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Fabrication and characterization of extruded and spheronized beads containing Carbopol® 974P, NF resin

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Abstract

Carbopol® 974P, NF resin is a synthetic, cross-linked, acrylic acid polymer. It becomes tacky when wetted, which introduces handling difficulties with techniques involving water or other fluid. To reduce tack, the water for wetting was replaced by an aqueous solution of a strong electrolyte. The effect of the concentration and type of electrolyte on the adhesive force of the wet mass was measured. A correlation was found between the charge density of the cation and the minimum salt concentration necessary to eliminate problems associated with tack. Beads containing chlorpheniramine maleate, Carbopol®, Avicel PH101, and electrolytes were successfully manufactured by extrusion-spheronization. The Carbopol® concentration, as well as the pH and ionic strength of the dissolution medium and the rotation speed of the paddles, can modify drug release.

Keywords: Carbopol®; Extrusion-spheronization; Beads; Pellets; Tack; Wet granulation

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1. Introduction

Carbopol® resins are cross-linked polyacrylic acids. They hydrate in the presence of water and the carboxylic acid groups in the molecules can dissociate in an aqueous system. The negative charges on the polymer backbone then repel each other to cause dramatic polymer expansion. Its swelling and hydrophilic characteristics allow three main pharmaceutical applications: (i) as a thickening agent (Lochhead and Warfield, 1985), (ii) as a suspending agent (Davidson and Collins, 1976), and (iii) as an emulsifying agent (Schwarz, 1962). Due to differences in molecular weight, polymerization reaction solvent, cross-linking agent and density, there are currently 17 different types of Carbopol® resins. Carbopol® 974P, NF is one of the newest products of the Carbopol® series. It offers advantages over its precursor, Carbopol® 934P, NF, since it is polymerized in ethyl acetate rather than benzene. In particular, polymerization in the non-toxic solvent makes Carbopol® 974P, NF a suitable resin for use in oral dosage forms.

Carbopol® 934P, NF has been used as a binder in direct compression tablets (Elsabbagh et al., 1978), and has been investigated as a controlled

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released modifying agent in tablets (Baun and Walker, 1971; Choulis and Papadopoulos, 1975; Choulis et al., 1976; Perez-Marcos et al., 1991; Durrani et al., 1992). Baun and Walker (1971) included Carbopol® 934P, NF in caramiphen hydrochloride tablets and in atropine sulfate tablets to prolong drug release. A viscous gel barrier was reported to have formed on the tablet surface. By preparing tablets with 5, 10 and 15% (w/w) Carbopol®, they determined that higher Carbopol® concentrations could provide slower drug release in simulated gastric or intestinal fluid. The cumulative amount of drug released was described as a linear function of the square root of time, indicating that slowing drug diffusion from the tablets was probably the sustained release mechanism.

Choulis and Papadopoulos (1975) prepared quinine sulfate tablets with 20–75% (w/w) Carbopol® 934P, NF content. Tablets with a lower Carbopol® content allowed more complete drug release in a 7.5-h dissolution study. Drug was reported to be liberated by a combination of diffusion and gel attrition processes. Tablets with lower Carbopol® content were more susceptible to attrition. By taking advantage of these two release mechanisms, drug release from sustained release tablets containing Carbopol® 934P, NF and a drug that is poorly soluble in water, furosemide or theophylline, could be described by zero-order kinetics (Perez-Marcos et al., 1991; Durrani et al., 1992).

Carbopol® 974P, NF is structurally similar to Carbopol® 934P, NF, differing in the polymerization solvent, crosslinking density, and the molecular weight range of the final product. As such, its behavior is similar to that of Carbopol® 934P, NF when exposed to a range of media. Carbopol® resins have not been employed in the preparation of extruded and spheronized beads. This study investigates the feasibility of employing this Carbopol® resin as a sustained-release modifying agent in beads manufactured by extrusion-spheronization.

