Dry Powder Coating of Pellets with Micronized Eudragit® RS for Extended Drug Release

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Purpose. To develop a novel powder coating technology for extended-release pellets based on the acrylic polymer, Eudragit® RS.
Methods. A mixture of micronized Eudragit® RS plus talc and a liquid feed (plasticizer plus binder solution) were sprayed separately onto propranolol hydrochloride-loaded pellets in a fluidized bed coater. The coated pellets were heat-cured under different conditions (40°C to 60°C, 2 h to 24 h). The coalescence (film formation) of the polymer particles was studied via the determination of the glass transition and the minimum polymer-softening temperatures (MST). The coated pellets were characterized with respect to their morphologic, release, and stability properties.
Results. The optimum plasticizer type and concentration and process temperatures could be identified by the determination of the MST. High concentrations of plasticizer (40% based on the polymer) and a thermal treatment were necessary to achieve complete film formation and extended drug release. Curing the pellets resulted in release profiles, which did not change during storage for 3 years. The coated pellets had a smooth, continuous surface and a dense film structure after curing.
Conclusions. This novel coating technique avoids the use of organic polymer solutions or latex dispersions, has short processing times, and results in stable extended-release profiles.

KEY WORDS: curing; dry powder coating; Eudragit® RS; extended release; pellets.

INTRODUCTION

Methacrylate copolymers are widely used as coating material for extended-release dosage forms. Eudragit® RS is referred to as ammoniomethacrylate copolymers in the USP/NF monograph and is prepared by copolymerization of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride with a mole ratio of 1:2:0.1. As a result of the quaternary ammonium functional groups, Eudragit® RS possesses a defined swelling capacity and permeability in water with pH-independent properties in the entire physiologic pH range (1–4).

The application of organic polymer solutions has been historically used for film coatings. Toxicity and environmental concerns associated with the use of organic solvents have pushed the pharmaceutical industry to explore alternative procedures. Many polymers have been formulated into aqueous colloidal polymer dispersions or aqueous micronized polymer dispersions (1,5–7). However, aqueous coatings are at times unsuitable. A fairly high energy of evaporation of water requires a higher coating temperature and/or long processing time, which may cause thermal degradation of heat-sensitive materials (8,9). Moisture-sensitive cores may also be deteriorated during the coating process on contact with water (10,11). In addition, drug migration into the coating could occur during aqueous-based coating, depending on the drug molecule (12).

To overcome these limitations of liquid-based coatings, a novel alternative coating technology based on polymer powder has been introduced. Hydroxypropyl methylcellulose acetate succinate (HPMCAS) powder, an enteric polymer, was coated onto drug-loaded pellets and tablets (13). Compared to an aqueous dispersion, the enterically coated pellets and tablets with HPMCAS powder required a higher polymer amount for achieving gastric resistance. However, the dry powder coating offered much shorter processing time. Thus, this new technique offers a new possibility of a coating system for extended-release dosage forms.

The major objective of this study was to investigate this powder coating technique with the nonenteric extended-release polymer Eudragit® RS powder. Specific objectives were (a) to investigate the formulation and processing variables for extended-release coated pellets with micronized Eudragit® RS powder, (b) to investigate the film-forming ability of Eudragit® RS powder, (c) to evaluate the curing conditions (curing temperature and time) and formulation factors (plasticizer concentration) for achieving a complete film coating and extended-release pattern of coated pellets, and (d) to evaluate the stability of the powder-coated pellets.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride (Abbott, Ludwigshafen, Germany), hydroxypropyl methylcellulose (HPMC, Methocel® E5, Colorcon, Orpington, UK), distilled acetylated monoglyceride (AMG, Myvacet® 9-45; Quest International, Bussum, The Netherlands), acetyltributyl citrate (ATBC), triethyl citrate (TEC) (Morflex, Greensboro, NC), polyethylene glycol 4000 (PEG 4000, BASF, Ludwigshafen, Germany), talc (Merck, Darmstadt, Germany), nonpareil beads (Suglets® sugar spheres NF, 710–850 μm, NP Pharma S.A., c/o Gustav Parmentier, Frankfurt, Germany). Eudragit® RS PO (Röhm Pharma, Darmstadt, Germany) was micronized with an air-turbulence mill (Axiva, Frankfurt, Germany).

Minimum Polymer-Softening Temperature

The determination of the minimum polymer-softening temperature (MST) was carried out on a heating bench (Kofler Heizbank, Type 7841, Vienna, Austria), which is equipped with a metal plate with a variable temperature gradient (30°–80°C) and a multisensor for the temperature measurement. The plasticizer (% w/w, based on the polymer) was gradually added to the polymer powder and mixed with a mortar and pestle. The micronized Eudragit® RS powders (plasticizer-free and plasticized) were applied on the metal plate. The MST is the temperature at which the polymer particles start to soften and stick to the surface of the heating plate.

