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Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes

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Summary

Chlorpheniramine maleate-loaded nonpareil seeds were coated in a fluidized bed with a commercial ethyl cellulose pseudolatex, Aquacoat, and ethyl cellulose pseudolatexes prepared by a microfluidization-solvent evaporation technique in order to investigate the effect of process variables (coating temperature, curing temperature and time) and formulation variables (surfactant concentrations) on the drug release in simulated gastric and intestinal fluids. Although curing and coating conditions did not affect the drug release in simulated gastric juice, dramatic increases in drug release were seen in simulated intestinal fluid with incompletely cured beads. The presence of the anionic surfactant, sodium lauryl sulfate, in the coating caused the pH-dependent drug release from ethyl cellulose pseudolatex-coated beads. The release from beads coated with surfactant-free pseudolatexes was insensitive to the pH of the dissolution medium. With cured beads, the faster initial drug release in simulated intestinal fluids was attributed to the better wetting of the beads, as indicated by contact angle measurements. The addition of cetyl alcohol as a cosurfactant decreased the drug release and pH sensitivity of the film.

Introduction

Acrylic and cellulosic polymers have been used extensively in the film coating of solid dosage forms to prepare oral sustained release formulations. While coating with organic polymer solutions is still widespread, aqueous colloidal polymer dispersions, called latexes or pseudolatexes, have been developed in order to eliminate the hazards associated with organic solvents (Banker and Peck, 1981; Lehmann, 1989). When compared to the film formation from organic polymer solutions, the film formation from aqueous latexes is a complex process. Various theories have been reported (Brown, 1956; Sheetz, 1965; Kast, 1985). In a simplified description, water evaporates and the colloidal polymer particles are forced together, deform and coalesce into a continuous film during the drying process.

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Ethyl cellulose is the most widely used water-insoluble polymer (Porter, 1989) and two aqueous latex dispersions, Aquacoat and Surelease, are commercially available. Aquacoat (30% w/w total solids) is prepared by a direct emulsification-solvent evaporation method (Vanderhoff and El-Asser, 1978; Steuernagel, 1989). The pseudolatex is stabilized with sodium lauryl sulfate and cetyl alcohol and requires the addition of plasticizers and possible dilution prior to use. Surelease (25% w/w total solids, ready for use) is prepared by a phase inversion in-situ emulsification technique (Moore, 1989). It contains ammonium oleate as a stabilizer and dibutyl sebacate as a plasticizer. Upon drying and film formation, ammonia evaporates leaving oleic acid as a plasticizer within the film.

The drug release from latex-coated dosage forms is strongly affected by variables influencing the coalescence of the polymer particles and hence the film formation process (Ghebre Sellassie, 1988; Harris and Ghebre-Sellassie, 1989). Process variables such as coating temperature (Yang and Ghebre-Sellassie, 1990), curing conditions (Goodhart et al., 1984; Ghebre-Sellassie et al., 1988), plasticization time (Lippold et al., 1989), and formulation variables such as the type and level of plasticizer (Steuernagel, 1989) have to be investigated in order to obtain reproducible drug release profiles.

With ethyl cellulose-coated beads, the drug release is expected to be pH-independent for drugs with pH-independent solubility characteristics. However, several studies with Aquacoat-coated beads showed a faster drug release in simulated intestinal fluid when compared to simulated gastric juice. Goodhart attributed the faster drug release to the ionization of sodium lauryl sulfate (Goodhart et al., 1984), while Lippold suggested that the presence of carboxyl groups on the polymer chain was responsible for the pH-dependent effects (Lippold et al., 1989; Sutter, 1987).

The objective of this study was to gain further insight into the effect of surfactant levels on the drug release in simulated gastric and intestinal fluids by coating drug-loaded beads with ethyl cellulose pseudolatexes of varying composition prepared by a microfluidization-solvent evaporation method. In addition to formulation variables, process parameters such as coating temperature and curing conditions were investigated. Chlorpheniramine maleate, a suitable candidate for an oral sustained release preparation, was selected because of its pH-independent solubility at physiological pH levels.

Materials and Methods

Materials

The following chemicals were obtained from commercial suppliers and used as received: chlorpheniramine maleate (Sigma Chemical Co., St Louis, MO), Aquacoat (FMC Corp., Princeton, NJ), ethyl cellulose (Ethocel STD 10 Premium, Dow Chemical Co., Midland, MI), sodium lauryl sulfate (Duponol C, DuPont Chemicals and Pigments Dept, Wilmington, DE), Cetyl Alcohol NF (Adol 520, Sherex Chemical Co. Inc., Dublin, OH), dibutyl sebacate (Eastman Kodak Co., Rochester, NY), nonpareil seeds (Nu-pareil PG sugar spheres NF, 18–20 mesh, Crompton & Knowles Corp., Pennsauken, NJ), Ethyl Alcohol, USP (Aaper Alcohol and Chemical Co., Shelbeville, KY), and hydroxypropyl methylcellulose, HPMC (Methocel E5 Premium Grade, Dow Chemical Co., Midland, MI).

