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THE EFFECT OF CURING ON DRUG RELEASE AND MORPHOLOGICAL PROPERTIES OF ETHYLCELLULOSE PSEUDOLATEX-COATED BEADS

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ABSTRACT

Drug-containing nonpareil beads were coated in a fluidized bed with a commercial ethylcellulose pseudolatex, Aquacoat. The drug release was investigated as a function of curing conditions (curing time and temperature) for a hydrophilic and lipophilic drug (chlorpheniramine maleate and ibuprofen) at different levels of plasticizer (triethyl citrate). Curing of coated beads at elevated temperatures immediately after the coating process significantly changed the drug release pattern. Both a retardation and an enhancement in drug release were seen, with the extent being dependent on the type of drug and curing conditions. With chlorpheniramine maleate, a drug with low affinity for the ethylcellulose coating, a curing step was necessary at intermediate plasticizer levels to obtain good film formation and a limiting drug release pattern, while the use of higher plasticizer levels eliminated the need for a curing step. With ibuprofen, a lipophilic drug with high solubility in the ethylcellulose coating, drug crystals were apparent on the bead surface after curing. Curing of ibuprofen beads as a function of time initially decreased but then substantially increased the drug release as a result of drug diffusion across the ethylcellulose membrane with subsequent crystallization on the bead surface. An intermediate seal coat reduced the diffusion of the drug into the ethylcellulose coating.

INTRODUCTION

Aqueous colloidal polymer dispersions (latexes or pseudolatexes) have been developed as an alternative to organic polymer solutions for the coating of solid dosage forms (1-3). Films or coatings of water-insoluble polymers can be prepared without toxic organic solvents. The mechanism of film formation from aqueous polymer dispersions is a complex process (4-8). During the spraying of the polymer dispersion onto solid dosage forms in a suitable coating equipment, water evaporates, forcing the colloidal particles together. Upon further evaporation, the particles deform and coalesce into a continuous polymer film at temperatures above the minimum film formation of the polymer dispersion. During storage or aging of the films, further gradual coalescence occurs whereby the polymer chains and segments in adjacent polymer particles diffuse across particle boundaries eventually leading to complete coalescence and disappearance of the individual particle contours (9-12). This final stage of the film formation process is time- and temperature-dependent (13-14).

An important task in the development of controlled release pharmaceutical dosage forms is the assurance of a stable drug release pattern during its shelf life. Changes in the drug release pattern have been observed with dosage forms coated with colloidal polymer dispersions (3, 15, 16). They have been attributed to the incomplete coalescence of the colloidal particles during the coating process and to their further coalescence upon storage. These aging phenomena affect the microstructure of the polymer coating and hence its permeability and drug release. To overcome this problem, a thermal treatment (curing) of the solid dosage forms immediately following the coating process is often recommended in order to further particle coalescence and achieve complete film formation, thus avoiding changes in the morphological and drug release properties during storage (15-18). During the curing step, the coated dosage forms are subjected to a heat treatment above the glass transition temperature of the polymer. This is achieved by either storing the coated dosage forms in an oven or through further fluidization in the heated fluidized bed coater immediately after the completion of the coating process for a short period of time. A hydrophilic overcoat of a water-soluble polymer such as hydroxypropyl methylcellulose may be applied to the coated substrate prior to the curing step in order to prevent particle sticking as a result of the softening of the polymer coating (19, 20).

The objective of this study was to investigate the effect of different curing conditions on the release and morphological properties of beads containing a hydrophilic or lipophilic model drug, chlorpheniramine maleate or ibuprofen, coated with a commercially available ethylcellulose pseudolatex, Aquacoat.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: chlorpheniramine maleate, ibuprofen (Sigma Chemical Co., St. Louis, MO), Aquacoat (25 %w/w aqueous ethylcellulose dispersion), (FMC Corporation, Newark, DE), triethyl citrate (Citroflex-2, Morflex Inc., Greensboro, NC), nonpareil seeds (Nu-Pareil PG sugar spheres NF, 18-20 mesh, Ingredient Technology Corp., Pennsauken, NJ), ethylcellulose (Ethocel STD 10 Premium, Dow Chemical Co., Midland, MI), ethyl alcohol, USP (Aaper Alcohol and Chemical Co., Shelbeville, KY), acetone, methylene chloride (Fisher Scientific Co., Fair Lawn, NJ), hydroxypropyl methylcellulose, HPMC (Methocel E5 Premium, Dow Chemical Co., Midland, MI).