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Table I. Glass Transition Temperature (T_g) of Organic-Cast Eudragit® RS Films Plasticized with Different Plasticizers (10% w/w, Based on the Polymer)

Plasticizer	T_g, °C
None	57.6 (0.2)
Acetylated monoglyceride	16.1 (0.8)
Acetyltributyl citrate	19.3 (0.2)
Triethyl citrate	15.9 (1.9)

Thermal Analysis

Thermograms of unplasticized and plasticized Eudragit® RS films were obtained by using a differential scanning calorimeter (Mettler Toledo DSC 821^e) and STAR® software (Mettler Toledo, Giessen, Germany) to determine the glass transition temperature (T_g) (n = 2–3). The temperature calibration was accomplished with the melting transition of indium. The samples (7–10 mg, stored in a vacuum-desiccator before analysis) were sealed in aluminum pans. The scanning rate was 10°C/min. All tests were run under a nitrogen atmosphere.

Particle Size Measurements

The particle size of Eudragit® RS was determined by laser light scattering including polarization intensity differential scattering (PIDS) technology (Coulter LS 230, powder module, Coulter Electronics, Krefeld, Germany). The relative frequency of the diameter of the particles was shown with the calculation based on volume distribution. The particle size at 50% of total fraction was used as average particle size. The particle size was the average of three measurements and was 9.4 μm for micronized Eudragit® RS.

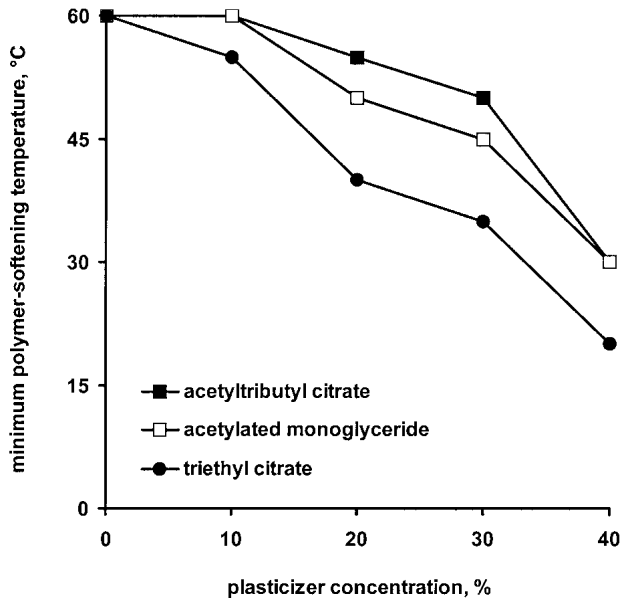

Fig. 1. Effect of plasticizer concentration (% w/w, based on the polymer) on the minimum polymer-softening temperature (MST) of Eudragit® RS powder.

Preparation of Drug-Loaded Pellets

A solution of propranolol hydrochloride (96 g) and PEG 4000 (0.45 g) in 300 ml ethanol/water (60% v/v) was mixed with 45 g of an aqueous 10% w/w HPMC E5 solution. Propranolol hydrochloride-loaded pellets (drug loading, 12% w/w) were prepared by layering the drug-binder solution onto nonpareil beads (800 g) using a fluidized bed coater (Glatt® GPCG-1, Wurster insert, Glatt GmbH, Binzen, Germany). The drug-layering conditions were: inlet air temperature, 45°C; product temperatures, 38°C-40°C; air flow rate, 80-90 m^3/h; spray rate, 4-6 g/min; atomizing air pressure, 1.2 bar; spray nozzle diameter, 1.2 mm.

Coating of Drug-Loaded Pellets

A mixture of Eudragit® RS and talc powder (1:1 w/w) was fed with a quantitative helix dosing feeder with a flexible hopper (Secudos-Type O, G.+K. Fuchs, Wiehl, Germany) and an emulsion of the plasticizer (36.8-75.0% w/w of total emulsion) in an aqueous 10% w/w HPMC binder solution (25.0-63.2% w/w or total emulsion) was sprayed through separate inlets onto drug-loaded pellets in a fluidized bed coater (Glatt® GPCG-1, Wurster insert). The processing parameters were: batch size, 1.2 kg; inlet air temperature, 40°C-45°C; product temperature, 34°C-36°C; outlet air tempera-

