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Extruded and spheronized beads containing Carbopol® 974P to deliver nonelectrolytes and salts of weakly basic drugs

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Abstract

The purpose of the study was to explore the utilization of Carbopol® 974P, NF, resin in a bead dosage form manufactured by extrusion and spheronization. It was possible to prepare beads in this study by using calcium chloride to overcome the tack problem associated with wetted Carbopol® 974P. The actives included both salts of weakly basic drugs (chlorpheniramine maleate and diphenhydramine hydrochloride) and nonelectrolytes (caffeine and dyphylline) which have a broad range of solubilities. Nonelectrolytes were released faster than the salts of weakly basic drugs. This is contrary to the behavior typically seen with a matrix system where the more soluble drug is released faster than a poorly soluble one. In the results of the present study, the solubility does not determine the drug release rate. Ionic interactions between the protonated amines of the salts and the carboxylates of the Carbopol resin are suggested to be the reason for the slower release of the salts of weakly basic drugs. Data from tack measurements confirm that this ionic interaction affects the behavior of the wetted Carbopol. In addition to the drug release profiles, bead average diameter, roundness, friability, and density were also determined.

Keywords: Carbopol; Carbomer; Extrusion–spheronization; Pellets; Beads

1. Introduction

Carbopol® 974P is one member of the Carbopol family of polymers that is suitable for use in oral bead dosage forms since it was polymerized in ethyl acetate, a relatively nontoxic solvent (Carbopol Resins Handbook, 1993). It is a water-swellable polyacrylic acid crosslinked with 0.75–2% allylsucrose. Due to their extremely efficient thickening and gelling characteristics, Carbopol resins have been widely used in various pharmaceutical applications, including gels and ointments (el Gendy et al., 2002; Moretti et al., 2000; Gurol et al., 1996; French et al., 1995; Ishida et al., 1983a,b), transdermal and nasal dosage forms (Najafabadi et al., 2004; Callens et al., 2003; Ugwoke et al., 2000a,b; Witschi and Mrsny, 1999; Morimoto et al., 1985), and tablets (Parojcic et al., 2004a,b; Elkheshen, 2001; Ceschel et al., 2001; Baun and Walker, 1971). The use of Carbopol in an extruded and spheronized bead has been described (Neau et al., 2000, 1996), but a study of the effect of Carbopol on release of different types of drugs from such beads has not been reported.

Carbopol® 974P becomes tacky when wetted, which introduces handling difficulties in the wet massing step found in the extrusion–spheronization method (Neau et al., 1996). At low pH, the carboxylic acid groups of Carbopol molecules would be uncharged and should have weak interactions, and the molecules are in the coiled form. In near neutral or alkaline media, carboxylates are formed and the negatively charged molecules repel each other and extreme expansion occurs, resulting in a hydrogel (Carbopol Resins Handbook, 1993; Park and Robinson, 1985). It has been shown that electrolytes can affect the hydration of the carboxylate groups, resulting in aqueous dispersions of low viscosity (Lin et al., 1993; Ünlü et al., 1992). Tack is evident when these carboxylates are formed. Decreasing the strength of the repulsive forces between the carboxylates or reducing the contact surface area should reduce the problem of tack. It has been reported that the inclusion of strong electrolytes can reduce the repulsive effect that neutralization has on the carboxylates (Kriwet and Kissel,

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1996) and can essentially eliminate the problems associated with the tack of wetted Carbopol (Neau et al., 1996).

Interestingly, the roundness and smoothness of beads containing Carbopol® 974P were dependent on the electrolyte type (Neau et al., 1996). Image analysis revealed that beads incorporating calcium chloride in the formulation were more spherical than beads containing potassium, sodium, magnesium, or aluminum chloride. Photomicroscopic images revealed that beads containing calcium chloride also had the smoothest surface. Therefore, calcium chloride was selected as the strong electrolyte for use in further studies. The minimum concentration of calcium chloride required in the formulation to essentially eliminate tackiness due to wetted Carbopol was shown to be dependent on the Carbopol® 974P content (Neau et al., 1996), as described in the following equation:

$$\%CaCl_2 \text{ concentration} = 0.635 \times 10^{0.0329C} \quad (1)$$

where C is the percentage of Carbopol in the dry mass. This minimum amount still allowed production of smooth, essentially spherical beads. The amount of water to prepare the wetted mass was based on R, the ratio of Carbopol® 974P to Avicel PH101 mass percentages in the formulation (Neau et al., 1996)

$$\text{ml of water} = 310–97.4R \quad (2)$$

These two equations, each based on a 300 g batch, were used in the present study to calculate the levels of these components to be used in the wetted mass.

Caffeine, dyphylline, chlorpheniramine maleate and diphenhydramine hydrochloride were selected for the present study to investigate the affect of the water solubility (Fig. 1) and the salt form of the drug on the release rate. In the case of nonelectrolytes, dyphylline was chosen as a water soluble xanthine derivative, 333 mg/ml, and caffeine as a less soluble one, 20 mg/ml (Gennaro, 2001). Chlorpheniramine maleate has a solubility, 160 mg/ml, that is approximately half that of dyphylline, whereas diphenhydramine hydrochloride was selected as a highly water soluble salt, 1000 mg/ml, with a solubility in excess of that of dyphylline (Gennaro, 2001). In this way, high and low solubilities are represented in both the nonelectrolytes and the salts, and a broad range of solubilities are considered. By taking advantage of drug pairs that are similar in molecular size and shape, the diffusivity of the molecules in the pair through the release medium would be expected to be similar. Since Fickian diffusion is typically a release mechanism from devices based on hydrophilic polymers, any differences in release rate or mechanism of release between the drugs in the pair should not be dependent on molecular size or shape.

