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Physicochemical and release properties of pellets coated with Kollicoat® SR 30 D, a new aqueous polyvinyl acetate dispersion for extended release

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Abstract

Kollicoat® SR 30 D is a new aqueous colloidal polyvinyl acetate dispersion used for extended release coatings. Kollicoat® SR 30 D is stable against sedimentation, has a low viscosity (54 mPas) and a negative zeta potential of −23.2 mV because of the presence of the anionic surfactant, sodium dodecyl sulfate. Because of its low minimum film formation temperature (MFT = 18 °C), plasticizer addition and a thermal after-treatment (curing) of coated pellets was not required. Coated pellets showed no aging or curing effect. The rate of release could be easily adjusted by varying the coating level. A subcoating layer of the hydrophilic polymer, polyvinyl alcohol, between an ibuprofen-containing core and the Kollicoat® SR coating prevented the diffusion of the lipophilic, low melting ibuprofen into the polymer coating during storage. The drug release from Kollicoat® SR 30 D coated pellets was almost independent of the pH and ionic strength of release medium.

Keywords: Aqueous colloidal polymer dispersions; Curing; Extended release; Kollicoat® SR 30 D; Pellets

1. Introduction

The coating of solid dosage forms with aqueous dispersions of cellulose and acrylate derivatives for extended drug release is widespread. The polymer dispersions offer the possibility to form films from water-insoluble polymers in an aqueous environment without organic solvents. However, film formation from aqueous polymer dispersions is a complex process (Lin and Meier, 1995). The film formation depends on the minimum film formation temperature (MFT) of the dispersion. The MFT is the minimum temperature above which a continuous film is formed during drying (ISO 2115/DIN 53787). Plasticizers are frequently added to reduce the MFT (Pagés and Lippold, 1995) and to improve the film formation (Bodmeier and Paeratakul,

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1992) and also to positively affect the mechanical properties of the resulting films (Bodmeier and Paeratakul, 1993). Plasticizers can also have a very pronounced effect on the drug release characteristics (Lippold et al., 1990; Bodmeier and Paeratakul, 1994a, 1997).

The coated dosage forms are often treated at elevated temperatures for short periods of time (curing) to complete film formation in order to obtain stable release profiles. Curing effects are known for the commercially available polymer dispersions, Eudragit® RS 30 D, Eudragit® RL 30 D, and Aquacoat® ECD, whereby the drug release decreases upon a thermal after-treatment. This is a result of the relatively high MFT of these dispersions (47, 39, and 81 °C, respectively) and the incomplete coalescence of the polymer particles during coating. To achieve constant drug release profiles during storage, a post coating thermal treatment step (curing) or higher plasticizer concentrations are recommended (Bodmeier and Paeratakul, 1991; Gilligan and Wan Po, 1991).

Eudragit® NE 30 D and Kollicoat® EMM 30 D have a low MFT (5 °C) and no curing effects have been reported. However, a higher tackiness during the coating process and during storage of the coated dosage form requires the addition of anti-tacking agents.

With extended release dosage forms, it is desirable to obtain a drug release, which is independent of pH or ionic strength of the release medium. The existing polymer dispersions have shown both pH and ionic strength effects. Aquacoat® ECD-coated pellets had pH-dependent release because of the presence of the anionic surfactant, sodium lauryl sulphate, which resulted in pH-dependent wettability (Bodmeier and Paeratakul, 1991). The release from Eudragit® RS/RL coated dosage forms was highly dependent on the anionic buffer species present in the release medium because of quaternary ammonium groups of the polymer acting as ion exchangers. The chloride counterions of the quaternary groups were exchanged with the anionic buffer species. The water uptake of the coated beads correlated well with the drug release (Sun et al., 2001; Lehmann, 1986; Watts et al., 1991; Bodmeier et al., 1996).

The objective of this study, was to investigate the properties of a new aqueous polyvinyl acetate dispersion, Kollicoat® SR 30 D with regard to processability and release properties as an alternative to existing polymer dispersions.

