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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

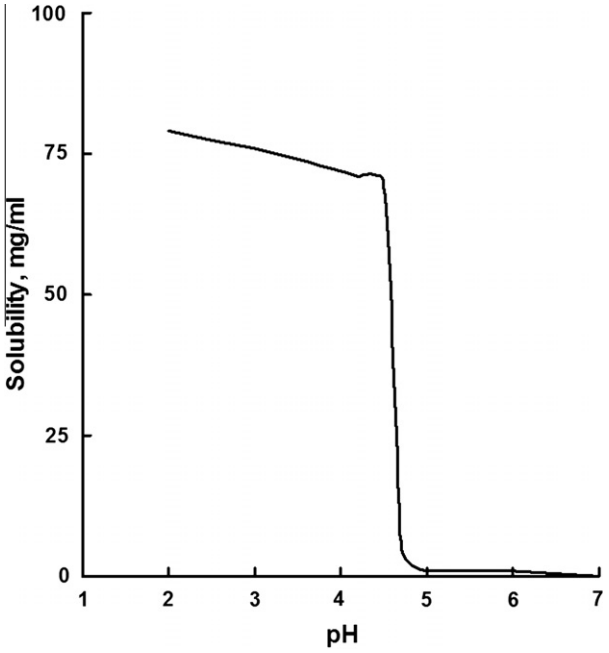

Fig. 1. Solubility–pH plot of the drug.