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RESEARCH PAPER

Improvement of the Low-Temperature Stability of an Aqueous Colloidal Ethylcellulose Dispersion, Aquacoat® ECD, and Preparation/Characterization of a Redispersible Aquacoat® ECD Powder

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ABSTRACT

Aquacoat® ECD, an aqueous ethylcellulose dispersion, is susceptible to low-temperature storage, resulting in irreversible coagulation as indicated by a strong increase in viscosity and particle size. This destabilization of the ethylcellulose dispersion is caused by the anionic surfactant sodium dodecyl sulfate, which precipitates at low temperatures because of its low Krafft point. This problem could be solved by using the more hydrophilic, ethoxylated, sodium dodecyl ether sulfate, which was an effective stabilizer at low temperatures. A redispersible ethylcellulose powder was prepared by freeze- or spray-drying of the original polymer dispersion (Aquacoat ECD). The pH of the dispersion medium had a strong influence on the redispersibility of the dried ethylcellulose particles because of the dissociation behavior. At a pH > 7, polymer dispersions in the colloidal size range were obtained. At lower pH values, the dried ethylcellulose agglomerates could not be redispersed. Drug release studies from pellets coated with the redispersed and the original dispersion showed a comparable release pattern when using alkalized aqueous dispersion systems. Higher plasticizer concentration and curing of the coated pellets improved the film formation of the redispersed polymer particles.

Key Words: Aquacoat® ECD; Colloidal polymer dispersion; Coating; Ethyl cellulose; Pseudolatex; Redispersibility; Spray-drying; Freeze-drying.

INTRODUCTION

Organic solvent-based polymer solutions have lost importance in the coating of multiparticulate dosage forms when compared with aqueous polymer dispersions, because of the high costs of solvents and solvent recovery systems and of ecological, toxicological, and explosion risks. Aqueous polymer

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dispersions are commercially available either in liquid form or are prepared just before coating from redispersible polymer powders. The dry powders are usually obtained by freeze-drying or spray-drying of the original aqueous polymer dispersions or by milling the polymer to the micrometer size range. Redispersible polymer powders have various advantages when compared with aqueous polymer dispersions. These include better chemical, physical, and microbiological stabilities; a more flexible formulation design; and reduced transport costs. Additionally, the polymer powders are not susceptible to heat or freezing, which can lead to unwanted flocculation/coagulation of aqueous dispersions. The challenges in the development of redispersible polymer powders are the aggregation of the polymer particles during drying and the redispersion process, whereby polymer dispersions with the original properties should be obtained.

Aquateric®, Aqoat®, and Eudragit® L100-55, L100, and S100 are commercially available redispersible enteric polymer powders.[1] Aquateric is a spray-dried pseudolatex of cellulose acetate phthalate (CAP), which contains acetylated monoglycerides as a barrier dispersant to prevent agglomeration/coalescence of the particles during the spray-drying process. The CAP powder can be redispersed to nearly the original particle size range.[2] Aqoat is a milled fine powder of hydroxypropylmethylcellulose acetate succinate, with an average particle size of 5 μm and is readily redispersed in water.[3] Eudragit L100-55 (methacrylic acid:ethyl acrylate, 1:1 copolymer) is the spray-dried powder of Eudragit L30D-55 in the form of loose agglomerates of the latex particles of around 50 μm. This powder can be reconstituted to a comparable particle size distribution of the original dispersion by adding small amounts of alkali, which neutralize 3–6 mol% of the carboxyl groups.[4] Aqueous colloidal dispersions of extended release methacrylic copolymers containing small amounts of quaternary ammonium groups (Eudragit RS/RL100) are prepared by direct emulsification of the bulk polymer in water heated to temperatures above the polymer's glass transition temperature.[5]

The acrylic or cellulosic enteric or nonenteric polymers, which are currently available as redispersible powders, all carry ionizable groups and are therefore well dispersed in water.

For extended release coatings, the nonionic polymer ethylcellulose is widely used. Two aqueous ethylcellulose dispersions are commercially available. Aquacoat ECD is a 30% w/w dispersion prepared by a direct emulsification-solvent evaporation method[6] and Surelease® is a 25% w/w dispersion prepared by a phase inversion-in situ emulsification technique.[7] Besides the aqueous ethylcellulose pseudolatexes, coating with an aqueous suspension of micronized ethylcellulose with a particle size of 5 μm has been described.[8] However, a redispersible colloidal ethylcellulose powder is currently not available.