2. Materials and methods

2.1. Materials

Kollicoat® SR 30 D (aqueous dispersion of polyvinyl acetate); polyvinyl pyrrolidone (PVP, Kollidon® 30, Kollidon® 90 F); polyvinyl pyrrolidone vinyl acetate copolymer (PVP-VA, Kollidon VA 64); polyethylene glycol (PEG, Lutrol® 4000); propylene glycol (PG, BASF AG, Ludwigshafen, Germany); triethyl citrate (TEC, Morflex, Greensboro, NC, USA); polyvinyl alcohol (Mowiol 4-88, Aventis, Frankfurt, Germany); hydroxypropyl methylcellulose (HPMC, Methocel® E5, Colorcon, Dratford, Kent, UK); sugar pellets (Suglets, 710–850 μm, NP Pharma, Bazainville, France); talc (Merck-Schuchardt, Hohenbrunn, Germany); colloidal silica (Aerosil 200, Degussa, Hanau, Germany). Propranolol HCl, ambroxol HCl and ibuprofen (Knoll AG, Ludwigshafen, Germany) were used as a model drugs.

2.2. Particle size and zeta potential measurements

The particle size and zeta potential of Kollicoat® SR 30 D were measured by laser light scattering using a Coulter LS 230 (Coulter electronics, Krefeld, Germany) and by photon correlation spectroscopy (Zetasizer 4, Malvern Instruments, Malvern Worcestershire, UK). Ten millilitres of the sample of dispersion were centrifuged for 1 h at 3000 rpm and stored within 5 months at ambient stationary conditions in tightly closed container and the particle size was measured.

2.3. Minimum film formation temperature

The MFT was determined according to ISO 2115/DIN 53787 with a temperature gradient block containing temperature sensors (Thermostair BL-MFT, Coesfeld GmbH, Dortmund, Germany). The dispersions were spread on the surface of an aluminum foil, which covered the block. The MFT was the lowest temperature, at which the film formation was complete and the films were without cracks.

2.4. Drug layering

The drugs (15%, w/v) were layered on sugar pellets using an ethanol/water (60:40, w/w) solution of HPMC

(Methocel® E5) (1.5%, w/v) as a binder and PEG (Lutrol® 4000) (10%, w/w based on HPMC) as a plasticizer in a fluidized bed coater (Glatt GPCG-1, Glatt GmbH, Binzen, Germany) to achieve a 10% (w/w) drug content. Propranolol HCl and Amboxol HCl were layered as solutions and ibuprofen as suspension. The layering conditions were: batch size = 800 g, inlet temperature = 30 °C, product temperature = 26 °C, air flow = 130 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 8.5 g/min, final drying at 40 °C for 15 min.

2.5. Coating of the drug-layered pellets

The drug-layered pellets were coated with Kollicoat® SR 30 D (15%, w/v solids content) in the fluidized bed coater Glatt GPCG-1 to obtain a predetermined weight gain. If necessary, additives [plasticizer (TEC) or talc] were incorporated. Coating conditions were: batch size = 800 g, inlet temperature = 45 and 55 °C, product temperature = 30 and 40 °C, air flow = 130 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 7.8 g/min, final drying at 40 °C for 15 min. 0.5% of colloidal silica (Aerosil 200) was admixed to the pellets after coating. The coated pellets were cured in an oven at 60 °C for 2 and 24 h.

2.6. Drug release

The drug release from coated pellets was investigated in a paddle apparatus (USP XXV) (Vankel VK 300, Vankel Industries, Edison., NJ, USA) (900 ml 0.1 N HCl or buffer pH 6.8 Pharm. Eur. 1997 or a release medium with modified osmolality by addition of sodium chloride, 100 rpm, 37 °C, $n = 3$). Samples were withdrawn at predetermined time points and measured UV-spectrophotometrically (propranolol HCl $\lambda = 269$ nm, ibuprofen $\lambda = 222$ nm, ambroxol HCl $\lambda = 246$ nm).