The first objective of the study was to continue to explore the utilization of Carbopol® 974P in a pellet dosage form and to expand the bead application to the delivery of different types of drugs. The second objective was to explore the release behavior of nonelectrolytes and salts of weakly basic drugs from Carbopol-containing beads. The effect of solubility on drug release and the effect of the drug on the level of tack were of particular interest. The third objective was to study the effect of the physicochemical properties of the counterion of the salt on drug release. In particular the effect of the counterion on the microenvironmental pH and ionic strength was considered.

2. Materials and methods

2.1. Materials

Carbopol® 974P (BFGoodrich, Cleveland, OH) was used as a drug release-modifying agent. Microcrystalline cellulose, available as Avicel PH101 (FMC Corporation, Philadelphia,

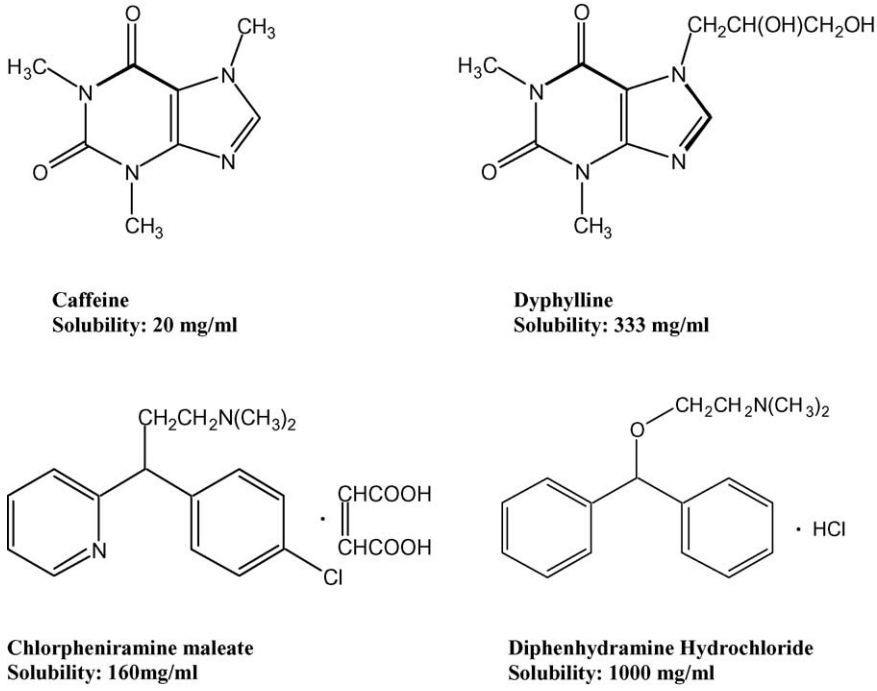

Fig. 1. Chemical structures and solubilities of the drugs used in the study.

PA), was used as the principal spheronization agent. Certified ACS reagent grade calcium chloride from Fischer Scientific (Fair Lawn, NJ) was chosen to essentially eliminate tack problems encountered upon wet massing. Chlorpheniramine maleate (CPM) was obtained from Napp Chemical, Inc. (Lodi, NJ). Caffeine (CAF) and dyphylline (DYP) were purchased from Sigma Chemical Co. (St. Louis, MO). Diphenhydramine hydrochloride (DPH) was purchased from Aldrich Chemical Company Inc. (Milwaukee, WI). Drugs were used as received. Distilled and deionized water was prepared using a Milli-Q Plus Ultra pure water system (Millipore Corporation, Bedford, MA).

2.2. Fabrication of beads

Powders were mixed in a Hobart Model N-50 Planetary mixer (Hobart Corporation, Troy, OH) for a minimum of 10 min to achieve a powder blend that was 20% Carbopol® 974P, 75% Avicel PH101 and 5% individual drug. Calcium chloride, in the amount based on the percentage concentration calculated using Eq. (1), was added as a solution in the volume of water calculated using Eq. (2), to yield a wetted mass with the proper consistency. The amounts of water calculated for a 300 g batch was doubled to allow the proper addition to a 600 g powder blend. The wetted mass was passed through a radial twin-screw extruder (Fuji Denki Kogyo Co., Osaka, Japan) fitted with a 1.5 mm screen and operated at 50 rpm. The cylindrical extrudate in each case was immediately spheronized in a Q400 Marumerizer (Fuji Denki Kogyo Co., Osaka, Japan) fitted with a plate with a radiating, cross-hatched groove pattern. The rotational speed was 880 rpm, and the residence time in the spheronizer was 10 min, which was necessary for the successful production of spherical beads (Neau et al., 2000, 1996). Beads were collected from the spheronizer, air dried for 2 h, and then oven dried at 40 °C for 6 h.

2.3. Bead characterization

Sieve analysis with U.S. standard sieves was used to evaluate product yield. Yield was defined as the percentage of beads that passed through sieve 14 and were retained by sieve 20. Beads in this 14/20 mesh cut (840–1410 μm in diameter) were used for further studies. Friability tests were conducted by rotating 50 g of beads with 50 glass beads of 3 mm diameter in a model 10805 Erweka friability tester (Chemical Pharmaceutical Industry Co. Inc., New York, NY) at 25 rpm for 10 min. The percentage loss of mass retained by sieve 20 was recorded as friability. The density of the beads was calculated by measuring the volume occupied by 80 g of beads after dropping the graduate cylinder 20 times from a height of 1.9 cm (Staniforth et al., 1988).