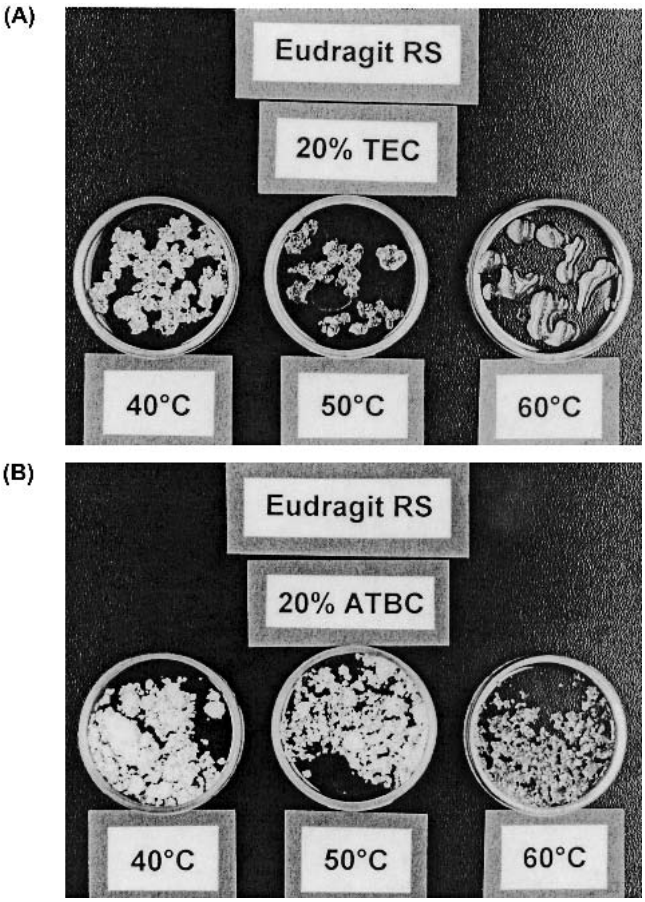

Fig. 2. Effect of temperature on the softening (film-forming) ability of mixtures of Eudragit® RS powder with different plasticizers (20% w/w, based on the polymer): (A) triethyl citrate; (B) acetyltributyl citrate.

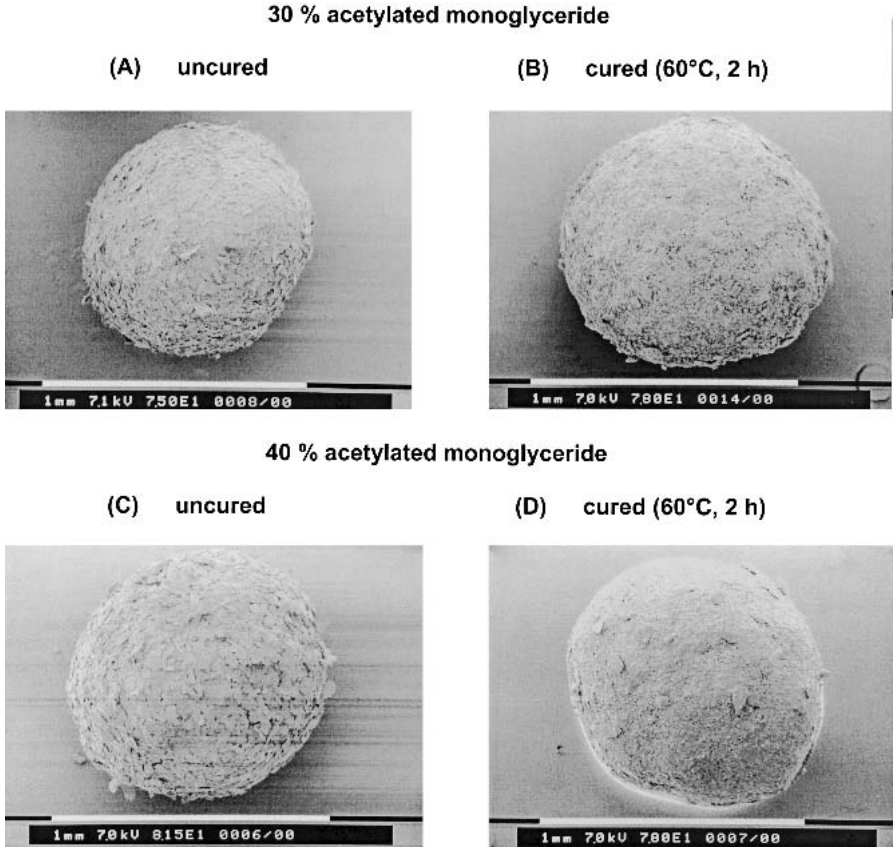

Fig. 3. Effect of plasticizer concentration on the surface morphology of Eudragit® RS–coated pellets: 30% acetylated monoglyceride (coating level, 8.6%), (A) uncured pellet, (B) cured pellet (60°C, 2 h); and 40% acetylated monoglyceride (coating level, 9.9%), (C) uncured pellet, (D) cured pellet (60°C, 2 h).

ture, 32°C-36°C; air flow rate, 60-80 m^3/h; spray rate, 3-5 g/min; atomizing air pressure, 1.2 bar; spray nozzle diameter, 1.2 mm; powder feed rate, 12-13 g/min.

After the coating process, the coated pellets were further fluidized for 10 min in order to stabilize the polymer particles onto the pellets prior to the curing step. The pellets were then oven-cured at different temperatures (40°C to 60°C) and times (2 h to 24 h). The coating level was calculated from the weight difference between the coated and the uncoated pellets and was based on the polymer weight gain. The coating efficiency (%) was calculated from the actual weight gain of the coated pellets divided by the theoretical weight gain.

