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European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 363–369
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Dry polymer powder coating and comparison with conventional liquid-based coatings for Eudragit® RS, ethylcellulose and shellac

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Received 17 April 2003; accepted in revised form 9 July 2003

Abstract

Drug-layered pellets were coated with micronized polymer powders (Eudragit® RS, ethylcellulose, and shellac) by a dry powder coating technique as an alternative to organic- and aqueous-based coatings (Eudragit® RS 30D, Aquacoat® ECD) were investigated. High plasticizer concentrations (40%) and a thermal after-treatment (curing) were necessary for the coalescence of the polymer particles and good film formation. Ethylcellulose required a higher curing temperature and time than Eudragit® RS because of its higher glass transition temperature (133 versus 58°C). A smaller polymer particle size also promoted film formation. In general, pellets coated with polymer powders required higher coating levels to obtain similar drug release patterns as pellets coated with organic polymer solutions and aqueous polymer dispersions.

Keywords: Dry powder coating; Film formation; Eudragit® RS; Ethylcellulose; Shellac

1. Introduction

Water-insoluble polymers for extended release coatings are generally applied to the solid cores from either an organic polymer solution or an aqueous polymer dispersion [1,2]. These coating techniques potentially suffer from problems such as the use of organic solvents, high energy consumption and aging phenomena during storage. Recently, dry powder coating has been developed as an alternative coating technology, whereby the dosage forms are coated directly with micronized polymer powder [3]. The advantages of powder coating include a reduction in processing time and environmental friendliness (no organic solvents, lower energy costs) [4,5]. The coating process requires higher amounts of plasticizer, which is sprayed simultaneously to the polymer powder feeding, for film formation. The plasticizer has to partially soften or dissolve the polymer particles.

Ethylcellulose and Eudragit® RS, which are frequently used polymers for extended release dosage forms, and shellac, which is a natural enteric polymer with thermoplastic properties [6], were evaluated for dry powder coating in this study.

The major objectives of this study were: (i) to study the mechanism of film formation by dry powder coating; (ii) to determine the effect of process and formulation variables on the drug release from coated pellets; and (iii) to compare dry powder coating to conventional liquid-based coatings.

2. Materials and methods

2.1. Materials

Acetaminophen, propranolol hydrochloride (Abbott, Ludwigshafen, Germany), Aquacoat® ECD (FMC c/o Lehmann and Voss Co., Hamburg, Germany), ethylcellulose (Ethocel®, standard 10 FP, premium grade, Dow Chemical, Midland, MI, USA), Eudragit® RS 30D and PO (Röhm Pharma, Darmstadt, Germany), hydroxypropyl methylcellulose (HPMC, Methocel® E5, Colorcon, Orpington, UK), shellac (SSB® 55 Pharma, de-waxed and decolorized shellac, fine powder, Stroever Schellack Bremen, Bremen, Germany), distilled acetylated monoglyceride (AMG, Myvacet® 9–45, Quest International,

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doi:10.1016/S0939-6411(03)00121-8

Bussum, The Netherlands), acetyltributyl citrate (ATBC), triethyl citrate (TEC) (Morflex, Greensboro, NC, USA), polyethylene glycol 4000 (PEG 4000, BASF, Ludwigshafen, Germany), talc, 25% ammonium hydroxide (Merck, Darmstadt, Germany), non-pareil beads (Suglets® sugar spheres NF, 710–850 μm, NP Pharma S.A., c/o Gustav Parmentier, Frankfurt, Germany). Eudragit® RS PO was ground by Axiva (Frankfurt, Germany).

2.2. Particle size measurements

The particle size of the polymer powders was determined by laser light scattering including polarization intensity differential scattering 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 the average particle size.

2.3. Thermal analysis

Thermograms of unplasticized and plasticized polymeric films were obtained by using a differential scanning calorimeter (Mettler Toledo DSC 821^e) and STAR® software (Mettler Toledo, Giessen, Germany) to determine the melting point or the glass transition temperature (Tg) ($n = 2–3$). 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.

2.4. Preparation of drug-loaded pellets

A solution of drug (96 g) and PEG 4000 (0.45 g) in 300 ml solvent [acetaminophen in ethanol (96% v/v) or propranolol hydrochloride in ethanol (60% v/v)] was mixed with 45 g of an aqueous 10% w/w HPMC solution. Propranolol hydrochloride-loaded pellets (12% w/w, drug loading) were prepared by layering the drug-binder solution onto non-pareil 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.

