International Journal of Pharmaceutics 361 (2008) 169–176

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

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

Safak Paker-Leggs, Steven H. Neau*

Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, 600 South 43rd Street, Philadelphia, PA 19104, United States

ARTICLE INFO

Article history:
Received 31 December 2007
Received in revised form 29 April 2008
Accepted 29 May 2008
Available online 12 June 2008

Keywords:
Beads
Carbopol
Drug release profiles
Extrusion
Pellets
Spheronization

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

* Corresponding author. Tel.: +1 215 596 8825; fax: +1 215 895 1161.
E-mail address: s.neau@usp.edu (S.H. Neau).

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doi:10.1016/j.ijpharm.2008.05.041

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

in order to reduce the tack generated by the carboxylate groups of Carbopol® 974P in the wetted mass (Chow, 1990; Neau et al., 2000; Bommareddy et al., 2006). After calcium chloride dihydrate was dissolved in distilled, de-ionized water, the solution was slowly introduced to the powder blend by a syringe while the blend was still being mixed. The wetted mass was immediately fed into a radial twin-screw extruder (Fuji Denki Kogyo Co., Osaka, Japan) with a 1.5 mm screen at a speed of 50 rpm. The extrudates were immediately transferred into a Q400 spheronizer (Fuji Denki Kogyo Co.) that had a cross-hatched plate, operated at a speed of 880 rpm for 10 min. The beads were air dried for 2 h, and then oven dried at 40 °C at least overnight.

2.6. Bead characterization

The moisture content in the dried beads was measured in triplicate using a Brainweigh Electronic Balance, MB301 (Ohaus, Pine Brook, NJ). Approximately 5 g of beads were accurately weighed and then exposed to 102 °C for 15 min. The mass of the sample was recorded at 5, 10, and 15 min to confirm that a consistent mass had been reached by at least 10 min. The moisture content of the samples was calculated by dividing the difference between the initial and final mass of the samples by the initial mass, and multiplying the result by 100 to express it as a percentage.

Sieve analysis of the beads was conducted using the entire batch and U.S. Standard Sieves Nos. 10–35. Yield equaled the fractional mass of beads in the 14/20 meshcut, expressed as a percentage. Average bead diameter, d_{avg}, was calculated based on the sieve analysis results:

$$d_{avg} = \sum \frac{(\text{MO} \times \%\text{Retained})}{100\%} \quad (1)$$

where MO is the mean sieve opening for each sequential pair of sieves in the nest of sieves. %Retained is the mass of beads retained on the sieve with the smaller aperture of the pair, which was expressed as a percentage of the total mass of beads in the sieve analysis. Only beads in the 14/20 meshcut, that includes beads of 840–1410 μm diameter, underwent further study. This range was isolated to minimize bead diameter effects on the characteristics studied subsequently, since the purpose of the study is to examine the effects of the drug form. This size range should also effectively result in uniform capsule fill.

Approximately 1 g of each bead sample and twenty-five 3 mm glass beads were placed in a model 1805 Erweka Friability Tester. Friability tests consisted of 100 rotations at 25 rpm. After the test, each sample was collected and sieved using a No. 20 sieve, and the sample remaining on the sieve was weighed. The difference between the initial and final mass was divided by the initial mass, and the result was multiplied by 100 to express friability as a percentage. Friability analysis for each batch was performed in triplicate.

The roundness of the bead samples was determined using a Retsch Technology Camsizer® (Jenoptik, Haan, Germany) that employs optical imaging with two adaptive full-frame matrix cameras. Approximately 20 g of the yield for each batch were analyzed in triplicate. The roundness of the beads was calculated using the following equation:

$$\text{Roundness} = \frac{4\pi A}{P^2} \quad (2)$$

where A is the area occupied by a single bead image, and P is its perimeter. The two-dimensional image of a sphere has a roundness score of 1. Other shapes have a roundness score less than 1.