In Vitro Drug Release Studies

In vitro drug release was determined using the USP XXV rotating paddle method [900 ml 0.1 N HCl; 100 rpm; 37°C; n = 3] (Vankel® 700, Vankel Industries, Edison, NJ, USA). At predetermined time intervals, samples were withdrawn (3 ml, not replaced) and assayed spectrophotometrically at 290 nm (UV-210PC, Shimadzu Europa, Duisburg, Germany). The drug release studies were repeated after storage for 7 and 14 days and 3 years (light-protected glass vials; room temperature) in order to evaluate the stability of the coated pellets.

Scanning Electron Microscopy

The morphology of the surfaces and cross-sections of the coated pellets were examined prior to and after curing by scanning electron microscopy (SEM). The cross-sections of the coated pellets were obtained by cutting the pellets with a razor blade. The dried samples were mounted onto the stages prior to coating for 230 s under an argon atmosphere with gold-palladium (SCD 040, Balzers Union, Lichtenstein), and then were observed with a scanning electron microscope (PW 6703/SEM 515, Philips, Eindhoven, The Netherlands).

RESULTS AND DISCUSSION

Eudragit® RS is a frequently used extended release polymer and usually coated onto solid dosage forms from either an organic polymer solution or an aqueous colloidal polymer dispersions (Eudragit® RS 30D). In this study, a novel polymer powder coating method was investigated, in which micronized Eudragit® RS powder was directly coated onto the pellets in the form of a dry powder.

The coating of the pellets was performed in a fluidized bed coater, into which the powder mixture (polymer plus talc) and a liquid mixture (plasticizer in an aqueous HPMC solution) were fed/sprayed simultaneously. The particle size of the Eudragit® RS powder as received from the supplier was too large (mean particle size = 159.2 μm) to obtain a coating layer around the core pellets. The thickness of polymer coating layers around pellets usually is in the range between 20-100 μm, therefore, a much smaller particle size was required to form films in this thickness range. The Eudragit® RS powder was micronized into a fine powder with a mean particle

size of 9.4 μm. Talc (mean particle size = 17.4 μm) was used as a glidant for the polymer powder to improve the powder flow into the spraying chamber and also as an anti-tacking agent during the coating process. Spraying the pure plasticizer and feeding the polymer powder resulted in sticking/agglomeration of the pellets because of high local concentrations of the plasticizer. Therefore, the plasticizer was added to a 10% w/w HPMC solution in order to spray the plasticizer in a more diluted form. The HPMC solution also acted as a binder solution for the polymer powder and therefore improved its adherence to the pellet surface.

For dry powder coating, a plasticizer is needed to reduce the glass transition temperature (T_g) in order to soften the polymer particles and to enhance coalescence of the particles into a film. At a level of 10% w/w (based on the polymer), the tested plasticizers, namely acetylated monoglyceride (AMG), acetyltributyl citrate (ATBC), and triethyl citrate (TEC), reduced the T_g of Eudragit® RS films from approx. 58°C to between 15°C and 20°C (Table I). In order to simulate the film formation from polymer powders more closely, the minimum polymer-softening temperature (MST) of Eudragit® RS powder was determined (Fig. 1). In general, the MST of Eudragit® RS powder was higher than the glass transition temperature (T_g) of the organic-cast Eudragit® RS film (Table I). With 10% plasticizer, the plasticized polymer powders had a MST of 55°–60°C, while the plasticized films had a T_g of 15.9°–19.3°C. An increase in the plasticizer concentration lowered the MST of polymer powders. At a plasticizer concentration of 20% w/w, the MST of the polymer powders was lowered from an original value of 60°C to 55°C (ATBC-plasticized) or to 40°C (TEC-plasticized). Higher plasticizer levels reduced the MST to 20°–30°C. The efficiency of the plasticizers was in the order of TEC > ATBC > AMG. Placing Eudragit® RS/plasticizer powder mixtures in ovens at different temperatures was a rapid screening method for identifying the proper plasticizer concentration and temperature for film formation. For example, 20% TEC resulted in clear softened polymer particles at 40°C (Fig. 2A), whereas 20% ATBC softened the powder at 50°C (Fig. 2B). On the basis of these results, Eudragit® RS powder was coated at an inlet air temperature between 40°C and 45°C, which was near or above the MST of the polymer powders.

With aqueous colloidal polymer dispersions, a thermal aftertreatment (curing) at elevated temperatures is often recommended to complete film formation and to avoid changes in the release profiles during storage (14–17). A curing step was also needed with Eudragit® RS powder-coated pellets. The polymeric coating was discontinuous, and uncoalesced polymer particles were visible throughout the surface of uncured pellets (Fig. 3A,C). Curing at 60°C for 2 h clearly resulted in a smoothing of the pellet surface, indicating further coalescence of the polymer particles (Fig. 3B,D). A higher concentration of the plasticizer AMG (40% vs. 30%) also resulted in a smoother, less porous surface (Fig. 3D vs. 3B).