3. Results and discussion

3.1. Characterization of Kollicoat SR 30 D

Kollicoat® SR 30 D is a new aqueous colloidal dispersion based on polyvinyl acetate (27%, w/v), polyvinyl pyrrolidone (2.5%, w/v) and sodium dodecyl sulfate (0.3%, w/v), which is prepared by an emulsification polymerization method. Kollicoat® SR 30 D was stable against sedimentation as indicated by the unchanged particle size distribution after either centrifugation at 3000 rpm for 1 h or storage for 5 months at ambient conditions (Fig. 1). The viscosity of the dispersion was low (54 mPas) and the zeta potential was

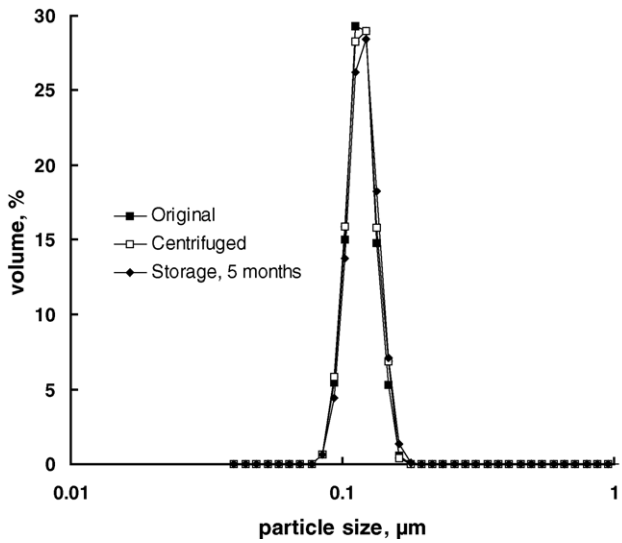

Fig. 1. Particle size distribution of Kollicoat® SR 30 D dispersions, original, after centrifugation for 1 h at 3000 rpm and after storage for 5 months.

Table 1
Physico-chemical properties of Kollicoat® SR 30 D

Parameter	Mean (S.D.)
Solids content (%, w/v)	30.3 (0.2)
Zeta potential (mV)	−23.2 (2.1)
Particle size (mean) (μm)	0.123
pH	4.5
Viscosity (mPas)	54
Minimum film formation temperature (°C)	18

negative with a value of −23.2 mV because of the presence of the anionic surfactant, sodium dodecyl sulfate (Table 1).

Kollicoat® SR 30 D has a low minimum film formation temperature (MFT) of only 18 °C when compared to other commercially available aqueous dispersions [Aquacoat® ECD (81 °C), Eudragit® RS 30 D (47 °C) or Eudragit® RL 30 D (39 °C)] (Lippold et al., 1990; Dressman et al., 1995; Lehmann, 1997). A low MFT is preferred because it results in easier coalescence of the colloidal polymer particles during coating at product temperatures between 30 and 40 °C and it may also eliminate the need for the addition of plasticizers, which have to be added in concentrations of 20–30% (based on the polymer) to the other dispersions for a reduction of the MFT. The addition of small amounts of plasticizer reduced the MFT further, whereby TEC was a more efficient plasticizer than propylene glycol (Table 2). Only Eudragit® NE 30 D and Kollicoat® EMM 30 D have a lower MFT (5 °C). However, as a result of the low MFT, sticking during coating or storage of the coated product may occur. Therefore, talc was added to the coating dispersion (shown below) or

Table 2
Minimum film formation temperature (MFT) of unplasticized and plasticized Kollicoat® SR 30 D

	Plasticizer (%)	MFT (°C)
None		18
Propylene glycol	2.5	18
	5	16
	10	14
	15	12
Triethyl citrate	2.5	10
	5	8
	10	1
	15	<0