The release studies were performed in triplicate in a Model 200 USP dissolution apparatus II (Distek Inc., Somerset, NJ) with a paddle speed of 50 rpm. The release medium was 900 ml of 0.05 M phosphate buffer at pH 6.8, maintained at 37 °C. An 800 mg sample of the 14/20 meshcut was used consistently in each of the release studies. At predetermined time points, 5 ml samples were withdrawn and immediately replaced with 5 ml of phosphate buffer. The absorbance of the samples was measured at 288 nm using a Hewlett Packard (Palo Alto, CA) 8451A UV/visible diode array spectrophotometer.

Content analysis was performed in triplicate to measure the propranolol in each type of bead. Accurately weighed bead samples of approximately 800 mg were crushed and stirred in 1000 ml of 0.05 M, pH 6.8, phosphate buffer for at least 24 h. The slurries were filtered and the absorbance measured at a wavelength of 288 nm using the UV/visible spectrophotometer. The percent released data was prorated for the total propranolol found per gram of each type of bead.

The internal and external morphology of the beads was investigated using a scanning electron microscope (SEM), Model S-530 (Hitachi, Tokyo, Japan), at 10 kV. Beads were mounted on aluminum studs as a whole bead, or after being sliced in half, and then sputter-coated with gold for approximately 1 min. The images of the beads were viewed at 50× magnification.

2.7. Data analysis

Each reproduced study had at least three replicates, and the results were analyzed using Sigma Stat software, version 3.1. Data sets were considered significantly different from each other when p was less than 0.05 in the statistical analysis.

In order to evaluate the similarity of the release profiles of the different batches, f_2, the similarity factor described by Moore and Flanner (1996) and Shah et al. (1998), was calculated for propranolol HCl and free base batches. Each of the triplicate batches for each form was treated as the reference batch. The equation used was:

$$f_2 = 50 \log \left\{ 100 \left[1 + \left(\frac{1}{n} \right) \Sigma (R_t - T_t)^2 \right]^{-0.5} \right\} \quad (3)$$

where R_t is the reference assay at time point t, T_t is the test assay at the same time point, and n is the number of sample points. It was suggested that, if the differences of the test assays at the same time points are less than 10%, where the f_2 values would not be less than 50, then it would be appropriate to call the two dissolution profiles "similar". Data points were limited to 85% released, since use of later data points can cause bias in the evaluation of the similarity of the batches by increasing the f_2 value (Shah et al., 1998).

2.8. Mathematical modeling of release profiles

Based on the shape of the release profile, the visual observation of gel formation on the surface of the beads, and the lack of particulate matter in the release vessel that would indicate erosion of beads during drug release, only diffusion of dissolved drug and polymer relaxation were the expected release mechanisms. This led to consideration of four release models to find the best fit to the data that can subsequently identify or confirm the release mechanisms.

2.8.1. Model 1

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} \quad (4)$$

In this equation, M_t/M_∞ is the fraction of the drug released, k_1 is a constant, and t is the release time (Higuchi, 1963). In this model, it was assumed that the only release mechanism is diffusion of the dissolved drug through a reasonably intact matrix. The data analysis was limited to 80% released data (Bommareddy et al., 2006).

Table 1
Physical characteristics of the batches of beads containing each type of propranolol

Drug	Yield (%)	Average diameter (mm)	Friability (%)	Roundness scores
Propranolol HCl	76.2 ± 3.7	1.10 ± <0.01	1.01 ± 0.26	0.95 ± <0.01
Propranolol free base	60.5 ± 1.4	0.90 ± <0.01	0.99 ± 0.18	0.97 ± <0.01
Propranolol maleate	77.8 ± 1.2	1.18 ± 0.01	1.00 ± 0.10	0.92 ± <0.01

2.8.2. Model 2

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \quad (5)$$

Fickian diffusion, which is represented by the first term on the right hand side of the equation, and polymer relaxation, represented by the second term, are acknowledged as contributions to the release mechanism (Harland et al., 1988). Only up to 90% released data was used in the data analysis (Bommareddy et al., 2006).

2.8.3. Model 3

$$\frac{M_t}{M_\infty} = k_1 t^m \quad (6)$$

The only difference between this model and Model 1 is that the exponent m is not fixed at 0.5 and is used as an indicator of the release mechanism (Ritger and Peppas, 1987). It was suggested that when m equaled 0.5, the likely release mechanism was Fickian diffusion. When m was between 0.5 and 1, the release mechanism was nonFickian diffusion or a combination of Fickian diffusion and at least one other release mechanism. Only up to 90% released data was used for the data analysis.