Table 1
Dissolution media with different pH and ionic strength

pH	Components	Ionic strength
1.5	HCl	0.0316
4.5	HCl + NaCl	0.0316
7.4	KH_2PO_4+ NaOH + HCl	0.0320
7.4	KH_2PO_4+ NaOH	0.0214
7.4	KH_2PO_4+ NaOH	0.0360
7.4	KH_2PO_4+ NaOH	0.0630
7.4	KH_2PO_4+ NaOH	0.1280

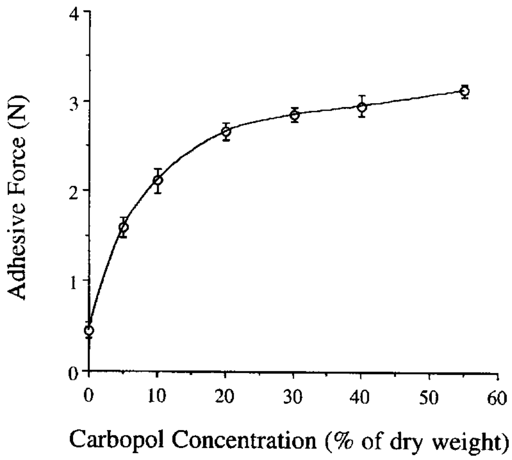

Fig. 1. Tack of Carbopol® 974P/Avicel PH101 wet mass. Water was employed as the granulating fluid. Data points are the mean of five replicates; the error bars present the standard deviation.

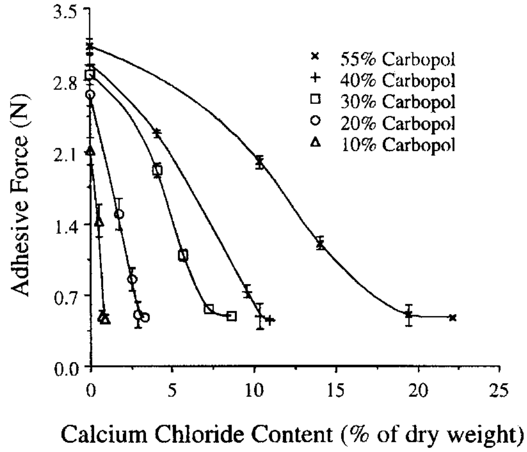

Fig. 2. Tack of Carbopol® 974P/Avicel PH101 wet mass as a function of calcium chloride content. Data points are the mean of five replicates; the error bars present the standard deviation.

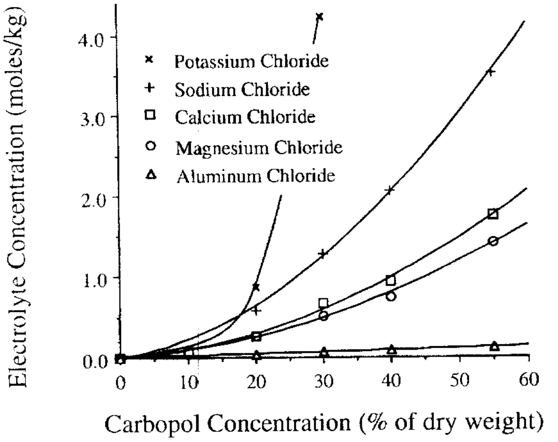

Fig. 3. Minimum amount of electrolyte to eliminate tack problems.

Carbopol® becomes tacky when wetted, which introduced handling difficulties in the wet massing step. Methods to eliminate tack during the manufacture of extruded and spheronized beads have not been published. The ability of strong electrolytes to reduce the tack of wetted Carbopol®, and the effects of the type of strong electrolyte on the roundness and smoothness of beads, were investigated. This is a unique approach since the use of strong electrolytes has been limited to reducing the viscosity of Carbopol® dispersions (Testa and Etter, 1973; Carbopol® Resins Handbook, 1993). The swelling of polyelectrolyte gels is known to be pH-sensitive, ionic strength-sensitive, and affected by the ionic composition of the medium (Kuhn et al., 1950; Abd-Elbary et al., 1981). For that reason, the effects of the pH and the ionic strength of the dissolution medium on the release of chlorpheniramine maleate from beads consisting of Carbopol®, Avicel PH101 and inorganic salt were also studied.

