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Propranolol forms affect properties of Carbopol-containing extruded-spheronized beads

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ABSTRACT

Drug release rates from extruded-spheronized beads containing Carbopol have been shown to be dependent on the chemical nature of different types of drugs. To further clarify solubility, salt counterion, pH, and ionic strength effects on Carbopol bead characteristics, including but not limited to the drug release profile, the present study utilizes propranolol in its free base, hydrochloride, and maleate forms. Different forms of propranolol resulted in different bead average diameter, roundness, and smoothness, but the ruggedness was not affected. Release profiles for the two salt forms were nearly superimposable, but the free base form was released more slowly. Mathematical analysis of the release data revealed that Fickian diffusion and polymer relaxation were contributing factors to the release mechanism in each case, although polymer relaxation was more influential with the free base form. In light of these results, the choice of the form of a drug should be considered carefully when preparing Carbopol-containing beads produced by extrusion-spheronization.

1. Introduction

Extrusion-spheronization is a pelletization technique that includes dry mixing, wet massing, extrusion, spheronization, and drying steps (Erkoboni, 2003). This is a process that offers immediate and controlled release profile alternatives for pharmaceutical products (Liu et al., 2003). Carbopol is one of the polymers recently studied in extrusion-spheronization (Neau et al., 2000; Gomez-Carracedo et al., 2001; Bommareddy et al., 2006). It is an ionizable, pH-sensitive, water-swellable polymer that is used in the pharmaceutical and cosmetic industry (Nobles, 1955). Composed of cross-linked poly(acrylic acid), Carbopol® 974P is a pharmaceutical grade approved for oral products, since the acrylic acid was polymerized in ethyl acetate instead of benzene (Carbopol Resins Handbook, 1993). It possesses very high thickening efficiency, with only a slight viscosity change over the 10–70 °C range, and a resistance to bacterial and fungal degradation (Nobles, 1955; Carbopol Resins Handbook, 1993) and chemical hydrolysis (Dittmar, 1957). These characteristics make Carbopol® 974P an excellent candidate for use in pharmaceutical products.

The effect of microenvironmental pH within a solid dosage form exposed to release medium has been studied extensively since it can affect drug solubility (Thoma and Zimmer, 1990; Brandl et al., 1995; Nykanen et al., 1999; Krogars et al., 2000; Badawy and Hussain, 2007) and the subsequent release rate. Microenvironmental pH gains importance especially when a formulation contains a pH-sensitive polymer (Krogars et al., 2000; Tatavarti et al., 2004) and/or a drug with a pH-dependent solubility (Thoma and Zimmer, 1990; Nykanen et al., 1999; Tatavarti et al., 2004; Guthmann et al., 2007).

In a recent study, the release of different actives from Carbopol-containing beads was compared (Bommareddy et al., 2006). Caffeine was released faster than chlorpheniramine maleate from these beads, although chlorpheniramine maleate is more soluble (160 mg/ml) than is caffeine (20 mg/ml). This was initially surprising because faster release from a matrix system is expected with a drug possessing a higher solubility when all other characteristics are comparable. The nonelectrolytes in the study, caffeine and dyphylline, were released at approximately the same rate, even before the swelling and gelling of Carbopol was visually observed, although the solubility of dyphylline (333 mg/ml) is substantially higher than that of caffeine. The slower release seen with chlorpheniramine maleate was presumed to be due to the interaction of its protonated amine with the carboxylate groups of Carbopol after the polymer had hydrated and gelled. Although released at a rate closer to that of chlorpheniramine than to that of the nonelectrolytes, diphenhydramine hydrochloride was released faster than chlorpheniramine. In the cases of diphenhydramine and

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chlorpheniramine, a protonated amine-bearing drug of comparable molecular weight and chemical structure is the diffusing species, but they differ in aqueous solubility and salt form counterion. The higher aqueous solubility of diphenhydramine hydrochloride (1000 mg/ml) would provide a faster release rate due to a faster dissolution rate, even if the diffusion rates of these two protonated basic drugs were comparable.

The microenvironmental pH should also be causing a difference in the release rate of these two amine salts. If the buffer capacity of the release medium is insufficient, an ionizable drug or the counterion of a drug salt might establish a new pH within the microenvironment of the hydrated bead that, in turn, affects the performance of the polymer. The effect of the counterion on microenvironmental pH was suggested by the lower pH for diphenhydramine hydrochloride in comparison to that for chlorpheniramine maleate at saturation, 5.73 and 5.81, respectively (Bommareddy et al., 2006). The lower pH results in fewer carboxylate groups on Carbopol (average pK_a 6.2, Riley et al., 2001) for interaction with the protonated amine-bearing drug and also the collapse, at least in part, of the gel that helps sustain drug release. The results of this study therefore led to several questions regarding the effects of microenvironmental pH, ionic strength effects and counterion effects on drug release from Carbopol-containing beads.