2.8.4. Model 4

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (7)$$

In this model, it was suggested that the value of the exponent for polymer relaxation was two times the value of the exponent for Fickian diffusion, regardless of the shape of the device (Peppas and Sahlin, 1989). By not restricting the value of m to 0.5, this model allows that exponent to more accurately reflect the influence of the aspect ratio on this parameter (Ritger and Peppas, 1987). Only up to 90% released data was used for the data analysis.

Using the number of data points considered in the model fitting (n), the sum of the squared residuals corresponding to the fit of the model to the data set (SSR), and the number of estimable parameters for that model (p), an examination of the model fitting was conducted. Using those three parameters, the Akaike Information Criterion (AIC) was calculated in order to find the model with the fewest estimable parameters that still fit the data well (Yamaoka et al., 1978):

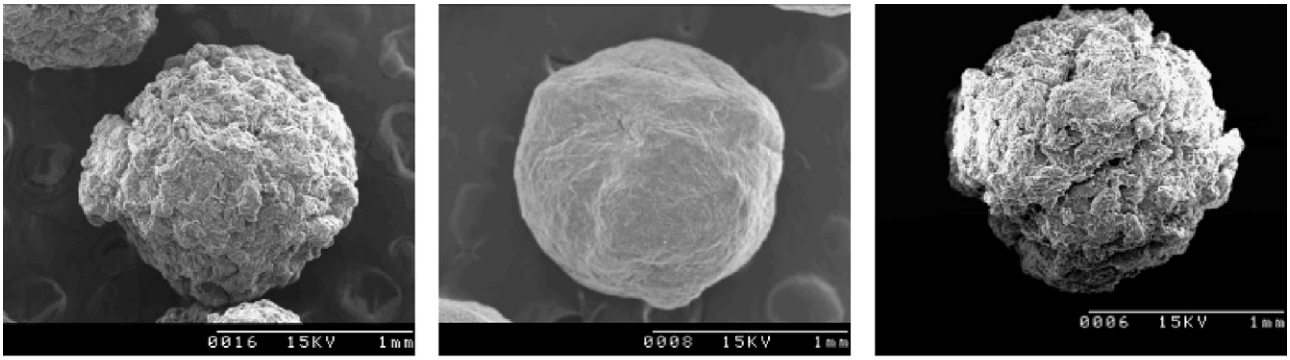
$$\mathrm{AIC} = n[\ln(\mathrm{SSR})] + 2p \quad (8)$$

3. Results

DSC studies revealed that the purity of propranolol HCl, free base, and maleate was 98.0 ± 0.1%, 99.7 ± 0.3%, and 97.9 ± 0.2%, respectively. The melting point for propranolol free base was 91.9 ± 0.2 °C, which confirms its identity since a reported melting point for propranolol free base with a purity of 99.2% was 92.9 °C (Neau et al., 1993). The room temperature solubility for propranolol free base and maleate was 0.12 and 7.03 mg/ml, respectively.

Force of detachment studies revealed that the tack generated by at least one of the wetted masses was different from the others ($p < 0.001$, Kruskal–Wallis one-way analysis of variance on ranks (De Muth, 1999). Using the Student–Newman–Keuls method as a post-test revealed that each result was statistically different ($p < 0.05$) from the other two. The highest tack was generated by the wetted mass that included propranolol free base, 17.90 ± 0.93 N. On the other hand, the least tacky wetted mass was the one with propranolol maleate, 2.68 ± 0.23 N. The wetted mass with propranolol HCl gave an intermediate tack level, 6.58 ± 0.25 N.