Methods

A mixture of placebo beads and beads containing drug (chlorpheniramine maleate or ibuprofen) (9:1 w/w) was coated with Aquacoat (solids content of dispersion, 15 %w/w; triethyl citrate concentration, 10, 15, 20, 25, 30, 35 %w/w of pseudolatex solids content; plasticization time, 2 h) in a fluid-bed coater (Uni-Glatt Laboratory Unit, Wurster insert, Glatt Air Technique, Ramsey, NJ; 400 g charge, inlet temperature = 45 - 50 °C, outlet temperature = 40 - 45 °C, spray rate = 2 ml/min for 10 minutes, then 3-5 ml/min, pre-heating time = 15 min, post-drying time = 5 min) to obtain a 5 or 10 % weight increase. The coated beads were cured at room temperature (uncured), 40, 50, or 60 °C for different time periods ranging from 0.5 to 24 h.

The USP XXI rotating paddle method (1.5 - 2.0 g beads, 37 °C, 50 rpm, 500 ml 0.1 M pH 7.4 phosphate buffer; 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 time intervals and assayed spectrophotometrically (ibuprofen, $\lambda = 222$ nm; chlorpheniramine maleate, $\lambda = 264$ nm).

The drug-containing films were prepared by codissolving ibuprofen (600 mg), ethylcellulose (400 mg), triethylcitrate (100mg) in methylene chloride (7 ml). The drug-polymer solution was cast into aluminum dishes (6 cm in diameter) and dried at room temperature for 48 h. The HPMC and Aquacoat films were prepared by casting and drying an aqueous polymer solution and a plasticized dispersion (triethyl citrate, 20 %w/w; plasticization time, 2 h), respectively, on a teflon protective overlay (Cole-Parmer Instrument Co., Chicago, IL) mounted on a glass plate (area of casting = 9.5 x 13.5 cm^2; casting volume = 40 ml; total solids content = 2.5 g). The films were oven-dried for 48 h at 40 °C. The dried films were peeled from the teflon surface and cut into 4 x 4 cm^2 test sections. The laminated films were prepared by wetting one side of the Aquacoat or HPMC film with acetone:ethanol (50:50 %v/v) and pressing it immediately onto the drug-containing films. A successive lamination step was also applied with a laminate of the HPMC / drug-containing layer, to obtain a three-layer laminate containing Aquacoat / HPMC / drug-containing layer. The laminates were oven-cured at 60 °C for 6 h.

The morphology of the surfaces and cross sections of polymeric laminates and coated beads were examined by scanning electron microscopy (SEM). A cross section of the coated beads was obtained by cutting the beads with a razor blade. The dried film and bead samples were mounted onto the stages prior to coating for 70 seconds under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and were then observed with a scanning electron microscope (Jeol JSM 35C).

RESULTS AND DISCUSSION

During coating of solid dosage forms with aqueous polymer dispersions, the coalescence of colloidal polymer particles into a homogeneous film is often incomplete. The exposure of the coated dosage form to temperatures above the glass transition temperature immediately following the coating step is recommended to complete the coalescence and film formation process. This curing or thermal treatment generally results in a reduction in drug release when compared to the drug release from uncured dosage forms (15, 17, 18, 20). In a previous study with chlorpheniramine maleate-loaded beads coated with ethylcellulose pseudolatexes, a limiting drug release pattern was approached after curing the beads for 1 h at 60 °C (18).

In this study, the effect of curing of multiparticulates containing a hydrophilic (chlorpheniramine maleate) or lipophilic (ibuprofen) drug and different levels of plasticizer on the drug release were investigated.

Besides curing conditions (curing temperature and time), formulation factors such as the plasticizer concentration will affect the film formation process. Chlorpheniramine maleate-beads were coated with Aquacoat, an ethylcellulose pseudolatex, containing different levels of triethyl citrate, a water-soluble plasticizer. Figure 1 shows the effect of triethyl citrate concentration and curing temperature on the chlorpheniramine maleate release in pH 7.4 buffer. The drug release was very rapid at a 10 % level of triethyl citrate (%w/w of polymer). This plasticizer concentration was insufficient to reduce the minimum film formation temperature below the coating temperature, which was a prerequisite for coalescence. Curing these beads at higher temperatures did not retard the drug release. At intermediate plasticizer levels (15 - 25 %w/w of polymer), curing of the beads resulted in a decrease in the drug release when compared to uncured beads, this effect becoming more dominant at higher curing temperatures (60 °C vs 40 °C). The drug release from uncured beads decreased above a triethyl citrate concentration of 15 % indicating at least partial film formation (Figure 2). The drug release approached a limiting pattern as the plasticizer concentration was increased to 25 - 35 %w/w (Figure 1). At plasticizer levels above 25 %, curing had little effect on the drug release, indicating good coalescence of the colloidal polymer particles during the coating step. In summary, a curing step was necessary at intermediate plasticizer levels to obtain good film formation and a limiting drug release pattern, while the use of higher plasticizer levels eliminated the need for a curing step.