Methods

Ethyl cellulose pseudolatexes were prepared by a high-pressure emulsification-solvent evaporation method. A solution of ethyl cellulose (48 g) in methylene chloride (260 ml) was emulsified into an aqueous phase (340 ml) containing sodium lauryl sulfate (0, 0.5, 4.0, and 6.0% w/w of total solids excluding plasticizer) with a homogenizer (Polytron, Brinkman Instruments, Westbury, NY) to form an o/w emulsion. Cetyl alcohol (0, 3.0, 6.0, and 9.0% w/w of total solids excluding plasticizer), the co-surfactant, and dibutyl sebacate (20% w/w of total solids including plasticizer), the plasticizer, were also dissolved in the organic phase prior to emulsification. The particle size of the internal phase was reduced into the colloidal size range by passing the emulsion through a microfluidizer (standard M-110 laboratory model, Microfluidics Corp., Newton, MA) to form the pseu-

dolatex (operating pressure = 7000 lb/inch^2 (psi), 5 cycles). The pseudolatexes were stirred for 48–72 h at room temperature and ambient pressure to evaporate the solvent. The standard formulation contained sodium lauryl sulfate, 4% w/w and cetyl alcohol, 9% w/w. The average particle size of the pseudolatexes was determined by photon correlation spectroscopy (BI-200SM goniometer, BI-2030 digital correlator, Brookhaven Instruments Corp., Holtsville, NY, Melles Griot 10 mW He–Ne laser) and was in the range of 120–140 nm for the self-prepared pseudolatexes.

A solution of chlorpheniramine maleate (82 g), HPMC (3 g), and PEG 3350 (0.3 g) in ethanol/water (60 : 40% w/w, 200 ml) was sprayed onto nonpareil seeds in a fluid-bed coater (Uni-Glatt Laboratory Unit, Wurster insert, Glatt Air Technique, Ramsey, NJ; 600 g charge; inlet temperature 45–50 °C; outlet temperature 40–45 °C; spray rate 2 ml/min) to obtain drug-layered beads (12 mg drug/100 mg beads). The pseudolatexes (15% w/v) were sprayed onto a mixture of drug-loaded and placebo beads (1 : 9 w/w) in the fluid-bed coater (400 g charge; inlet temperature, 45–50 °C, outlet temperature, 40–45 °C; spray rate, 1 ml/min for 10 min, then 3–5 ml/min; pre-heating time, 15 min, post-drying time, 5 min) until a 10% w/w weight gain was achieved. With Aquacoat, dibutyl sebacate was emulsified into the pseudolatex 2 h prior to coating. The coated beads were cured at room temperature, 40, 50, or 60 °C for different time periods (1, 3, 6, 15, and 24 h).

The USP XXI rotating paddle method (1.5–2.0 g beads, 37 °C, 50 rpm, 500 ml 0.1 M HCl or 0.1 M pH 7.4 phosphate buffer used as simulated gastric juice or intestinal fluid; $n = 3$, coefficient of variation $< 5\%$) was used to study the drug release from the coated beads. The samples (2 ml, not replaced) were withdrawn at predetermined intervals and assayed spectrophotometrically at $\lambda = 263$ nm.

To determine the chlorpheniramine maleate solubility, excess amount of drug was placed in contact with the two release media. The samples ($n = 2$) were shaken for 48 h at 37 °C, filtered and assayed spectrophotometrically.

For contact angle measurement, pseudolatexes (6 ml) were cast into aluminum petri dishes (6 cm in diameter) and dried for 24 h at 60 °C. The dried films were cut and mounted on the glass slides (25 × 25 mm^2) with a silicone adhesive sealant (GC Electronics, Rockford, IL). The contact angle was measured using the NRL contact angle goniometer (Model 100-00) equipped with a micro-syringe attachment (Rame-Hart, Inc., Mountain Lakes, NJ). The glass slide was placed on an adjustable platform and a drop of the medium (2 μl) was applied on the film using a micrometer syringe (Gilmont Instruments, Great Neck, NY). The drop was allowed to rest for 2 min before the contact angle measurement. The contact angle was measured in four places on each test film.

Results and Discussion

Whereas true latexes are prepared from monomers by emulsion polymerization techniques (Lehmann, 1989), pseudolatexes are prepared by direct emulsification of preexisting polymers, either from solution or melt (Chang et al., 1987). In this study, ethyl cellulose pseudolatexes similar in composition to the commercially available Aquacoat were prepared by a microfluidization-solvent evaporation technique. These colloidal polymer dispersions were used to coat chlorpheniramine maleate-loaded beads in order to investigate the effect of process and pseudolatex formulation variables on the drug release.

The glass transition temperature of ethyl cellulose has been reported to be at 135 °C (Porter, 1989) and is above the coating or bed temperature attainable in a fluid bed coater. Several plasticizers with levels between 20 and 30% are recommended to reduce the glass transition and hence minimum film formation temperature (Aquacoat Handbook). During plasticization, the plasticizers diffuse into and soften the polymeric particles to promote their deformation and coalescence into a continuous film. The plasticization time (time elapsed between addition of plasticizer to the latex and coating process) was shown to affect the drug release (Lippold et al., 1989). In this study, the plasticizer, dibutyl sebacate, was incorporated into the colloidal polymer particles by dissolving di-

butyl sebacate directly into the organic polymer solution prior to emulsification of the organic phase into the aqueous phase. This eliminated any time-dependent effects and maximized the amount of plasticizer in the polymer phase.