The roundness and equivalent diameter of the beads were determined by an image analysis system consisting of a camera, model JE-7442 (Javelin Electronics, Los Angeles, CA), and Quantimet 500+ Version VO2.00 software (Leica Cambridge Ltd., Cambridge, UK). Roundness was calculated using the following equation:

$$\text{roundness} = \frac{p^2}{4\pi A \times 1.064} \tag{3}$$

In this formula, the perimeter, p, is the total length of the boundary of the bead image; A is the square area of the image, defined as the total number of detected pixels within the feature; and the adjustment factor of 1.064 corrects the perimeter for the effect of the corners produced by the digitization of the image. A roundness score of 1 corresponds to the image of a perfect sphere in two dimensions, and an increase in the roundness score indicates that the beads are less spherical. The equivalent diameter is based on the square area of the image

$$\text{equivalent diameter} = 2\sqrt{\frac{A}{\pi}} \tag{4}$$

The smoothness of the bead surface was evaluated using an Olympus research stereomicroscope SZH 10 with a magnification of 7.5×. The beads were wetted in a 0.05 M pH 7.4 phosphate buffer for 30 min before the images of wetted beads were taken.

To investigate drug release from the beads, USP dissolution method 2 was conducted using a Distek Model 2000 (Distek Inc., Somerset, NJ) and a paddle rotation speed of 50 rpm. Release studies were carried out in 900 ml of 0.05 M pH 7.4 phosphate buffer at 37 ± 0.5 °C. The mass of beads added to each vessel was consistently 480 mg. The UV absorbance of samples containing caffeine, dyphylline or chlorpheniramine was measured at the appropriate wavelength using a Hewlett Packard 8451A diode array spectrophotometer. HPLC analysis of the samples for diphenhydramine was accomplished using a Varian 9010 System with a Varian 9050 UV detector. The mobile phase used was acetonitrile, water, and triethylamine (50:50:0.5). The pH of the mobile phase was adjusted to 6.5 with glacial acetic acid. The column was a Spherisorb® cyano 5 μm column (4.6 mm × 25 cm) (Alltech, Deerfield, IL), and the detection wavelength was 254 nm.

2.4. Mathematical modeling

Mathematical modeling was limited to three models that are commonly applied to drug release data from bead dosage forms. In each case, model fitting was accomplished using Microsoft Office Excel software. In model I, the assumption is that the bead is a matrix which remains intact during drug delivery. Release medium penetrates the matrix and dissolves the drug. The dissolved drug then diffuses through the matrix to exit the bead. This was considered a reasonable model to test because no evidence of erosion, disintegration, or dissolution of the bead was observed during drug release (Peppas and Sahlin, 1989; Peppas, 1985). Tablets containing 15% Carbopol 934 formed a viscous, translucent gel layer in simulated intestinal fluid that exhibited no fragmentation or deformation over the 4 h release study. The model is typically expressed as

$$\frac{M_t}{M_\infty} = kt^{1/2} \tag{5}$$

In this equation, M_t/M_∞ is the fraction of drug released (limited to ≤0.80 in this study) at time t, k is a reaction rate constant, t is the elapsed time after introduction of the beads to the release medium. Release of the drug occurs by Fickian diffusion of the

dissolved drug through a nondissolving, noneroding matrix due to a chemical potential gradient (Ritger and Peppas, 1987a,b).

In model II, an additional drug release mechanism is polymer relaxation, represented by the term in Eq. (6) involving k_2 (Harland et al., 1988)

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \quad (6)$$

The assumption here is that release of drug is also dependent on polymer hydration and swelling. This could be a more relevant model since the beads are observed to swell and gel on the surface. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers that swell in water or biological fluids (Peppas and Sahlin, 1989; Peppas, 1985). In Eq. (6), the first term on the right is the Fickian contribution and the second term is the Case-II relaxation contribution. M_t/M_∞ was limited to ≤ 0.90 when applying this model.

In model III, the exponent in Eq. (5) is not fixed at 0.5 (Korsmeyer et al., 1983), but rather the value of n is estimated following model fit to the data:

$$\frac{M_t}{M_\infty} = kt^n \quad (7)$$

Peppas (1985) claimed that this equation could adequately describe release of actives from spheres, and indeed the value of n is an indicator of release mechanisms. If n is approximately 0.5, Fickian diffusion is the controlling mechanism. If $0.5 < n < 1.0$, nonFickian transport, or anomalous transport resulting from more than one mechanism, is evident. If n approximates 1.0, polymer swelling, dissolution, or chain disentanglement is the likely mechanism (Harland et al., 1988). M_t/M_∞ was again limited to ≤ 0.90 when applying this model.

Since these different mathematical models might have different numbers of estimatable parameters, three criteria were used to judge the model that best fit the data: (1) examination of the fit of the predicted curve to the data and the sum of the squared residuals (SSR), (2) comparison of the Akaike information criterion (AIC) (Yamaoka et al., 1978) for each model fit, and (3) examination of the validity of the final parameter estimates (including magnitude and confidence intervals). The AIC can be calculated using the number of experimental points, n, the SSR, and the number of parameters to be estimated, p

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

The more negative the AIC, the better the model describes the data. Since the AIC is based on both the fit to the data and on the number of estimated parameters, if two models both fit the data well, the AIC will be more negative for the model with fewer estimated parameters. Thus, the AIC can help in selecting the simplest model that still describes the data well.

2.5. Tack measurement

Powder blends (20% Carbopol® 974P, 75% Avicel PH101, and 5% of the drug under consideration) were mixed using the Hobart mixer. Distilled and deionized water (calculated using Eq. (2), based on a 300 g batch) was added. The force of detachment was measured using a Chatillon Model No. DFM-10 digital force gauge. The surface area of the upper compression plate was 20.41 cm^2. To achieve consistent contact with each sample mass, the force of compression of the upper plate with the platform of the test stand was 20 N for 3 min. The force of detachment (N) was measured while lowering the platform at a constant rate of 1 mm/min.

