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Research paper

pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat® SR 30 D and the enteric polymer dispersion Kollicoat® MAE 30 DP

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Abstract

The objective of this study was to obtain pH-independent release profiles from coated pellets containing drugs with pH-dependent solubility. pH-independent release of the basic model drug verapamil HCl was achieved by coating with a combination of the neutral polymer dispersions Kollicoat® SR 30 D (aqueous dispersion of polyvinyl acetate) and the enteric polymer dispersion Kollicoat® MAE 30 DP (aqueous dispersion of methacrylic acid and ethyl acrylate copolymer; methacrylic acid copolymer type C). The two polymers where applied either as separate layers (enteric polymer + extended release polymer or vice versa) or as a polymer blend. A careful balance of the ratios of the polymers allowed the achievement of a pH-independent release. Higher amounts of the enteric polymer in the polymer blend resulted in a reversal of the pH-dependency, e.g. a faster release at pH 6.8 than in 0.1 N HCl.

Keywords: Enteric polymers; Extended release; Multiparticulates; pH-independent release; Polyvinyl acetate; Kollicoat®SR 30 D

1. Introduction

Many drugs, being weak bases, acids or salts thereof demonstrate pH-dependent release from extended release formulation, for example coated pellets. At the low pH in the stomach, weakly basic drugs are freely soluble resulting in fast release rates. However, the release rate can decrease dramatically once the dosage forms reach the higher pH-regions of the intestinal tract [1]. Opposite conditions may hold for weakly acidic drugs. Differences in the release rate in different parts of the gastrointestinal tract may cause in vivo variability and bioavailability problems.

In principal, two approaches exist to overcome the pH-dependent drug release. First, the addition of buffering agents to the core to maintain a constant pH and solubility and therefore constant concentration gradient across the polymeric coating independent of the surrounding pH, or, secondly, an increase in the permeability of the coating to counteract the decreased solubility. pH-adjusters, such as organic acids of sufficient acidic strength (fumaric, succinic, adipic, tartaric, citric acid) [1–5], alkaline substances such as magnesium oxide [6] or mixtures such as disodium hydrogen orthophosphate/citric acid [7] are added to the drug-containing core in order to create a favourable pH-microenvironment. This approach has been applied to reservoir systems (coated dosage forms) [2,6,8] as well as to matrix tablets [3–5,7,9,10]. Matrix systems based on a hydrophilic polymer (e.g. HPMC E50) and an enteric polymer (Eudragit® L) have been patented [3]. In acidic medium, the enteric polymer is insoluble and acts as part of the matrix and thus contributes to the retardation of the drug release. In intestinal fluids, the enteric polymer dissolves and, thus, increases the permeability of the dosage form.

Depending on the core and polymer used as extended release membrane, the pH-adjusting substances are also released from the dosage forms and the buffering capacity decreases with time. Often, higher amounts of acids (up to 500% relative to the drug) have to be used to achieve pH-independent drug release over a long period of time [1,2]. The addition of organic acids lead to sigmoidal drug release

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profiles from multiparticulate systems coated with Eudragit® RS [11,12]. This anomalous behaviour was explained mostly by an osmotic pumping mechanism [13].

In the second approach, the permeability of the coating is increased to balance the decreased drug solubility. This was achieved by using a mixture of water-insoluble polymers (e.g. ethylcellulose) with enteric polymers (e.g. hydroxypropyl methylcellulose phthalate or -acetate succinate) for the coating of pellets, which contained basic drugs [14]. The enteric polymer remains in the coating at low pH (high drug solubility) and increases the permeability at higher pH (low drug solubility), for example by leaching.

The objective of this study was to achieve pH-independent release of the basic model drug verapamil HCl from pellets coated with an aqueous polyvinyl acetate dispersion, Kollicoat® SR 30 D [15], which recently became commercially available, and the enteric polymer dispersion, Kollicoat® MAE 30 DP.

2. Materials and methods

2.1. Materials

Kollicoat® SR 30 D (aqueous dispersion of polyvinyl acetate); Kollicoat® MAE 30 DP (aqueous dispersion of methacrylic acid and ethyl acrylate copolymer; methacrylic acid copolymer type C); polyethylene glycol, PEG (Lutrol® 4000) (BASF, Ludwigshafen, Germany); triethyl citrate, TEC (Morflex, Greensboro, NC, USA); sugar spheres, 710–850 μm (Suglets, NP Pharm, Bazainville, France); hydroxypropyl methylcellulose, HPMC (Methocel® E5, Colorcon, Orpington, England); verapamil HCl (BASF AG, Ludwigshafen, Germany).