In order to investigate the effect of process variables on the film formation and hence drug release, the drug-loaded beads were coated at two temperatures (outlet temperatures of 40 or 45 °C) with self-prepared ethyl cellulose pseudolatexes similar in composition to Aquacoat. The coalescence of latex particles is often incomplete after the coating process, and a curing step has been recommended with ethyl cellulose pseudolatexes to accelerate further coalescence and formation of a homogeneous film (Bindschaedler et al., 1983; Harris and Ghebre-Sellassie, 1989; Lippold et al., 1989). In this study, the coated beads were oven-cured at 40, 50, or 60 °C for curing periods between 1 and 24 h. As can be seen in Fig. 1A and B, the drug release in 0.1 M HCl was almost independent of the investigated coating and curing conditions. On the contrary, the drug release in pH 7.4 buffer was strongly affected by the curing condition and to a lesser extent by the coating temperature (Fig. 2). Uncured beads coated at either 40 or 45 °C released the drug much faster in pH 7.4 buffer, when compared to the release in 0.1 M HCl. Although the bed temperature was above the minimum film formation temperature of the pseudolatex (Sutter, 1987), evaporation of water during the coating process could result in a cooling effect and may have kept the temperature on the bead surface below the minimum film formation temperature. Coating at temperatures above 45 °C was not possible because of sticking and agglomeration of the beads. While curing at 40 °C for 24 h was insufficient, curing at either 50 or 60 °C resulted in a significant reduction in drug release in simulated intestinal fluids. The limiting drug release pattern was approached after curing the beads for 1 h at 60 °C for both coating temperatures. At a curing temperature of 50 °C, longer curing times were required to approach the limiting drug release pattern, the required curing times being shorter for beads coated at the higher temperature. All following samples were cured at 60 °C for 1 hour. As an alternative to oven-curing,

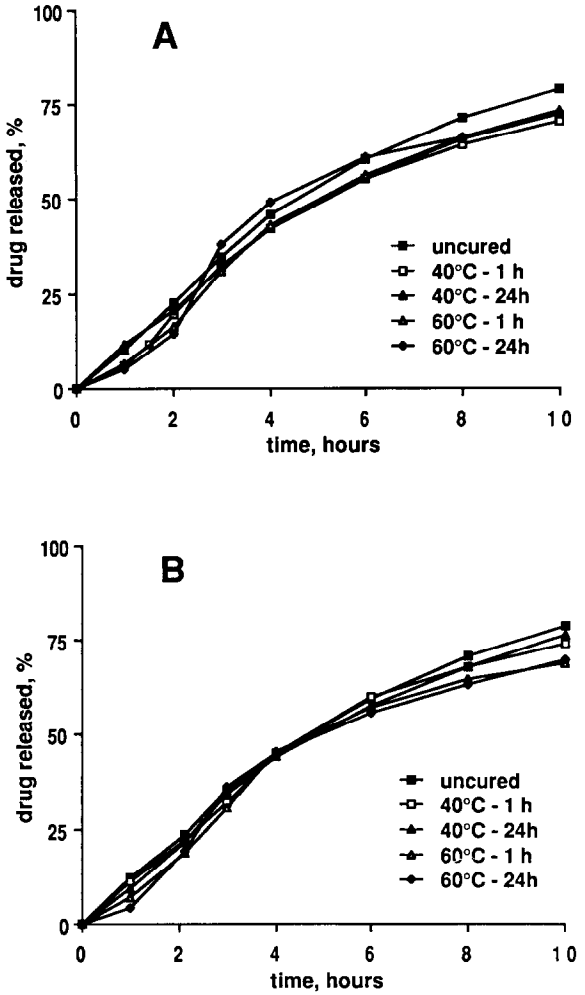

Fig. 1. Effect of coating temperature, (A) 40 °C and (B) 45 °C, and curing conditions (curing temperature-curing time) on the chlorpheniramine maleate release in 0.1 M HCl.

Aquacoat-coated beads have been cured directly in the fluidized bed after coating the beads with a thin layer of hydroxypropyl methylcellulose (Harris, 1986). The overcoat prevented the sticking and agglomeration of the beads at higher temperatures.

Similar results were obtained with beads coated with the commercially available ethyl cellulose pseudolatex, Aquacoat (Fig. 3). To explain the differences between the drug release in simulated gastric and intestinal fluids, various factors had to be considered. Drug solubility could be eliminated