Table 1
Roundness scores and equivalent diameters for beads containing nonelectrolytes and salts of weakly basic drugs

Drug	Dry beads		Wetted beads[a]	
	Roundness score	Equivalent diameter (mm)	Roundness score	Equivalent diameter (mm)
CAF	1.13 ± 0.08	0.93 ± 0.14	1.15 ± 0.11	1.19 ± 0.22
DYP	1.19 ± 0.09	1.05 ± 0.18	1.25 ± 0.14	1.38 ± 0.26
CPM	1.13 ± 0.09	0.88 ± 0.17	1.11 ± 0.09	0.99 ± 0.19
DPH	1.12 ± 0.09	0.94 ± 0.17	1.12 ± 0.13	1.11 ± 0.19

[a] Wetted beads were generated by placing dry beads in a 0.05 M pH 7.4 phosphate buffer for 30 min before the images were taken.

3. Results

For the roundness and the equivalent diameter evaluations, more than 800 beads from each batch were measured. For the other responses, data were the average of at least three experimental replicates. Tables present results as the mean and the standard deviation.

Data in Table 1 reveal that the dry beads had roundness scores that are considered to be within the acceptable range for good flow (1–1.2). It appears that beads containing the nonelectrolytes were more swollen at the end of a 30 min time period than were those containing drug salts (Table 1). The tack associated with the samples involving the nonelectrolytes was higher than that with the salts (Table 2). The tapped densities reported in Table 2 indicate that a difference in densities is possible even with related pairs of drugs. A linear relationship ($r^2 = 0.992$) exists between tapped density and the equivalent diameter of the dry beads, confirming that a larger equivalent diameter results in less dense packing (Banker and Anderson, 1986). The percent friability value is low for each batch of beads (Table 2), revealing rugged bead products that are capable of handling further processing. Bead images in Figs. 3–6 present the surfaces as well as the roundness for each type of bead.

Table 2
Tack values of wetted powder blends, and bead tapped densities and friabilities for samples involving nonelectrolytes and salts of weakly basic drugs

Drug	Force of detachment (N)	Tapped density (g/cm^3)	Friability (%)
CAF	5.62 ± 0.18	0.811	0.40
DYP	5.52 ± 0.18	0.666	0.20
CPM	4.26 ± 0.17	0.882	0.60
DPH	4.33 ± 0.13	0.789	0.80

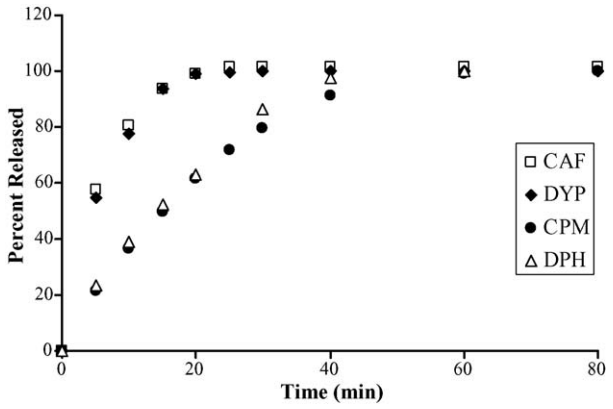

Fig. 2. Release profiles for Carbopol beads containing nonelectrolyte or weakly basic drugs.

Nonelectrolytes were released faster than were the salts of weakly basic drugs (Fig. 2). Caffeine and dyphylline differ in aqueous solubility (Fig. 1), but there was no significant difference ($p < 0.01$, t-test at each time point) in their release profiles. The release profiles of the drug salts were also similar, although their profiles are different from those of the nonelectrolytes.

4. Discussion

4.1. Release mechanisms and model fitting

Bead images (Figs. 3–6) indicate that the drug salts provide a smoother surface. These figures and data presented in Table 1 reveal that hydration does not noticeably alter the roundness of the beads, although the equivalent diameter is increased. The release of drugs from the Carbopol® 974P-containing beads is largely dependent on the level of hydration, the swelling, and the gelling of the Carbopol. As the near neutral dissolution medium enters the beads, the beads hydrate and the carboxylic acid groups on the Carbopol would be expected to lose their protons to form the carboxylate ions to a greater extent than already occurred during wet massing with the calcium chloride solution. The hydration and then repulsion between these carboxylate ions causes the Carbopol® to swell and gel. Such a gel can act as a rate-controlling barrier to further fluid permeation and subsequent drug release (Wan et al., 1991; Baun and Walker, 1971), but the gel structure is undoubtedly a more open and less tortuous pathway for drug diffusion than was the original hydrated matrix.

It is likely that permeating release medium dissolves the nonelectrolyte drug particles and dissolved drug is being released through hydrating, swelling, and gelling beads. Hydration would allow both Avicel and Carbopol particles to swell and this would reduce the tortuosity of the bead, allowing rapid diffusion of dissolved nonelectrolyte drug as the release study progressed (Fig. 2). The principal release mechanism of release for the nonelectrolytes then should be Fickian diffusion of the drug. This is confirmed by the AIC data in Table 3 that shows that the fit of model III to the release data for both dyphylline and caffeine is the best. The value of n is so close to 0.5 in both cases that Fickian diffusion by the drug is the likely mechanism and model I should also be a good fit. Yet model II for both caffeine and dyphylline has a more negative value for the AIC, indicating a better model than model I. However, the negative values for k_2 for caffeine indicates the inappropriate application of model II to this data, since contributions to the release should be additive (Peppas and Sahlin, 1989). So model II is ruled out for caffeine. For dyphylline, k_1 and k_2 for model II are both positive, indicating the validity of the model. However, upon closer examination, the term involving k_2 contributes less than