2.5. Coating of drug-loaded pellets

The formulations for the coating with dry polymer powders (Eudragit® RS, ethylcellulose, shellac) and the process parameters are shown in Tables 1 and 2. The powders (polymer plus talc) and an emulsion of liquid materials (plasticizer plus 10% w/w HPMC solution) were fed/sprayed separately onto drug-loaded pellets in a fluidized bed coater (Glatt® GPCG-1, Wurster insert). The coated pellets were cured in an oven at different temperatures (40–80°C) and times (2–24 h).

Table 1
Formulations for the coating of pellets with polymer powders in a fluidized bed coater (Glatt® GPCG-1, Wurster insert)

Formulation	Composition,% w/w		
	Ethylcellulose	Eudragit® RS	Shellac
Powders			
Polymer	76.9	50.0	50.0
Talc	23.1	50.0	50.0
Total	100.0	100.0	100.0
Liquids			
Plasticizer	50.0–75.0	36.8–75.0	50.0–75.0
10% w/w HPMC solution	25.0–50.0	25.0–63.2	25.0–50.0
Total	100.0	100.0	100.0

With aqueous polymer dispersions, Eudragit® RS 30D and Aquacoat® ECD were plasticized with TEC (20 and 25% w/w, based on the polymer, respectively) for 24 h prior to coating. The polymer content of the plasticized dispersion was then adjusted to 15% w/w by dilution with water.

For ethanolic ethylcellulose solution, the coating formulation consisted of a solution of ethylcellulose (5% w/v) and TEC (20% w/w, based on the polymer) in ethanol (96% v/v). A 10% w/v ethanolic solution of shellac was prepared by dissolving shellac in ethanol (96% v/v). The ethanolic shellac solution was plasticized with 5% TEC and 30% talc was added as anti-tacking agent.

To prepare a 10% w/w aqueous solution with a degree of neutralization of 0.8, shellac was added to an aqueous

Table 2
Physical properties of polymer powders and processing parameters of the dry powder coating in a fluidized bed coater (Glatt® GPCG-1, Wurster insert)

	Ethylcellulose	Eudragit® RS	Shellac
Physical properties			
Glass transition temperature, °C	133.4 (1.8)	57.6 (0.2)	50.4 (0.3)
Polymer particle size, μm	6.1 (4.6)	9.4 (1.4)	27.1 (2.5)
Processing parameters			
Batch size, kg	1.2	1.2	1.2
Inlet air temperature, °C	55–60	40–45	60–65
Product temperature, °C	45–47	34–36	50–52
Outlet air temperature, °C	40–41	32–36	40–45
Air flow rate, m^3/h	60–80	60–80	60–80
Atomizing air pressure, bar	1.2	1.2	1.2
Spray nozzle diameter, mm	1.2	1.2	1.2
Spray rate, g/min	3–5	3–5	3–5
Powder feed rate, g/min	10–14	12–13	11–12
Drying temperature, °C	45	35	50
Drying time, min	10	10	10
Curing condition, in oven	80°C, 24 h	60°C, 2 h	80°C, 24 h

Table 3
Processing parameters of organic- and aqueous-based coatings in a fluidized bed coater (Glatt® GPCG-1, Wurster insert)

	Aqueous Eudragit® RS 30D dispersion	Ethanolic ethylcellulose solution	Aqueous ethylcellulose dispersion, Aquacoat® ECD	Ethanolic shellac solution	Aqueous shellac solution
Batch size, kg	1.2	1.2	1.2	1.2	1.2
Inlet air temperature, °C	35–40	30–35	45–50	23–25	50–55
Product temperature, °C	31–33	29–31	41–43	23–25	38–42
Outlet air temperature, °C	27–29	27–30	35–39	22–23	34–37
Air flow rate, m^3/h	80–90	80–100	80–90	80–100	80–90
Atomizing air pressure, bar	1.2	1.2	1.2	1.2	1.2
Spray nozzle diameter, mm	1.2	1.2	1.2	1.2	1.2
Spray rate, g/min	2–10	2–6	2–10	2–6	2–10
Drying temperature, °C	35	30	45	20	50
Drying time, min	10	10	10	10	10

ammonium hydroxide (15% v/v) solution. The shellac suspension was agitated and heated (50–60°C) until a clear solution with a pH 7–8 was obtained. For all liquid-based coatings, the final coating formulations were sprayed onto drug-loaded pellets in a fluidized bed coater (Glatt® GPCG-1, Wurster insert). The processing parameters are given in Table 3. After coating with aqueous dispersions, the coated pellets were cured in an oven at 60°C for 2 h (Eudragit® RS 30D) and 24 h (Aquacoat® ECD).