Aquacoat ECD was incorporated as model nanoparticles into various oral solid dosage forms (e.g., tablets, granules, and pellets) to study their release and redispersibility from the dry dosage forms into the original particles. The colloidal ethylcellulose nanoparticles (Aquacoat ECD) were incompletely released from the solid dosage forms and were also poorly redispersible, when the dosage forms were brought in contact with water. This was explained with the poor wettability of the ethylcellulose particles, which do not carry ionizable functional groups like Eudragit RL, which was almost completely released in the form of the original colloidal particles and had good wettability.[9]

The objective of this study was to prepare and evaluate a redispersible ethylcellulose powder having similar properties and performance to the original polymer dispersion (Aquacoat ECD). In addition, the temperature sensitivity of the ethylcellulose dispersion toward coagulation was investigated.

EXPERIMENTAL

Materials

The following materials were obtained from commercial suppliers and were used as received: Aquacoat ECD (FMC Corporation, c/o Lehmann and Voss, Hamburg, Germany), micronized ethylcellulose (Ethocel 10 Standard FP, The Dow Chemical Company, Midland, MI, USA), Surelease (Colorcon Ltd., Orpington, UK), triethylcitrate (TEC) (Morflex, Inc., Greensboro, NC, USA), theophylline pellets (82.83% drug content, drug layered on nonpareils, Byk-Gulden Lomberg Chemische Fabrik GmbH, Konstanz, Germany), nonpareil beads 710–850 μm (Hanns G. Werner, Tornesch, Germany), propranolol HCl (Knoll AG, Ludwigshafen, Germany), hydroxypropylmethylcellulose (Methocel E5®, Colorcon Ltd., Orpington, UK), PEG 4000 (Lutrol E 4000, BASF AG, Ludwigshafen, Germany), sodium dodecyl ether sulfate (SDES) (Texapon N70, Henkel KGaA, Düsseldorf, Germany), sodium dodecyl sulfate (SDS) (Smith

Kline & Beecham, Worthing, UK), cetyl alcohol (Lanette 16, Henkel KGaA, Düsseldorf, Germany), sodium hydroxide (E. Merck KGaA, Darmstadt, Germany), and ethanol (Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany).

Preparation of Ethylcellulose Dispersions

Ethylcellulose pseudolatex dispersions were prepared by a solvent-evaporation method [organic phase: ethylcellulose, 21.75 g; cetyl alcohol, 2.25 g; methylene chloride, 130 mL; aqueous phase: SDS or SDES, 1.0 g; water, 170 g]. After prehomogenization of the aqueous and organic phases by a rotor stator homogenizer (Ultra-Turrax, Janke & Kunkel GmbH, Staufen, Germany), this pre-emulsion was passed through a high-pressure homogenizer (3 cycles at 1,000 bars; Micron Lab 40 homogenizer, APV Gaulin, Lübeck, Germany) to reduce the particle size into the colloidal size range. Pseudolatex was stirred for 1 week (room temperature at ambient pressure) to evaporate the organic solvent. The solids content of the dispersion was determined gravimetrically by drying a sample at 60°C.

Drying of the Aqueous Ethylcellulose Dispersion, Aquacoat ECD

A fine powder of Aquacoat ECD was obtained by drying the original dispersion in a spray-dryer (Büchi 190 Mini Spray Dryer,Buchi Laboratoriums Technick, Eislingen, Germany) (inlet temperature: 100°C, outlet temperature: approximately 50°C, aspirator setting: 50% of maximum, nozzle diameter: 0.7 mm) or in a freeze-dryer (alpha I-5, Christ GmbH, Osterode, Germany) (drying temperature: −10°C (−20°C) for 48 hr, postdrying: 20°C for 4 hr). After freeze-drying, a cake of Aquacoat ECD was obtained, which was gently broken into a flowable powder with a mortar and pestle. The polymer powders were stored in a desiccator with silica gel.

Redispersibility Studies

One gram of the polymer powder was added to 10 mL of water-filled glass vials (pH adjusted with NaOH or HCl to different pH values) at a solids content of 10% w/w in a horizontal shaker at 200 rpm for 1 hr. After standing for predetermined time intervals, a sample of 1 g of the supernatant was taken, dried at 60°C to constant weight, and the solids content of the supernatant was determined gravimetrically ($n = 2$). A redispersion index was defined as the fraction of solids content of the supernatant/theoretical solids content.