As expected, curing of the pellets also affected the release profiles. With both types of plasticizers—AMG (water-insoluble plasticizer, Fig. 4A) and TEC (water-soluble plasticizer, Fig. 4B)—the release was fastest from the uncured pellets because of the incomplete film formation and therefore porous nature of the coating. The drug release decreased with increasing curing temperature and time. A shorter curing at higher temperature (60°C, 2 h) resulted in the same release

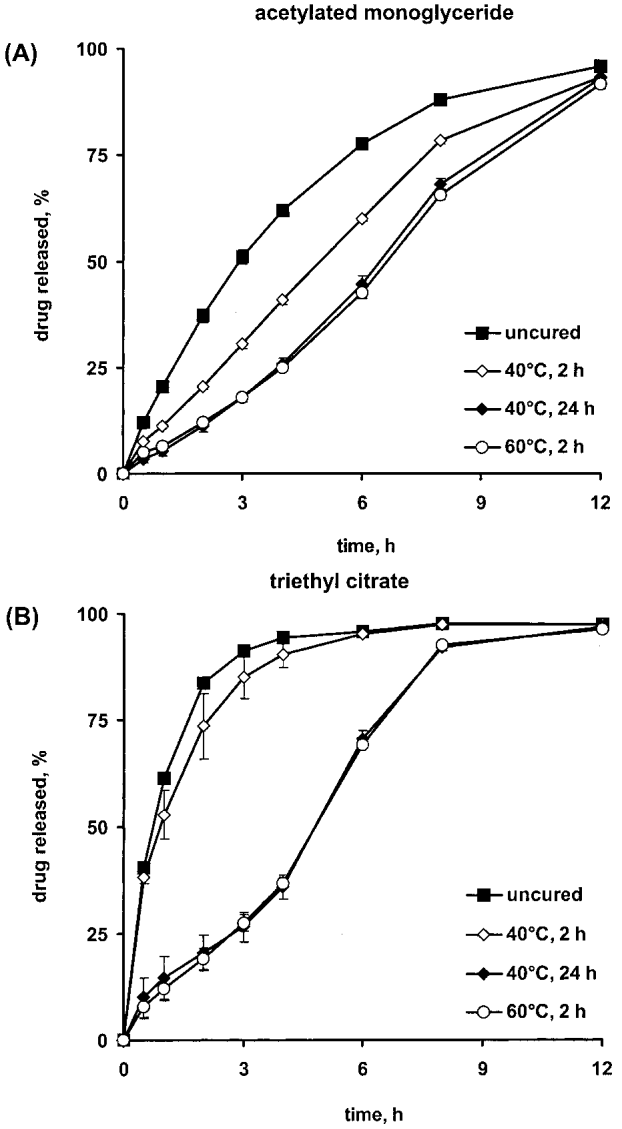

Fig. 4. Effect of curing on the propranolol hydrochloride release from Eudragit® RS–coated pellets: (A) 40% acetylated monoglyceride (coating level, 14.5%); (B) 40% triethyl citrate (coating level, 15.0%).

profile as were obtained with a longer curing at a lower temperature (40°C, 24 h). The drug release was faster with TEC than with AMG pellets; the water-soluble TEC probably leached from the coating during the release studies, while the water-insoluble AMG remained in the film. Curing longer than 2 h at 60°C resulted in sticking of the pellets, they could not be separated without damaging the film coating. Thus, all following samples were cured at 60°C for 2 h.

The importance of the curing step for obtaining a stable drug release profile is shown in Fig. 5. The drug release from the uncured pellets decreased significantly over a 3-year storage period; changes in the release profile occurred within 1 week (Fig. 5A). In contrast, the profile of the cured pellets remained unchanged (Fig. 5B). With uncured pellets, further coalescence of the polymer particles occurred during storage caused by a better distribution of the plasticizer within the polymer layer and by the subsequent interdiffusion of polymer molecules across particle boundaries. This resulted in

