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Development of extended release multiple unit effervescent floating drug delivery systems for drugs with different solubilities

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ABSTRACT

The purpose of this study was preparation and evaluation of extended release multiple unit floating drug delivery systems based on CO_2 formation with rapid and extended floating and good control over the release for drugs with different solubilities. The pellet systems were prepared by fluidized bed layering/coating techniques and evaluated by floating, drug release, medium uptake and swelling studies in 0.1 N HCl. Two different pellet systems were evaluated; the first consisted of drug-layered sugar cores, $NaHCO_3$-layer and a polymeric top-coating, which ideally controlled both floating and release properties. The second, modified system consisted of drug-containing Eudragit® RS 30 D coated extended release pellets coated with $NaHCO_3$-layer and Eudragit® RL 30 D top-coating. The Eudragit® RL coating resulted in sufficient medium penetration, a prerequisite for CO_2 formation, and in high CO_2 entrapment efficiency. Floating was maintained over a wide range of Eudragit® RL/RS combinations. Extended release from the first system could be achieved only for low solubility, high dose drugs because of high Eudragit® RL permeability. For high solubility drugs, separating floating and release "functions" was successful. Extended release pellets were used to achieve better drug release control, while floating was achieved by an Eudragit® RL top-coat.

1. Introduction

Gastroretentive dosage forms are interesting extended release delivery systems for drugs with a narrow window of absorption in the upper intestine, for drugs with pH-dependent solubility [12], for drugs degraded by higher pH intestinal fluids [2,24] or for drugs with local action in the proximal part of the GI tract, such as antibiotic administration for *Helicobacter pylori* in the treatment of peptic ulcer [16,26].

Several approaches to prolong gastric retention have been investigated: Magnetic systems [8], high density systems [18], mucoadhesive systems [4], swelling [6,19] and expanding systems [14] as well as floating systems [1,21].

Floating systems are either based on an inherently low density or on effervescence. Non-effervescent systems have their inherent low density due to the entrapment of air, as with low density hollow microspheres [2,13], incorporation of low density material (sponges) [21] or due to swelling [7,20]. In contrast, effervescent systems, have an initially high density, which decreases upon contact with the acidic environment due to CO_2 formation [11].

Besides frequently investigated single unit dosage forms, which have a high variability in GI transit time due to their all-or-nothing emptying process [22], multiple unit floating systems have been developed to overcome this problem due to their more uniform emptying from the stomach [5], as well as reducing the risk of dose dumping [10]. Multiple unit effervescent systems utilizing ion exchange resins beads [1], matrix minitablets [9], as well as extruded-spheronized pellets [23] have been previously developed.

In the present study, floating reservoir-type pellets based on CO_2 formation were developed for drugs with different solubilities, characterized in vitro and their stability under various conditions was evaluated.

2. Materials and methods

2.1. Materials

Non-pareils 710–850 μm (Suglets sugar spheres NF, NP Pharm S.A., Bazainville, France), propranolol HCl, theophylline anhydrous (BASF SE, Ludwigshafen, Germany) and micronized carbamazepine

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(Fabrica Italiana Sintetici, Alto de Monte Vecchio, Italy) as model drugs, sodium hydrogen carbonate ($NaHCO_3$) (Merck KGaA, Darmstadt, Germany) as effervescent agent, polyvinyl acetate aqueous dispersion (Kollicoat® SR 30 D; BASF AG, Ludwigshafen, Germany), methacrylic copolymers with varying ratios of trimethylammonioethyl methacrylate as functional group, Type A and B (Eudragit® RL 30 D and Eudragit® RS 30 D respectively; Evonik Industries AG, Darmstadt, Germany), triethyl citrate (TEC) (Morflex, Greensboro, NC, USA), talc (Luzenac Europe, Toulouse, France), hydroxypropyl methylcellulose (HPMC) (Methocel E5; Colorcon, Orpington, UK), polyethylene glycol 6000 (Lutrol E 6000, BASF AG, Ludwigshafen, Germany), and silicon dioxide (Aerosil 200; Evonik Industries AG, Darmstadt, Germany) were used as received. All other reagents were of analytical grade and were used without further purification.

2.2. Preparation of pellets

2.2.1. Preparation of the three-layer pellet system

Drug loaded pellets were prepared by layering drug suspensions in isopropyl alcohol: water (88: 12 w/w) for carbamazepine and theophylline and solution in ethanol: water (70: 30 w/w) for propranolol HCl using HPMC E5 as binder (10%, w/w, based on drug) onto sugar pellets in a fluidized bed coater GPCG1 (Glatt Process Technology GmbH, Binzen, Germany) to achieve a 10% (for all drugs) or 50% (for carbamazepine) drug content based on the initial pellet weight. The layering conditions were, batch size: 900 g, inlet temperature: 38–44 °C (carbamazepine), 32–36 °C (theophylline) and 42–46 °C (propranolol HCl); product temperature: 32–36 °C (carbamazepine), 30–32 °C (theophylline) and 38–42 °C (propranolol HCl); air flow: 80–90 m^3/h; nozzle diameter: 1.2 mm; spray pressure: 1.2 bar; spray rate: 9–12 g/min (carbamazepine), 8–10 g/min (theophylline and propranolol HCl); final drying at 40 °C for 15 min.