The coating level (based on polymer in coating) was calculated from the weight difference between the coated and the uncoated pellets. The coating efficiency (%) was calculated from the actual weight gain of the coated pellets divided by the theoretical weight gain.

2.6. In vitro drug release studies

In vitro drug release was determined using the USP XXV rotating paddle method [900 ml 0.1 N HCl or phosphate buffer pH 6.8; 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 the following wavelengths: 244 nm (acetaminophen), 290 nm (propranolol hydrochloride) in 0.1 N HCl; 243 nm (acetaminophen) in phosphate buffer pH 6.8, respectively (UV-210PC, Shimadzu Europa, Duisburg, Germany).

3. Results and discussion

Coating of solid dosage forms with polymer powders is an interesting alternative to the coating with organic polymer solutions or aqueous polymer dispersions. The dry powder coating process used in this study was a modified fluidized bed Wurster-process. The polymer powder was fed via a powder feeder into the coating chamber, while the plasticizer/HPMC solution is bottom-sprayed simultaneously from the liquid container. The fluidization of the pellets and of the polymer powder results in good product motion/mixing and initiates particle collisions between the liquid droplets and pellets and polymer particles.

The film formation from polymer powders occurred via several steps. First, polymer particles had to adhere to the surface of the heated pellets. This adhesion was achieved by spraying simultaneously to the powder feeding an aqueous HPMC solution containing the plasticizer. The polymer particles and the pellet surface were wetted thus promoting adhesion of the particles to the surface and cohesion of subsequently fed particles to the already adhering particles. The process was also performed at elevated temperatures, which resulted in the softening of the polymer particles and plasticizer uptake and sticking of the particles to each other on the pellet surface. However, the particles did not coalesce into a homogeneous film during the coating process. Like with aqueous colloidal polymer dispersions, a thermal after-treatment (curing) at elevated temperatures was necessary for the coalescence of the plasticized polymer particles and good film formation. To complete the film formation, all coated pellets were oven-cured at 60°C for 2 h (Eudragit® RS) and at 80°C for 24 h (ethylcellulose). Ethylcellulose ($Tg = 133$°C) has a much higher glass transition temperature (Tg) than Eudragit® RS ($Tg = 58$°C) and therefore required higher curing temperatures and longer curing times [7]. Shellac had a larger particle size than the other two polymers and was therefore also cured at higher temperatures.

After adhesion to the pellet surface, the polymer particles could already partially coalesce during the coating process. In order to promote film formation and to remove residual water present from the binder solution, ethylcellulose-coated pellets were further fluidized in the coating chamber at 45 and 65°C for 10 min after the powder feeding was finished. Higher temperatures were not possible, because the coated pellets agglomerated during drying, causing poor fluidization in the coating chamber. The drug release was affected by the additional fluidization step only with the uncured pellets (Fig. 1). The release was lower for the sample treated at 65°C than for the sample treated at 45°C because of a better film formation. Curing the pellets in an oven at 80°C for 24 h resulted in a sharp decrease in

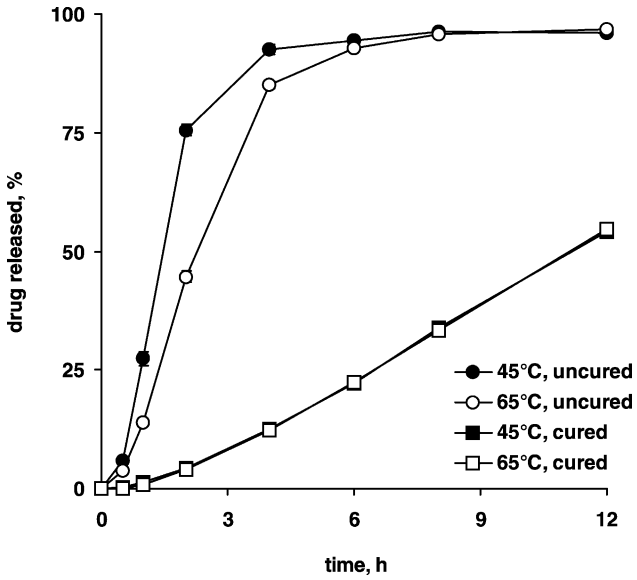

Fig. 1. Effect of drying temperature in the coater and oven-curing on the propranolol hydrochloride release in 0.1 N HCl from ethylcellulose-coated pellets (coating level, 30.3%; 40% acetylated monoglyceride; drying time, 10 min; curing at 80°C for 24 h).