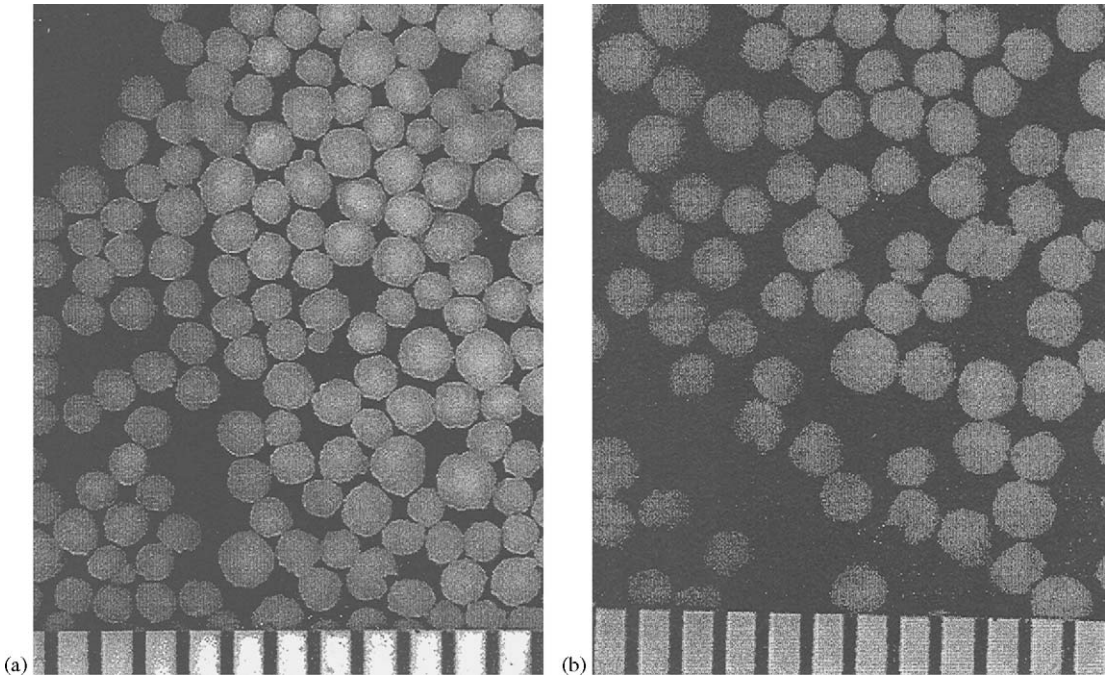

Fig. 3. (a) Microscopic image of dry caffeine beads. (b) Microscopic image of wetted caffeine beads.

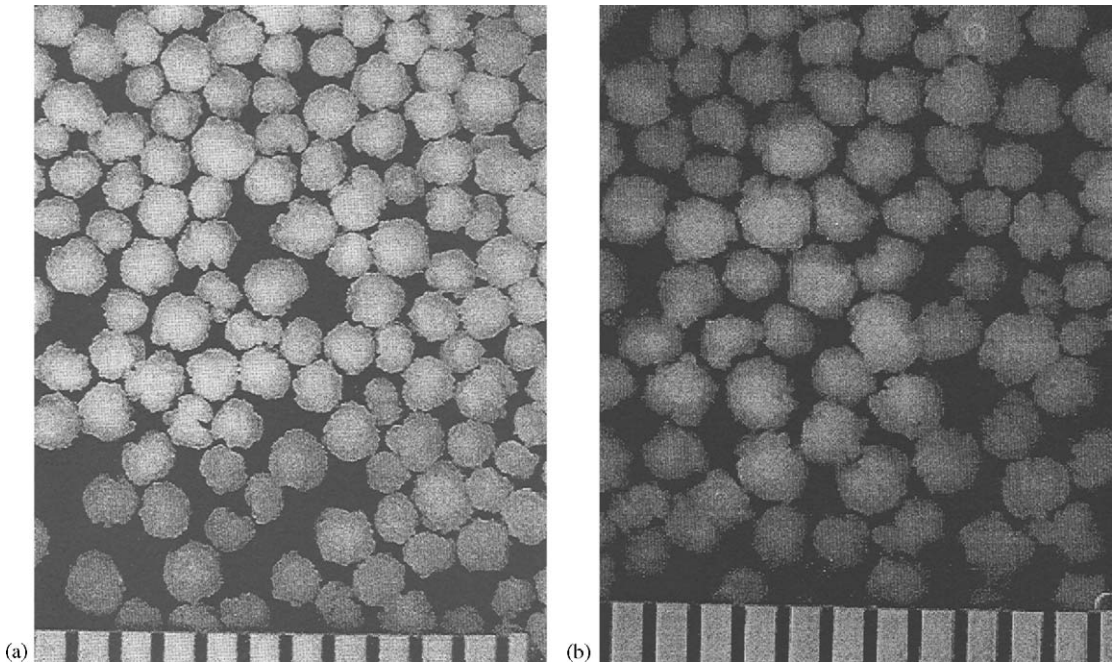

Fig. 4. (a) Microscopic image of dry dyphylline beads. (b) Microscopic image of wetted dyphylline beads.

2% to the fraction released at any point in time where M_t/M_∞ is less than 0.80. Thus the model essentially collapses to model I. Fickian diffusion, described in model I, is judged to be the mechanism for nonelectrolyte drug release with a negligible, if any, contribution from polymer relaxation. Fit of model I to the nonelectrolyte release data is also evident in the initial linear portion of the release data as a function of the square root of release time (Fig. 7). Note that the release profiles for the drug salts are not initially linear in Fig. 7.