Moisture content was less than 1% for each of the batches of dried beads. The average diameter of the batches of beads (see Table 1) differed from each other ($p < 0.001$, one-way ANOVA). The propranolol free base batches revealed the smallest average diameter, whereas propranolol maleate batches had the highest average diameter. The shift of the propranolol free base beads to smaller diameters resulted in a lower yield than found with the other forms (one-way ANOVA, $p < 0.001$, followed by Student–Newman–Keuls method, $p < 0.001$). However, there was no statistically significant difference between the yield values for propranolol HCl and maleate beads (Student–Newman–Keuls method, $p = 0.431$). Each batch of beads had a very low friability value (see Table 1) that did not reveal any statistically significant difference from the other two (one-way ANOVA, $p = 0.990$). The batches that included propranolol free base provided the highest roundness scores,



(a) Propranolol HCl bead (b) Propranolol free base bead (c) Propranolol maleate bead

Fig. 1. Scanning electron micrographs of representative beads from batches containing each type of propranolol: (a) propranolol hydrochloride; (b) propranolol free base; and (c) propranolol maleate.

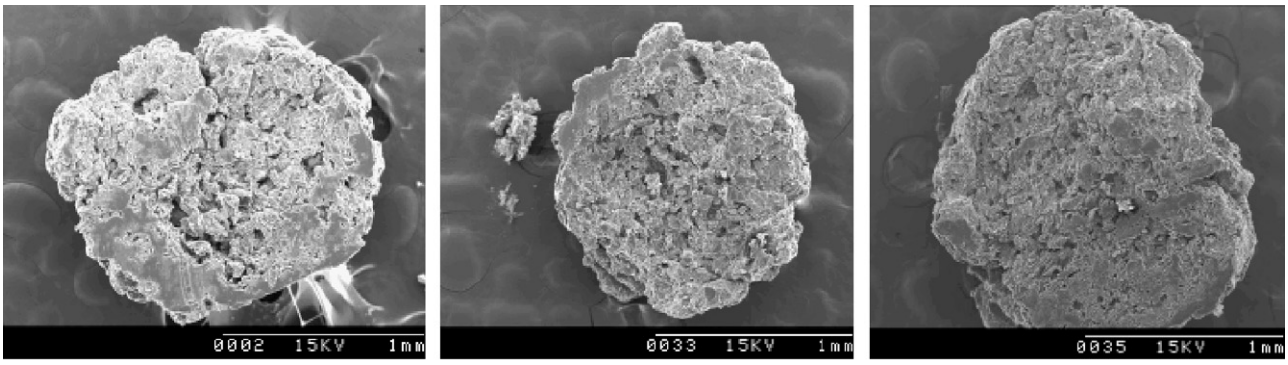


Fig. 2. Scanning electron micrographs of the interior of split representative beads from batches containing each type of propranolol: (a) propranolol hydrochloride; (b) propranolol free base; and (c) propranolol maleate.

whereas propranolol maleate batches provided the least spherical beads, resulting in statistically different roundness scores for the three types of beads (one-way ANOVA, $p < 0.001$, followed by Student–Newman–Keuls method, $p < 0.001$).

SEM analysis revealed that the beads with propranolol free base had the smoothest surface (Fig. 1b). On the other hand, the beads with the maleate salt had the roughest surface (Fig. 1c). Interestingly, the consistency of the interior matrix was similar for beads containing each of the three forms (Fig. 2).

The f_2 values for propranolol HCl and free base batches were at least 81.7 and 78.2, respectively, indicating the reproducibility of release profiles for beads with the same form of propranolol. The drug release rate from the beads that included propranolol free base revealed a slower release than the beads with either HCl or maleate salts (Fig. 3). Mathematical modeling for the first three models is presented in Table 2. When using Model 4, k_1 approximated zero and the model collapsed to Model 3. The similarity of the k_2 and 2 m values associated with Model 4 to k_1 and m of Model 3, respectively, confirmed that Model 4 had collapsed to Model 3.