While curing of the Aquacoat-coated chlorpheniramine maleate beads resulted in a retardation of the drug release, curing of Aquacoat-coated ibuprofen beads unexpectedly resulted in a significant increase in drug release (Figure 3). The thermal treatment of coated beads did not only positively affect the coalescence of the colloidal polymer particles in a homogeneous film, but could also enhance the interaction of the drug core with the polymer coating. The increase in drug release, which increased with increasing curing temperature and time, could be explained with the migration of ibuprofen from the bead interior to the bead surface during the curing step. Scanning electron microscopy was used to characterize the surface morphology of the beads (Figure 4). The surface of the uncured beads was uniform and smooth and no crystals were visible. However, large drug crystals could be

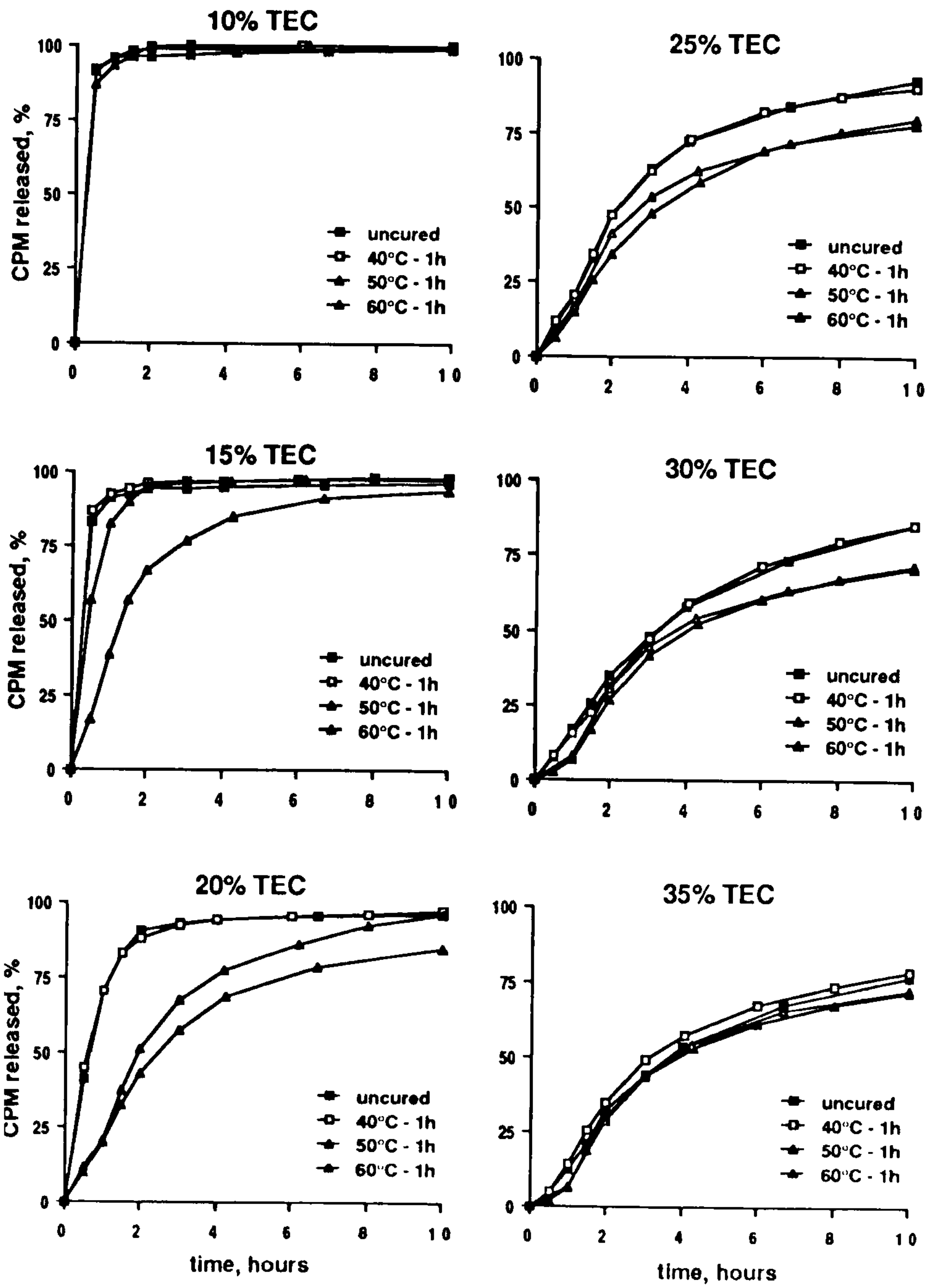

FIGURE 1
Effect of triethyl citrate concentration and curing conditions on chlorpheniramine maleate release in 0.1 M pH 7.4 buffer from Aquacoat-coated beads.