If the beads could be considered simple matrix beads, the effect of an improved aqueous solubility should have been an increase in the release rate, reflected by an increase in the model I k value. This is not seen with these nonelectrolytes (Fig. 8). This is likely due to the fact that water penetration into the beads and the hydration of the polymers are the rate limiting steps and not the dissolution of the drug. Thus, these nonelectrolyte drugs will dissolve readily and diffuse through a hydrating matrix that limits the release rate. Dissolution could be the rate limiting step

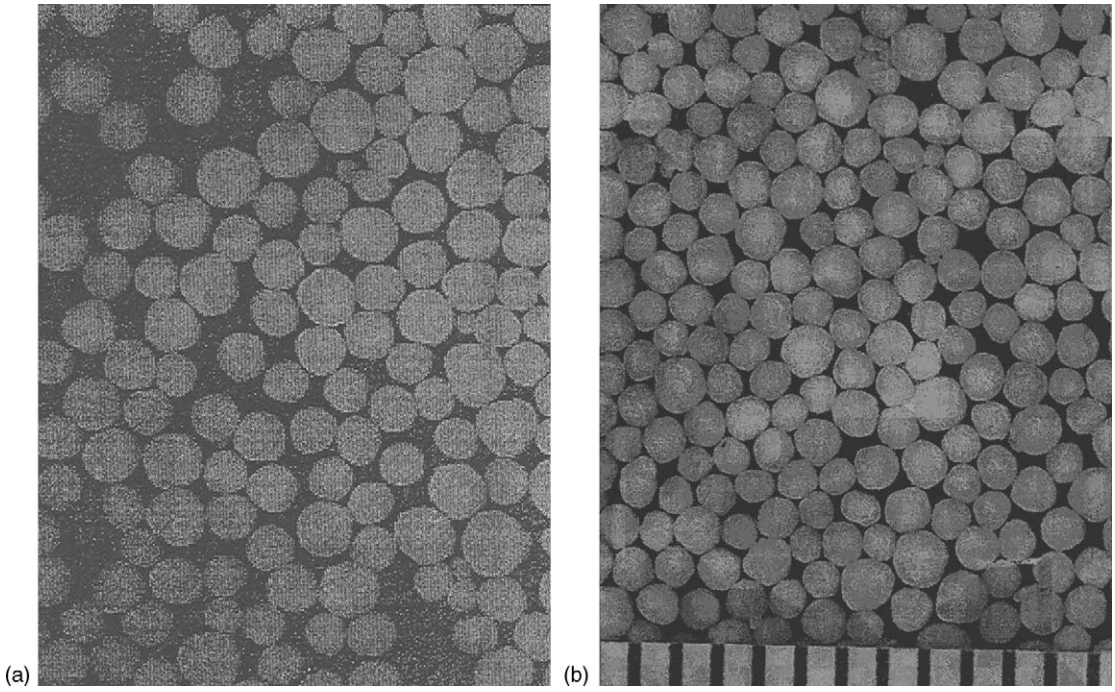

Fig. 5. (a) Microscopic image of dry chlorpheniramine maleate beads. (b) Microscopic image of wetted chlorpheniramine maleate beads.

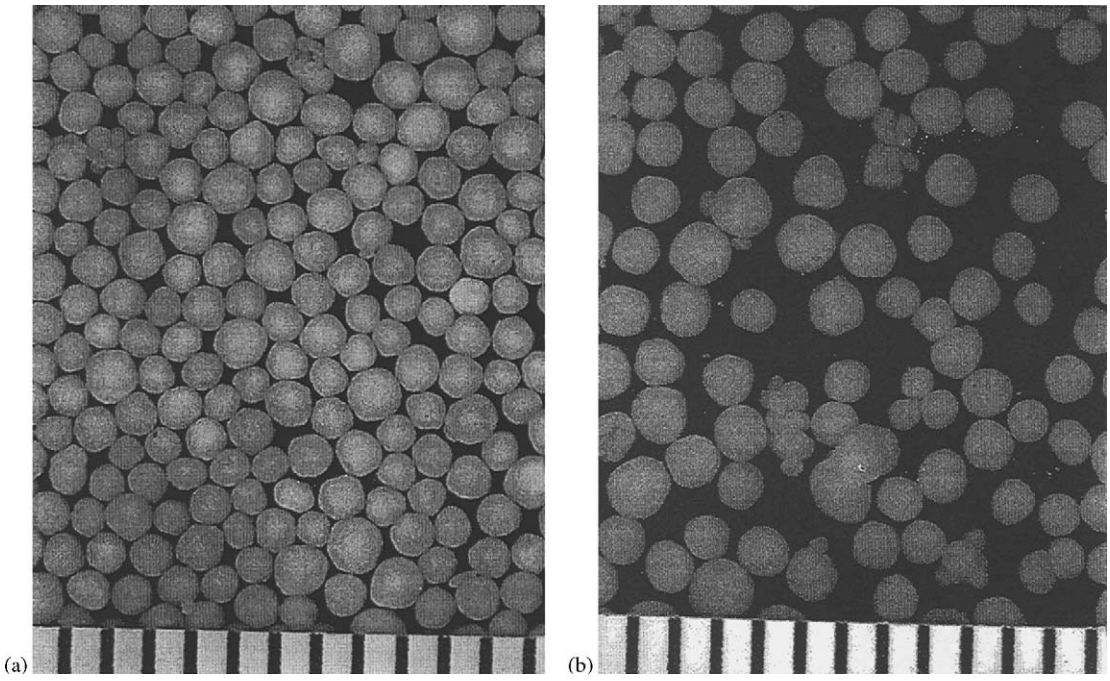

Fig. 6. (a) Microscopic image of dry diphenhydramine hydrochloride beads. (b) Microscopic image of wetted diphenhydramine hydrochloride beads.

Table 3
Reaction rate constants, regression values and AIC values from models I, II, and III fit to release data

Drug	Model I				Model II					Model III				
	k	r^2	SSR (10^{-5})	AIC	k_1	k_2	r^2	SSR (10^{-5})	AIC	k	n	r^2	SSR (10^{-5})	AIC
CAF	0.256	0.999	3.094	−29.2	0.265	−0.0033	0.999	0.01251	−43.7	0.265	0.483	0.999	0.000422	−53.9
DYP	0.245	0.999	0.4916	−34.7	0.241	0.0013	0.999	0.00926	−44.6	0.241	0.507	0.999	0.000392	−54.1
CPM	0.136	0.966	1629	−26.8	0.0739	0.0136	0.998	87.50	−45.3	0.0673	0.734	0.999	60.47	−47.9
DPH	0.133	0.982	423.7	−25.3	0.0837	0.0129	0.999	2.250	−49.5	0.0826	0.683	0.998	65.10	−32.7

Units for k in model I are $\text{min}^{-1/2}$; for k_1 and k_2 in model II are $\text{min}^{-1/2}$ and min^{-1}, respectively; and for k in model III are min^{-n}.

with release of nonelectrolyte drugs of lower solubility from Carbopol-containing solid dosage forms.