4. Discussion

4.1. Microenvironmental conditions

Initially, as the release medium enters the surfaces of the beads, they become hydrated. The release medium continues to move into the individual beads (see the moving front in Fig. 4) and dissolution of the drug and other soluble components takes place at a rate appropriate for the environmental conditions that control the dissolution rate for that component, such as its solubility and the pH of the medium at the moving front. As time progresses, the hydrated Avicel and Carbopol begin to swell and the Carbopol gels if the pH in the hydration and dissolution layer (see Fig. 4) is high enough that carboxylic acid groups have been deprotonated and the negative charges of the carboxylates thus formed cause repulsive forces that move stretches of the Carbopol molecules apart (Carbopol Resins Handbook, 1993). This is a gel that holds much water (Carbopol Resins Handbook, 1993; Colombo et al., 2000; Islam et al., 2004) and, in the gel layer (see Fig. 4), that water is expected to be the release medium solution. Because of the high release medium content in this gel layer and the diluted components of the original bead, the release medium should manage to control the pH in the gel layer. This means that the Carbopol gel in the gel layer will be similar for beads involving the different forms of propranolol. This is a reasonably stable gel that does not readily erode due in large part to the crosslinked nature of Carbopol® 974P (Peppas et al., 2000).

The pH and ionic strength at the moving front in the present study are likely to depend on the dissolution rate of the soluble components and the hydration and deprotonation rates of the Carbopol at that site. Once the drug is dissolved in the hydration and dissolution layer, however, the diffusing species will in each case be the protonated form of propranolol. The diffusion rate of the dissolved components, however, will depend on their interactions with the gelled Carbopol, as discussed below. Therefore, possible effects of the different forms of propranolol at the moving front, in the hydration and dissolution layer, and in the gel layer will be discussed below.

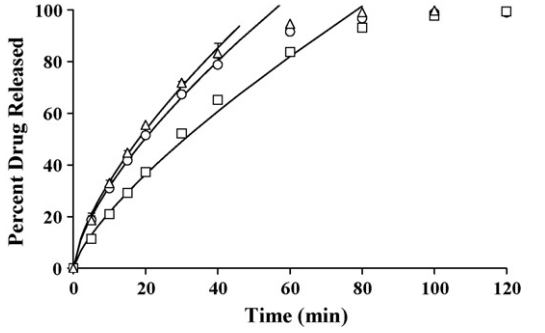


Fig. 3. Release profiles for batches of beads for each type of propranolol. The profile with circles presents the results for propranolol hydrochloride, with squares the results for propranolol free base, and with triangles the results for propranolol maleate. Error bars present the standard deviations associated with the triplicate results. The curves are predicted values based on Model 3 parameters.

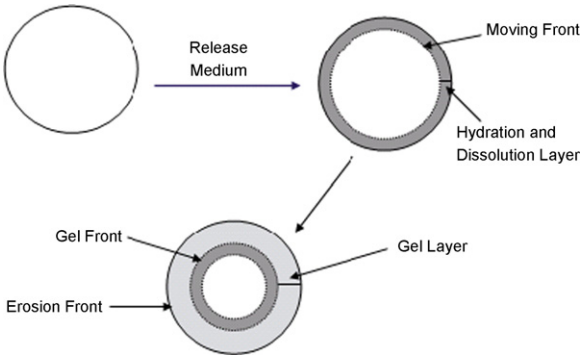


Fig. 4. A diagram showing the generation of the different fronts and regions of the hydrating, swelling, gelling, and drug releasing bead.

Table 2
Parameter values from model fitting to the release data for batches of beads containing each type of propranolol and the assessment of the fit