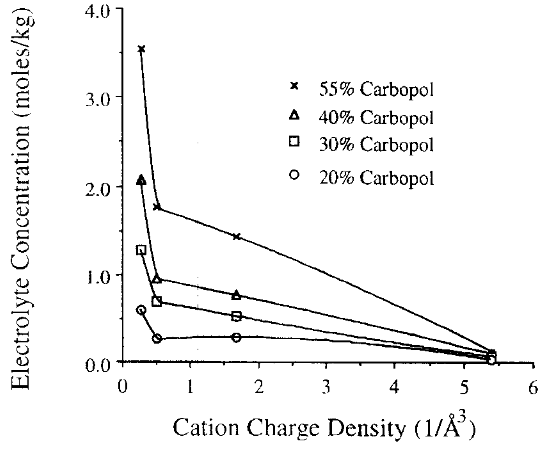

Fig. 4. Minimum amount of electrolyte as a function of the cation charge density.

2. Materials and methods

2.1. Measurement of tack

Carbopol® 974P, NF resin (BFGoodrich Specialty Chemicals, Cleveland, OH) and Avicel PH101 (FMC Corporation, Portsmouth, NH) were mixed in a beaker for 5 min. The powder blends contained 10, 20, 30, 40 or 55% (w/w) Carbopol®. Distilled and deionized water was added to the powder mixture to achieve the consistency appropriate for a successful wet granulation. The tack of the wet mass was measured using an Instron 4201 (Instron Corporation, Canton, MA). A stainless steel, 23-mm diameter disk probe was brought into contact with the surface of the wet mass which had been applied to a steel rod. The force required to pull the probe away from the surface of the wet mass was reported as the adhesive force in Newtons (N). To evaluate the reduction in tack, the tack of the wetted powder blend, measured after water was used as a granulating fluid, was compared to that after an inorganic salt solution was incorporated as the granulating fluid into a powder mixture of the same composition. NaCl, KCl, $MgCl_2$, $CaCl_2$, and $AlCl_3$ solutions were selected for this study.

2.2. Fabrication of beads

Powder mixtures containing Carbopol® and Avicel PH101, with or without 5% chlorpheniramine maleate (Napp Chemical Inc., Lodi, NJ), were blended for 5 min in a Hobart model N-501 planetary mixer (Hobart Corporation, Troy, OH). The minimum amount of salt was added as a dilute solution to yield a wet mass with the proper