The drug-loaded pellets were coated with $NaHCO_3$, as the gas-generating agent, suspended in aqueous HPMC solution, which was plasticized with Lutrol E 6000 (10%, w/w, based on the solids content of HPMC). The ratio of $NaHCO_3$ to HPMC was 2:8 w/w, the solids content of the coating suspension was kept constant at 12% w/w and coating was performed in a fluidized bed coater, Glatt GPCG-1 to a weight gain of 15%. The layering conditions were: batch size: 900 g; inlet temperature: 44–48 °C; product temperature: 36–40 °C; air flow: 80–90 m^3/h; nozzle diameter 1.2 mm; spray pressure: 1.2 bar; spray rate: 6–6.5 g/min and final drying at 40 °C for 15 min.

As top-coat, Eudragit® RL 30 D, RS 30 D or Kollicoat® SR 30 D were coated from an aqueous polymer dispersion, plasticized with 20% TEC (w/w, based on the total dry polymer weight of Eudragit® RL 30 D and Eudragit® RS 30 D and their combination) or 10% TEC (w/w, based on the dry Kollicoat® SR 30 D weight). 35% Talc (w/w, based on polymer content) was used as antitacking agent. The polymer content was adjusted to 15% (w/w) with purified water and the coating was done in a fluidized bed coater Mini Glatt (Glatt GmbH, Binzen, Germany) to a weight gain of 10–20% (w/w). The coating conditions were: batch size: 100 g; inlet temperature: 32–34 °C (Eudragit® RL 30 D: RS 30 D) and 34–38 °C (Kollicoat® SR 30 D); product temperature: 28–30 °C; air flow: 0.2 bar; nozzle diameter 0.5 mm; spray pressure: 0.9 bar; spray rate: 1 g/min and final drying at 40 °C for 15 min. 1% Aerosil was added to the coated pellets, which were oven-cured at 60 °C directly after the coating step using dry heat, with no controlled humidity for 2 h (Table 1). The samples were put into a desiccator until further tested.

2.2.2. Preparation of the modified multiple unit drug delivery system

Propranolol HCl loaded pellets were prepared by layering drug-binder solution in ethanol: water (70: 30, w/w) using HPMC E5 as binder (10%, w/w, based on drug) onto drug free sugar pellets in a fluidized bed coater GPCG1 (Glatt Process Technology GmbH, Binzen, Germany) to achieve a 10% drug content based on the initial pellet weight. The layering conditions were, batch size: 900 g, inlet temperature: 42–46 °C; product temperature: 38–42 °C; air flow: 80–90 m^3/h; nozzle diameter: 1.2 mm; spray pressure: 1.2 bar; spray rate: 8–10 g/min; and final drying at 40 °C for 15 min (Table 2).

The propranolol HCl loaded pellets were further coated with an aqueous colloidal polymeric dispersion of Eudragit® RS 30 D in a fluidized bed coater Glatt GPCG-1 to a predetermined weight gain. The dispersion was plasticized with 20% TEC (w/w, based on the dry Eudragit® RS 30 D weight). 35% Talc (w/w based on the dry polymer weight) was used as antitacking agent. The polymer content was adjusted to 15% (w/w) with purified water. The coating conditions were batch size: 900 g, inlet temperature: 38–42 °C, product temperature: 30–34 °C, air flow: 70–80 m^3/h, nozzle diameter 1.2 mm, spray pressure: 1.2 bar, spray rate: 8–10 g/min and final drying at 40 °C for 15 min. Samples of the coated pellets were oven-cured directly at 60 °C after the coating step using dry heat, with no controlled humidity for 2 h, after adding 1% Aerosil and put into a desiccator until further tested.

The extended release uncured pellets were further coated with $NaHCO_3$ (15 or 20%, w/w, based on the initial pellet weight) and finally with Eudragit® RL 30 D (to a predetermined weight gain) as top-coat, using the same procedure as previously mentioned. 1% Aerosil was added to the coated pellets, which were oven-cured at 60 °C for 2 h directly after the coating step (Table 2). The samples were put into a desiccator until further tested.

2.3. Floating properties

The floating abilities of the pellets was determined in 50 ml prewarmed 0.1 N HCl or deionized water at 70 rpm, 37 ± 0.2 °C for 18 h, using a shaker apparatus (GFL shaking incubator 3033; GFL GmbH, Burgwedel, Germany) (n = 2). One hundred pellets ($n_{initial}$) were placed in the medium; the number of floating pellets (n_t) over the tested time range was measured by visual observation. The percentage of floating pellets was calculated as follows:

$$\text{Floating pellets}(\%) = \frac{n_t}{n_{initial}} * 100$$

Alternatively, the floating lag time (time at which all pellets started floating) and the% floating pellets at 18 h was determined.

2.4. Drug release

The drug release was investigated in a USP paddle apparatus (VK 700, Vankel Industries, Edison, NJ, USA), 900 ml of 0.1 N HCl, deionized water, deionized water + 0.01 N $NaHCO_3$ or + 0.1 N $NaHCO_3$ (100 rpm, 37 °C, $n = 3$). The weight of pellets used was equivalent to about 50 mg of propranolol HCl, and 20 mg for theophylline and carbamazepine. At predetermined time intervals, 3 ml samples were withdrawn and analyzed with UV spectrophotometry (UV-2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA), propranolol HCl, λ = 290 nm; theophylline, λ = 270 nm and carbamazepine, λ = 283 nm.

2.5. Medium uptake and mass loss of pellets

One hundred pellets were weighed ($weight_{initial}$), put into 50 ml prewarmed 0.1 N HCl, and shaken at 37 ± 0.2 °C, 70 rpm for 18 h, using a shaker apparatus (GFL shaking incubator 3033; GFL GmbH,