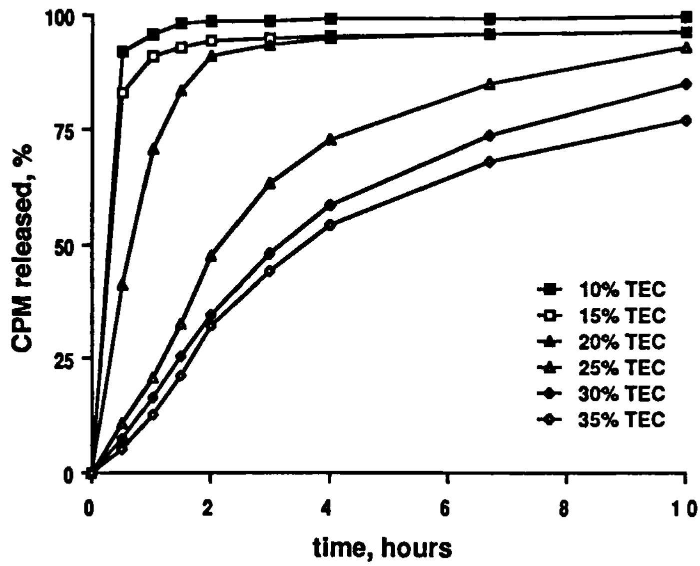

FIGURE 2
Effect of triethyl citrate concentration on chlorpheniramine maleate release in 0.1 M pH 7.4 buffer from uncured Aquacoat-coated beads.

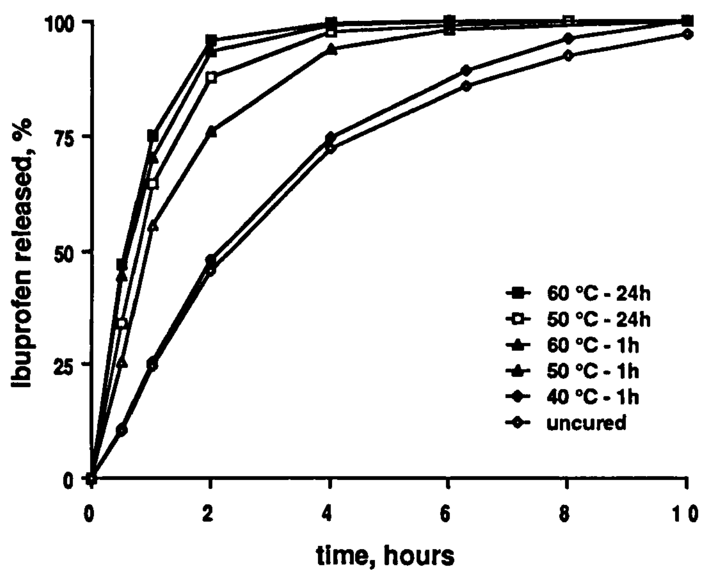

FIGURE 3
Effect of curing conditions on ibuprofen release in 0.1 M pH 7.4 buffer from Aquacoat-coated beads.