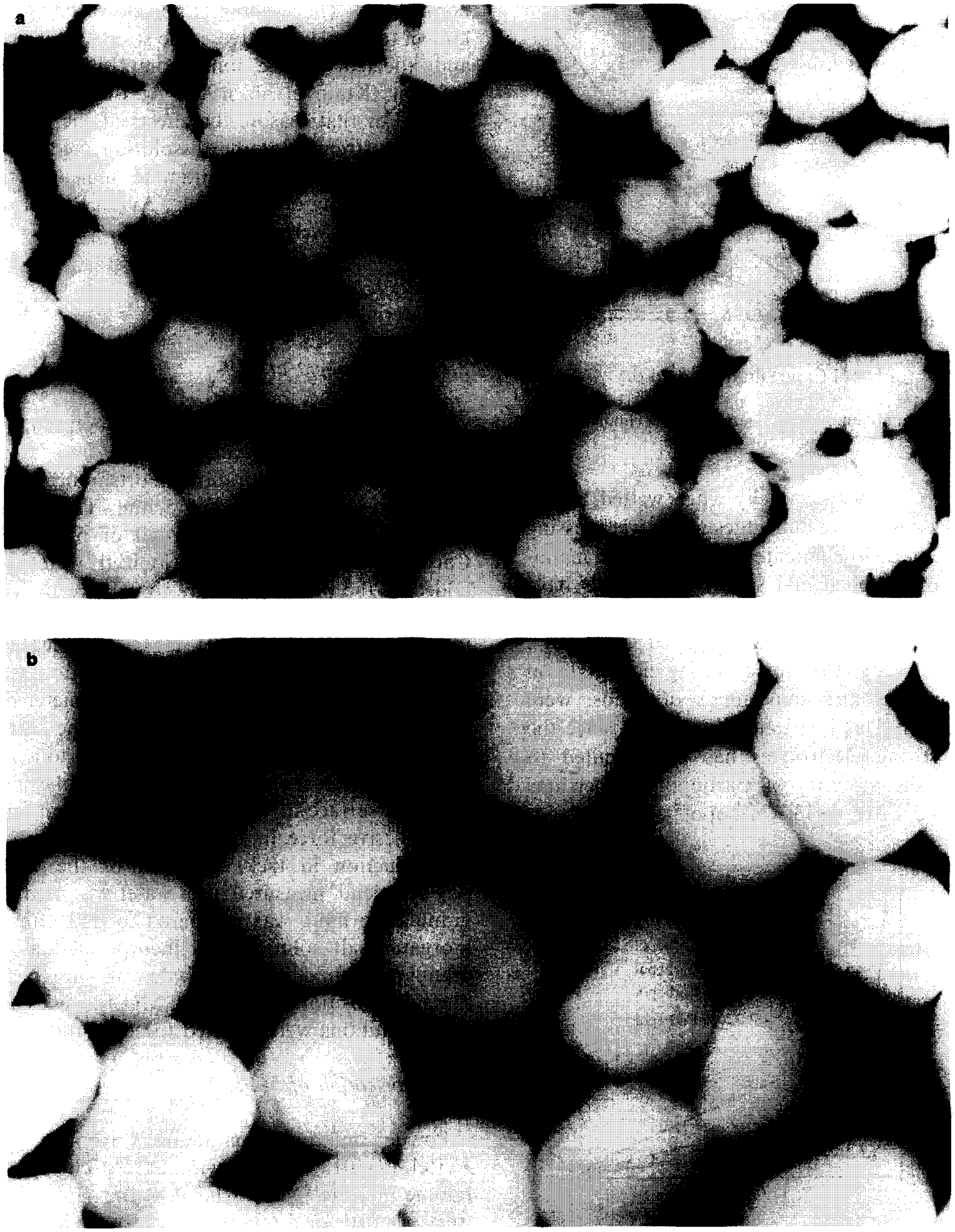

Fig. 5. Microscopic Images of Carbopol® 974P/Avicel PH101 Beads (7.5 × magnification). (a) Magnesium chloride; (b) sodium chloride; (c) aluminum chloride; and (d) calcium chloride.

