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Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique

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Abstract

Pellets were coated with ethylcellulose powder to achieve extended release. The film forming ability of ethylcellulose powder and the effect of formulation factors (plasticizer type and concentration) and curing conditions (curing temperature and time) were investigated. The coating formulation was divided into two components consisting of a powder mixture (polymer plus talc) and a mixture of liquid materials (plasticizer plus binder solution), which were sprayed separately into the coating chamber of a fluidized bed coater (Glatt® GPCG-1, Wurster insert). The coated pellets were oven-cured under different conditions (60–80 °C, 2–24 h) without and with humidity (100% relative humidity). Propranolol hydrochloride was used as a model drug, and drug release was studied in 0.1N HCl at 37 °C (USP XXV paddle method). Despite the high glass transition temperature of ethylcellulose (133.4 °C), micronized ethylcellulose powder can be used for dry powder coating by adjusting the coating temperature, amount and type of plasticizer applied, and curing conditions. 40% plasticizer and a curing step (80 °C, 24 h) were required to achieve complete coalescence of the polymer particles and extended drug release of coated pellets. Although ethylcellulose-coated pellets had an uneven surface, extended drug release could be obtained with coating level of 15%. Because of its high glass transition temperature, ethylcellulose-coated pellets showed unchanged drug release profiles upon storage at room temperature for 3 years.

Keywords: Curing; Dry powder coating; Ethylcellulose; Film formation; Extended release

1. Introduction

Ethylcellulose is frequently used as a polymeric coating material for extended drug release applications (Dahl, 1994; Savage and Rhodes, 1995; Bodmeier, 1997; Wheatley and Steuernagel, 1997; Rhodes and Porter, 1999). Ethylcellulose has been originally applied to solid dosage form in the form of an organic solution (Rowe and Forse, 1980; Rowe, 1986; Narisawa et al., 1994a,b). Besides toxicity and environmental concerns, the viscosity of organic polymer solutions sharply increases with increasing molecular weight and concentration of ethylcellulose (Banker and Peck, 1981). Thus, only a small amount of polymer can be applied per volume of coating solution, resulting in long processing times. Alternatively, ethylcellulose can be coated from aqueous dispersions, the viscosity of which is independent of the molecular weight and concentration of the polymer. Two colloidal ethylcellulose dispersions are commercially available, namely Aquacoat® ECD and Surelease® (Fukumori, 1994; Rekhi et al., 1995; Bodmeier et al., 1997). These

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aqueous dispersions avoid organic solvents and are highly concentrated in polymer (approximately 30%). The coating with aqueous micronized ethylcellulose dispersions has also been reported (Nakagami et al., 1991; Keshikawa and Nakagami, 1994).

The mechanism of film formation from organic- and aqueous-based systems is fundamentally different (Osterwald, 1985; Iyer et al., 1990; Lehmann, 1994; Sun et al., 1999; Wesseling and Bodmeier, 1999). With organic solutions, ethylcellulose is molecularly dissolved, film formation occurs simply by a loss of organic solvent during the drying process and contact of individual polymer molecules. In contrast, polymer particles have to coalesce into a homogeneous film during the coating with aqueous polymer dispersions. Plasticizers often have to be added to reduce the minimum film formation temperature (Bodmeier and Paeratakul, 1991; Bodmeier et al., 1997) and a thermal after-treatment (curing) is also necessary to complete film formation and to avoid aging phenomena (Bodmeier and Paeratakul, 1994; Bodmeier et al., 1997). Since there is a big difference in size between the micronized ethylcellulose powder and colloidal ethylcellulose particles, the former needs more plasticizer to achieve complete film formation (Nakagami et al., 1991; Keshikawa and Nakagami, 1994).

In addition to liquid-based coatings, a new dry powder coating has been introduced (Obara et al., 1999). This technique directly attaches polymer particles onto the surface of a solid substrate without organic solvents and large volumes of water. Softening, melting and curing are the principal stages in the film formation during dry powder coating (Leong et al., 1999; Wulf et al., 2000; Belder et al., 2001; Pfeffer et al., 2001). Because of the absence of large amounts of solvents or water, the processing times are much shorter. This technique has been investigated with hydroxypropyl methylcellulose acetate succinate (HPMCAS), an enteric polymer.

The objectives of this study were: (i) to develop a dry powder coating technique for ethylcellulose, a polymer, which results in extended release; (ii) to investigate the film forming ability of micronized ethylcellulose powder on pellets; and (iii) to evaluate the effect of formulation factors (plasticizer type and concentration) and curing conditions (curing time and temperature) on the drug release from powder-coated pellets.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride (Abbott, Ludwigshafen, Germany), ethylcellulose (Ethocel®, standard 10 FP, premium grade, Dow Chemical, Midland, MI, USA), 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, USA), 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).