Particle Size Determination

The particle size of the self-prepared dispersions was determined by photon correlation spectroscopy (Malvern Zetasizer 4, Malvern Instruments, GB-Malvern, Germany) after appropriate dilution of the samples. The intensity of the scattered light was measured at an angle of 90°. The dispersion was measured at a sample time of 200 sec, consisting of 10 subruns per 20 sec and characterized by mean particle size and polydispersity index.

The mean particle size of the redispersed dispersions was examined by laser light scattering, including PIDS technology (Coulter LS 230, Coulter Electronics, Krefeld, Germany; small volume module) in deionized water to determine the particle size in the micrometer range. The relative frequency of the diameter of the particles is obtained with the calculation based on volume distribution.

Scanning Electron Micrographs

Dried powders were examined by scanning electron microscopy (SEM) (PW 6703/SEM 515, Philips, Eindhoven, the Netherlands). The samples were coated for 230 sec under an argon atmosphere with gold-palladium (SCD 040, Balzers Union, Liechtenstein).

Viscosity Measurements of the Ethylcellulose Dispersion

The viscosity of the dispersions was measured with Ubbelohde capillary viscosimeters (Schott-Geräte GmbH, Hofheim, Germany) at 23°C ($n = 2$).

Preparation of Drug-Layered Beads

Propranolol HCl containing beads (drug content: 8.2%) were produced by layering 450 g solution [ethanol (96%) 200 g, water 145 g, drug 100 g, hydroxypropylmethylcellulose (Methocel E5) 5 g, and PEG 4,000 0.5 g] onto 1,000 g of nonpareil beads

(Wurster insert, inlet temperature: 66°C, product temperature: 54°C, outlet temperature: 48°C, air flow: 100 m^3/hr, spray rate: 8 g/min, atomization pressure: 1.8 bars, and spray nozzle diameter: 1.2 mm). The drug-layered pellets were dried for 24 hr at 40°C in an oven.

Coating of the Drug-Layered Beads with the Original or Redispersed Ethylcellulose Dispersions

A mixture of drug-containing beads and nonpareils (theophylline pellets:nonpareils: 1:4, propranolol HCl pellets:nonpareils: 2:3, batch size: 600 g) were coated in a fluidized-bed coater (GPCG1, Wurster insert, Glatt GmbH, Binzen, Germany) using either the original or the redispersed dispersions (15% polymer solids content, 20% or 30% TEC based on polymer dry weight).

The redispersed dispersion was prepared by suspending and stirring the dried ethylcellulose powder in water or in 0.001 N NaOH for 2 hr, followed by plasticizer addition and an additional stirring for 2 hr before to coating the pellets.

The following process parameters were used for the coating—inlet air temperature: 48–55°C, product temperature: 36–40°C, outlet air temperature: 34–36°C, air flow: 50–70 m^3/hr, spray rate: 4–7 g/min, atomization pressure: 1.8 bars, and spray nozzle diameter: 1.2 mm. The pellets were dried for 10 min fluidizing in the column (product temperature at approximately 45°C). The beads were then cured in an oven at 60°C for different periods of time (1 or 24 hr).

In Vitro Release Studies

The drug release studies were conducted in 0.1 N HCl or 0.1 M phosphate buffer (pH 7.4) using the USP XXIII rotating paddle method (Van Kel VK 700, Van Kel Industries, Edison, NJ, USA, $n = 3$; 100 rpm; 900 mL; 37°C). After the release experiments, the pellets were crushed with an Ultra-Turrax (Janke & Kunkel GmbH, Staufen, Germany) and stirred for at least 2 hr to determine the total amount of drug within the sample of pellets (100% release value). Samples (3 mL, not replaced) were withdrawn at predetermined time intervals, filtered or centrifuged, and then analyzed UV spectrophotometrically with a UV-2101PC (Shimadzu Europe GmbH, Duisburg, Germany) (propranolol HCl: 289 nm, theophylline: 244 nm).