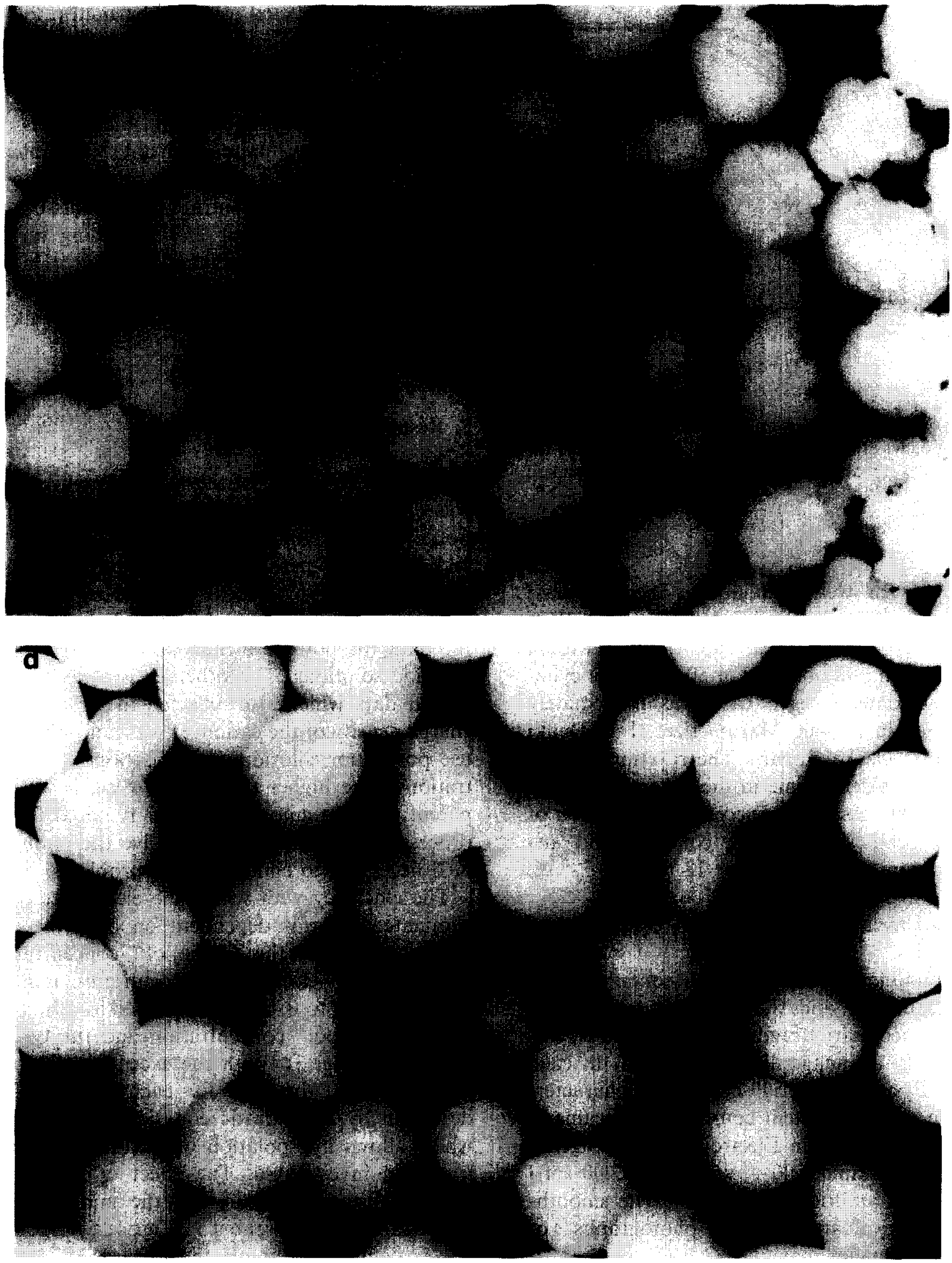

Fig. 5C and 5D.

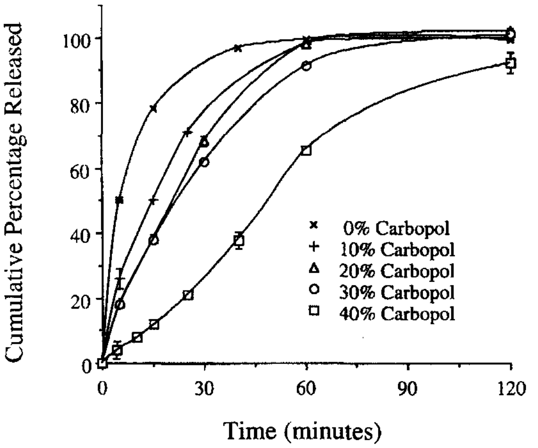

Fig. 6. Carbopol® effect on chlorpheniramine release in pH 7.4 phosphate buffer at 0.128 ionic strength. Data points are the mean of three replicates; the error bars present the standard deviation.

consistency for wet granulation. The wet mass was passed through a 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). The rotational speed of and the residence time in the spheronizer were adjusted as necessary for successful production of spherical beads. Beads were collected and air-dried at room temperature for 12 h.