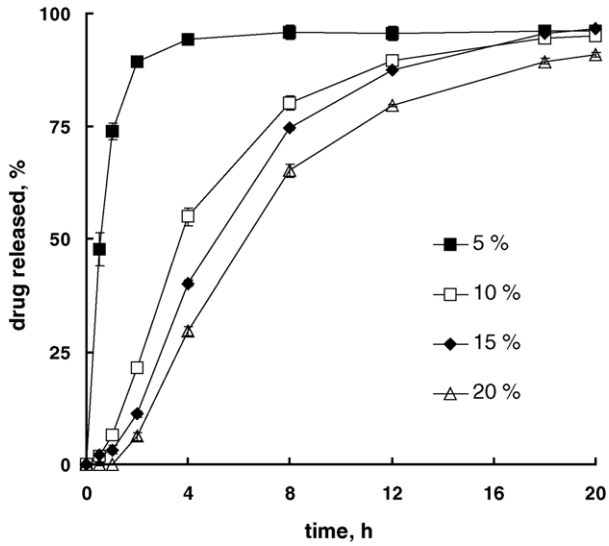

Fig. 2. Effect of coating level on the propranolol HCl release in 0.1 N HCl from Kollicoat® SR 30 D-coated pellets.

0.5% of colloidal silica (Aerosil 200) was admixed to the pellets after coating.

3.2. Effect of various formulation and process parameters on the drug release from Kollicoat SR 30 D-coated pellets

The propranolol HCl release from Kollicoat® SR 30 D coated pellets decreased with increasing coating level (Fig. 2). A 12 h release profile was obtained at coating levels between 10 and 15% with this water-soluble drug. The release profile was sigmoidal in shape. The short lag time was probably caused by the time required for the dissolution medium to diffuse through the coating and for the drug concentration gradient across the film coating to be established.

In general, plasticizers reduce the MFT of aqueous polymer dispersions and thus promote film formation during the coating process. The drug release is often reduced because of the formation of a denser film (Pagés and Lippold, 1995; Bodmeier and Paeratakul, 1992, 1993, 1994a; Lippold et al., 1990). In the case of Kollicoat® SR 30 D, the addition of the hydrophilic plasticizers, triethylcitrate or propylene glycol (5 or 10%, w/w based on the polymer) did not result in different release profiles when compared to the plasticizer-free coated pellets (Fig. 3 A). Kollicoat®

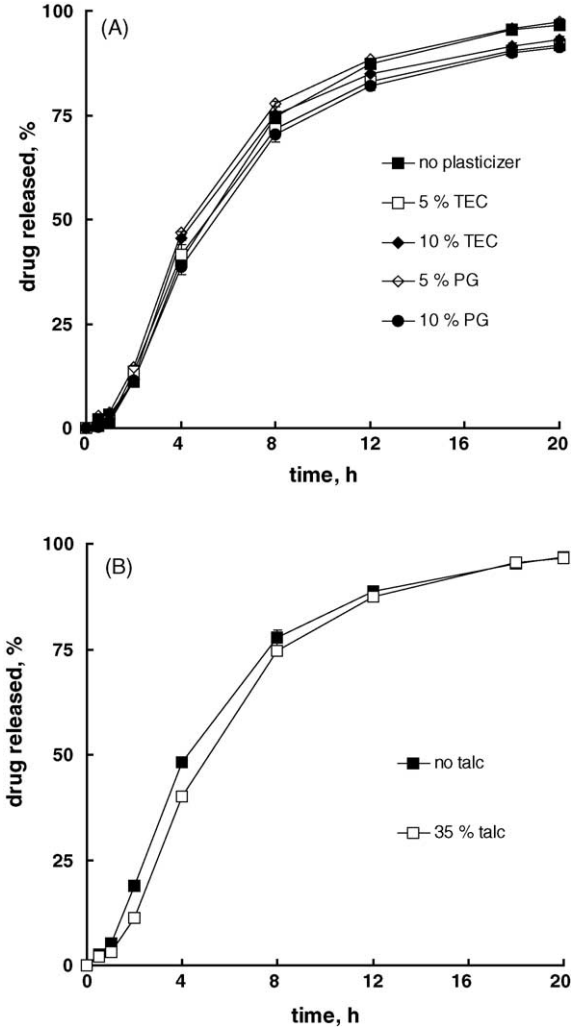

Fig. 3. Effect of: (A) plasticizers and (B) talc addition on the propranolol HCl release in 0.1 N HCl from Kollicoat® SR 30 D-coated pellets (15% coating level).