2.2. Drug layering

Verapamil HCl was layered on sugar pellets using an ethanol/water (60:40 w/w) binder solution of HPMC (Methocel® E5) (1.5% w/v) with PEG as a plasticizer (Lutrol® 4000) (10% w/w based on HPMC) in a fluidized bed coater Glatt GPCG-1 (Glatt GmbH, Binzen, Germany) to achieve a 10% w/w drug content. The layering conditions were: batch size: 800 g, inlet temperature: 30 °C, product temperature: 26 °C, air flow: 130 m^3/h, nozzle diameter: 1.2 mm, spray pressure: 1.2 bar, spray rate: 8.5 g/min, final drying at 40 °C for 15 min.

2.3. Coating of layered pellets

The drug-layered pellets were coated with Kollicoat® SR 30 D (15% w/w solids content) without plasticizer and with Kollicoat® MAE 30 DP (15% w/w solids content) with 10% w/w TEC (based on solids) either sequentially or simultaneously using a ball coater Hüttlin HKC 05 (Hüttlin Coating-Technik, Steinen, Germany). When sprayed simultaneously, two separate nozzles were used because of the incompatibility of the aqueous dispersions Kollicoat® SR 30 D and Kollicoat® MAE 30 DP (they coagulated/flocculated in contact with each other). The coating conditions were: batch size: 600 g, inlet temperature: 46 °C, product temperature: 39 °C, nozzle diameter: 0.8 mm, spray pressure: 0.5 bar, microclimate pressure: 0.2 bar, spray rate (total for both nozzles): 5.2 g/min, final drying at 40 °C for 15 min.

2.4. Drug release

The drug release from the coated pellets was investigated in a paddle apparatus (USP XXIV) (Vankel VK 300, Vankel Industries, Edison., NJ, USA) (900 ml 0.1 N HCl or buffer pH 6.8 Pharm. Eur. 1997, 100 rpm, 37 °C, $n = 3$). Samples were withdrawn at predetermined time points and measured UV-spectrophotometrically at $\lambda = 278$ nm).

3. Results and discussion

Extended release dosage forms should ideally release the drug independent of the conditions in the gastrointestinal tract, and, in particular, independent of pH. Extended release polymers, such as ethylcellulose, Eudragit® RS/RL or polyvinyl acetate (Kollicoat® SR) generally result in pH-independent drug release for drugs with pH-independent solubility. However, many drugs are ionisable and therefore show pH-dependent drug release. For example, a basic drug has a higher solubility at low pH and a lower solubility at high pH. The drug release would therefore be higher in gastric than in intestinal fluids.

Verapamil HCl was selected as a model basic drug because of its pH-dependent solubility. The solubility is greater than 100 mg/ml at pH-values below 6.35, at pH 6.45 it decreases to about 50 mg/ml, and at pH 6.8 it equals 2.7 mg/ml [10]. As expected, the drug was released faster from Kollicoat® SR 30 D-coated pellets in 0.1 N HCl than in pH 6.8 buffer (Fig. 1). The concentration gradient across the polymeric membrane decreased with increasing pH resulting in a reduction in verapamil HCl release.

In this study, pH-independent drug release was attempted by influencing the permeability of the coating through the addition of an enteric polymer. Enteric polymers carry acidic functional groups and are insoluble in gastric medium, but dissolve in intestinal fluids. Three possibilities of incorporating the enteric polymer in the coating layer were investigated: (1) Sequential coating: extended release polymer (Kollicoat® SR) + enteric polymer (Kollicoat® MAE), (2) Sequential coating: enteric polymer + extended release polymer, and (3) Coating with a blend of extended release and enteric polymers (Fig. 2).

First, pellets were coated with the extended release polymer (Kollicoat® SR) and subsequently with the enteric polymer (Kollicoat® MAE) (Fig. 2A). In 0.1 N HCl, both polymers were insoluble and therefore contributed to