2.2. Particle size measurements

The particle size of ethylcellulose 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 employed as average particle size. The particle size was the average of three measurements and was 6.1 μm for ethylcellulose.

2.3. 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 (30–150 °C) and a multi-sensor 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 ethylcellulose powders (plasticizer-free or 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.

2.4. Thermal analysis

Thermograms of unplasticized and plasticized ethylcellulose films (cast from an 5% w/v ethanolic ethylcellulose solution, drying for at least 48 h at room temperature and an additional 24 h at 40 °C) 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 prior to analysis) were sealed in aluminum pans. The scanning rate was 10 °C/min. All tests were run under a nitrogen atmosphere.

2.5. Contact angle measurements

Micronized ethylcellulose powder (desiccator-dried under vacuum before use) was compressed into tablets by direct compression. The flat-faced tablets (diameter: 10 mm, hardness: 100–150 N, weight: 500 mg) were prepared with a single punch press (EK-0, Korsch, Berlin, Germany). The contact angle was measured using a contact angle goniometer equipped with a micro-syringe attachment (Krüss G1 Goniometer, Hamburg, Germany). The compressed tablet was placed on an adjustable platform and a drop of the plasticizer (2 μl) was applied on the tablet using a micrometer syringe. The contact angle was measured after 1 min ($n = 6$).

2.6. Preparation of drug-loaded pellets

A solution of propranolol hydrochloride (96 g) and the plasticizer, 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 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, 38–40 °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.

2.7. Coating of drug-loaded pellets

A mixture of ethylcellulose and talc (76.9 and 23.1% w/w) and an emulsion of the plasticizer (50–75% w/w based on total emulsion) in an aqueous 10% w/w HPMC binder solution (25–50% w/w based on total emulsion) were fed 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, 55–60 °C; product temperature, 45–47 °C; outlet air temperature, 40–41 °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, 10–14 g/min.

After the coating process, the coated pellets were further fluidized for 10 min in order to stabilize the polymer particles onto the cores prior to the curing step. The pellets were then oven-cured at different temperatures (60–80 °C) and times (2–24 h). With heat-humidity curing, the pellets were conditioned in a desiccator at 100% relative humidity (RH) at different temperatures (60–80 °C) and times (2–24 h). The coating level was calculated from the weight difference between the coated and the uncoated pellets and was based on the polymer gain. The coating efficiency (%) was calculated from the actual weight gain of the coated pellets divided by the theoretical weight gain.

2.8. In vitro drug release studies

In vitro drug release was determined using the USP XXV rotating paddle method [900 ml 0.1N 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 (UV-210PC, Shimadzu Europa, Duisburg, Germany). The drug release studies were repeated after storage for 7 or 14 days and 3 years (light-protected glass vials; room temperature) in order to evaluate the short- and long-term stability of the coated pellets.

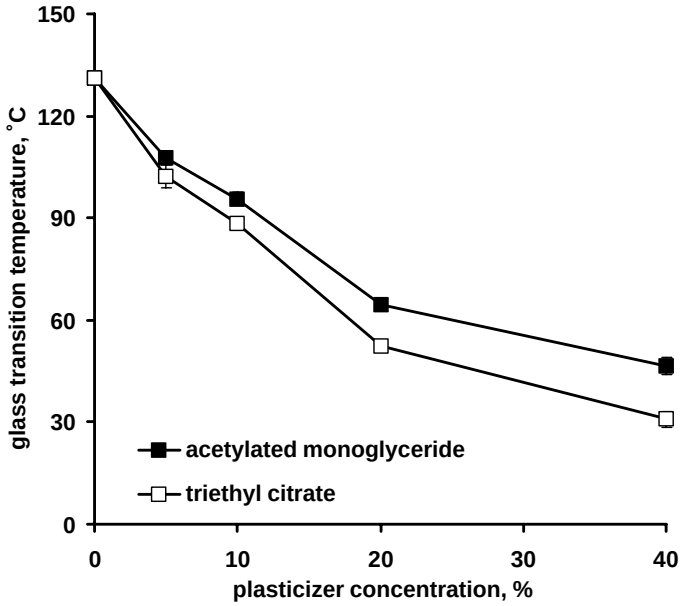

Fig. 1. Effect of plasticizer concentration (% w/w, based on the polymer) on the glass transition temperature (T_g) of ethanol-cast ethylcellulose films.