2.3. Characterization of beads

The roundness of beads, which contained 40% (w/w) Carbopol® and the minimum amount of electrolyte necessary to reduce tack to 0.45 N, was measured by an image analysis method. In each image analysis, at least 500 beads were characterized. The imaging system consisted of a camera, model JE-7442 (Javelin Electronics, Los Angeles, CA), and Quantimet 500+ version VO2.00 software (Leica Cambridge Ltd., UK). The smoothness was evaluated using photographs of microscopic images magnified 7.5 × .

To investigate the effect of various parameters on drug release, dissolution tests (U.S.P. Apparatus 2) were conducted using a pharmatest PTWII (Scientific Instruments and Technology Corp., Englishtown, NJ). The paddle rotation speed was consistently 50 rpm, except in the study of the effect of paddle rotation speed, and the dissolution medium was maintained at 37°C. Calcium chloride was selected as the salt for these dissolution studies. Drug concentration in the dissolution media was measured at 264 nm using an HP 8451A diode array spectrophotometer (Hewlett Packard, Palo Alto, CA). Several dissolution media were prepared to investigate the effect of pH and ionic strength (Table 1).

3. Results and discussion

The adhesive force of the wet mass when water was employed as the granulating fluid is a function of the Carbopol® concentration (Fig. 1). The tack of the wet mass decreased dramatically in the presence of strong electrolytes and in each case asymptotically approached 0.45 N. Fig. 2 presents the data for powder blends wetted with calcium chloride solutions. The other electrolytes yielded similar data which also reflected the effect of the charge density of the cation. It was not possible to use potassium chloride when Carbopol® concentrations were higher than 30% (w/w); it was apparent that the amount of water required for the process was insufficient to dissolve the minimum KCl necessary to eliminate tack problems.

The efficiency with which the electrolyte could eliminate tack was dependent on both the electrolyte type and the Carbopol® concentration. The minimum electrolyte concentration required to reduce tack to 0.45 N was plotted as a function of the Carbopol® concentration and the type of electrolyte (Fig. 3). With the exception of potassium chloride, the data for each salt could be described by a quadratic equation ($r^2 > 0.992$) which allows interpolation to mixtures that have not been investigated. The effect of the charge density of the salt cation on the minimum salt concentration is presented in Fig. 4. Charge density is defined as the absolute charge of the ion divided by its volume, based on the reported ionic radius (Handbook of Chemistry and Physics, 1969). The effect is attributed to the local ionic strength which can disturb ionic interactions with the carboxylate groups of Carbopol®, thereby reducing tack.

The roundness and smoothness of beads were dependent on the electrolyte type. Roundness was calculated using this formula:

$$R = \frac{P^2}{4.256\,\pi\,A}$$

where R is the roundness, P is the perimeter, and A is the area of the bead in the image. A roundness value of 1, as reported by the image analysis software, corresponds to the image of a perfect sphere. An increase in the roundness value indicates that the beads is less spherical. Roundness mean and standard deviation values were 1.25 ± 0.18, 1.15 ± 0.11, 1.24 ± 0.10 and 1.28 ± 0.15 for beads containing sodium, calcium, magnesium and aluminum chloride, respectively. Although these roundness values are not statistically different, only one salt was selected for further studies. Employing calcium chloride yielded the beads with the lowest mean values for roundness, and one of the lowest standard deviations for that parameter. Microscopic images (Fig. 5) reveal that beads containing calcium chloride also had the smoothest surface. Therefore, calcium chloride was chosen as the strong electrolyte to prepare drug-containing beads to be used in the dissolution studies.