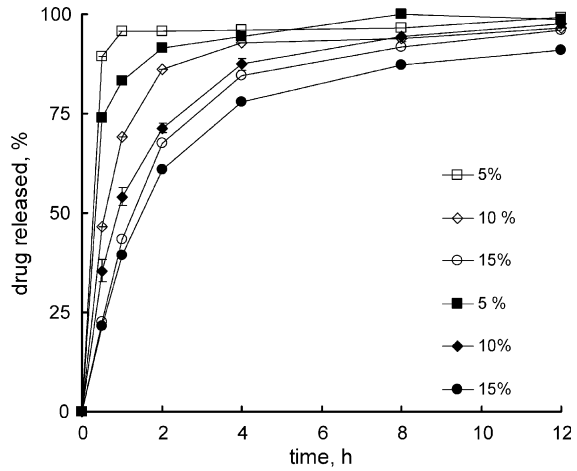

Fig. 1. Verapamil HCl release from pellets coated with Kollicoat® SR 30 D. Open symbols: 0.1 N HCl, closed symbols: phosphate buffer, pH 6.8.

diffusional hindrance; the drug release was controlled by both polymers. The drug release in 0.1 N HCl decreased with increasing amount of enteric polymer as top coating. In phosphate buffer, pH 6.8, the enteric polymer dissolved quickly and the drug release was controlled only by the Kollicoat® SR coating and was independent of the amount of enteric polymer applied on top (Fig. 3).

In the case of pellets coated with 10% Kollicoat® SR (Fig. 3A), a top coating of 5% Kollicoat® MAE resulted in a pH-independent release (Fig. 3A). Higher coating levels of the enteric polymer (10%) reversed the pH-dependent drug release, now the drug was released slower at low than at high pH because of the top enteric film layer.

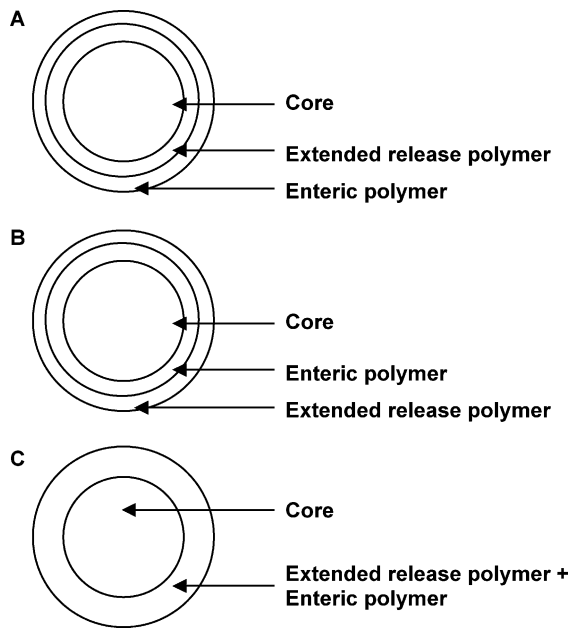

Fig. 2. Schematic presentation of different coating layers: (A) extended release polymer followed by enteric polymer, (B) enteric polymer followed by extended release polymer and (C) blend of extended release and enteric polymers.

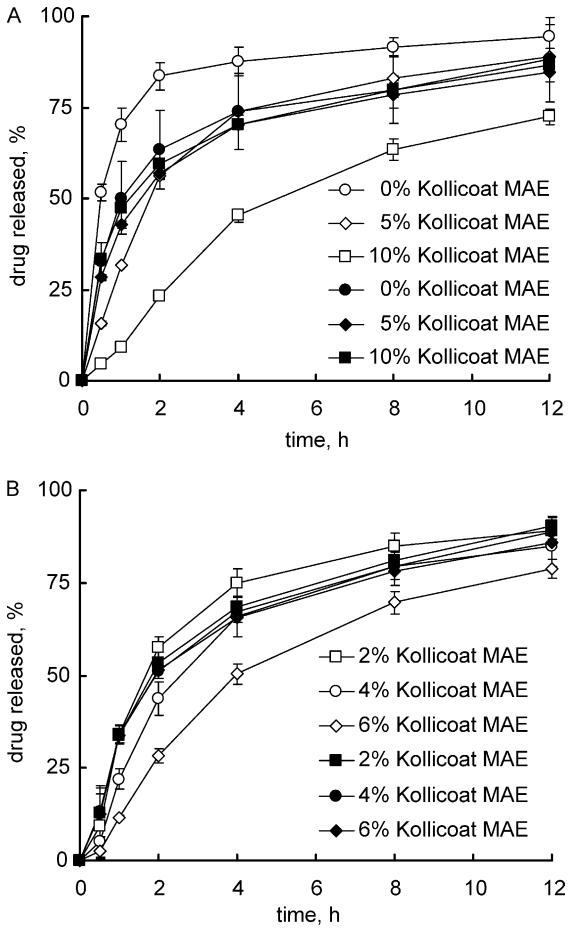

Fig. 3. Verapamil HCl release from pellets coated with (A) 10% Kollicoat® SR 30 D and 0, 5, or 10% Kollicoat® MAE 30 DP (top coating), (B) 15% Kollicoat® SR 30 D and 2, 4, or 6% Kollicoat® MAE 30 DP (top coating). Open symbols: 0.1 N HCl, closed symbols: phosphate buffer, pH 6.8.