Propranolol form	$k_1 \pm$ standard error	$k_2 \pm$ standard error	$m \pm$ standard error	r^2	SSR	AIC
		Model 1				
HCl	0.113 ± 0.006	–	–	0.928	0.0101	−21.0
HCl	0.117 ± 0.007	–	–	0.913	0.0140	−19.3
HCl	0.113 ± 0.006	–	–	0.915	0.0128	−19.8
Free base	0.089 ± 0.006	–	–	0.875	0.0248	−20.2
Free base	0.092 ± 0.006	–	–	0.897	0.0202	−21.4
Free base	0.087 ± 0.006	–	–	0.885	0.0207	−21.3
Maleate	0.120 ± 0.007	–	–	0.918	0.0137	−19.4
		Model 2				
HCl	0.0733 ± 0.007	0.00854 ± 0.001	–	0.995	0.0013	−35.9
HCl	0.0722 ± 0.009	0.00962 ± 0.002	–	0.992	0.0023	−32.5
HCl	0.0693 ± 0.008	0.00959 ± 0.002	–	0.994	0.0017	−34.3
Free base	0.0424 ± 0.007	0.00891 ± 0.001	–	0.993	0.0027	−37.4
Free base	0.0521 ± 0.007	0.00759 ± 0.001	–	0.992	0.0031	−36.5
Free base	0.0444 ± 0.006	0.00804 ± 0.001	–	0.993	0.0025	−38.0
Maleate	0.0779 ± 0.011	0.00910 ± 0.002	–	0.990	0.0029	−31.1
		Model 3				
HCl	0.0673 ± 0.005	–	0.672 ± 0.021	0.997	0.00067	−39.9
HCl	0.0664 ± 0.006	–	0.687 ± 0.028	0.995	0.00135	−35.6
HCl	0.0639 ± 0.005	–	0.691 ± 0.024	0.997	0.00092	−37.9
Free base	0.0382 ± 0.004	–	0.760 ± 0.025	0.996	0.00147	−41.7
Free base	0.0454 ± 0.004	–	0.716 ± 0.026	0.996	0.00166	−40.8
Free base	0.0393 ± 0.004	–	0.742 ± 0.024	0.996	0.00131	−42.5
Maleate	0.0713 ± 0.007	–	0.673 ± 0.031	0.994	0.00178	−34.0

4.2. At the moving front and in the hydration and dissolution layer

It is interesting that propranolol HCl and propranolol maleate demonstrated comparable release profiles (see Fig. 3). It is apparent that this is due to compensating contributions of solubility, pH, and ionic effects in the microenvironments. Because of the soluble calcium chloride in the formulation, the common ion effect of the chloride ions should reduce the solubility and dissolution rate of propranolol HCl. This common ion effect should not be evident with either of the other two drug forms. Propranolol HCl with its higher solubility in water (50 mg/ml, Beringer et al., 2005) should dissolve faster at the hydration and diffusion layer than propranolol maleate with its lower solubility in water. However, the common ion effect would diminish this effect of the higher solubility of propranolol HCl, possibly to the extent of making the effect of the solubility difference negligible.

When propranolol HCl or maleate is dissolved, the protonated propranolol molecules would retain their acidic protons, since propranolol has a higher pK_a than the average pK_a of Carbopol (6.2, Riley et al., 2001) or the second pK_a of phosphate (7.2) at room temperature. This would result in neither encouragement nor discouragement of the gel formation of Carbopol because there is a lack of a pH effect on the part of the dissolving propranolol. On the other hand, when propranolol maleate is dissolved, many of the maleate molecules would be further deprotonated, because its second pK_a of 6.23 (Harmon et al., 1998) is lower than the pH of the entering release medium. The acidity of the maleate molecules would thus cause a lowering of the microenvironmental pH at the moving front and possibly even extend this effect into the hydration and dissolution layer. Consequently, the deprotonation and subsequent gel formation of Carbopol would be discouraged, at least to some extent, and a more tortuous matrix pathway would exist at the moving front for the dissolved drug molecule to diffuse through, as opposed to the more open matrix for propranolol HCl.

Positive contributions to the ionic strength by the two salt forms of propranolol in the microenvironment should also be considered. Although calcium and chloride ions would be present as the calcium chloride dissolves and diffuses out of the beads in each case, propranolol HCl provides even more chloride ions that can enhance the ionic interference with the ionic interaction between the protonated propranolol and carboxylate groups of the Carbopol due to transient ion–ion interactions, and this would encourage a faster release rate. However, this interference would be stronger in the case of the propranolol maleate form, since both monovalent and divalent maleate molecules should be formed when the drug is dissolved. Monovalent maleate ions would have an ionic strength effect comparable to chloride ions, but the higher charge density of the divalent ions would more strongly attract the cationic propranolol molecules to allow the establishment of even fewer and/or shorter duration interactions between the cationic propranolol and the carboxylates of Carbopol. Divalent maleate molecules can in effect escort protonated propranolol molecules as they both diffuse, which can cause a faster release rate due to fewer interactions with Carbopol, but slower rates due to a larger ion pair than found with propranolol and chloride ion.