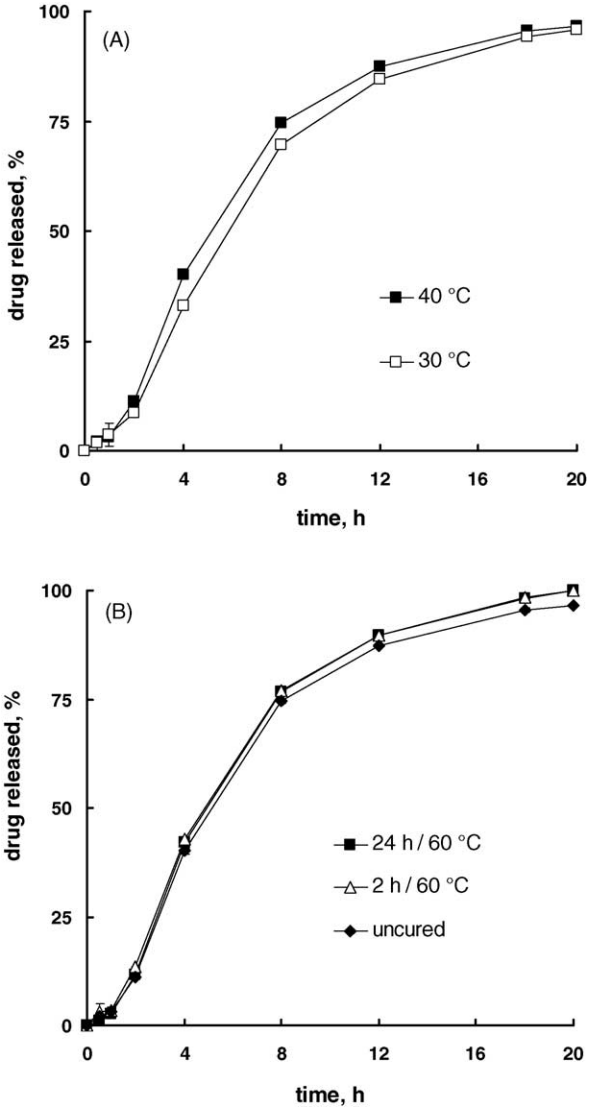

Fig. 4. Effect of: (A) product temperature and (B) curing on the propranolol HCl release in 0.1 N HCl from Kollicoat® SR 30 D-coated pellets (15% coating level).

SR 30 D has already a low MFT of 18 °C, which is sufficient for complete film formation during the coating process. A further reduction in MFT through the addition of plasticizers was not required in the case of propranolol HCl pellets. However, the addition of up to 10% plasticizer has been recommended for Kollicoat® SR-coated pellets, which are intended to be compressed into tablets, because the addition of a plasticizer significantly increased the flexibility of the otherwise brittle Kollicoat® SR coatings (Dashevsky et al., 2004).

With plasticizers, the coatings could be tacky during coating or storage because of the low glass transition temperature, potentially resulting in unwanted agglomeration. Talc is often added as an anti-tacking agent to avoid this problem. The addition of 35% talc did not affect the drug release from Kollicoat® SR-coated propranolol HCl pellets (Fig. 3B).