ζ-Potential Measurements

The ζ-potential of the aqueous dispersions was measured with a Malvern Zetasizer 4, 7032 Multi-8-Correlator (Malvern Instruments, Herrenberg, Germany) in a ZET 5104 capillary with a diameter of 4 mm. The samples were diluted with deionized water, with a conductivity of 50 μsec/cm (adjusted with NaCl). The measured electrophoretic mobility at an electric field strength of 20 mV/cm was converted into the ζ-potential by the Helmholtz-Smoluchowski equation.

RESULTS AND DISCUSSION

Temperature-Dependent Stability of Ethylcellulose Dispersions

Aquacoat ECD is susceptible to irreversible coagulation at storage temperatures below 0°C and above 38°C. The commercial supplier of Aquacoat ECD, FMC, does not ship the dispersion in cold weather without temperature control. Storage of the dispersion at 2°C leads to an increase in viscosity, the dispersion became semisolid and, on warming to room temperature, did not return to its original rheological behavior.

The anionic surfactant, SDS (4% w/w of total solids) together with cetyl alcohol (9% w/w of total solids) are used as stabilizers in Aquacoat ECD. They stabilize pseudolatex during manufacturing and also prevent agglomeration and coalescence of the particles during storage. Aquacoat ECD has a ζ-potential of −55 mV and pH in the range of 4–7, indicating adsorption of the anionic surfactant at the polymer particle surface resulting in a strong stabilization of the dispersion at room temperature.

A reason for the observed viscosity increase of Aquacoat ECD at low temperatures could be the temperature-dependent solubility of SDS. Cooling a clear aqueous SDS solution (1.3% w/w, a concentration equivalent to the concentration of SDS in Aquacoat ECD) resulted in a turbid system, indicating precipitation of SDS. The solubility of SDS decreases with decreasing temperature, and SDS becomes insoluble below its Krafft temperature, which is 12°C.[10] Precipitation of the SDS in Aquacoat ECD at low temperatures obviously leads to destabilization of the polymer dispersion, thus explaining the viscosity increase because of flocculation of the dispersion.

Table 1. Properties of ethylcellulose dispersions prepared with SDS or SDES stored at room temperature (RT) or at 2°C for 24°hr.

Dispersion	Solids content (%)	Kinematic viscosity (cSt)	Mean particle size (nm)	Polydispersity index	ζ-Potential (mV)
SDS-RT	30.5	6.4	201.0	0.127	−53.3
SDS-2°C	30.5	762.3	(397.3)	0.519	−46.4
SDES-RT	28.6	10.6	252.9	0.140	−57.7
SDES-2°C	28.6	20.5	297.8	0.230	−50.7

To reduce the temperature sensitivity of ethylcellulose dispersions, the more hydrophilic anionic surfactant, SDES, was evaluated. Because of its ethoxylation, SDES is more hydrophilic and therefore more soluble at low temperatures than SDS and has a Krafft temperature below 0°C.[11] It was speculated that the more hydrophilic character of SDES should result in better stability of the ethylcellulose dispersion at low temperatures. Ethylcellulose dispersions were prepared by the solvent-evaporation method to compare the influence of the surfactants SDS and SDES on the stability of the dispersion at low temperatures. The self-prepared ethylcellulose dispersion with SDS as surfactant had a slightly lower viscosity and a smaller particle size than dispersions with SDES (Table 1). The ζ-potential of both dispersions was similar to Aquacoat ECD (Table 1).

After storage at 2°C for 24 hr, the self-prepared ethylcellulose dispersion containing SDS showed a more than 100-fold increase in viscosity and also an increase in the polydispersity index and a decreased ζ-potential, indicating aggregation of the particles. On the contrary, the viscosity and particle size of the dispersion stabilized with the more hydrophilic SDES remained almost unchanged, indicating its stabilizing effect also at low temperatures (Table 1).

In summary, the more hydrophilic surfactant, SDES, was an effective stabilizer at low temperatures because of its higher water solubility for ethylcellulose dispersions when compared with SDS.