The maximum concentration of Carbopol® 974P, NF that could be successfully incorporated into beads was 55% (w/w). Above that level, the wet mass formed a gel in the extruder before passing through the screen, and substantial heat was generated. When calcium chloride was incorporated into the beads, an increase in the Carbopol® content could be employed to slow the release rate (Fig. 6).

If the pH of the dissolution medium was increased, the release rate could be diminished even though the ionic strength was consistently 0.032 M (Fig. 7). At a higher pH, the carboxylic acid groups on Carbopol® are more likely to be dissociated. Repulsion due to negative charges causes expansion of the molecules, which thereby form a gel which can slow drug release (Carbopol® Resins Handbook, 1993). Interactions between the negatively charged polymer and the positively charged drug are also more likely to increase at higher pH in this range. Therefore, at least to a limited extent, at a higher pH the release rate can be reduced.

When the ionic strength of the dissolution medium was increased, the release rate increased (Fig. 8). High ionic strength in the dissolution medium weakens the structure of the Carbopol® gel by masking the repulsive forces between the charged polymer molecules (Lochhead and Warfield, 1985). The loss of gel structure could also account for the particles observed sloughing off bead surfaces exposed to the mechanical forces in the dissolution medium. The increase in surface area would result in a faster drug release rate. Increasing the paddle rotation speed increased these mechanical forces within the dissolution fluid and resulted in a faster release rate (Fig. 9).

4. Conclusions

The results of this study indicate that it is feasible to incorporate Carbopol® 974P, NF into beads manufactured by extrusion-spheronization. The adhesive force of wetted mixtures of Carbo-

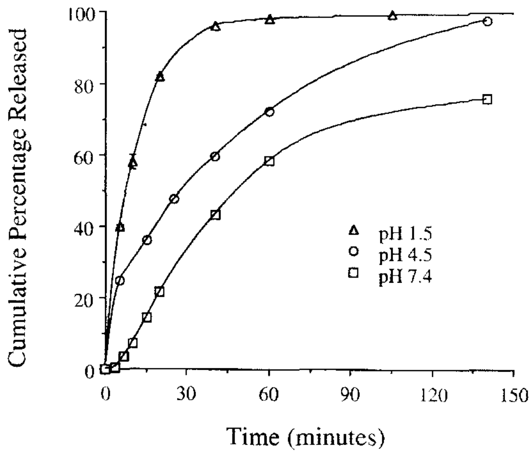

Fig. 7. pH effect on chlorpheniramine release at 0.032 ionic strength. Data points are the mean of three replicates; the error bars present the standard deviation.

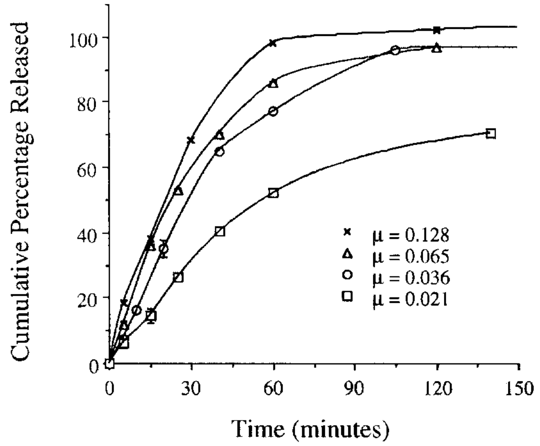

Fig. 8. Ionic strength effect on chlorpheniramine release in pH 7.4 phosphate buffer. Data points are the mean of three replicates; the error bars present the standard deviation.

pol® 974P, NF and Avicel PH101 was decreased dramatically in the presence of strong electrolytes. The charge density of the salt cation profoundly influenced the minimum salt concentration required to eliminate handling problems due to tack. Electrolyte type also affected the smoothness of the beads. The concentration of Carbopol® in bead formulations, the paddle rotation speed, and the pH and ionic strength of the dissolution medium affected the drug release rate.

