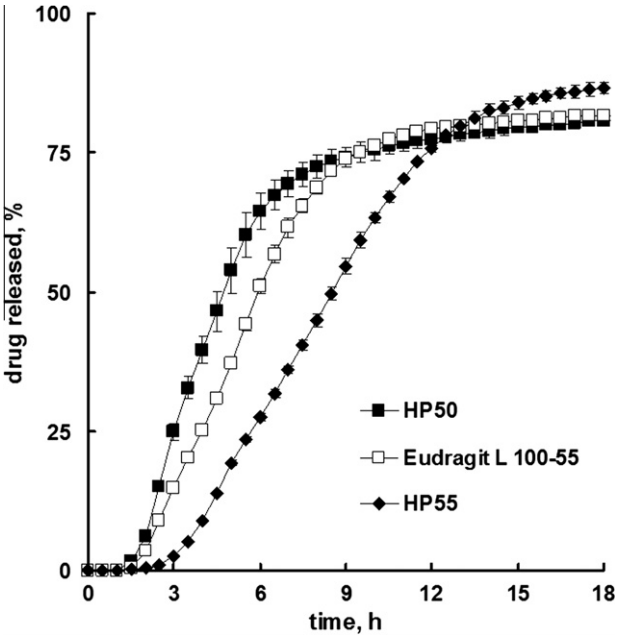

Fig. 11. Drug release of pellets coated with enteric polymer (10%) and top-coated with 10% ethylcellulose/hydroxypropyl cellulose 70:30 as a function of the enteric polymer type.

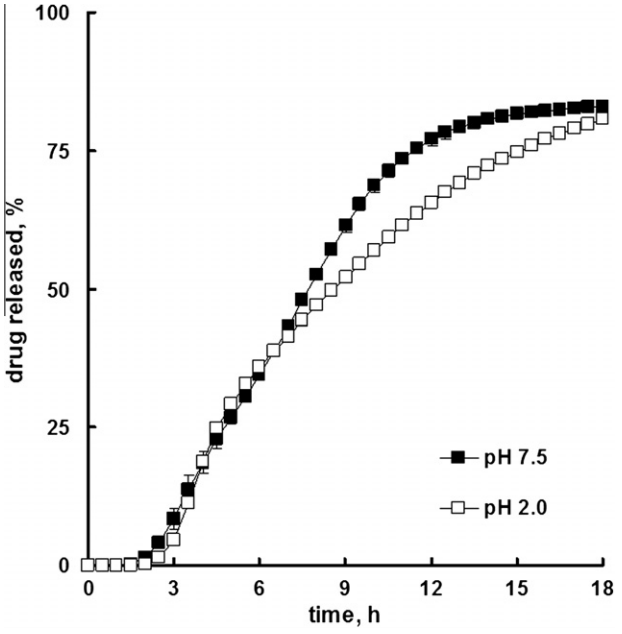

Fig. 12. Drug release of pellets coated with 10% Eudragit L and top-coated with 15% ethylcellulose/hydroxypropyl cellulose 70:30 as a function of medium pH.

A slightly increased completeness of drug release was also obtained (Fig. 11), if Eudragit L was replaced by the more acidic enteric polymer HPMCP-55 ($pK_{a\ app}$ 4.5 vs. 6.9; [18,19]). Interestingly, a higher release was obtained with HP-55 compared to HP-50, which dissolve at pH 5.0 and 5.5, respectively. A more efficient acidification with HP-55 than with HP-50 correlated thereby with the higher acid number (123 gKOH/g vs. 84 gKOH/g) at comparable pK_a values (pK_a 4.35 ± 0.15) reported in the literature [19,20].

Overall, flexible release patterns for 80% of the drug loading over 18 h with a slight (F2 similarity factors 42–49) or negligible (F2 similarity factors: 50–55) pH-dependence were achievable upon incorporation of only 10% Eudragit L into EC/HPC-coated pellets (Fig. 12).

4. Conclusion

Pellets containing a high loading of a salt of a weakly basic drug with a strongly pH-dependent solubility (factor 4000) were subjected to three approaches towards pH-independent release. The incorporation of aspartic acid and coating with a blend of ethylcellulose/Eudragit L failed to significantly improve the extended release of pellets towards pH-independent release. The incorporation of enteric polymers into EC/HPC-coated drug cores, however, facilitated the flexible and pH-independent release of the drug over 18 h.

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