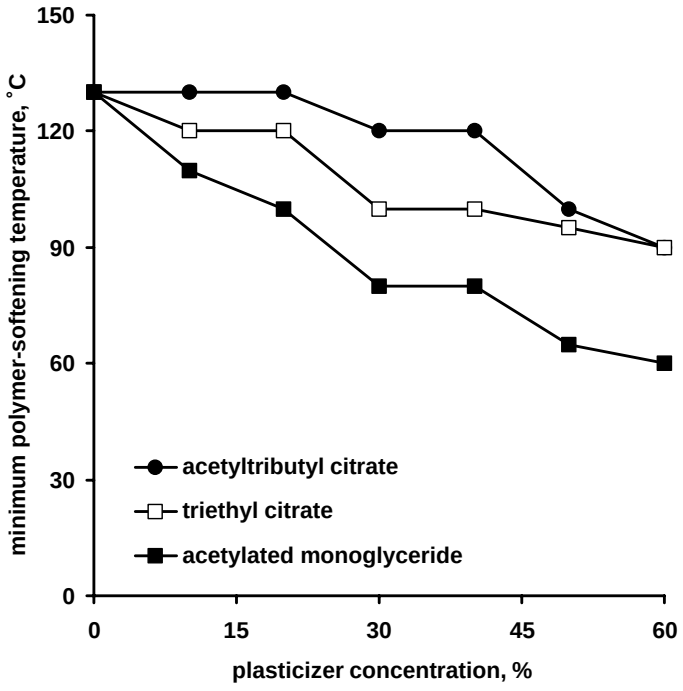

Fig. 2. Effect of plasticizer concentration (% w/w, based on the polymer) on the minimum polymer-softening temperature (MST) of ethylcellulose powder.

2.9. 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).

3. Results and discussion

A novel coating technique with ethylcellulose based on the coating with micronized ethylcellulose powder was investigated in order to achieve extended drug release. Ethylcellulose has a high glass transition temperature of approximately 130 °C. A plasticizer therefore had to be sprayed in parallel to the feeding of the polymer powder into the coating chamber in order for the micronized polymer particles to coalesce into a film. The plasticizer was added to an aqueous HPMC solution, which also assisted in the adhesion of the polymer