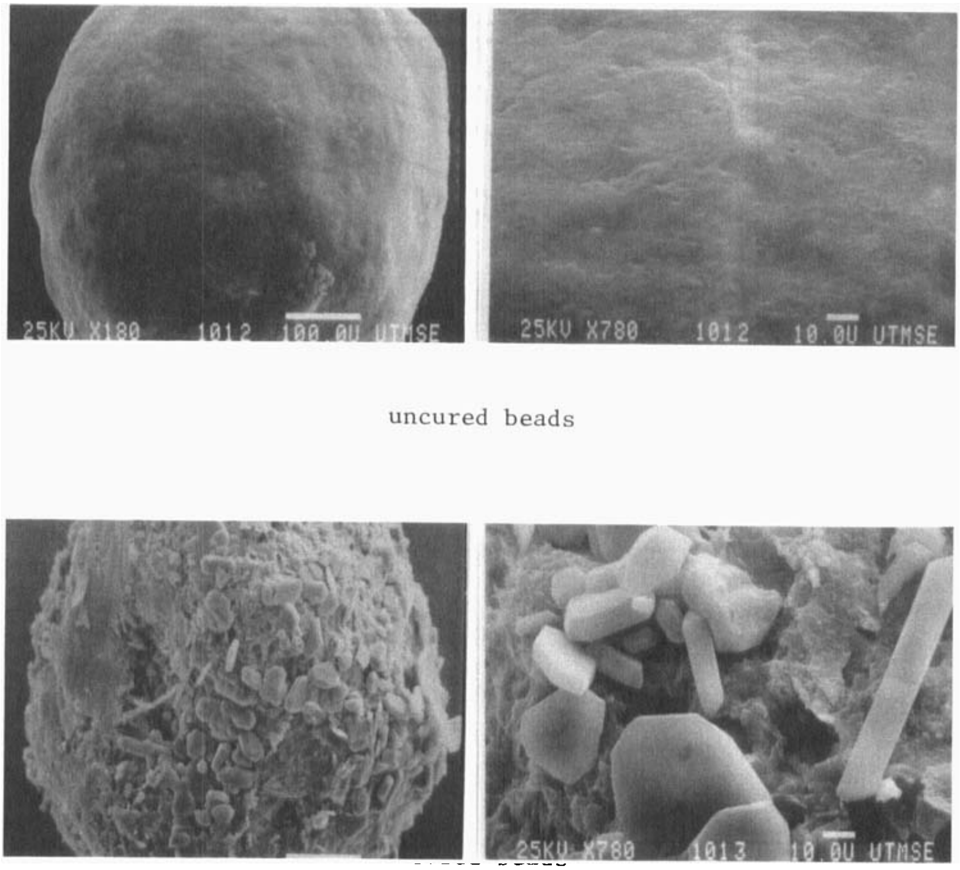

FIGURE 4
Scanning electron micrographs of surfaces of uncured and cured Aquacoat-coated ibuprofen beads.

observed on the surface of beads cured at 50 °C for 24 h, indicating the migration of ibuprofen during the thermal treatment with subsequent crystallization on the bead surface.

The diffusion of ibuprofen across the Aquacoat membrane during thermal treatment was confirmed by preparing a laminate comprised of an ibuprofen-containing reservoir and the Aquacoat membrane. The drug reservoir layer containing 60 % w/w ibuprofen was cast from an organic solution of ethylcellulose and drug. The Aquacoat film, prepared by casting and drying a plasticized dispersion (20 %w/w triethyl citrate), was laminated onto the reservoir layer. Figure 5A shows the surface of the laminated film after curing for 6 hours at 60 °C. A large number of scaly drug crystals and aggregates appeared on the film surface, which was smooth prior to the curing step.

The appearance of ibuprofen crystals on the film or bead surface could be explained with the high affinity of the drug for the polymer. Polymeric films containing different amounts of ibuprofen or chlorpheniramine maleate were prepared by solvent-casting. The drug, polymer and plasticizer were codissolved in a common organic solvent prior to casting and drying to obtain the drug-containing polymeric films. Clear transparent films indicated that the drug was at least macroscopically soluble in the polymer, while opaque films were the result of drug crystallization in the polymer matrix. The approximate data on the solubility of the drugs in the polymer films were confirmed by differential scanning calorimetry (drug melting endotherm absent - drug soluble in polymer) and polarized light microscopy. Ibuprofen, a lipophilic drug, had a solubility in excess of 20 % in the polymeric films, while with chlorpheniramine maleate, a hydrophilic drug, crystals were visible at concentrations of less than 5 %. Due to its high solubility in the polymer, ibuprofen dissolved in and diffused across the polymer film followed by crystallization on the surface. In addition, ibuprofen has a low melting point (75-77 °C), which promoted the observed phenomena.

The rapid crystallization of ibuprofen on the bead surface could be explained with the change in drug solubility in the polymeric coating during and after the curing step. The solubility and diffusivity of the drug in the polymer were enhanced by the elevated temperature during the curing step. After the cured beads were cooled to room temperature, the drug solubility decreased; the amount of drug present in the film exceeded the drug solubility, resulting in drug crystallization. Crystallization of ibuprofen was observed not only with cured beads but also with uncured beads which have been stored for several months. This again confirmed the high affinity between the drug and the film coat. With beads stored at room temperature, the ibuprofen crystallization was probably induced by temperature fluctuations or other factors potentially causing nucleation such as as changes in humudity. On the contrary, chlorpheniramine maleate, a hydrophilic drug with low solubility in the polymer, did not diffuse into the polymer coating during the curing