For the drug salts, although the fit of model I to the release data is adequate (Table 3), their release data presented in Fig. 7 hint that a lag time could be involved. No improvement in the fit is provided when a lag time is included, i.e., $(t - t_{\text{lag}})$ replaces t in Eq. (5) (Gazzaniga et al., 1993; Ford et al., 1991). However, there is an improvement in the fit to the release data (r^2 increases) when model II was applied (Table 3), and indeed the AIC indicates that model II is the best model to describe the release data for diphenhydramine hydrochloride. This is not surprising when considering that beads containing drug salts are not as swollen at 30 min as are beads containing nonelectrolyte

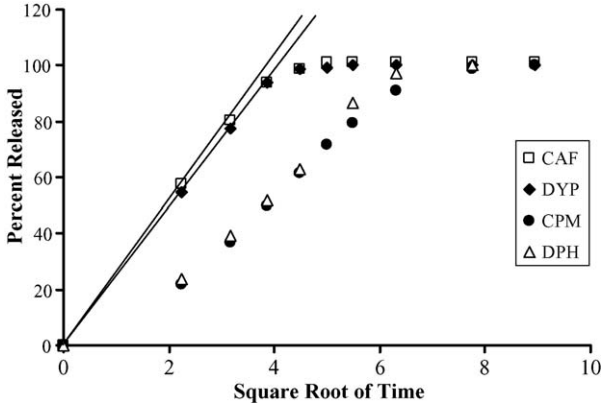

Fig. 7. Percent released for nonelectrolytes and salts of weakly basic drugs as a function of the square root of the release time presented in Fig. 2.

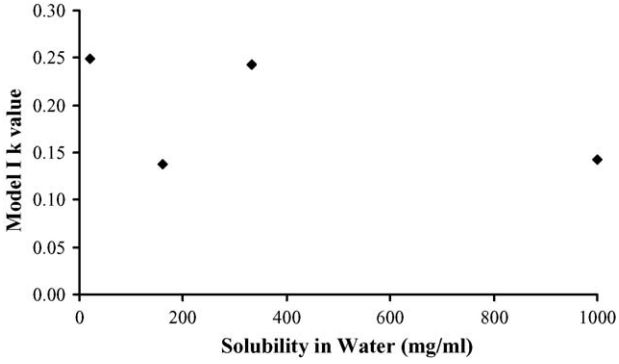

Fig. 8. Model I k value as a function of drug solubility in water.

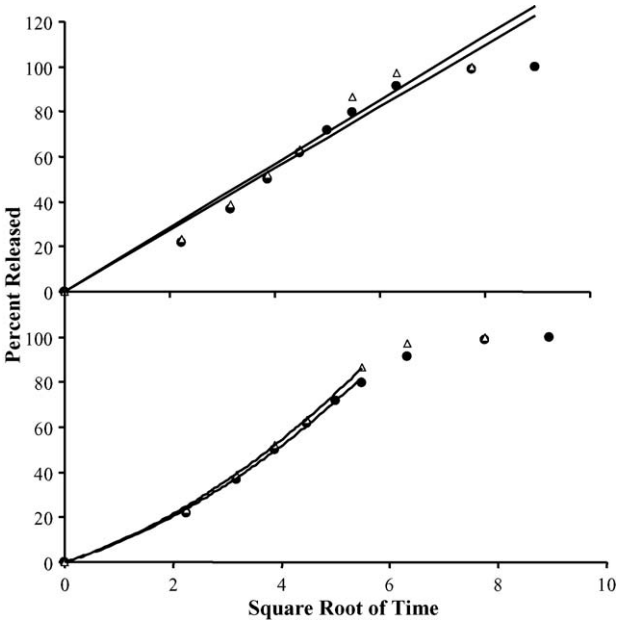

Fig. 9. Release data for chlorpheniramine (circles) and diphenhydramine (triangles) as a function of the square root of the release time presented in Fig. 2. In the upper plot, the predictive lines are based on model I. In the lower plot, the predictive curves are based on model II.

drugs (see equivalent diameters of wetted beads in Table 1), providing evidence that there is something mechanistically different about drug release from Carbopol beads that contain these drugs salts. A slower swelling rate for the polymers should result in a more profound effect of polymer relaxation on the release profile. Elkheshen (2001) suggested that the main reason behind the reduced swelling of a Carbopol® 934P tablet when verapamil hydrochloride content was increased was due to an increased incidence of the interaction of Carbopol carboxylate groups with the protonated amines of the drug molecules, forming insoluble complexes. Table 3 shows how the additional polymer relaxation term allows r^2 to improve to greater than 0.99 for each salt. The improved fit of model II to the release data is presented in Fig. 9. Fickian diffusion of dissolved drug is still the likely principal release mechanism. Polymer relaxation, i.e., the swelling of Avicel and Carbopol upon hydration, would be a secondary mechanism that contributes to a greater extent as release time progresses. This is confirmed by the excellent fit of model III to the salt data (the best model for chlorpheniramine, based on the AIC), with a value of n between 0.5 and 1.0 that indicates anomalous transport, since diffusion and Case-II transport are both involved.