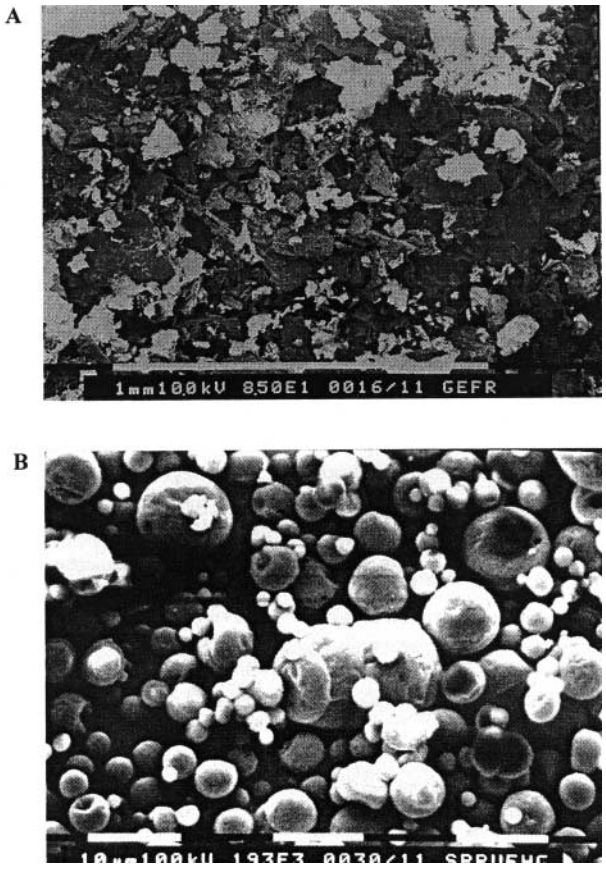

Figure 1. Scanning electron micrographs of freeze-dried (A) and spray-dried (B) Aquacoat ECD dispersions.

Drying of the Ethylcellulose Dispersion, Aquacoat ECD

Aquacoat ECD was converted into a dry polymer powder by either freeze-drying or spray-drying techniques. Ideally, the polymer powder should then redisperse in water into a dispersion having the same properties as the original Aquacoat ECD dispersion. Freeze-drying of Aquacoat ECD lead to irregularly shaped, large agglomerates (Fig. 1A).

Freeze-drying of dispersed systems is a complex process with different phases, including the freezing step and the sublimation/drying step. Freezing colloidal systems, such as liposomes[12,13] or emulsions,[14] can lead to instabilities, such as coagulation of the thawed system, fusion of the particles, or drug

leakage. Fast freezing rates produce a fine network of the product and a higher surface area, which leads to a better reconstitution when compared with slowly frozen products.[15,16]

For Aquacoat ECD dispersion, freezing is not the major problem of the freeze-drying process with regard to redispersibility. Freezing the Aquacoat ECD dispersion to −60°C and thawing it at room temperature did not lead to a change in the particle size distribution of the ethylcellulose particles (Fig. 2). Therefore, the particle aggregation occurred during the sublimation step and not during the freezing process. Shock-freezing Aquacoat ECD in liquid nitrogen did not lead to more favorable products with regard to the redispersibility in water.

Spray-drying Aquacoat ECD resulted in a fine powder of round particles with a particle size between 1–10 μm (Fig. 1B). During the spray-drying process, the particles are only in short contact with the heated air and are immediately dried, so that the time period for potential coalescence of the colloidal particles within the atomized droplets into larger particles is fairly short. When the polymer dispersion is sprayed below its minimum film formation temperature (MFT), the particles are not expected to coalesce. The high glass transition temperature (T_g) of ethylcellulose (128°C) and the MFT of Aquacoat ECD (81°C)[17] prevent a coalescence and film formation of the particles during spray-drying.

Spray-drying and freeze-drying of Surelease, another commercially available ethylcellulose dispersion, lead to an agglomerated powder. Surelease is already plasticized with dibutyl sebacate or fractionated coconut oil and ammonium oleate and is therefore a ready-to-use dispersion for coating.[7]

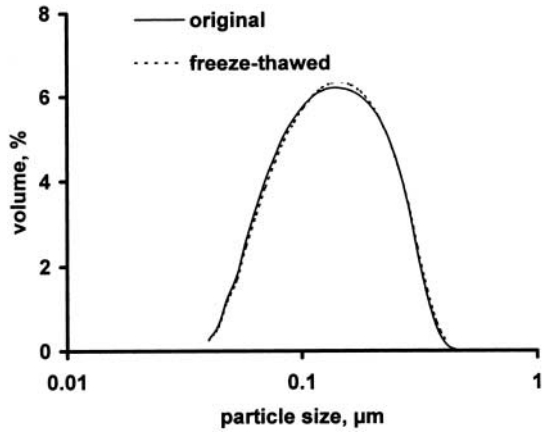

Figure 2. Particle size distribution of original and freeze-thawed Aquacoat ECD dispersions.