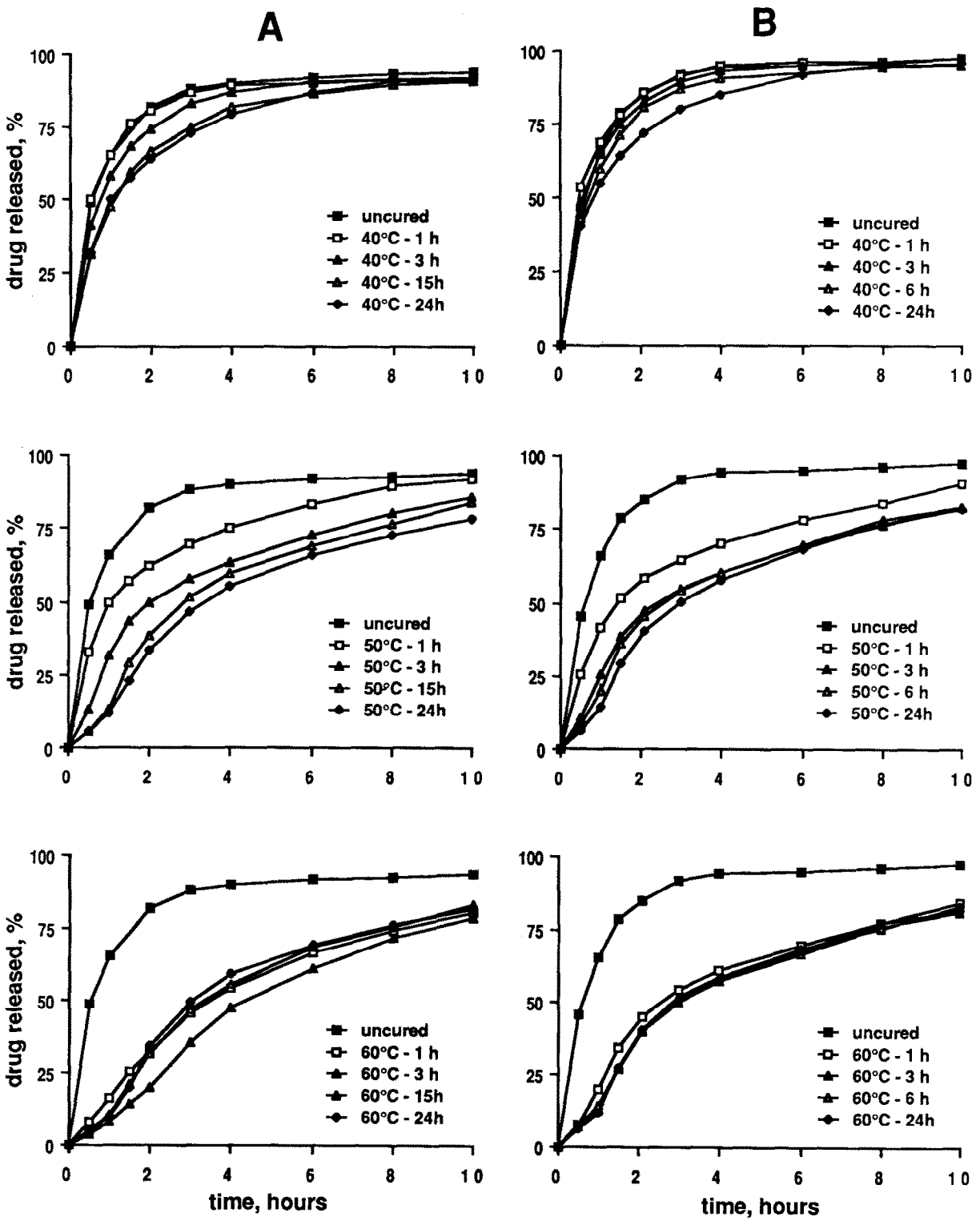

Fig. 2. Effect of coating temperature, (A) 40 °C and (B) 45 °C, and curing conditions (curing temperature-curing time) on the chlorpheniramine maleate release in 0.1 M pH 7.4 phosphate buffer.

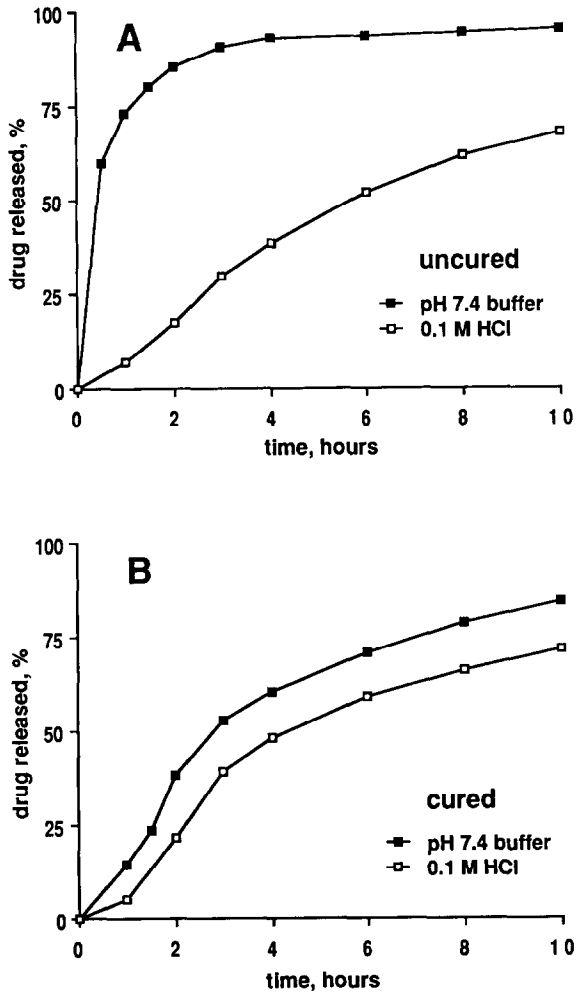

Fig. 3. Chlorpheniramine maleate release from (A) uncured and (B) cured Aquacoat-coated beads in 0.1 M pH 7.4 phosphate buffer and 0.1 M HCl.