Similar findings were obtained at a higher Kollicoat® SR coating level of 15% Kollicoat® SR (Fig. 3B). In this case, a pH-independent release was obtained with a 4% Kollicoat® MAE top coating. With this approach, relatively small changes in coating level of the enteric top coating led to remarkable pH-dependence in release.

In the second approach (Fig. 2B), the pellets were first coated with the enteric polymer (Kollicoat® MAE) followed by coating with the extended release polymer (Kollicoat® SR). The drug-loaded pellets were first coated with either 2.5 or 5% of the enteric polymer Kollicoat® MAE followed by coating with different levels of Kollicoat® SR (Fig. 4). Coating with 2.5% Kollicoat® MAE was not sufficient and the drug release in acidic medium was still faster than in pH 6.8 (Fig. 4A). The gastric residence time for pellets with the diameter of approx. 1 mm was reported to be up to 150 min [16]; pH independent release should therefore be achieved for at least the first 2–3 h. A pH-independent verapamil release was obtained with a first coating of 5% Kollicoat® MAE and a second coating with 5 or 10% Kollicoat® SR (Fig. 4B). Increasing the Kollicoat® SR coating level to 15% resulted in slightly lower release at low pH. In 0.1 N

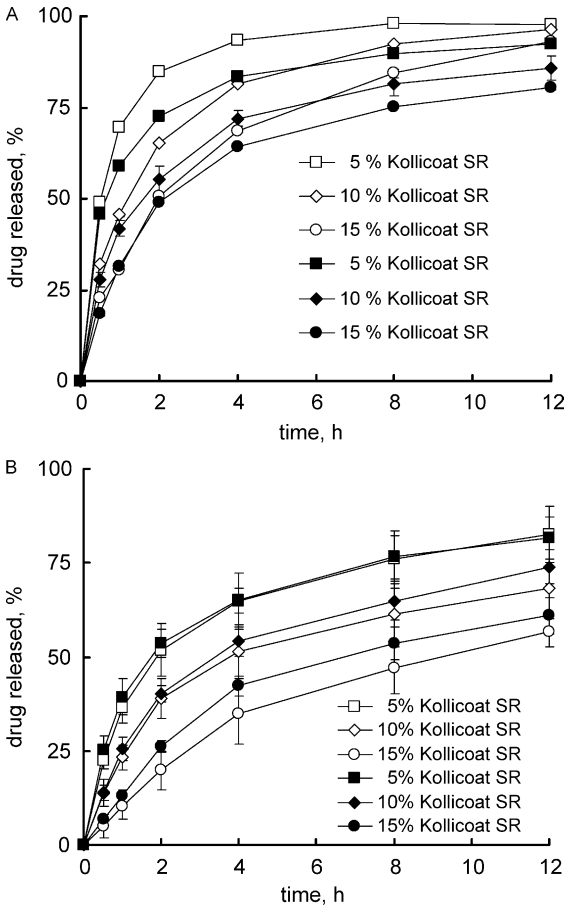

Fig. 4. Verapamil HCl release from pellets coated with (A) 2.5% and (B) 5% Kollicoat® MAE 30 DP (sub coating) and 5, 10, or 15% Kollicoat® SR 30 D (top coating). Open symbols: 0.1 N HCl, closed symbols: phosphate buffer, pH 6.8.

HCl, the drug had to diffuse through both the enteric and extended release coatings, while in phosphate buffer, pH 6.8, the enteric polymer dissolved, but probably did not diffuse through the outer coating. However, the permeability of this swollen or dissolved enteric layer is higher at pH 6.8, thus increasing the overall permeability of the two coating layers. In addition, the enteric polymer will also give an acidic microenvironmental pH, thus keeping the drug solubility and the concentration gradient higher.