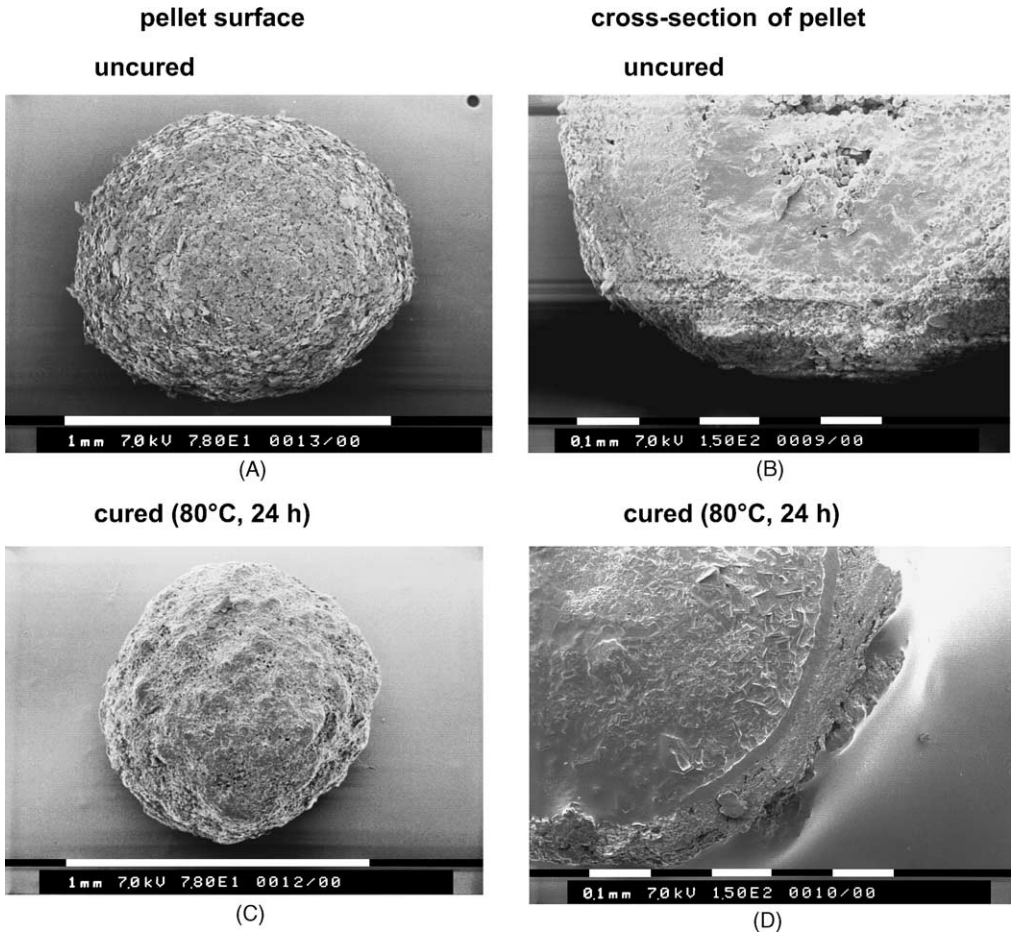

Fig. 3. Curing effects on the morphology of ethylcellulose powder-coated pellets: (A) pellet surface of uncured pellet; (B) cross-section of uncured pellet; (C) pellet surface of cured pellet; and (D) cross-section of cured pellet (coating level, 20.4%; 40% acetylated monoglyceride; curing at 80 °C for 24 h).

particles to the surface of the pellets prior to film formation.

First, a suitable plasticizer had to be identified. The glass transition temperature (T_g) of ethanol-cast ethylcellulose film could be lowered by the addition of acetylated monoglyceride (AMG) or triethyl citrate (TEC) from more than 130 °C to less than 60 °C (Fig. 1), which was a temperature obtainable in the coating chamber. In order to closer simulate the film formation process from polymer powders, the minimum polymer-softening temperature (MST) of ethylcellulose powder containing different concentrations of different plasticizers was determined with a heating plate method. The MST generally declined as the plasticizer concentration increased and the efficiency of the plasticizers to lower the MST was in the order of acetylated monoglyceride (AMG) > triethyl citrate (TEC) > acetyltributyl citrate (ATBC) (Fig. 2). For example, the MST of ethylcellulose powder was lowered from an original value of approximately 130–120 °C (40% ATBC) and 100 °C (40% TEC). AMG was the best plasticizer, 30–40%