as a variable influencing the drug release because of similar solubilities of chlorpheniramine maleate ($pK_a = 9.2$) in the two dissolution media (574 mg/ml in 0.1 M HCl and 562 mg/ml in 0.1 M pH 7.4 phosphate buffer at 37 °C). The pH-dependent drug release from solid dosage forms coated with Aquacoat has also been observed by other workers and has been attributed either to the presence of the surfactant (Goodhart et al., 1984) or to the ionization of carboxylic groups present in the polymer (Lippold et al., 1989). In Aquacoat, sodium lauryl sulfate (4% w/w of total solids), an anionic surfactant, is used in combination with cetyl alcohol (9% w/w of total solids) to stabilize the colloidal ethyl cellulose dispersion. The surfactants are used to lower the interfacial tension between the organic polymer solution and the aqueous phase during pseudolatex formation and to prevent agglomeration and coalescence of the dispersed polymer particles during storage. However, the surfactants will also be present in the coating after drying and therefore can modify the film properties.

To investigate the contributions of sodium lauryl sulfate or the polymer to the pH-dependent

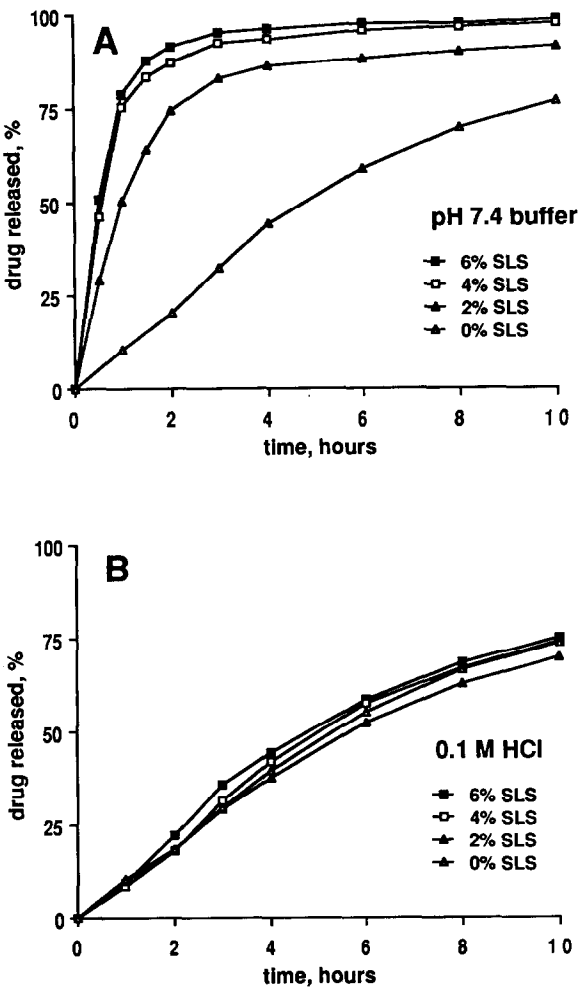

Fig. 4. Effect of sodium lauryl sulfate (SLS) concentration (% w/w of coating) on the chlorpheniramine maleate release in (A) 0.1 M pH 7.4 phosphate buffer and (B) 0.1 M HCl from uncured beads.

drug release, ethyl cellulose pseudolatexes were prepared with varying surfactant concentrations. Ethyl cellulose pseudolatexes, which were stable for a few days, could be prepared without sodium lauryl sulfate. The effect of sodium lauryl sulfate concentration in the coating on the drug release from uncured and cured beads is shown in Figs 4 and 5. With uncured beads, the amount of sodium lauryl sulfate in the film coat had no effect on the drug release in 0.1 M HCl but resulted in significant increases in drug release in pH 7.4 buffer (Fig. 4). Polymeric flakes from the coatings containing sodium lauryl sulfate could be seen in pH 7.4 buffer but not in 0.1 M HCl, indicating incomplete film formation. No flakes were seen with sodium lauryl sulfate-free coatings or cured beads. With cured beads, the difference between the drug release in the two media increased with increasing concentration of sodium lauryl sulfate (Fig. 5), however to a lesser extent when compared with the uncured beads. By visually comparing the release profiles in the two media at higher sodium lauryl sulfate concentrations, it appeared that the release profiles in 0.1 M HCl were similar to the release profiles in pH 7.4 buffer after a lag time. The faster initial drug release in pH 7.4 buffer