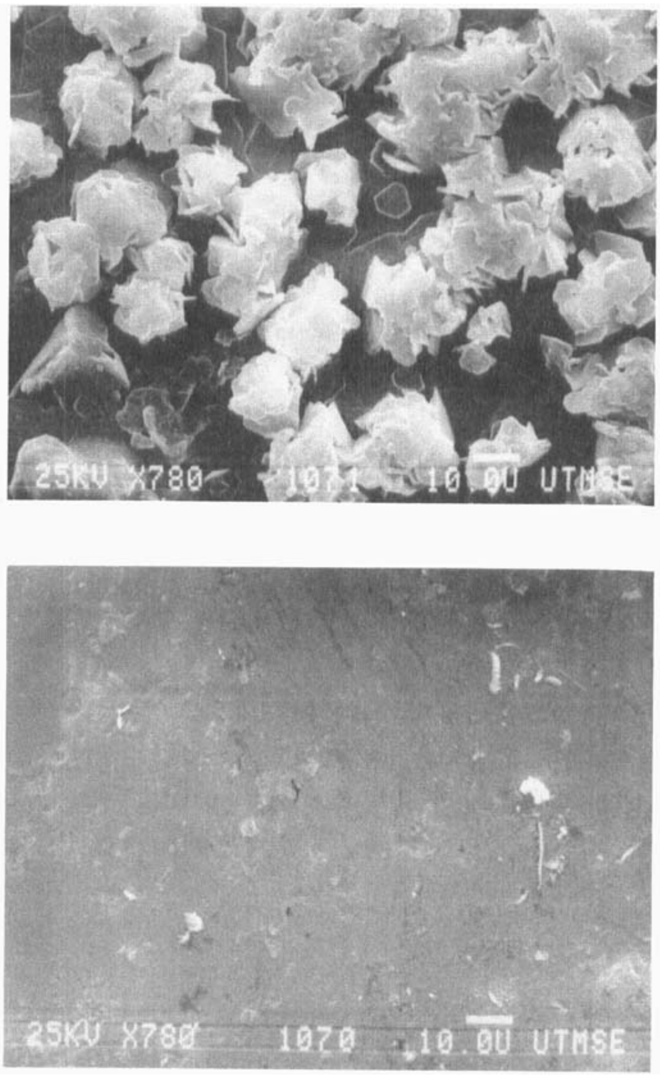

FIGURE 5
Scanning electron micrographs of the surfaces of cured ibuprofen (60 %w/w) - ethylcellulose films laminated with (A) Aquacoat membrane and (B) HPMC / Aquacoat membranes (curing conditions, 60 °C - 6 hours).

step. Drugs with low affinity for the polymer can therefore be cured without taking precautions directed toward the migration of drug into the polymer film.

Various approaches appear reasonable to eliminate the drug migration into the polymer film during storage or curing. One reasonable approach includes the application of an intermediate coating, which separates the drug core from the polymer coating. The intermediate material should consist of a polymer in which the drug is not soluble, thus eliminating the diffusion of the drug to the bead surface via the second coating. Hydroxypropyl methylcellulose (HPMC), a hydrophilic cellulose ether, was selected. The HPMC film, obtained by casting and drying an aqueous polymer solution, was first laminated onto the ibuprofen-containing layer followed by lamination of the Aquacoat membrane onto the surface of the HPMC film. Figure 5B shows the surface of this three layered laminate after curing at 60 °C. The surface was smooth and without any visible drug crystals. This indicated that the intermediate HPMC film prevented the diffusion of ibuprofen into the Aquacoat film and, hence, to the laminate surface.

The same principle using an intermediate HPMC layer was then investigated in the coating of ibuprofen pellets. The ibuprofen beads were first seal-coated with a thin layer of HPMC prior to the Aquacoat application. The application of the intermediate HPMC layer (4 %w/w HPMC based on total bead weight) showed a reduction in drug crystallization on the bead surface when compared to the previous HPMC-free batches. However, as described below, despite the application of the intermediate HPMC coating, the diffusion of ibuprofen across the Aquacoat film could not be eliminated completely at this HPMC coating level. This was probably due to the porous nature of the sprayed HPMC films. Unlike the cast films described above, which had a dense and homogeneous structure, sprayed films are generally more porous because of the presence of small air pockets and/or areas of irregularities (21-22).

The migration of ibuprofen through the two layered HPMC-Aquacoat coatings was a function of curing temperature and time. The effect of the curing conditions was investigated by oven-curing the beads at 50 °C and 60 °C for time periods ranging from 15 minutes to 24 hours. Figures 6 and 7 show the effect of curing time on ibuprofen release from the beads cured at 50 °C and 60 °C. At a curing temperature of 50 °C, the drug release initially decreased with increasing curing time up to a curing period of 4 h (Figure 6A), but then increased with curing times in excess of 4 h (Figure 6B). Curing at 60 °C for 15 min resulted in a