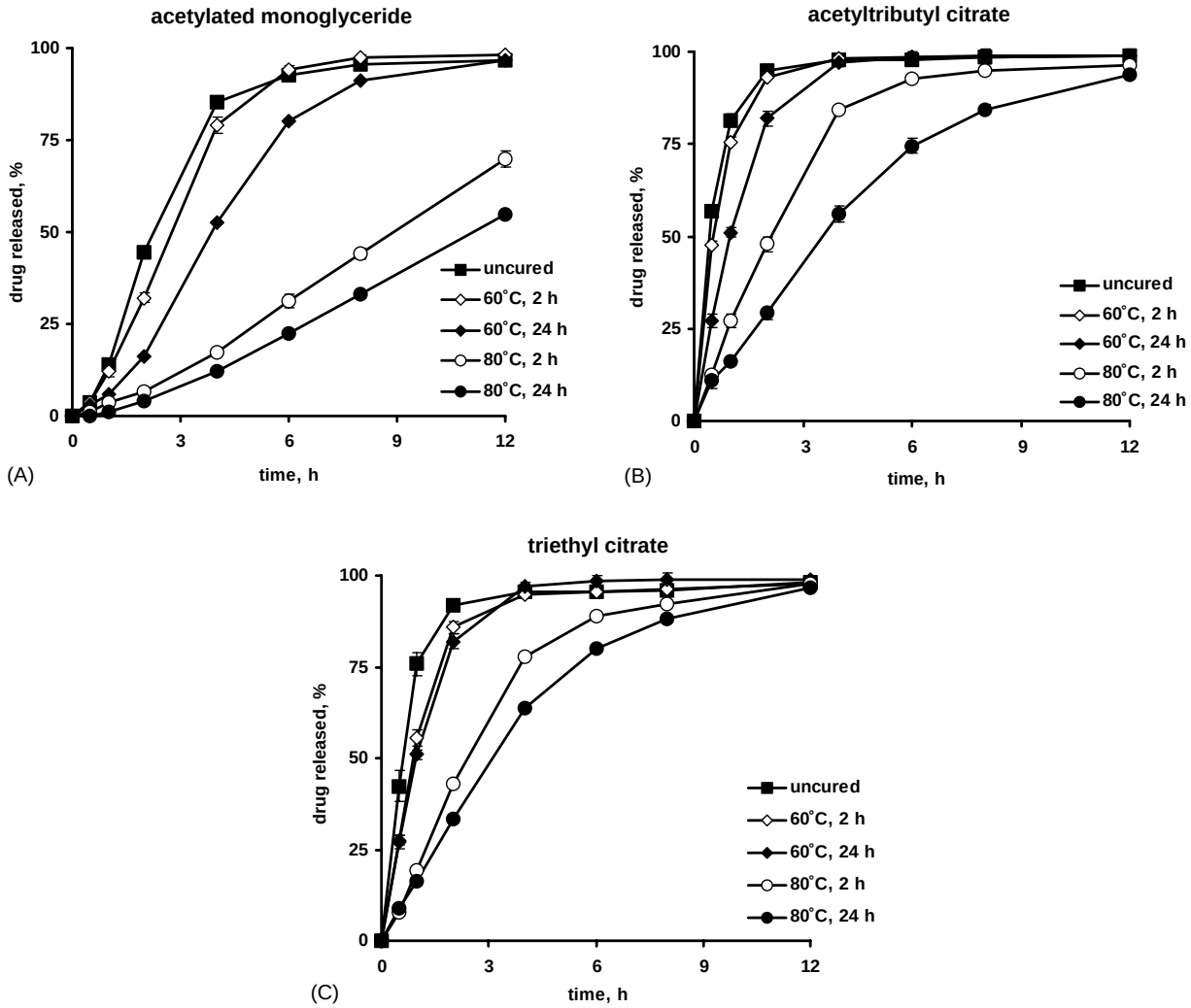

Fig. 4. Curing effects on propranolol hydrochloride release from ethylcellulose powder-coated pellets: (A) 40% acetylated monoglyceride (coating level, 30.3%); (B) 40% acetyltributyl citrate (coating level, 18.1%); and (C) 40% triethyl citrate (coating level, 18.9%).

AMG lowered the MST to 80 °C and 60% AMG to 60 °C.

As expected, the MST of the ethylcellulose powder was higher than the T_g of ethanol-cast ethylcellulose film, because the plasticizer was more uniformly distributed between the polymer chains within the films than with the powder. At 20–40% plasticizer, the ethylcellulose powders had a MST of 80–130 °C (Fig. 2) while the plasticized ethylcellulose films had a T_g of 30.9–64.4 °C (Fig. 1). The plasticizer initially wetted and softened the particle surface and then diffused into the particles. The wettability of the polymer powder by the plasticizer was therefore important. AMG resulted in a lower contact angle on ethylcellulose tablets than TEC (20.3° versus 32.7°), indicating better wetting with AMG (Hiemenz, 1986; Buckton, 1995). This could possibly explain the lower MST for AMG than with TEC. In this study, dry powder coating with ethylcellulose powder was operated at coating temperatures near the T_g of plasticized ethylcellulose (55–60 °C).

Scanning electron micrographs revealed that the surface of uncured powder-coated pellets was not smooth (Fig. 3A) and that the film—as seen on a cross-section of the pellet—was porous (Fig. 3B). This indicated that the micronized ethylcellulose particles did not coalesce into a smooth film during the coating process. The particles adhered well to the surface of the pellets, however, the film formation had to be improved. As commonly done after the coating with aqueous colloidal polymer dispersions, a thermal after-treatment (curing in an oven) was used to improve the film formation process. During the thermal treatment, the plasticizer further diffused into and softened the polymer particles and therefore enhanced their coalescence (fusion) into a denser film. The surface and cross-section of cured pellets (80 °C, 24 h) (Fig. 3C and D) was smoother, denser and more uniform than those of the uncured pellets. The surface of cured pellets was homogeneous, however, irregular structures were visible (Fig. 3D). When compared to pellets coated with an aqueous colloidal ethylcellulose dispersion (Bodmeier and Paeratakul, 1994; Wheatley and Steuernagel, 1997; Wesseling and Bodmeier, 1999), the film of the powder-coated pellets was more porous and inhomogeneous. This indicated a poorer film formation from the polymer