drug release and no differences were seen between the fluidization temperatures. For the oven-curing step, 10% talc (based on the pellet weight) was added to avoid agglomeration and sticking of the pellets. The film formation was therefore achieved primarily during the curing and not during the coating process.

A plasticizer concentration of 40% based on the polymer was necessary to obtain good film formation for Eudragit® RS and ethylcellulose [7–9]. Various plasticizers (AMG, ATBC, TEC at a level of 40% w/w based on the polymer) were evaluated in the coating formulations for dry powder coating (Eudragit® RS, Fig. 2A) and (ethylcellulose, Fig. 2B). Extended drug release was achieved with coating levels of 10% for Eudragit® RS and 15% for ethylcellulose. Because of their different water solubility, plasticizers significantly affected the drug release from coated pellets. Propranolol hydrochloride (a water-soluble drug) was released in the order of TEC > ATBC > AMG. TEC has the highest water-solubility and therefore leached from the coating and created pores, thus resulting in the faster release when compared to the water-insoluble plasticizers, ATBC and AMG.

The drug release from pellets coated with polymer powders was compared to the release from pellets coated with commercially available aqueous dispersions of the polymers, Eudragit® RS 30D [10] or Aquacoat® ECD [11,12]. Similar release patterns were obtained with the Eudragit® RS-coated pellets for both the dry powder and the aqueous dispersion (Fig. 3A). With both Eudragit® RS coating systems, the pellets were cured at 60°C for 2 h. An 8 h extended release profile was obtained at a coating level of 15%. A higher plasticizer level was used with the powder coating system (40 versus 20% TEC for Eudragit® RS 30D).

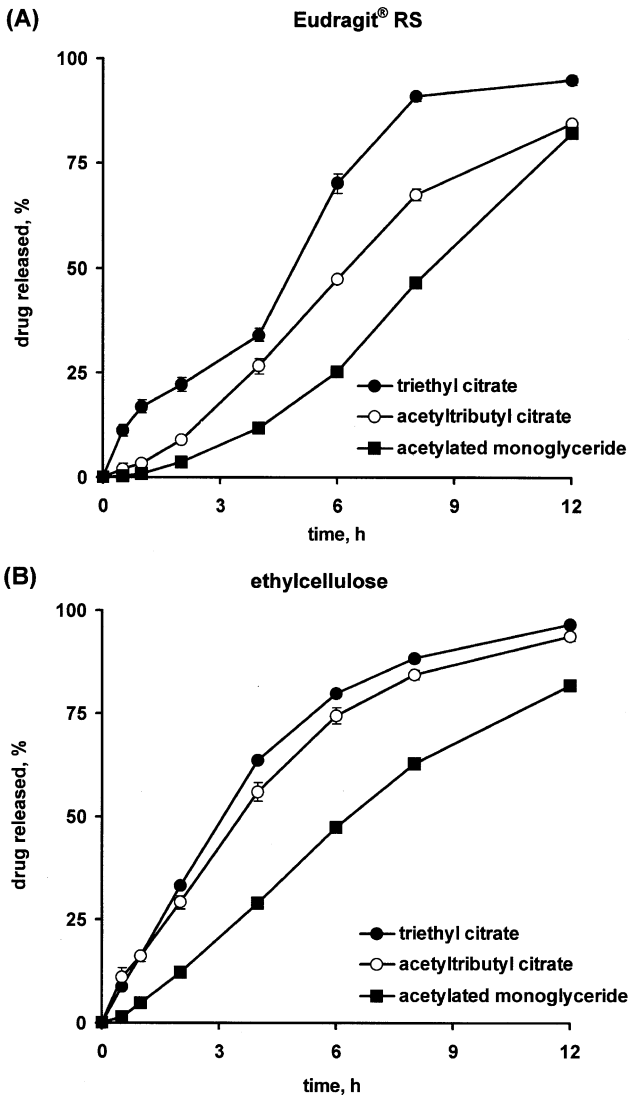

Fig. 2. Effect of the type of plasticizer (40% w/w, based on the polymer) on the propranolol hydrochloride release in 0.1 N HCl from pellets coated with: (A) Eudragit® RS; coating level, 12.2–14.9%; curing at 60°C for 2 h; and (B) ethylcellulose; coating level, 18.1–20.4%; curing at 80°C for 24 h.