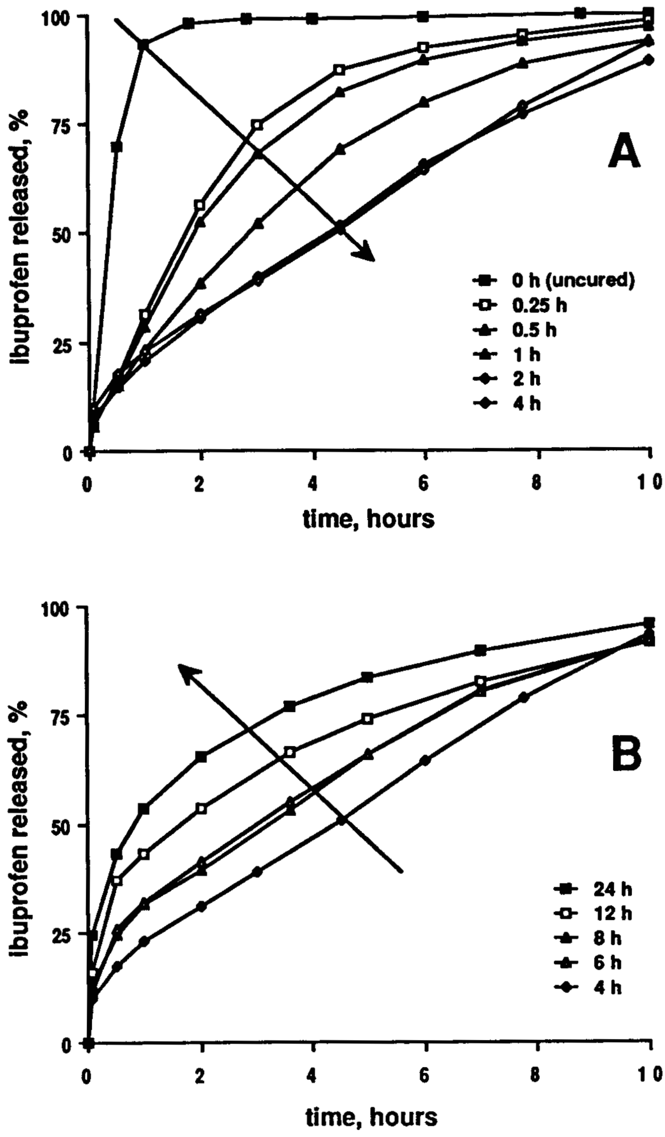

FIGURE 6

Effect of curing time (A, 0 - 4 h; B, 4 - 24 h) at 50 °C on ibuprofen release in 0.1 M pH 7.4 buffer from Aquacoat-coated beads with HPMC seal coat.

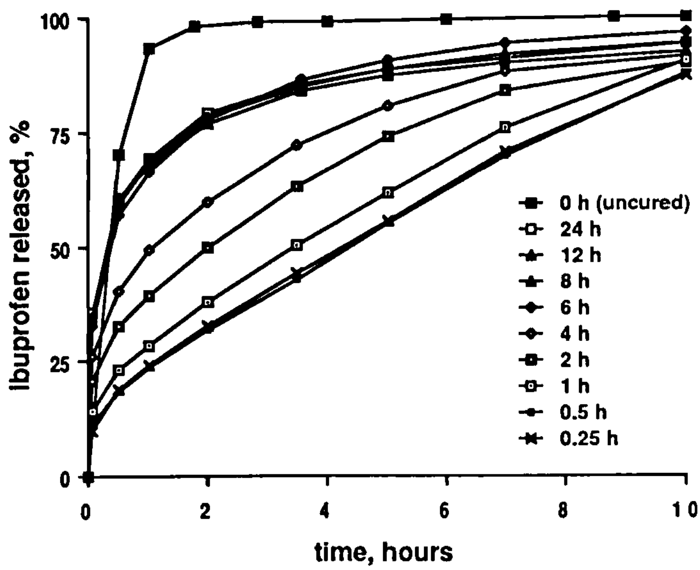

FIGURE 7
Effect of curing time at 60 °C on ibuprofen release in 0.1 M pH 7.4 buffer from Aquacoat-coated beads with HPMC seal coat.

reduction in drug release, however, the drug release then increased at longer curing times (Figure 7). The initial reduction in drug release at both curing temperatures was caused by the improved coalescence of the colloidal particles and, hence, film formation. Most drug release profiles were characterized by an initial rapid drug release phase (burst) followed by a linear portion indicating a region of constant drug release. The burst phase was caused by ibuprofen crystals present on the surface of the beads, while the constant or zero-order drug release phase was caused by a constant concentration gradient across the polymeric film. Ibuprofen has a fairly low solubility in pH 7.4 buffer thus upholding the concentration gradient as long as excess solid drug was present in the core. The linear drug release phase was not observed with beads cured for 12 and 24 h at a curing temperature of 50 °C (Figure 6B) and with beads cured in excess of 2 h at a curing temperature of 60 °C (Figure 7), indicating that the amount of drug present in the core was not sufficient to establish a constant concentration gradient under these curing conditions. At a curing temperature of 60 °C, the drug release profiles did not change at curing times in excess of 6 h. This probably indicated the saturation of the bead surface with drug.

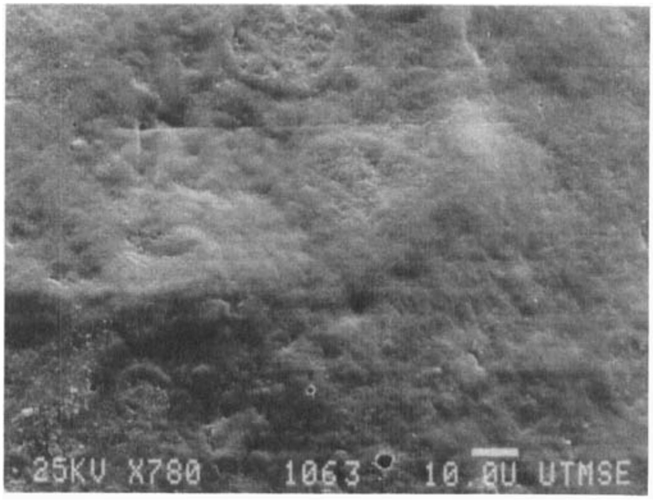

FIGURE 8
Scanning electron micrograph of the surface of a cured Aquacoat-coated ibuprofen bead (curing conditions, 60 °C - 24 hours) after exposure to 0.1 M pH 7.4 buffer for 5 minutes.