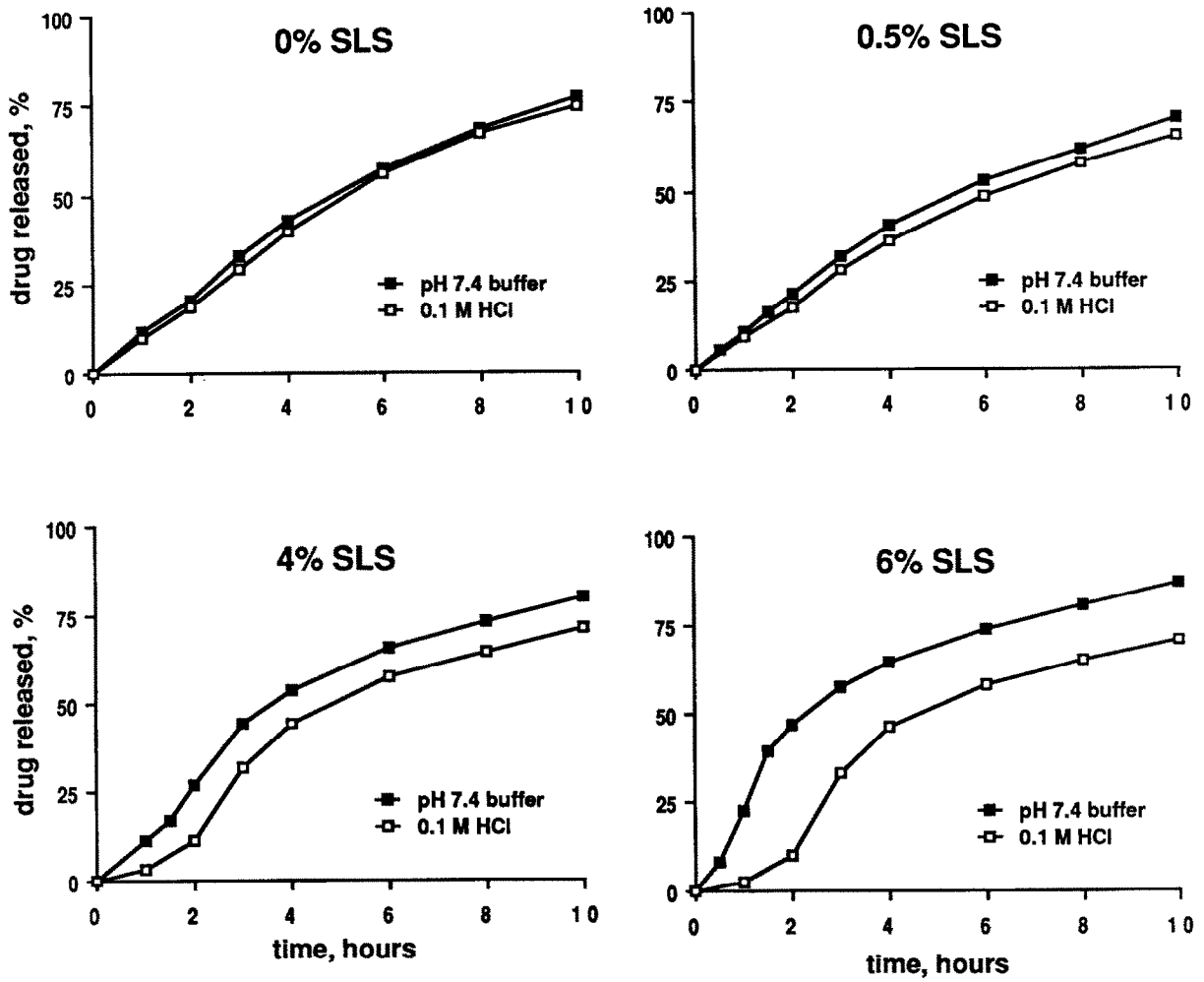

Fig. 5. Effect of sodium lauryl sulfate (SLS) concentration (% w/w of coating) on the chlorpheniramine maleate release in 0.1 M pH 7.4 phosphate buffer and 0.1 M HCl from cured beads.

TABLE 1

Contact angles between ethyl cellulose pseudolatex-cast films and 0.1 M HCl or pH 7.4 buffer

	0.1 M HCl	pH 7.4 buffer
Aquacoat	67.9 ± 3.9	40.8 ± 3.8
Sodium lauryl sulfate (%)		
0	63.6 ± 2.1	63.1 ± 1.9
2	62.3 ± 0.6	38.6 ± 3.0
4	50.4 ± 3.1	31.0 ± 1.8
6	47.9 ± 1.5	24.1 ± 0.8
Cetyl alcohol (%)		
0	17.5 ± 1.3	10.4 ± 1.4
9	50.4 ± 3.1	31.0 ± 1.8

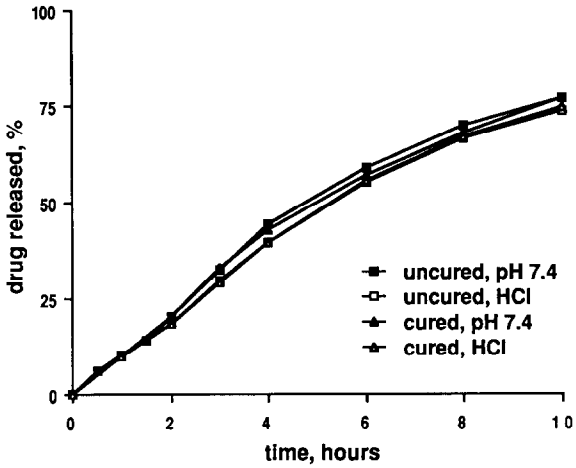

Fig. 6. Chlorpheniramine maleate release in 0.1 M pH 7.4 phosphate buffer and 0.1 M HCl from uncured and cured beads coated with sodium lauryl sulfate-free ethyl cellulose pseudolatexes.