The low solubility of propranolol free base will slow the release rate since it should have the slowest dissolution rate of the three forms of propranolol. Once dissolved at the moving front and in the hydration and diffusion layer, propranolol free base would raise the microenvironmental pH by taking up protons from both $H_2PO_4^-$ molecules and carboxylic acid groups of Carbopol. This would encourage gel formation, which, in comparison to either of the salt forms of propranolol, would result in less tortuous pathways for the drug molecules to diffuse to the gel layer. In addition, there is an ionic strength effect because the $H_2PO_4^-$ molecules deprotonated by the dissolving propranolol free base would now be divalent. The higher charge density of divalent phosphate would allow it to interfere more effectively than would monovalent phosphate with the interaction between the protonated propranolol molecules and the carboxylates of Carbopol to encourage faster diffusion in the hydration and diffusion layer.

Since diffusion is concentration gradient driven, drug loading can have a tremendous effect on the release rate (Kim et al., 1992; Upadrashta et al., 1993; Katikaneni et al., 1995; Kim, 1998). Although the propranolol free base product had the highest moles of drug in the formulation, it would probably achieve its solubility at the moving front even at low loading (as seen by Colombo

et al., 1999), resulting in no improvement in the release rate due to its higher drug loading in comparison to the salt forms of propranolol. It is clear that the formulation with propranolol maleate had fewer moles of drug molecules than does the propranolol HCl product. The comparable release rates of propranolol maleate and propranolol HCl, therefore, could also be the result of a lower concentration gradient developed by the maleate salt that counters the effect of the divalent maleate ions on the diffusion rate.

4.3. In the gel layer

Once the gel is established, the pH is likely maintained by the release medium buffer and, therefore, any pH change by dissolution of the propranolol forms is expected to be negligible in the gel layer. However, the ionic strength effects of the chloride and maleate counterions should still be in effect, since the ions should interfere with the interaction between protonated propranolol and the carboxylate groups of Carbopol as they did at the moving front and in the hydration and dissolution layer. This interference results in a faster diffusion rate in comparison to the situation with propranolol free base-containing beads. For propranolol maleate, this ionic interference should be more profound in the gel layer than it was at the moving front and in the hydration and diffusion layer, since a higher percentage (approximately 76%) of the maleate ions should be divalent at the higher pH, 6.8. In the case of propranolol free base, there would not be interference from a salt form counterion, and this would allow the interaction of protonated propranolol with the carboxylate groups of Carbopol to slow the drug diffusion through the gel layer and consequently slow its release rate.

4.4. Characterization and release studies

Force of detachment studies revealed that the wetted mass with propranolol free base clearly is the tackiest, which can be attributed to the encouragement of deprotonation of carboxylic acid groups of Carbopol by the free base (Chow, 1990; Neau et al., 1996). In the case of propranolol hydrochloride and maleate, the wetted masses are less tacky, since there is less encouragement of carboxylate formation, since propranolol in these two forms is already in its acid form when it is hydrated or dissolved. Although a tackier wetted mass was observed with the free base form in comparison to the hydrochloride or maleate forms, a higher net loss of mass in the extruder or spheronizer due to tacky mass adhering to the surfaces was not observed. Moisture content results revealed that each type of bead is dried to essentially the same extent (<1%). This would indicate that no particular type of bead provided a greater deterrent to release medium influx due to a higher moisture level.

Since the free base form encourages the formation of carboxylates on Carbopol that cause repulsive forces that move stretches of the Carbopol molecules apart, the wetted mass would be somewhat expanded and the extrudate entering the spheronizer would in effect be less dense than found with the salt forms of propranolol. When placed in the spheronizer, the less dense extrudate would undergo reduction in volume to a greater degree than would occur with the salt forms, and this would cause relatively smaller beads (see Table 1). Although the data analysis revealed that the average diameters of beads involving the three types of propranolol are statistically different from one another ($p < 0.001$), beads involving the free base were markedly smaller. The lower yield for the beads containing the free base form is undoubtedly due to the shift of the average bead diameter to lower values. The rounder beads (Table 2) and the smoother surfaces (see the SEM images in Fig. 1a–c) may also be due to the greater gel regions on the surfaces of the free base-containing extrudates that are rounded up and smoothed in the spheronizer. The gelled Carbopol should be easier to smooth and round up than would be the simply hydrated Avicel or Carbopol since water would have a higher mobility in the gelled Carbopol.