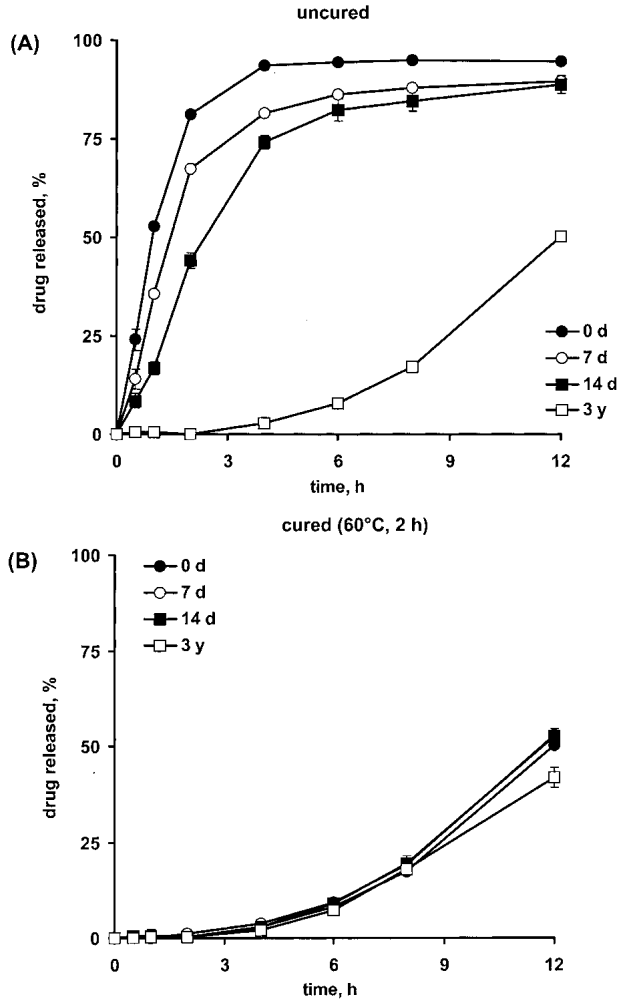

Fig. 5. Effect of storage time on the propranolol hydrochloride release from Eudragit® RS–coated pellets after storage at room temperature: (A) uncured pellets; (B) cured pellets (coating level, 22.4%; 40% acetylated monoglyceride; curing at 60°C for 2 h).

denser films and slower drug release profiles. This stage of the film formation process, which is known as "further gradual coalescence" (FGC), has been reported for aqueous colloidal polymer dispersions and can proceed for a long time after coating (14,15). The T_g of 40% AMG-plasticized Eudragit® RS films was below room temperature (8.4°C). Time-dependent changes therefore occurred because the coated pellets were stored at temperatures above the T_g of the polymer (16,17) as in this study at room temperature. A curing step for 2 h at 60°C improved the film formation, reduced the drug release, and resulted in release profiles that did not change during the stability study. This indicated good film formation during the curing step.

The type of plasticizer (AMG, ATBC, TEC) and concentration (20, 30, 40%) also strongly affected the drug release (Fig. 6). With 20-30% AMG or ATBC (Fig. 6A,B), the drug release was unaffected by the plasticizer increase, whereas an increase in the TEC concentration from 20 to 30% resulted in a decrease in drug release (Fig. 6C). This correlated well with the MST data (Fig. 1), where TEC was the most efficient plasticizer in lowering the MST. Increasing the plasticizer concentration to 40% resulted in a decrease in

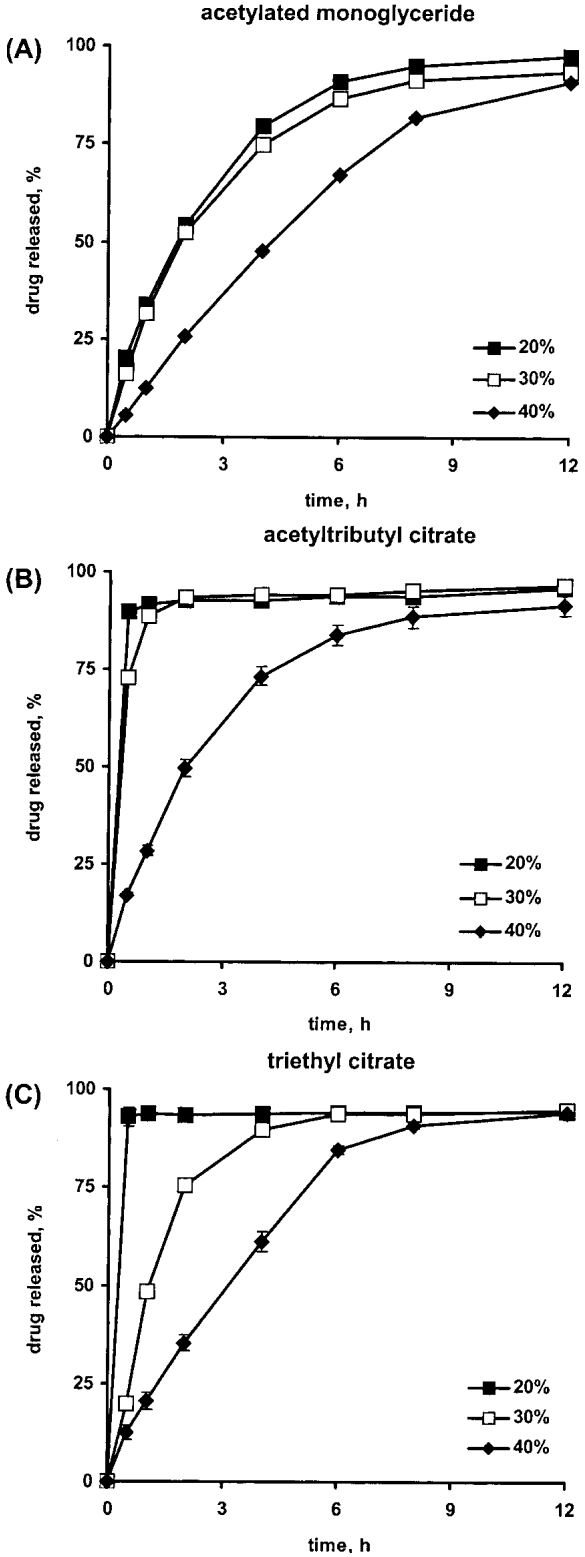

Fig. 6. Effect of plasticizer concentration on the propranolol hydrochloride release from Eudragit® RS–coated pellets (curing at 60°C for 2 h, coating levels 7.7–10.1%): (A) acetylated monoglyceride; (B) acetyltributyl citrate; and (C) triethyl citrate.

release for all plasticizers and better film formation; therefore, denser films were obtained. Thus, a plasticizer concentration of 40% w/w was used for dry powder coating in order to obtain a dense coating film and an extended release profile.