may be an indication of better wetting of the beads with this medium when compared to 0.1 M HCl. Sodium lauryl sulfate, an anionic surfactant with a pK_a of 1.9 (conjugate acid), will be surface active only in the ionized state. It is approx. 10% ionized in 0.1 M HCl when compared to complete ionization in pH 7.4 buffer. The wetting hypothesis was confirmed by measuring the contact angles between pseudolatex-cast ethyl cellulose films and the two dissolution media. As shown in Table 1, the contact angle was the same on surfactant-free ethyl cellulose films. The contact angle decreased with increasing concentration of sodium lauryl sulfate in the film and was significantly lower on films wetted with pH 7.4 buffer than on films wetted with 0.1 M HCl. A lower contact angle indicated better wetting and therefore explained the inital faster drug release in pH 7.4 buffer.

No effects of curing and of the pH of the dissolution media were seen with the drug release profiles from beads coated with surfactant-free ethyl cellulose pseudolatexes indicating good film formation during the coating of the beads (Fig. 6). Besides the plasticizer, the surfactant system may have a significant influence on the coalescence of the polymer particles. Although a surfactant is needed to stabilize the pseudolatex, sodium lauryl sulfate may interfere with the coalescence during the coating process. The surfactant is located at the particle surface and in the aqueous phase and repulsive forces have to be overcome during fusion of the latex particles. These results clearly demonstrated that the pH-dependent drug release was caused by the presence of the anionic surfactant, sodium lauryl sulfate, and not the polymer.

Cetyl alcohol, a long-chain fatty alcohol, is present in Aquacoat as a co-surfactant (9% w/w of total solids) to stabilize the pseudolatex. Its effect on the drug release was investigated by dissolving different amounts into the organic polymer-plasticizer solution prior to emulsification of the organic phase into the aqueous phase during pseudolatex formation. An increase in the amount of cetyl alcohol resulted in a significant decrease in drug release (Fig. 7). The presence of cetyl alcohol rendered the film coat more hydrophobic, as indicated by an increased contact angle (Table 1). The pH-sensitivity of the films decreased with increasing amount of cetyl alcohol. Additionally, cetyl alcohol may have a plasticizing effect on ethyl cellulose, or may melt within the film during dissolution studies at 37 °C. Cetyl alcohol (melting point 46–49 °C) melts and dissolves in the plasticizer, dibutyl sebacate, at 37 °C.

In conclusion, it was shown that the pH-dependent drug release from ethyl cellulose pseudolatex-