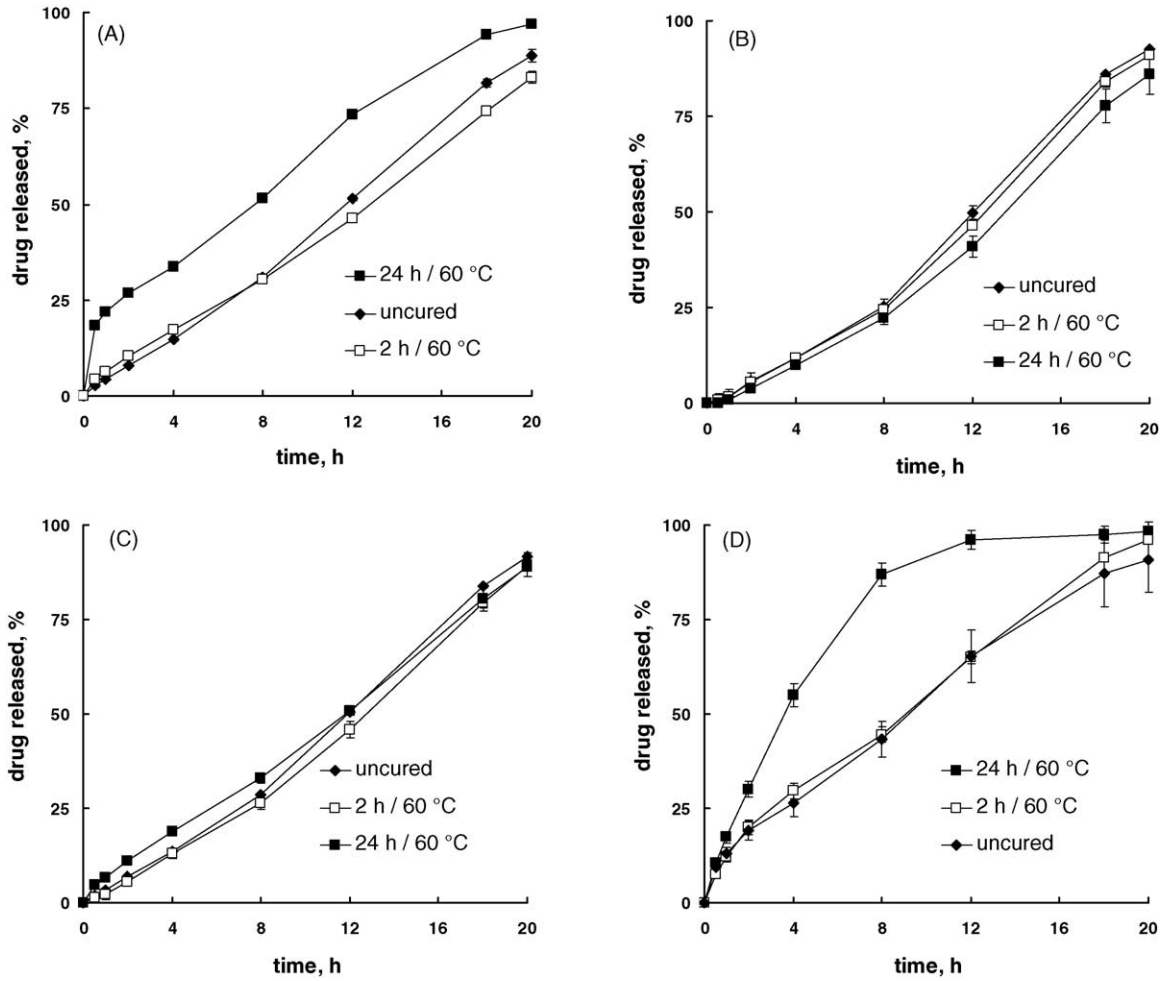

Fig. 5. Effect of curing on the ibuprofen release in buffer pH 6.8 from Kollicoat® SR 30 D-coated pellets (10% coating level): (A) without subcoating, (B) 5% Mowiol® 4–88 subcoating, (C) 5% Methocel E5 subcoating and (D) 5% Kollidon VA 64 subcoating.

The product temperature during coating should be approximately 20 °C above the minimum film formation temperature in order for good film formation to occur. With various aqueous polymer dispersions, the film formation often was not complete after the coating process and a thermal after-treatment (curing) at elevated temperatures was necessary to complete film formation and to avoid changes in the drug release profiles during storage because of further gradual coalescence (Bodmeier and Paeratakul, 1991; Gilligan et al, 1991). Alternatively, higher plasticizer concentrations could be used to obtain good film formation already during coating, thus eliminating a curing step (Bodmeier and Paeratakul, 1994a). Propranolol HCl pellets coated with Kollicoat® SR 30 D at product temperatures of 30 and 40 °C showed identical drug release profiles (Fig. 4A). Curing the pellets at 60 °C for 2 or 24 h did also not change the release profile (Fig. 4B). Thus, the drug release from Kollicoat® SR 30 D-coated pellets was independent of the product temperature in the range investigated and a curing of the pellets was not necessary, this being the result of the low MFT of the polyvinyl acetate dispersion.