In comparison, the ethylcellulose-coated pellets prepared by the dry powder coating required a higher coating level (20% ethylcellulose) than pellets coated with the aqueous dispersion, Aquacoat® ECD, or with an ethanolic ethylcellulose solution (only 5% ethylcellulose) to achieve a similar extended release profile (Fig. 3B). Also, a higher amount of plasticizer was used with the dry powder coating (40 versus 25% TEC with the aqueous dispersion and 20% for the ethanolic solution). Pellets coated with the ethanolic ethylcellulose solution had the slowest release. Ethylcellulose films prepared from ethanolic solution had a dense, compact film structure [13]. While Eudragit® RS coated pellets had similar release profiles for powder and aqueous dispersion-coated systems, a higher coating level was required with ethylcellulose. This could be explained with the higher Tg of ethylcellulose (133°C) when compared with Eudragit® RS (58°C). Ethylcellulose formed inferior

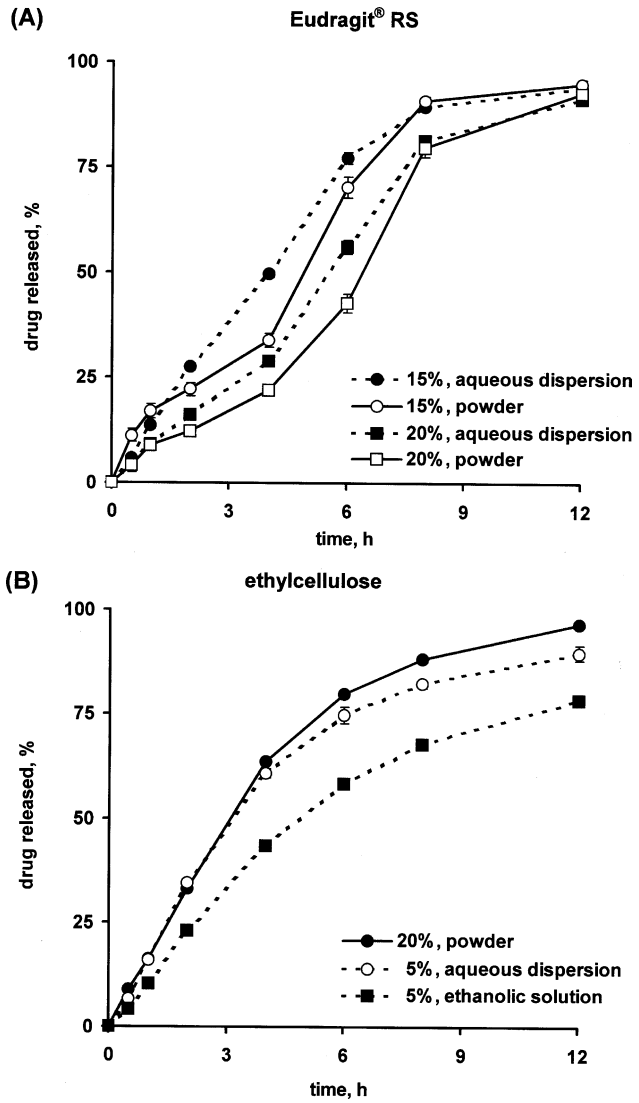

Fig. 3. Propranolol hydrochloride release in 0.1 N HCl from pellets coated with different polymer formulations (% coating level): (A) Eudragit® RS 30D, 20% triethyl citrate, curing at 60°C for 2 h; Eudragit® RS powder, 40% triethyl citrate, curing at 60°C for 2 h; and (B) ethanolic ethylcellulose solution, 20% triethyl citrate; Aquacoat® ECD, 25% triethyl citrate, curing at 60°C for 24 h; ethylcellulose powder, 40% triethyl citrate, curing at 80°C for 24 h.