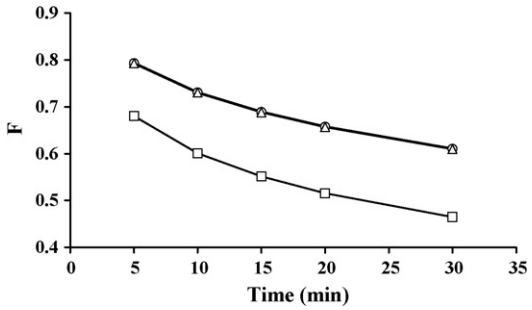


Fig. 5. The fraction of the drug being released by a Fickian diffusion mechanism as it changes with time for batches of beads for each type of propranolol. The data with circles presents the results for propranolol hydrochloride, with squares the results for propranolol free base, and with triangles the results for propranolol maleate. The curves are simple interpolations between the symbol values.

The rougher surfaces seen on the propranolol HCl and maleate beads (see Fig. 1a–c) increase the surface area available for release medium influx. Once the gel layer is formed on the surface of the bead, the differences in initial smoothness and possibly even the bead size might have a limited effect on the release rate. This is what has been described by Huber and Christenson (1968). However, the smaller bead size means that propranolol free base-containing beads are greater in number in the release medium in comparison to beads containing the salt forms since the same mass of beads entered each dissolution vessel. Therefore, the overall bead surface area available for release medium entry is greatest and the diffusion pathlength is shortest for the beads containing the free base form. Since both of these attributes should increase the release rate, these results indicate that the lower solubility and the effects in the gel layer must be quite profound in terms of reducing the release rate for this form of propranolol.

Data analysis of the release study results revealed that diffusion is not the only mechanism, since r^2 values increase and AIC values decrease when applying models that acknowledge other mechanisms (see Table 2). Upon closer examination, Model 3 is the best fit since r^2 values are highest and AIC values are the lowest. The magnitude of the exponent m indicates that a release mechanism other than Fickian diffusion is likely to be involved. There is a good fit of Model 2 to the release data and the second term on the right hand side of Model 2, k_2t, suggests polymer relaxation as a second mechanism that becomes more influential as time progresses. Peppas and Sahlin (1989) proposed an equation, based on Model 4, that can estimate the fraction of drug release by a diffusion mechanism, F, as a function of time:

$$F = \frac{1}{1 + (k_2/k_1)t^m} \tag{9}$$

Since Model 4 collapsed to Model 3 in this study, m was fixed at 0.5, based on the fit of Model 2 to the release data, and k_1 and k_2 were taken from the results for Model 2. Fig. 5 provides evidence that the contribution of Fickian diffusion diminishes with time as polymer relaxation becomes more influential. Note also that the fraction is lower at each time point for the free base form. Visual observation during release studies confirmed gel formation on the bead surfaces for each type of the bead, but, as discussed above, gel formation will be more profound with propranolol free base. Gel formation is evidence of polymer relaxation (Colombo et al., 2000).

5. Conclusion

Different forms of propranolol resulted in different bead diameters, roundness, smoothness, and release rates. However, the ruggedness of the beads was not affected, perhaps due to the low drug loading and the inherent ruggedness of microcrystalline cellulose beads. The slowest release rate was observed with the formulation that included propranolol free base, but the beads containing the salt forms exhibited comparable release rates, likely due to compensating effects. Fickian diffusion and polymer relaxation were contributing factors in 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 drug-loaded beads by extrusion-spheronization.

Acknowledgments

Generous gifts of Avicel PH 101, Carbopol® 974P, and propranolol hydrochloride from FMC Corporation, Lubrizol Incorporated and Novopharm Limited, respectively, are acknowledged. The authors would like to thank Dr. Ruy Tchao and Dr. Laura Pontiggia from the University of the Sciences in Philadelphia for guidance in the SEM analysis and the statistical analysis, respectively. Dr. Grant Heinicke from Actavis provided training and also access to the Camsizer® for the roundness analysis.

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