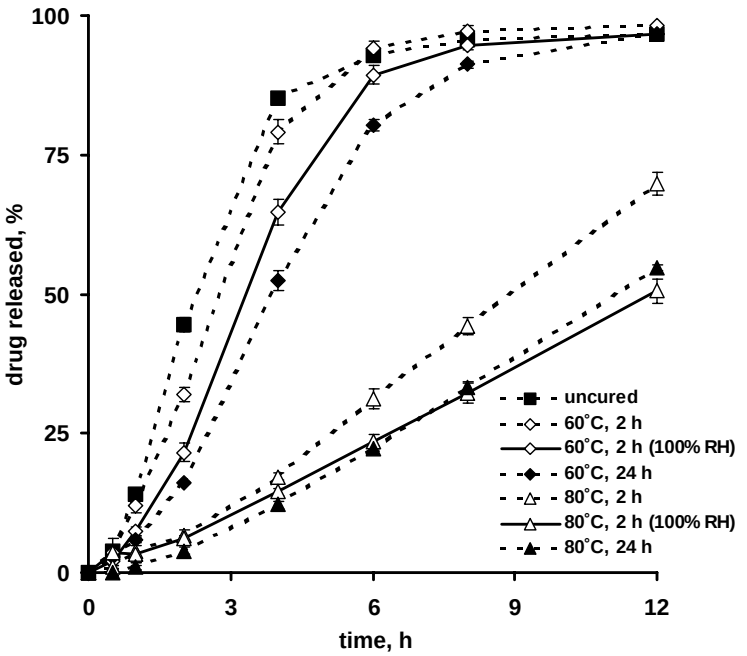

Fig. 5. Curing effect (heat-only vs. heat-humidity) on propranolol hydrochloride release from ethylcellulose powder-coated pellets (coating level, 30.3%; 40% acetylated monoglyceride).

powder than from the colloidal polymer dispersion. The reasons for this inferior film formation behaviour were probably the large particle size of the ethylcellulose powder (micronized versus colloidal particles), the irregular shape of the powder when compared to the spherical shape of the colloidal polymer particles, and the high T_g of ethylcellulose.

The ethylcellulose powder-coated pellets were cured at either 60 or 80 °C for 2 or 24 h to improve the coalescence of the polymer particles. The drug release was fast from the uncured pellets and decreased with increasing curing temperature and increasing curing time (Fig. 4). Similar curing effects were therefore seen with powder-coated pellets as have been observed with pellets coated with aqueous colloidal ethylcellulose dispersions, namely a decrease in release with increasing curing temperature and time (Fukumori, 1994; Rekhi et al., 1995; Bodmeier et al., 1997; Wheatley and Steuernagel, 1997). The coatings plasticized with AMG resulted in a slower release than the coatings plasticized with either TEC or ATBC. This correlates well with data on the