4.2. Effect of microenvironmental conditions

Although chlorpheniramine and diphenhydramine have comparable molecular weight, size and shape, they differ in aqueous solubility (Fig. 1). Although the release of dyphenhydramine is greater than that of chlorpheniramine at certain times, the difference in the release rates does not reflect the substantially higher aqueous solubility of diphenhydramine. This is not surprising since there was no marked difference in release rates between caffeine and dyphylline, although they too differ in solubility. From the release profiles and Fig. 8, it was evident that it is not solely the aqueous solubility of the active that controls the release rate for salts of weakly basic drugs. A common ion effect, from the chloride of the calcium chloride, would reduce the solubility and more importantly the dissolution rate of the diphenhydramine hydrochloride at the release medium moving front, and this could account in part for the similarity in these two drug salt release profiles.

The release profile clearly depends on the diffusing species. The potential for release rates that depend on the drug type was suggested in the Carbopol product literature (Carbopol Resins Handbook, 1993). The fact that the tack associated with the samples involving the nonelectrolytes was higher than that seen with the salts (Table 2) lends credence to the hypothesis that each of the two salts is able to reduce the tack by interacting with the carboxylates of the Carbopol gel. The sensitivity of wetted Carbopol adhesion to the presence of miscellaneous ions has been reported (Neau et al., 1996). This interaction could also be the reason for the slower release of these salts in comparison to the nonelectrolytes. Evidence for the effectiveness of this interaction was provided by Jimenez-Kairuz et al. (2003) in the low release rate of metoclopramide from a dilute (≤0.25%, w/v) Carbopol gel consisting only of drug, water, and Carbopol that had been neutralized by the basic drug. The authors claimed that only the free base form of metoclopramide was released into water because the protonated form of the drug was retained by ion pairing with the carboxylates of Carbopol. The ion pairing could be disrupted by an ionic strength effect when using normal saline as the release medium. Ion exchange has been suggested as one possible means to disrupt the ionic interaction between a cation and the carboxylates of Carbopol (Jimenez-Kairuz et al., 2003; Kriwet and Kissel, 1996). It has also been suggested that release rates are controlled by the relatively slow dissociation of such ion pairs and not by the concentration of free base form, unless the concentration of free base becomes high enough to provide a substantial concentration gradient as the driving force, which occurs when an increase in pH approaches the pK_a of the drug (Jimenez-Kairuz et al., 2001). The percentage of procaine hydrochloride released from a dilute Carbopol gel (≤3%, w/v) into a pH 7.4 phosphate buffer exhibited the linear relationship with the square root of release time ($r^2 > 0.998$) that is indicative of a diffusion mechanism (Realdon et al., 1998). The proximity of this pH to that of the pK_a of procaine (8.7) was considered responsible for generating the base form that was diffusing through the gel.

Release of the drug salts from these Carbopol-containing beads would be expected to be a somewhat different situation. Loss of protons by the amines of the salts in the present study to generate the base form would not be successful since the pK_a of Carbopol, ~6.2 (Riley et al., 2001), and that of the permeating phosphate in the release medium, 7.2 (Martin, 1993), are both lower than that of these drugs, about 9.2, indicating the presence of acids far stronger than the protonated

drug as dissolution occurs. The diffusing species in both cases, then, would be the protonated form of the drug. Since the drug molecules essentially do not deprotonate, there is no effect of dissolving drug on the microenvironmental pH that is established by deprotonation of the Carbopol at the moving front (Tatavarti et al., 2004). As the diffusing drug molecule works its way outward toward regions where the penetrating phosphate buffer has allowed the Carbopol to gel by carboxylate formation, the ionic interaction could take place that hinders diffusion of cationic drug molecules through Carbopol gels (Jimenez-Kairuz et al., 2003; Kriwet and Kissel, 1996). This interaction is likely to also reduce the swelling of the gel, even as weak base drugs made a poly (L-lactic/glycolic acid) matrix less swollen (Miyajima et al., 1998). This reduction in swelling will also slow free cationic drug diffusion through the gel, in comparison to nonelectrolyte diffusion through a more open gel.

As the drug salt dissolves, the counterion to the protonated chlorpheniramine, maleate, with its second pK_a of 6.3 (Martin, 1993) that is comparable to the pK_a of Carbopol, could more substantially reduce the microenvironmental pH than could the Carbopol alone. This further reduction in pH could diminish the gelling of Carbopol by discouraging to some extent its deprotonation. This acidic contribution would not be evident with the chloride associated with diphenhydramine and the Carbopol would be more likely to swell and gel when in the presence of dissolving diphenhydramine. This might account in part for the faster release rate of diphenhydramine than of chlorpheniramine. In addition, if the maleate undergoes deprotonation of the second acid group, its divalent nature would make it a greater contributor to the ionic strength of the microenvironment as the chlorpheniramine dissolved, in comparison to the chloride contribution to ionic strength with diphenhydramine. An increase in the ionic strength of an aqueous environment has been shown to diminish the gelation of Carbopol (Carbopol Resins Handbook, 1993), probably by reducing the repulsive forces due to shielding of the carboxylate charges by miscellaneous ions (Elkheshen, 2001). This additional contribution to a lower gelation of Carbopol would also reduce the release rate of chlorpheniramine in comparison to diphenhydramine where drug is first dissolving at the moving front. However, an increase in ionic strength has also been shown to reduce the pK_a of Carbopol® 934P (Nakanishi et al., 1998), a structurally related Carbopol product. Such a reduction in pK_a would cause the Carbopol in the present study to more likely deprotonate and gel, countering the effect of shielding the repulsive forces. The effect of this difference in ionic strength at the moving front, therefore, is apparently not profound enough to make a notable difference in the release profiles of the drug salts (Fig. 2), indicating that the interaction with the carboxylates of Carbopol is likely the rate controlling mechanism here.

More than one mechanism, then, can reduce the release rate of drug from a Carbopol-containing bead into a near neutral phosphate medium. The most effective mechanism appears to be the interaction of a cationic form of the drug with the carboxylates of the gelled Carbopol, with additional effects due to the reduction of the swelling and gelling of Carbopol by an acidic or ionic strength effect.

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