(more permeable) films from the micronized powder than from the aqueous colloidal polymer particles, higher coating levels were therefore required.

For liquid-based coating (either solution or dispersion), the length of the coating time depends on the polymer concentration in the coating formulation and the drying efficiency of the coater used [3]. Large amounts of solvents had to be removed and the coating times therefore were quite long (Table 4). In contrast, with dry powder coating, only small amounts of water are used in the plasticizer/HPMC solution and the processing times are therefore much shorter. For example, the coating time for Eudragit® RS-coated pellets at a coating level of 15% was reduced from 128 min (aqueous-based coating) to 31 min (dry powder coating). With ethylcellulose coatings, although a much higher coating level had to be used to achieve comparable release profiles, the processing time was still shortest with the dry powder coating technique. With the organic ethylcellulose solution, only a very diluted solution (5% w/v) could be sprayed because of viscosity restrictions [12,14]. The processing time therefore was also longer than with the Aquacoat® ECD-based coating, where a 15% w/v dispersion was sprayed.

Table 4
Coating time for the film coating of pellets with dry polymer powders or organic- and aqueous-based coatings (Glatt® GPCG-1, Wurster insert)

Coating formulation	Coating level, %	Coating time, min
Eudragit® RS		
Dry powder coating	15	31
	20	41
Aqueous-based coating	15	128
	20	171
Ethylcellulose		
Dry powder coating	20	30
Aqueous-based coating	5	44
Organic-based coating	5	111

Besides the synthetic polymers, Eudragit® RS and ethylcellulose, shellac is an interesting polymer for enteric coating applications, because it is the only approved enteric polymer for food additives. In preliminary experiments, shellac was fed into the coating chamber at coating temperatures of 40–45°C. Although this temperature was near the Tg shellac (50.4°C), a polymer layer could not be deposited around the pellets. This could be explained with the larger particle size of shellac (27.1 μm) when compared with Eudragit® RS (9.4 μm) and ethylcellulose (6.1 μm) powders. A critical parameter, which was responsible for the powder deposition onto the pellets was not only the softening (glass transition) temperature of the polymer, but also the particle size of the polymer powder. The coating efficiency could be raised to more than 80% when the coating temperatures was increased to 60–65°C. This was above the Tg of shellac (approx. 50°C). Being thermoplastic polymer, sticky shellac particles formed at this temperature, which then adhered to the heated pellet surface. The disadvantage of larger polymer particles could therefore be minimized by using higher temperatures.

The shellac-coated pellets (coating levels, 18.1–25.2%) were oven-cured at different curing conditions (40–80°C, 2–24 h) (Fig. 4). Interestingly, the uncured pellets already gave extended release patterns in 0.1 N HCl. With 40% plasticizer, curing at 40°C was insufficient to promote a better coalescence of polymeric particles, the drug release profiles from the 40°C-cured pellets were similar to those of the uncured pellets. This was similar with pellets cured at 60°C for 2 h, however, the drug release significantly decreased when the coated pellets were cured for 24 h. The drug release was further decreased by increasing the curing temperature to 80°C (2–24 h). Since the powder particle