The incorporated plasticizers decrease the MFT of the polymer dispersion, which lead to partial film formation of the dried powder. The agglomerated Surelease particles were not redispersible in water or diluted sodium hydroxide solutions.

Redispersibility of the Dried Aquacoat Dispersions

Because particle agglomeration during drying was visible by SEM, it would be desirable to optimize the redispersion process and to deagglomerate the particles to achieve a stable dispersion without sedimentation. Dispersing the freeze-dried or spray-dried ethylcellulose powder in pure water did not result in colloidal dispersions; the large agglomerates could not be dispersed, and sedimentation occurred resulting in a low redispersion index.

The dried Aquacoat ECD powder also contains SDS as an anionic stabilizer, its degree of dissociation depends on the pH of the medium. The polymer powders were therefore redispersed in aqueous media of different pH. The redispersion index was determined after 1 and 24 hr. The polymer dispersions are normally used within 1 day for coating and therefore do not need to have a long-term physical stability after redispersion. The freeze-dried ethylcellulose powder could be well redispersed at alkaline pH values higher than 7; the redispersion index was close to 100% and did not change during 24 hr (Fig. 3A). Below this neutral pH value, most of the polymer powder sedimented already after 1 hr.

Particle-size measurements corresponded well with the data on the redispersion index (Fig. 4). Colloidal particles (particle size $< 1\,\mu m$) were obtained at the alkaline pH values, while larger agglomerates ($> 5\,\mu m$) were detected at acidic pH-values. The freeze-dried, larger polymer agglomerates obviously disintegrated into colloidal particles only at alkaline pH values.

Although ethylcellulose is a neutral polymer, the redispersion in water showed a strong pH-dependent behavior. Ethylcellulose was reported to have residual carboxylic acid groups, which could explain the observed pH phenomena. A $pK_a = 6.3$ of the Aquacoat ECD dispersion was measured.[17] Deprotonation of residual carboxylic groups can lead to a mutual repulsion of the ethylcellulose particles to overcome the attraction forces of the loosely agglomerated particles, leading to a deaggregation into colloidal particles and therefore

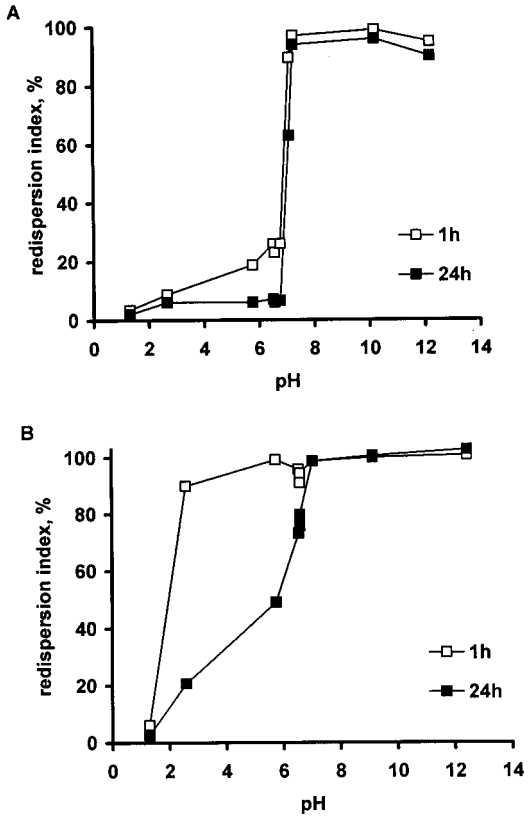

Figure 3. Redispersion index of (A) freeze-dried and (B) spray-dried Aquacoat ECD particles as a function of pH of the aqueous dispersion medium after 1 hr and 24 hr.