A stability problem was reported for Aquacoat® ECD coated ibuprofen pellets (Bodmeier and Paeratakul, 1994b). Ibuprofen diffused into the ethylcel-

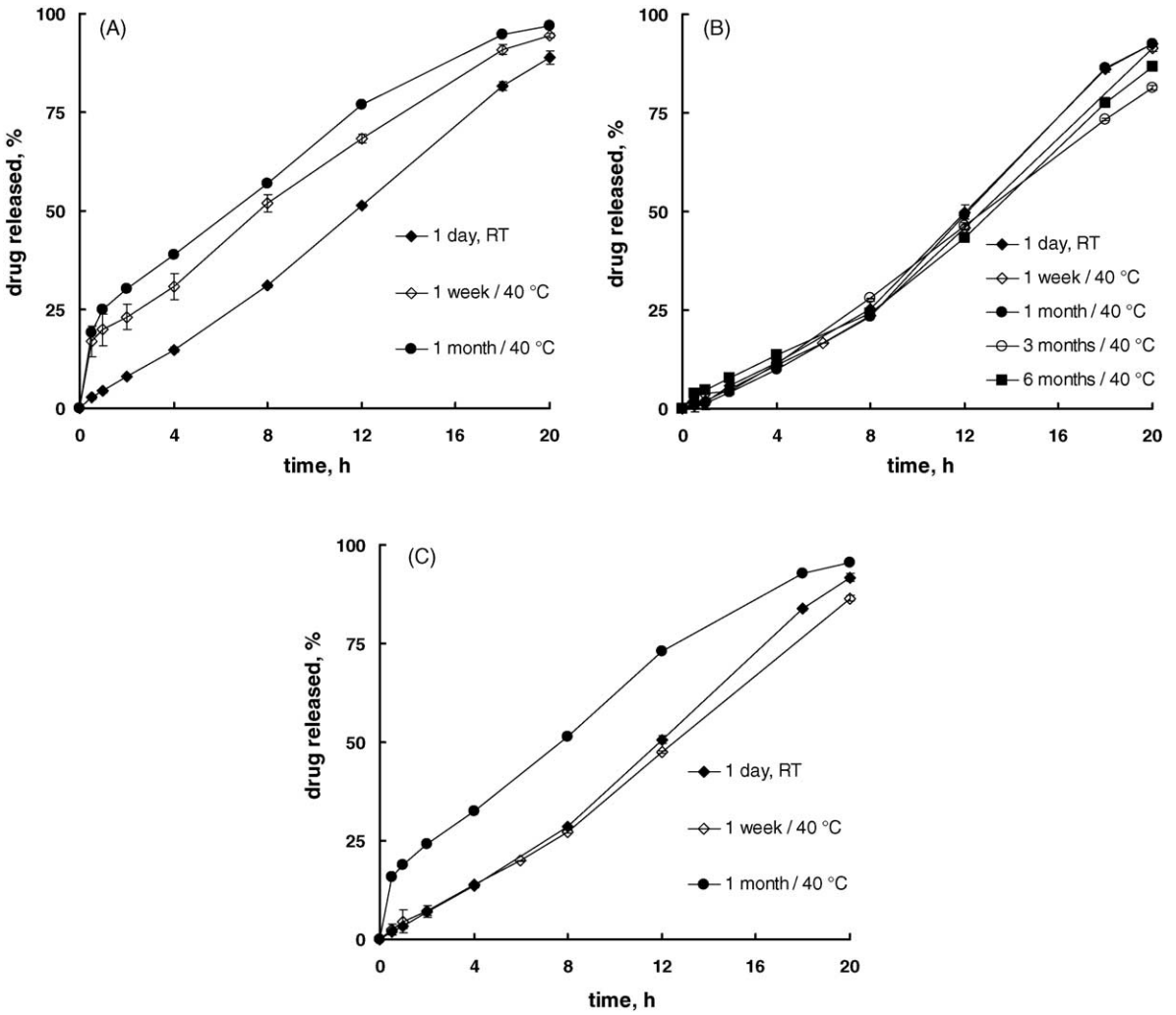

Fig. 6. Effect of storage at 40 °C on the ibuprofen release in buffer pH 6.8 from Kollicoat® SR 30 D-coated pellets (10% coating level): (A) without subcoating, (B) 5% Mowiol® 4–88 subcoating and (C) 5% Methocel E5 subcoating.

lulose coating during curing and storage because of its low melting point and its high affinity to the ethylcellulose film (ethylcellulose is the film-forming polymer in Aquacoat® ECD), resulting in the crystallization of the drug on the pellet surface. This resulted in an increase in drug release. The same phenomenon was also observed for Kollicoat® SR 30 D-coated ibuprofen pellets (Fig. 5A). Curing for 24 h at 60 °C (in order to stress the pellets) resulted in an increase in drug release, again probably because of the high affinity of the drug for and diffusion in the polymer film. Various hydrophilic polymer layers [HPMC (Methocel® E5), PVP-VA (Kollidon® VA 64), PVA (Mowiol® 4–88) at a coating level of 5%, w/w] were investigated as subcoatings between the ibuprofen pellets and the Kollicoat® SR coating with the aim to eliminate diffusion of ibuprofen into the coating during storage. PVA (Mowiol® 4–88) and HPMC (Methocel E5) successfully prevented changes in drug