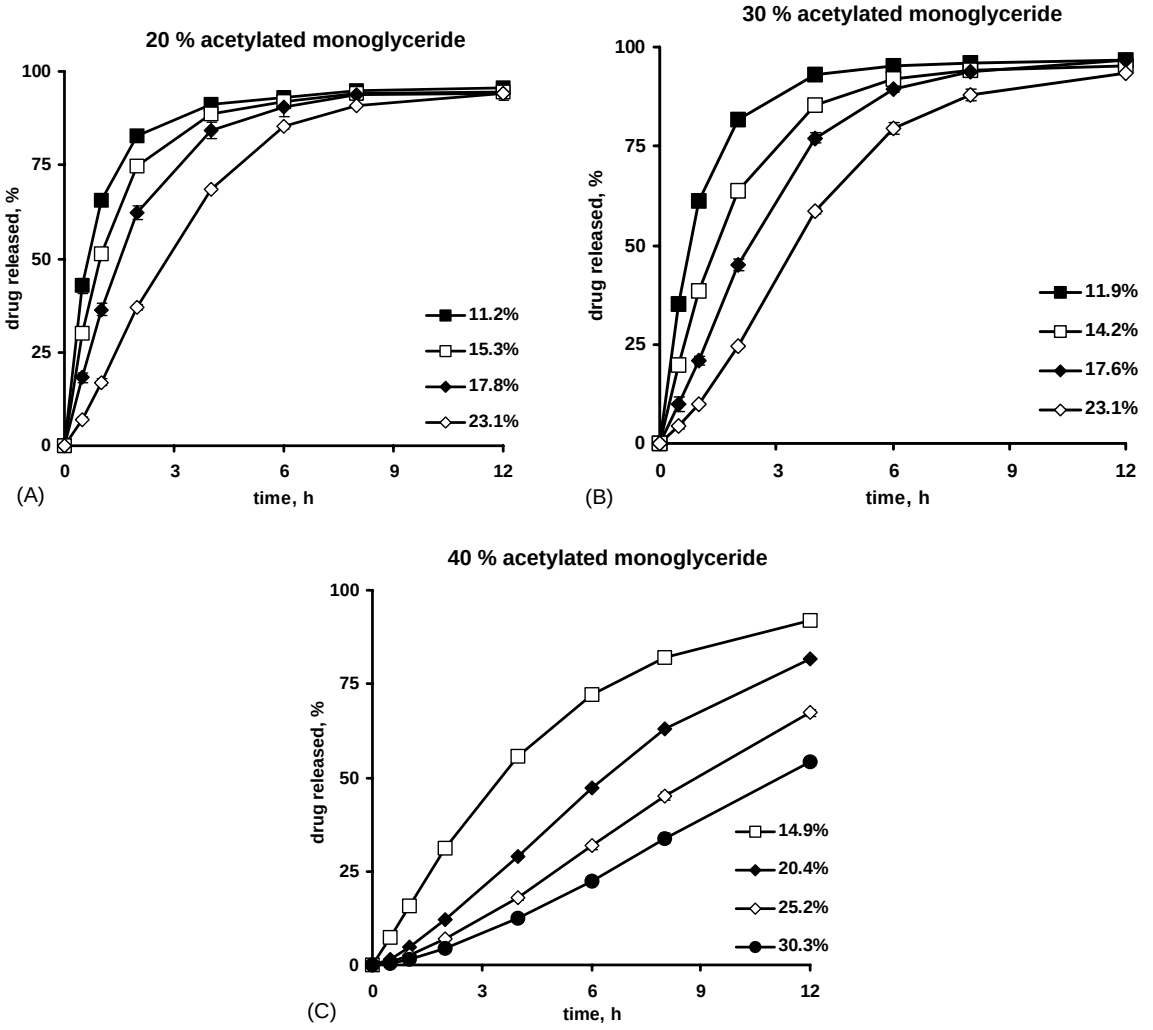

Fig. 6. Effect of plasticizer (acetylated monoglyceride) concentration and coating level on propranolol hydrochloride release from ethylcellulose powder-coated pellets: (A) 20% AMG; (B) 30% AMG; and (C) 40% AMG (curing at 80 °C for 24 h).

minimum softening temperature (Fig. 2). A thermal after-treatment was therefore necessary for ethylcellulose powder-coated solid dosage forms in order to promote film formation of the polymer particles and to obtain extended drug release.

To identify suitable curing conditions for optimum film formation, powder-coated pellets were cured at ambient humidity or 100% RH at different temperatures (60–80 °C) and times (2 or 24 h) (Fig. 5). Curing under higher humidity conditions decreased the drug