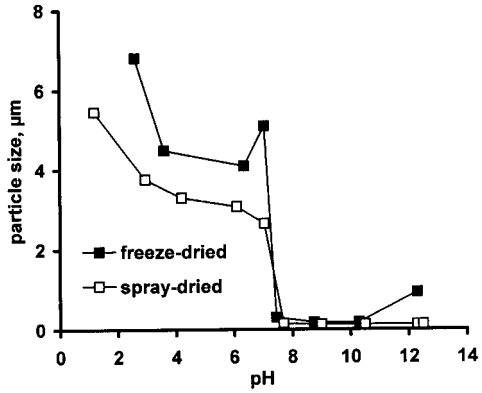

Figure 4. Mean particle size of spray-dried and freeze-dried Aquacoat ECD particles in the supernatant of the redispersion media after 1 hr sedimentation time as a function of pH.

better redispersion and lower particle sizes. Apparently, the low amount of residual carboxylic groups of 25 µval/g[18] must be sufficient to induce this deagglomeration. The hydrophilic carboxylic groups are assumed to be concentrated on the hydrophilic surface of the polymer particles.[19]

Redispersion of the spray-dried Aquacoat ECD powder gave similar results as with the freeze-dried powder. The spray-dried Aquacoat ECD particles had a smaller diameter, compared with the freeze-dried particles (Fig. 4). They were therefore easier to redisperse and had a lower tendency to sediment, as indicated by the higher redispersion index after 1 and 24 hr (Fig. 3B). No strong sedimentation was measured after 1 hr down to a pH value of 2. The redispersion index in 0.1 N HCl (pH 1) was less than 10% after 1 hr. The reason for this poor redispersion at this low pH value was the protonation of the anionic surfactant SDS, which has a pK_a of 1.9, and was therefore partially undissociated and not surface-active. This resulted in poor wettability of the powder. Adjusting the pH of the original Aquacoat ECD dispersion to 1.5 with 0.1 N HCl resulted in agglomeration and particles with a mean particle size of 19 µm. The mean particle size remained in the colloidal range, when Aquacoat ECD was adjusted to pH 3.5. No significant increase in particle size occurred, when the dispersion was mixed with 0.1 N NaCl or 0.1 N NaOH. Therefore, the low pH and protonation of SDS were the reasons for agglomeration of the colloidal particles and not the high electrolyte concentration.

The ζ-potential was measured for the ethylcellulose dispersions at different pH values (Fig. 5). A ζ-potential of -55 mV was measured for the original Aquacoat ECD dispersion. This negative value

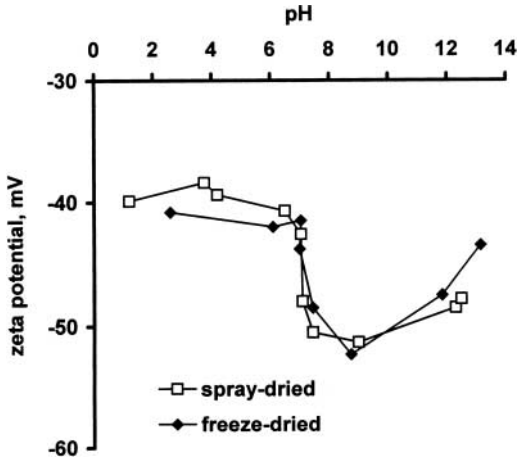

Figure 5. ζ-potential of dispersions prepared from freeze-dried or spray-dried Aquacoat ECD as a function of pH of the aqueous dispersion medium.

decreased when the dispersion was adjusted to acidic pH values for both freeze-dried and spray-dried dispersions, thus also explaining the higher sedimentation and poorer redispersibility with decreasing pH values. Stronger alkaline pH values also lead to a reduced ζ-potential of the dispersion. This was caused by the higher electrolyte concentration, which compressed the diffuse layer and reduced the electrostatic repulsion forces of the particles.

Coating Experiments

Next, coating experiments were performed with both the original Aquacoat ECD and the redispersed Aquacoat dispersions to evaluate the coating quality of the redispersed polymer powder. Theophylline, a drug with low water solubility, and propranolol HCl, with a higher water solubility, were used as model drugs. The solubilities in 0.1 N HCl at 37°C are 15 mg/mL for theophylline and 220 mg/mL for propranolol HCl, respectively.[20] Ideally, the drug release from pellets coated with the redispersed dispersions should be the same as from pellets coated with the original dispersions.

The drug release was faster from pellets coated with the redispersed polymer dispersion than from pellets coated with the original Aquacoat ECD, whereby theophylline was released slower than propranolol HCl because of its lower solubility (Figs. 6 and 7). Although the release was slightly faster from pellets coated with the redispersed dispersions, when compared with the original Aquacoat ECD, extended release profiles were easily achieved.