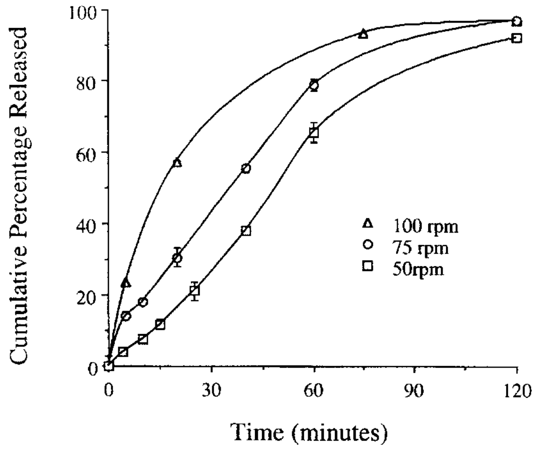

Fig 9. Paddle rotation speed effect on drug release in pH 7.4 phosphate buffer at 0.128 ionic strength. Data points are the mean of three replicates; the error bars present the standard deviation.

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References

Abd-Elbary, A., Mansour, F.F. and Foda, N., Interaction of Carbopol 934 with certain antihistaminic drugs. *Pharmazie*, 36 (1981) 356–358.

Baun, D.C. and Walker, G.C., The prolonged release of caramiphen hydrochloride and atropine sulfate from compressed tablets containing Carbopol 934. *Pharm. Acta Helv.*, 46 (1971) 94–113.

Carbopol® Resins Handbook, BFGoodrich Company, Specialty Polymers and Chemicals Division, Cleveland, OH, 1993.

Choulis, N.H. and Papadopoulos, H., Timed-release tablets containing quinine sulfate. *J. Pharm. Sci.*, 64 (1975) 1033–1035.

Choulis, N.H., Papadopoulos, H. and Choulis, M., Long acting methadone. *Pharmazie*, 31 (1976) 466–470.

Davidson, J.A. and Collins, E.A., Microrheology of thickened suspensions. *J. Colloid Interface Sci.*, 55 (1976) 163–169.

Durrani, M.J., Todd, R., Andrews, A., Whitaker, R.W., Greenberg, E. and Benner, S.C., Polymer concentration effects on Carbopol® 934P tablets for controlled release. *Proc. Int. Symp. Controlled Release Bioact. Mater.*, 19 (1992) 411–412.

Elsabbagh, H., Sakr, A. and Abd-Elhadi, S., Effect of guar gum on the dissolution rate of ephedrine hydrochloride and sulphadimidine tablets. *Pharmazie*, 33 (1978) 730–731.

Handbook of Chemistry and Physics, 50th edn., Weast, R.C. (Ed.), The Chemical Rubber Co., Cleveland, OH, 1969.

Kuhn, W., Hargitay, B., Katchalsky, A. and Eisenberg, H., Reversible dilation and contraction by changing the state of ionization of high-polymer acid network. *Nature*, 165 (1950) 514–516.

Lochhead, R.Y. and Warfield, D.S., Carbomers as thickeners and suspending agents in shampoos. *Soap Cosmet. Chem. Spec.*, 61 (1985) 46–54.

Perez-Marcos, B., Gutierrez, C., Gomez-Amoza, J.L., Martinez-Pacheco, R., Souto, C. and Concheiro, A., Usefulness of certain varieties of carbomer in the formulation of hydrophilic furosemide matrices. *Int. J. Pharm.*, 67 (1991) 113–121.

Schwarz, T.W., Emulsion with hydrocolloids. *Am. Perfum. Cosmet.*, 77 (1962) 85–88.

Testa, B. and Etter, J.C., Application of rheology to the study of interactions between Carbopol molecules as well as to the semiquantitative determination of the ionic strength of their dispersions. *Pharm. Acta Helv.*, 48 (1973) 378–388.