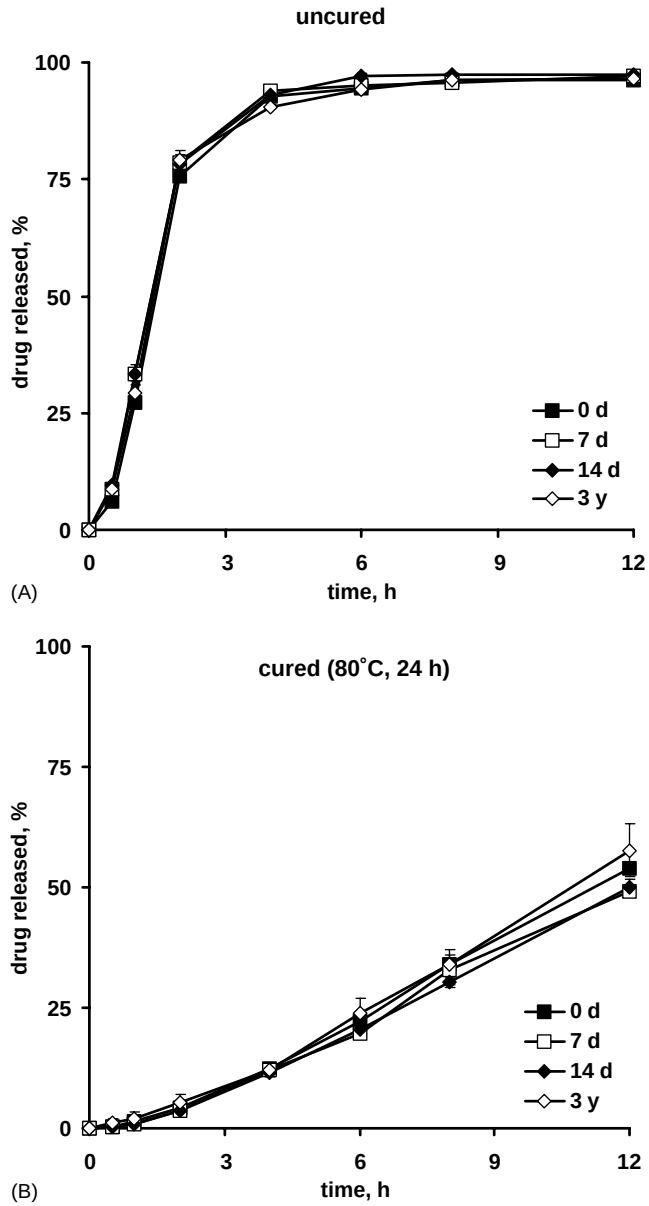

Fig. 7. Effect of short- and long-term storage at room temperature on propranolol hydrochloride release from ethylcellulose powder-coated pellets: (A) uncured pellets; and (B) cured pellets at 80 °C for 24 h (coating level, 30.3%; 40% acetylated monoglyceride).

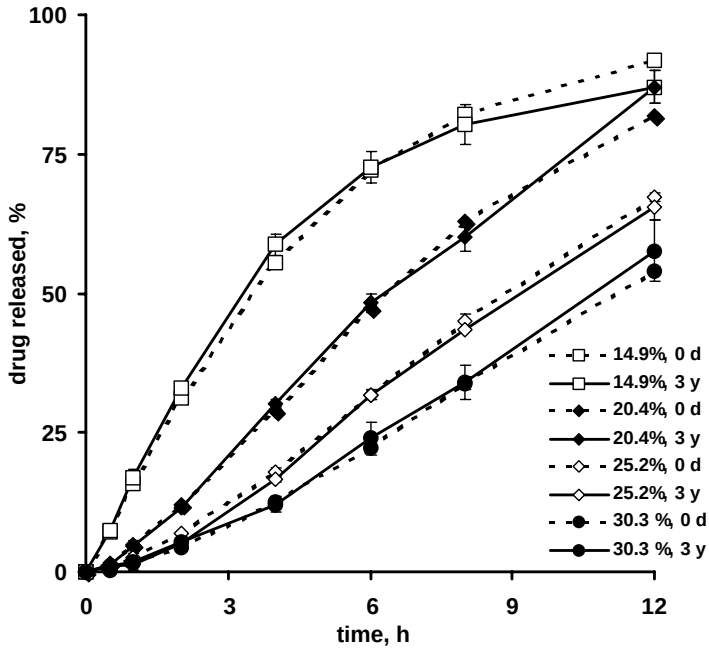

Fig. 8. Propranolol hydrochloride release from ethylcellulose powder-coated pellets at different coating levels after storage at room temperature for 3 years (40% acetylated monoglyceride, cured at 80 °C for 24 h).

release. Besides the plasticizer, water probably acted as a plasticizer (Williams and Liu, 2000), thus enhancing film formation. With combined heat-humidity curing, pellets cured for 24 h agglomerated and could not be separated without damaging the film coating. Curing at 80 °C/100% RH for only 2 h significantly did not result in agglomeration and lowered the drug release. The same release profile was obtained as with pellets cured at ambient humidity at 80 °C, but for 24 h. Curing at higher humidities might therefore be a tool to shorten the curing time and temperature, thus reducing potential non-moisture related chemical stability problems.

The drug release decreased with increasing plasticizer (AMG) concentration (20–40%) and, as expected, decreased with increasing coating level (Fig. 6). Higher plasticizer concentrations lowered the T_g and MST and therefore improved the film formation, thus resulting in a slower drug release. For example, a useful 12 h release profile could be obtained with 40% AMG and a coating level of 14.9%.

Long-term stability studies revealed that the drug release profiles of uncured and cured pellets did not change within a 3 year storage period at room temperature (Fig. 7). With uncured pellets, the rapid drug release profile did not change during storage, indicating no further coalescence of the incompletely coalesced polymer particles (Fig. 7A). The T_g of ethylcellulose was probably too high and the size of the micronized particles too large for further film formation to occur, the porous nature of the coating and therefore the rapid release were maintained. Good storage stability was seen with cured pellets, the release profile did not change (Fig. 7B). After 3 years of storage, the ethylcellulose powder-coated pellets showed unchanged drug release profiles at different coating levels (15–30%) (Fig. 8). Powder-coated solid dosage forms may therefore be a more storage stable than solid dosage forms coated with colloidal polymer dispersions, where further coalescence of particles occurs much easier during storage because of the smaller, colloidal size. This, however, needs to be investigated in more detail.

4. Conclusion

Micronized ethylcellulose powder can be coated on pellets by a dry powder coating technique to provide

extended drug release. The process has many advantages when compared to classical coating techniques (e.g. coating with organic polymer solutions or aqueous dispersions), such as shorter processing times.

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