In order to possibly further improve film formation of the Eudragit® RS powder, the powder-coated pellets were overcoated/sprayed with a plasticizer/HPMC liquid mixture. Spraying up to 20% w/w plasticizer (based on the polymer) did not alter the release profile, irrespective of the plasticizer type (Fig. 7). This confirmed that spraying 40% plasticizer in parallel with the polymer powder feeding and the subsequent curing step (60°C, 2 h) was sufficient to obtain good film formation, and the overcoating with more plasticizer did not have an effect.

The drug release from the powder-coated pellets could be controlled over a wide spectrum of release profiles by just varying the coating level (Fig. 8). Coating with Eudragit® RS powder achieved extended drug release with coating levels of 8.1–9.9%, irrespective of the plasticizer type. At still lower coating levels, the drug was rapidly released. Coating levels of 9.9% and 19.6% resulted in a film thicknesses of approxi-

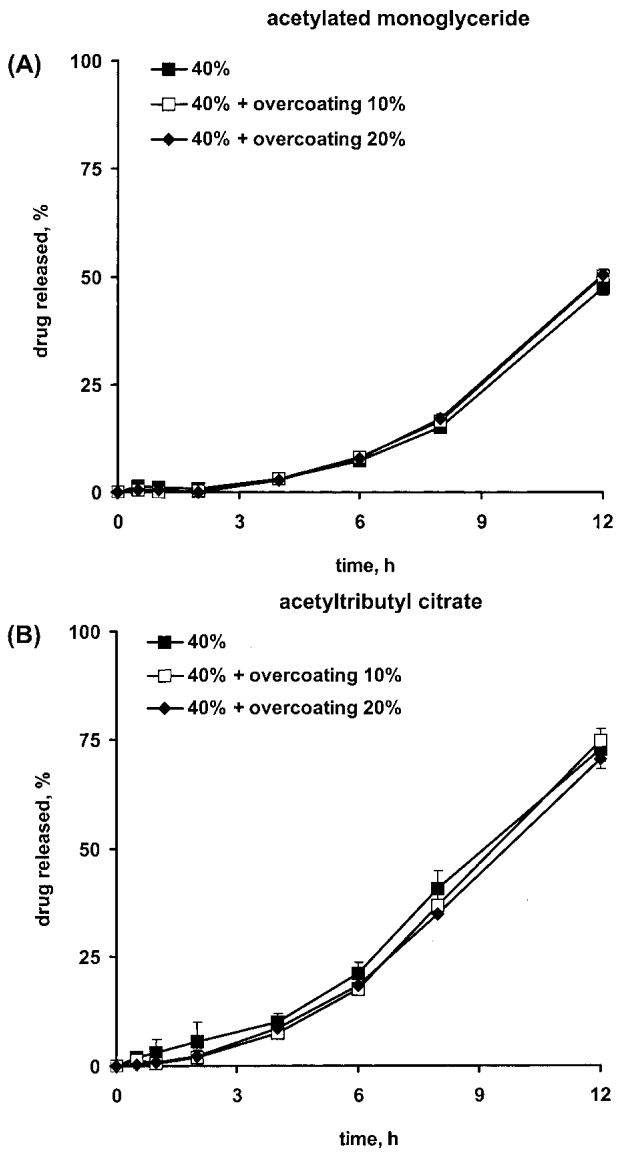

Fig. 7. Effect of plasticizer/HPMC overcoating on the propranolol hydrochloride release from Eudragit® RS–coated pellets (curing at 60°C for 2 h): (A) acetylated monoglyceride (coating level, 22.4%); (B) acetyltributyl citrate (coating level, 17.2%).