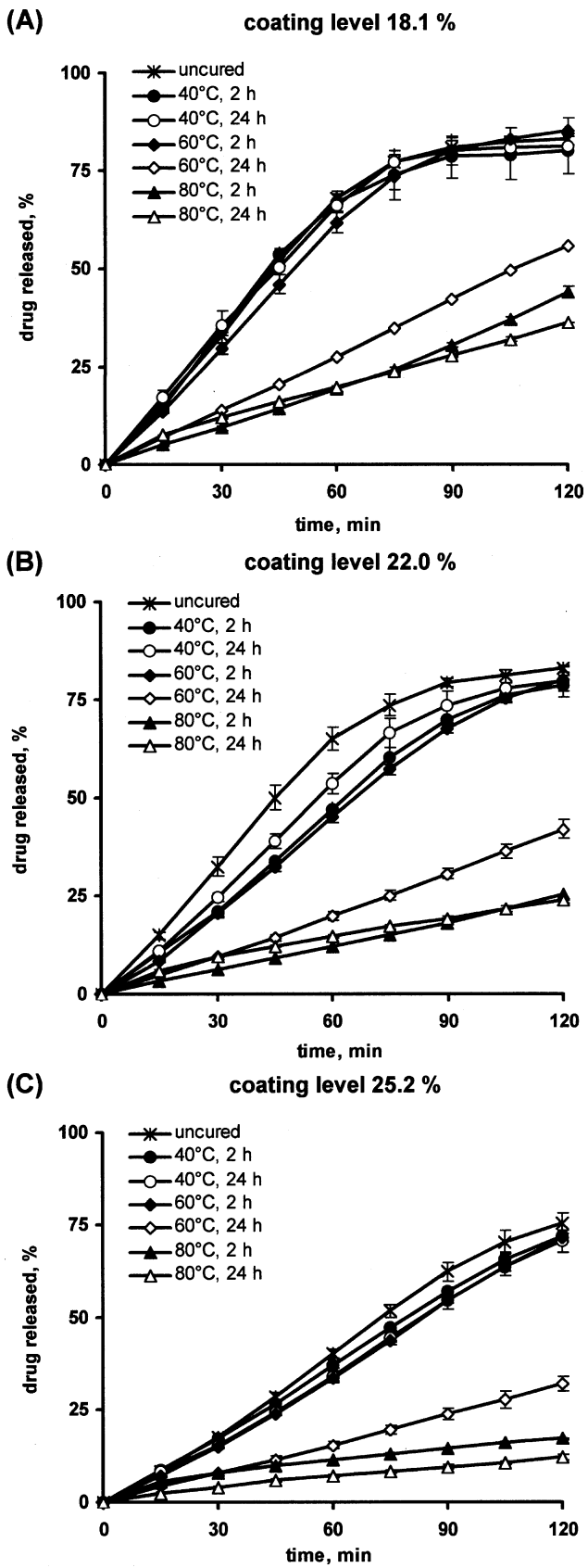

Fig. 4. Effect of curing conditions on the acetaminophen release in 0.1 N HCl from shellac-coated pellets containing 40% acetylated monoglyceride at different coating levels: (A) 18.1%; (B) 22.0%; and (C) 25.2%.

size was a parameter, which affected film coalescence, the modulus of the polymer must be decreased. This can be achieved by increasing the curing temperature [13], the limiting release pattern was then approached. Therefore, all following shellac-coated pellets were cured at 80°C for 24 h. The drug release also decreased with increasing coating level. For gastric protection (< 10% drug released within 120 min in 0.1 N HCl), a coating level of 25% was required.

The effect of plasticizer on the decrease in drug release in 0.1 N HCl was compared between a hydrophilic (TEC) and a lipophilic (AMG) plasticizer (Fig. 5). Gastric protection could only be achieved with the cured AMG pellets. A drug