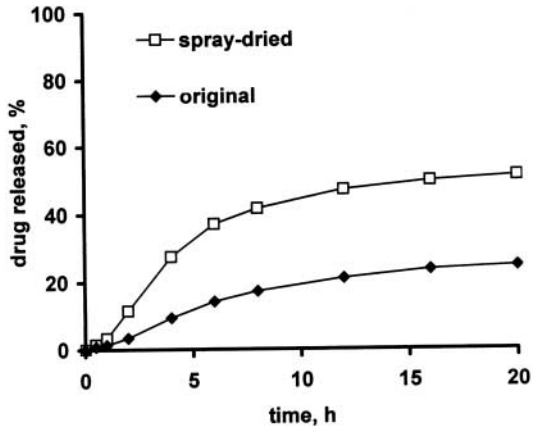

Figure 6. Release from theophylline pellets coated with original or redispersed (spray-dried) Aquacoat ECD in 0.1 N HCl (coating level: 10% w/w; 20% TEC; curing: 24 hr, 60°C).

To improve the film formation process with the redispersed ethylcellulose dispersions, the plasticizer concentration was increased from 20 to 30% with propranolol HCl pellets. In addition, a postthermal treatment step of the coated pellets (curing) is often recommended to promote further coalescence of incompletely formed films. The coated pellets were cured at 60°C for either 1 hr or 24 hr after the coating. Drug release was similar from pellets coated with dispersions prepared from both the freeze-dried and spray-dried ethylcellulose powders; however, their release was faster when compared with pellets coated with the original Aquacoat ECD at a curing time of 1 hr (Fig. 7A). These differences in drug release became smaller at a longer curing time of 24 hr, indicating better film formation (Fig. 7B). Longer curing times and higher plasticizer

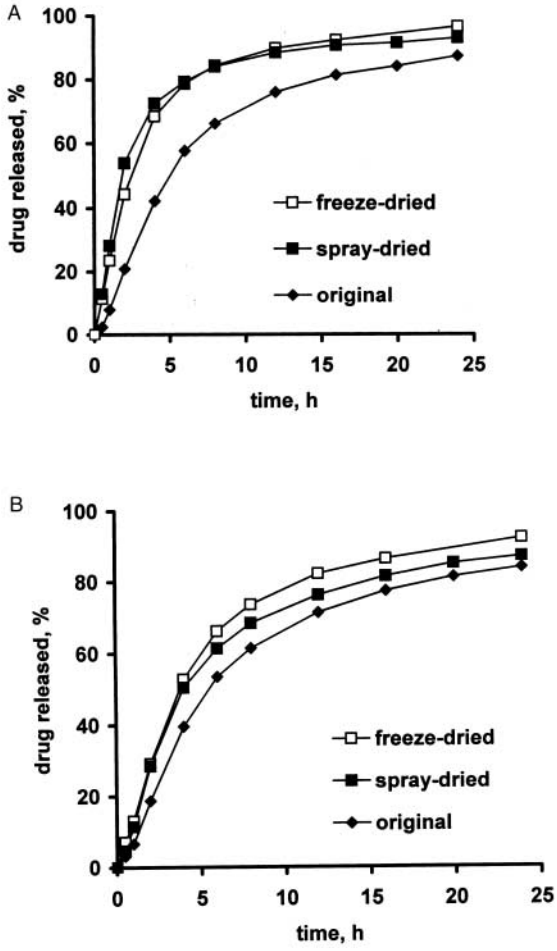

Figure 7. Release from propranolol HCl pellets coated with original, freeze-dried and spray-dried Aquacoat ECD in pH 7.4 and curing for: (A) 1 hr at 60°C and (B) 24 hr at 60°C (coating level: 10% w/w; 30% TEC).

concentrations therefore diminished the differences in the drug release between pellets coated with the original and redispersed Aquacoat ECD.

In conclusion, spray-dried and freeze-dried Aquacoat ECD could be redispersed well in alkaline aqueous media. Higher plasticizer concentrations and a curing step improved the film formation and resulted in similar release profiles between pellets coated with the original and redispersed dispersions. Storage stability problems of Aquacoat ECD at low temperatures could be avoided with redispersible dispersions or with replacing SDS with the more hydrophilic surfactant SDES.

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