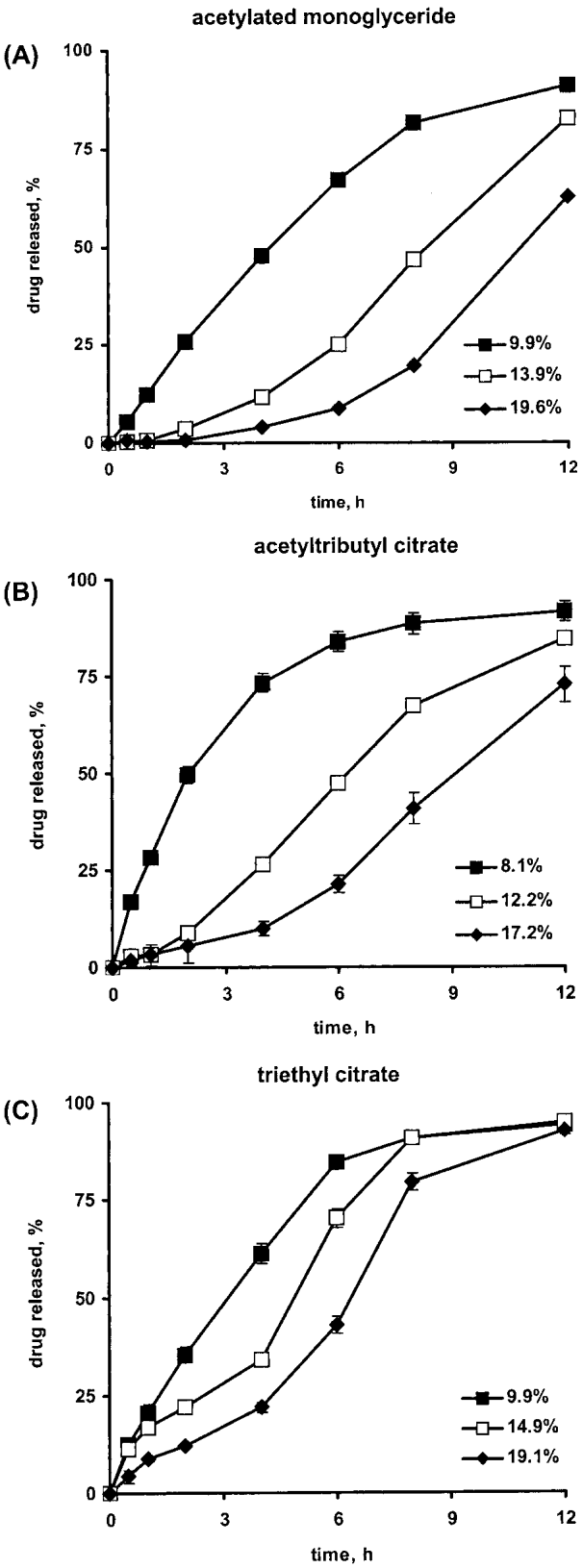

Fig. 8. Effect of coating level on the propranolol hydrochloride release from Eudragit® RS–coated pellets (curing at 60°C for 2 h), plasticizer concentration, 40% w/w: (A) acetylated monoglyceride; (B) acetyltributyl citrate; and (C) triethyl citrate.

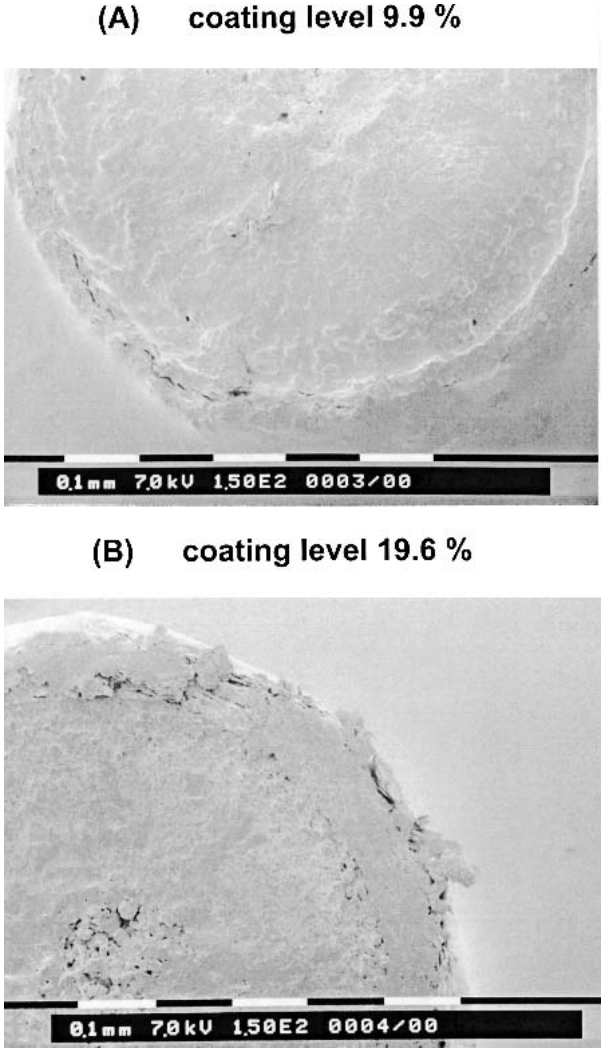

Fig. 9. Cross-section of Eudragit® RS–coated pellets at two coating levels (40% acetylated monoglyceride; curing at 60°C for 2 h): (A) coating level, 9.9%; (B) coating level, 19.6%.

mately 50 and 100 μm (Fig. 9). The cross sections of the coated pellets also revealed a dense structure of the Eudragit® RS coating.

CONCLUSIONS

Micronized Eudragit® RS powder can be used for dry powder coating. A high plasticizer amount (40% w/w, based on the polymer) and thermal treatment were necessary to achieve complete film formation. Extended release was obtained with a coating level of 10%. The limiting drug release profile was approached after curing the coated pellets at 60°C for 2 h. After curing, Eudragit® RS-coated pellets showed unchanged drug release profiles upon storage.

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