The objective of this study is to investigate the effect of the form of the drug when the diffusing species is identical. This can be achieved by preparing batches of beads using different forms of the same drug and then comparing the characteristics and performance of the different products. Salts of the same drug with different effects on the microenvironmental pH, with different effects on the ionic environment within the polymer gel region at the surface of the beads, and with different solubility in water were selected. Different forms of the weakly basic drug, propranolol, will be tested in this study, viz. the free base, the hydrochloride, and the maleate forms. Since the release medium pH of 6.8 is more than two pH units below the pK_a of propranolol of 9.45 (Beringer et al., 2005), the diffusing species in each case would be the protonated form of propranolol and thereby the identical diffusing species would have the same size and shape in each case. Differences in the bead characteristics would therefore be the result of the effect of the different forms of propranolol on the chemical and physical microenvironment within the wetted mass, extrudate, or wet bead as the bead is being formed; in the finished dried bead; or at the surface of the bead or within the bead as the drug is being released.

2. Materials and methods

2.1. Materials

Propranolol HCl, a gift from Novopharm Ltd. (Scarborough, Ontario, Canada), was used as a model drug. Tetrahydrofuran (THF) (Sigma–Aldrich, St. Louis, MO), anhydrous methyl-*t*-butyl ether (Fisher Scientific, Pittsburgh, PA), and maleic acid (Fisher Scientific), each with at least 99% reported purity, were used in the synthesis of propranolol maleate. Generous gifts of Carbopol® 974P resin from Lubrizol Inc. (Cleveland, OH) and of Avicel PH 101 from FMC Corporation (Philadelphia, PA) were used in the bead formulations. Calcium chloride dihydrate (Fisher Scientific) was used to reduce the tack that occurred during the wetted mass processing. Distilled, de-ionized water was generated by a Milli-Q Plus Ultra water system (Millipore Corporation, Bedford, MA).

2.2. Propranolol free base and propranolol maleate synthesis

Propranolol HCl was dissolved in water and the pH of the solution was gradually increased to approximately 11.5 by the slow addition of concentrated sodium hydroxide solution while the solution was vigorously stirred. Propranolol precipitated in its free base form as the pH of the solution was increased. The precipitate was filtered with a glass fiber filter and washed with distilled de-ionized water at least three times to eliminate residues that might remain in the precipitate. The precipitate was oven dried at 40 °C for at least 48 h. Purity analysis of the precipitate was performed in triplicate by differential scanning calorimetry (DSC), using a DSC 2910 (TA Instruments, New Castle, DE). UV analysis was performed using a Hewlett Packard 8451A diode array spectrophotometer at a wavelength of 288 nm to backcalculate and verify the purity of the propranolol.

Propranolol maleate synthesis was accomplished by a method described by Brown (1998). Equal moles of propranolol free base and maleic acid were weighed and dissolved in THF. The slurry was gently heated until the chemicals were completely dissolved. Methyl-*t*-butyl ether was gradually added to the solution while the solution was stirred vigorously. Acting as a nonsolvent, the methyl-*t*-butyl ether causes the precipitation of the maleate salt. The precipitate was filtered and washed with THF at least three times to eliminate residues. The precipitate was oven dried at 40 °C for at least 48 h. To find the purity of the propranolol maleate, DSC studies and UV analysis were performed as described above for the free base form.

2.3. Solubility studies for propranolol free base and maleate forms

Solubility studies were performed in triplicate at room temperature. Excess amounts of propranolol free base or maleate were stirred vigorously in water for 24 h. Using a Shimadzu UV-1601 UV–visible spectrophotometer (Columbia, MD) at 288 nm, the propranolol concentrations in the solutions were measured at 12 and 24 h to ensure that the concentration was consistent, indicating an equilibrium had been reached.

2.4. Force of detachment test

Powder blends that contained each of the different forms of propranolol were prepared. Each 25 g blend, composed of 5% propranolol form, 20% Carbopol® 974P, and 75% Avicel PH 101, was mixed for 5 min and wetted with 90 ml of water using a syringe to produce a consistency where the tack could be measured. The wetted masses were mixed manually for 5 min so that a uniform mixture was achieved. Force of detachment tests were conducted using a Chatillon LTC force gauge (Amtek, Largo, FL) and two 3 in. diameter GF8 peel strength grips. The wetted mass was applied to each of the grips and the grips were brought together to allow only a 1 mm gap. After removing any excess of the wetted mass from the periphery of the grips, the grips were slowly pulled apart and the force of detachment was measured at the time the grips were separated. Six replicates were conducted for each form of propranolol.

2.5. Production of beads

The bead formulation consisted of 5% propranolol form, 20% Carbopol® 974P, and 75% Avicel PH 101. The powder ingredients were mixed in a Model N-50 planetary mixer (Hobart Corporation, Troy, OH) for 10 min. The powder batch size was 600 g. Every 5 min, the mixer was stopped to scrape the walls of the bowl and to mix manually any material found below the blade at the bottom of the bowl. A 5.78 g mass of calcium chloride dihydrate was dissolved in 568 ml of water and the entire mixture was consistently used as the wetting fluid for each of the batches of the different drug forms. It was important to include calcium in the wetting fluid