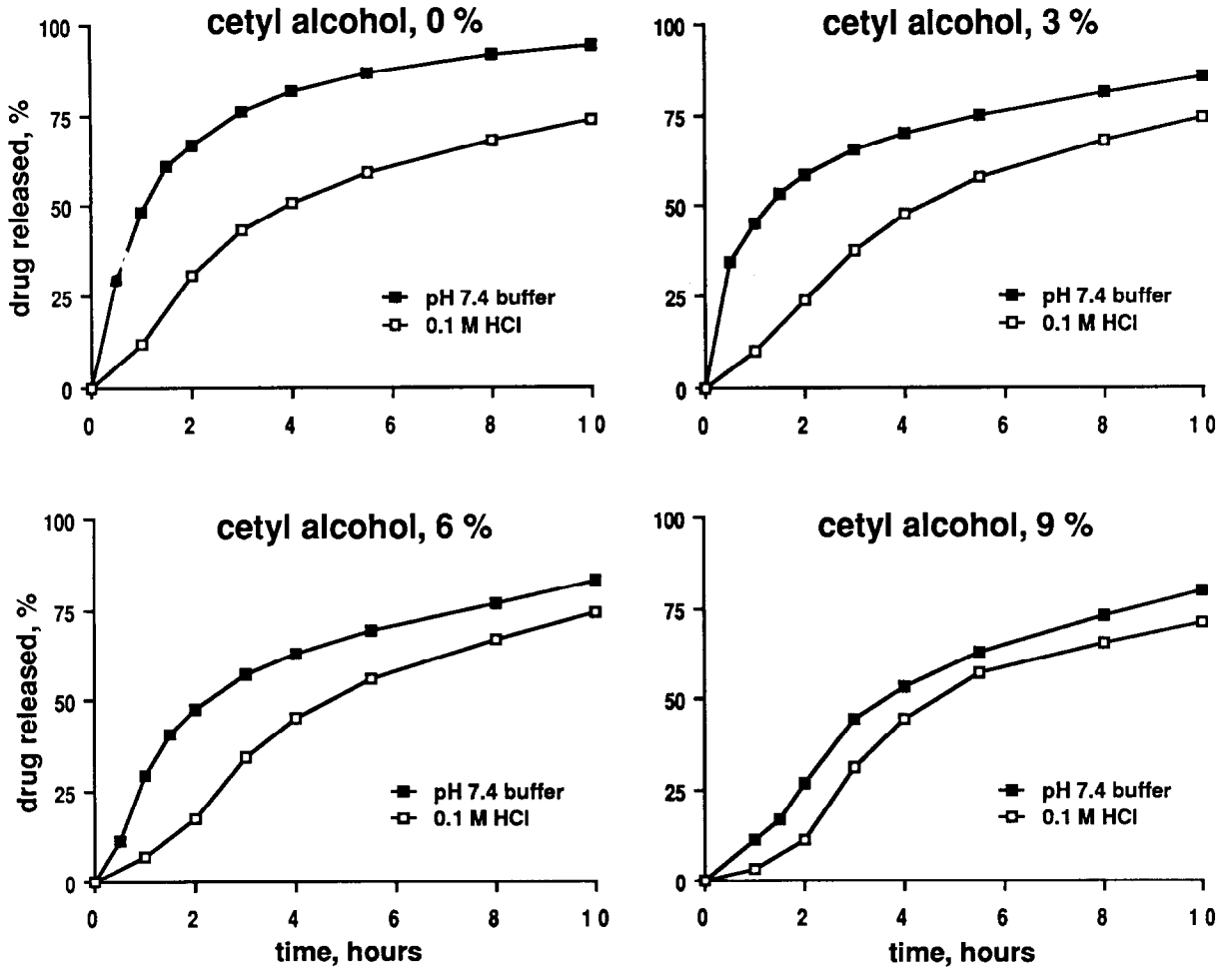

Fig. 7. Effect of cetyl alcohol concentration (% w/w of coating) on the chlorpheniramine maleate release in 0.1 M pH 7.4 phosphate buffer and 0.1 M HCl from cured beads.

coated beads was caused by the presence of the anionic surfactant, sodium lauryl sulfate, and not the polymer. Although curing and coating conditions did not affect the drug release in simulated gastric juice, dramatic increases in drug release were seen in simulated intestinal fluid with incompletely cured beads. With cured beads, the faster initial drug release in simulated intestinal fluids was attributed to the better wetting of the beads. The selection of the surfactant system is an important task to be considered when developing aqueous colloidal polymer dispersions because of its potential dramatic impact on film formation and permeability, and other film characteristics.

References

Aquacoat Handbook, FMC Corp., Philadelphia, PA, 1982.

Banker, G.S. and Peck, G.E., The new, water-based colloidal dispersions. *Pharm. Technol.* 5 (1981) 55–61.

Bindschaedler, C., Gurny, R. and Doelker, E., Theoretical concepts regarding the formation of films from aqueous

microdispersions and application to coating. *Lab. Pharm. Probl. Technol.*, 31 (1983) 389–394.

Brown, G.L., Formation of films from polymer dispersions. *J. Polym. Sci.*, 22 (1956) 423–434.

Chang, R.-K., Hsiao, C.H. and Robinson, J.R., A review of aqueous coating techniques and preliminary data on release from a theophylline product. *Pharm. Technol.*, 11 (1987) 56–68.

Ghebre-Sellassie, I., Recent advances in modified-release coating utilizing aqueous polymeric dispersions. Proceedings of Pharmaceutical Technology Conference, NJ, September 26–28, 1988.

Ghebre-Sellassie, I., Iyer, U., Kubert, D. and Fawzi, M.B., Characterization of new water-based coatings for modified-release preparations. *Pharm. Technol.*, 12 (1988) 96–106.

Goodhart, F.W., Harris, M.R., Murthy, K.S. and Nesbitt, R.U., An evaluation of aqueous film-forming dispersions for controlled release. *Pharm. Technol.*, 8 (1984) 64–71.

Harris, M.R., Ghebre-Sellassie, I. and Nesbitt, R.U., A water-based coating process for sustained release. *Pharm. Technol.*, 10 (1986) 102–107.

Harris, M.R. and Ghebre-Sellassie, I., Aqueous polymeric coating for modified-release pellets. In McGinity, J.W. (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Dekker, New York, 1989, pp. 63–79.

Kast, H., Aspects of film formation with emulsion copolymers. *Makromol. Chem. Suppl.*, 10/11 (1985) 447–461.

Lehmann, K.O.R., Chemistry and application properties of polymethacrylate coating systems. In McGinity, J.W. (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Dekker, New York, 1989, pp. 153–245.

Lippold, B.H., Sutter, B.K. and Lippold, B.C., Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersions. *Int. J. Pharm.*, 54 (1989) 15–25.

Moore, K.L., Physicochemical properties of Opadry, Coateric, and Surelease. In McGinity, J.W. (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Dekker, New York, 1989, pp. 303–315.

Porter, S.C., Controlled-release film coatings based on ethyl cellulose. *Drug Dev. Ind. Pharm.*, 15 (1989) 1495–1521.

Sheetz, D.P., Formation of films by drying of latex. *J. Appl. Polym. Sci.*, 9 (1965) 3759–3773.

Steuernagel, C.R., Latex emulsions for controlled drug delivery. In McGinity, J.W. (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Dekker, New York, 1989, pp. 1–61.

Sutter, B., Aqueous ethyl cellulose dispersions for preparing microcapsules with controlled drug release. Ph.D. Thesis, University of Düsseldorf, Germany, 1987.

Vanderhoff, J.W. and El-Asser; M.S., *U.S. Patent* 4,177,177 (1978).

Yang, S.T. and Ghebre-Sellassie, I., The effect of product bed temperature on the microstructure of Aquacoat-based controlled-release coatings. *Int. J. Pharm.*, 60 (1990) 109–124.