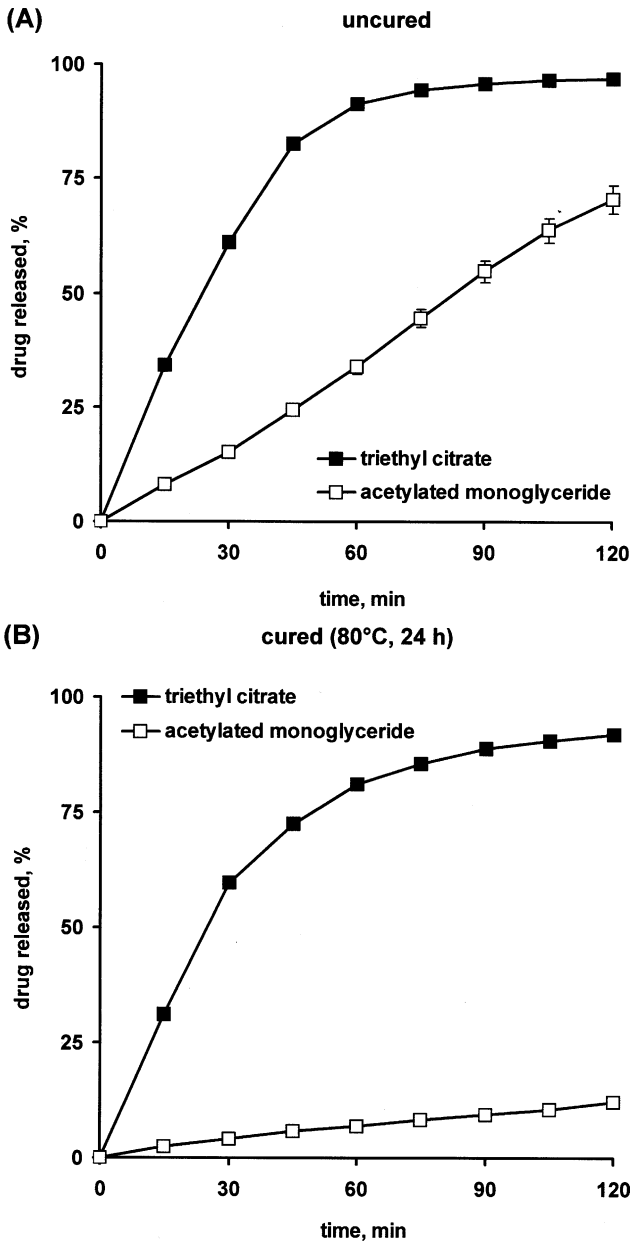

Fig. 5. Effect of the type of plasticizer (40% w/w, based on the polymer) on the acetaminophen release in 0.1 N HCl from shellac-coated pellets at coating levels of 23.9–25.2%: (A) uncured pellets; and (B) cured pellets (80°C, 24 h).

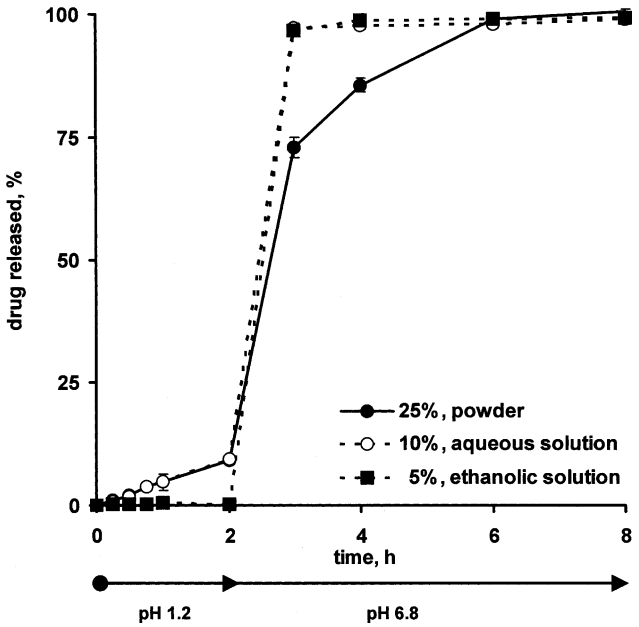

Fig. 6. Drug release from pellets coated with different shellac-coated formulations (% coating level): ethanolic shellac solution, 5% triethyl citrate; ammoniated aqueous shellac solution, no plasticizer; shellac powder, 40% acetylated monoglyceride, curing at 80°C for 24 h (release medium change after 2 h).

release of less than 10% within 120 min was obtained. The TEC-pellets, either cured or uncured, released the drug rapidly and also faster than the AMG-pellets because of the leaching of the water-soluble TEC.

The gastric protection and drug release of shellac-coated pellets was compared for the three different coating formulations: an ethanolic solution, an ammoniated aqueous solution and a dry powder coating (Fig. 6). Traditionally, an ethanolic shellac solution has been using for enteric coating. Due to the compact, homogeneous film structure [15], a coating level of 5% provided gastric protection, followed by a rapid release in pH 6.8 buffer. Shellac can also be coated from an aqueous solution by neutralizing the polymer with an alkaline solution (ammonium hydroxide). With the water-soluble salt of the polymer [15,16], gastric protection was achieved at a coating level of 10%, the drug release in the following pH 6.8 buffer was also rapid. In comparison, shellac-coated pellets prepared by dry powder coating required the highest polymer coating level (25%). Because of the higher coating level, the drug was released slower in pH 6.8 buffer. This indicated, that the film obtained from the shellac powder was inferior to films prepared from either aqueous or organic solutions. A reduction in particle size probably would improve the film formation from the shellac particles and lower coating levels would be required.

In conclusion, dry powder coating can be used for extended release coating with Eudragit® RS and ethylcellulose powders, and for enteric coating with shellac powder. Compared to the liquid-based coatings, the coated pellets prepared from dry powder coating required higher coating levels to obtain a similar drug release, however, the coating time can be significantly shorten.

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