The amount of drug present on the surface (causing the burst effect) was quantitated through equating it with the amount of drug released after 5 min of dissolution studies. Figure 8 verifies the absence of drug crystals on the bead surface after exposure of the cured beads to the dissolution fluid for 5 min. The percent drug released in 5 min was plotted as a function of curing temperature and time in Figure 9A. At the same curing time, the amount of drug present on the bead surface was higher at higher curing temperatures (60 °C vs 50 °C). The amount of drug on the bead surface, which was available for rapid release, increased in a linear fashion with increasing curing time at a curing temperature of 50 °C while it levelled off after 6 h at 60 ° C, caused probably by a saturation of the bead surface with drug.

The constant or zero-order drug release phase was characterized through the zero-order release rate constant, k, which was calculated from the linear portion of the release curve by linear regression analysis. The release rate constant was plotted vs. curing time in Figure 9B. The release rate initially decreased with increasing curing temperature and time and, interestingly, plateaued at a similar value for both curing temperatures. This plateau was reached after a shorter curing period at the

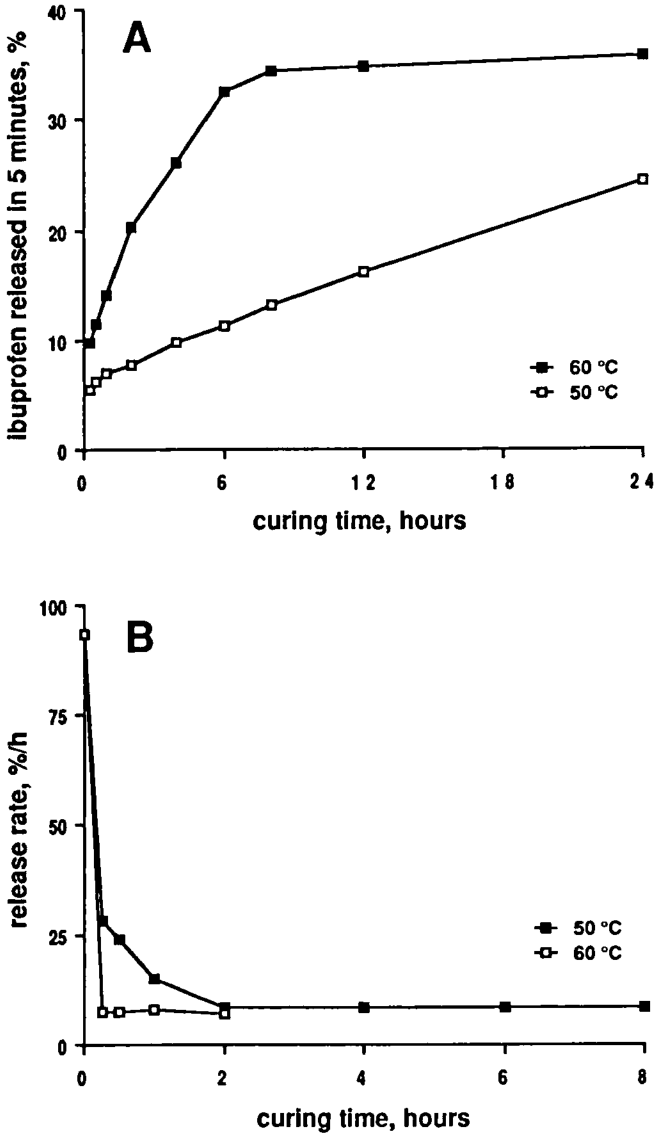

FIGURE 9
Effect of curing time on (A) percent of ibuprofen released in 5 minutes and (B) release rate constant of ibuprofen release from Aquacoat-coated beads (curing temperature, 50 or 60 °C).

higher curing temperature (60 °C). The plateaued region of the release rate in the case of ibuprofen, or the limiting drug release profile in the case of chlorpheniramine maleate beads could correspond to the completion of the coalescence or film formation process of the colloidal particles.

In conclusion, curing of coated beads at elevated temperatures immediately after the coating process significantly affected the drug release pattern. Both a retardation and an increase in drug release were seen, with the extent being dependent on the type of drug and curing conditions. Potential interactions of drugs with the polymer coating are potentiated during the thermal treatment.

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