In the last approach (Fig. 2C), the pellets were coated with a blend of the extended release polymer (Kollicoat® SR) and enteric polymer (Kollicoat® MAE) at ratios of 90/10, 80/20 and 70/30 (Fig. 5). Because of their incompatibility, the two polymer dispersions were sprayed in parallel through two nozzles. The two polymers were therefore present together in the same coating layer and not in separate layers, like in the previous compositions. As expected, the drug release decreased in both media with increasing coating level. In 0.1 N HCl, drug diffused through the polymeric barrier of both polymers. In phosphate buffer, pH 6.8, the enteric polymer dissolved, and either remained in the film in a hydrated state or leached out, thus increasing the permeability of the coating.

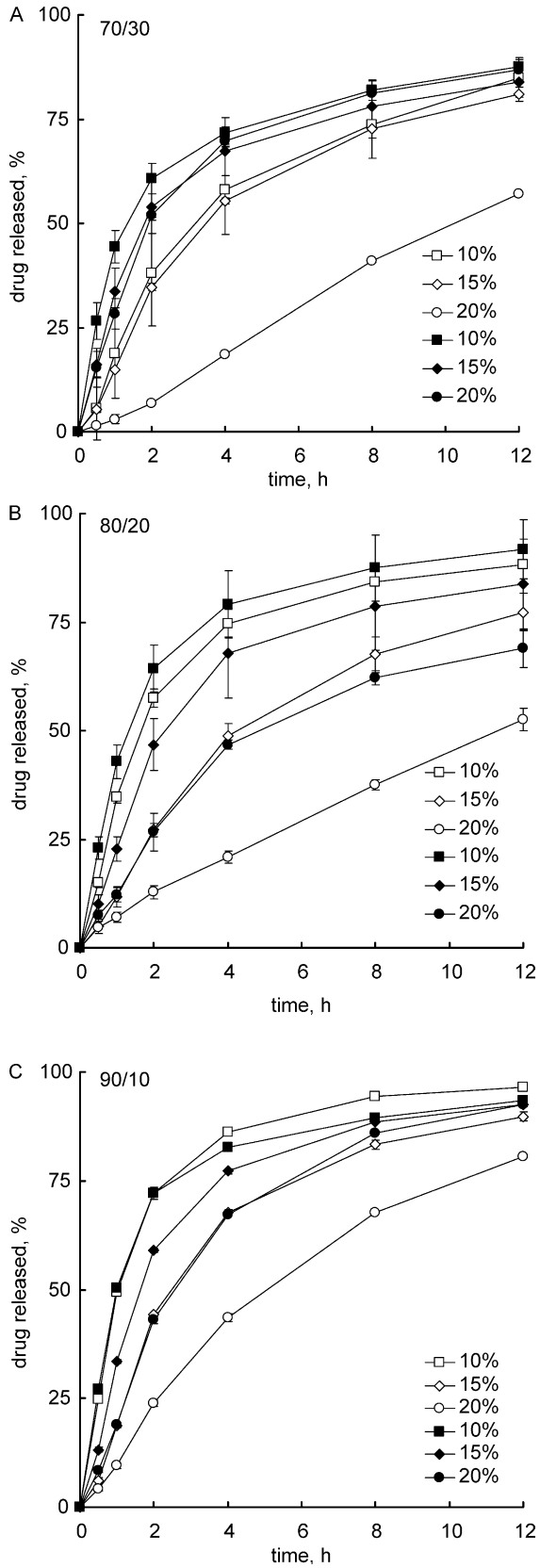

Fig. 5. Verapamil HCl release from pellets coated with Kollicoat® SR 30 D/Kollicoat® MAE 30 DP mixtures: (A) 70/30, (B) 80/20, (C) 90/10 (coating level 10, 15, 20%). Open symbols: 0.1 N HCl, closed symbols: phosphate buffer, pH 6.8.

The ratio of Kollicoat® SR to Kollicoat® MAE influenced the rank order of the release in 0.1 N HCl or pH 6.8. With increasing portion of the enteric polymer, the release in pH 6.8 buffer became faster than in 0.1 N HCl. The lower solubility of verapamil HCl in pH 6.8 was overcompensated at enteric polymer levels of 20 and 30% (Fig. 5A and B). At a ratio of Kollicoat® SR to Kollicoat® MAE of 90:10 and at coating levels of 15 and 20%, the release was slower in pH 6.8 buffer (Fig. 5C). The amount of enteric polymer was not sufficient to compensate the lower solubility of the drug. With all options, a pH-independent release was only achieved at a coating level of 10% at a polymer ratio of 90/10. Overall, this approach was the least suitable one, pH-independent release was not achieved at polymer ratios of 80/20 or 70/30.

Acknowledgements

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