release during curing at 60 °C (Fig. 5). However, only PVA (Mowiol® 4–88) resulted in stable release profiles during subsequent storage at elevated temperature (40 °C) for 6 months because of the inhibition of drug diffusion into the Kollicoat® SR film (Fig. 6). Applying subcoatings

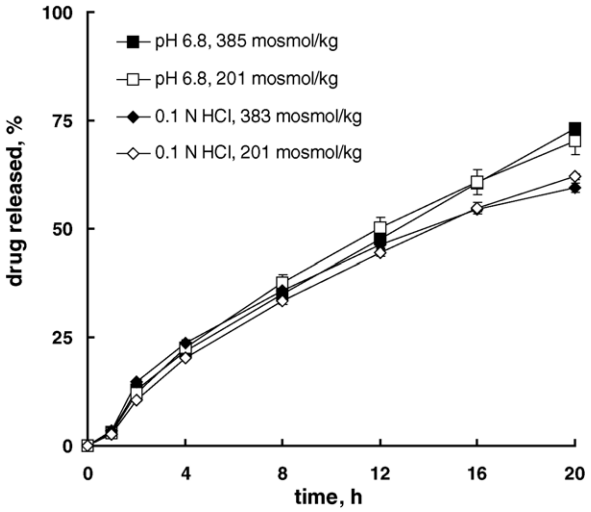

Fig. 7. Ambroxol HCl release from Kollicoat® SR 30 D-coated pellets in different release media.

drug release at the early stages was slightly reduced (Figs. 5 and 6), because it acts as additional diffusional barrier during the time needed to dissolve the water-soluble subcoating.

3.3. Effect of release medium on drug release

Besides the pH of the medium, other parameters such as buffer species, buffer strength or ionic strength could influence the drug release from coated pellets. This has been reported in particular for Eudragit® RS/RL, which contains quaternary ammonium groups and works as an ion exchange resin (Sun et al., 2001; Lehmann, 1986; Watts et al., 1991; Bodmeier et al., 1996). With Kollicoat® SR-coated pellets, the release of ambroxol HCl was independent of the osmolarity of the release medium in the investigated range (201–385 mosmol/kg) in both pH media (Fig. 7). The drug release was slightly lower in 0.1 N HCl than in pH 6.8 buffer. This could not be explained by solubility differences of ambroxol HCl (pH 2–14.1 mg/ml, and pH 6.8–10.9 mg/ml). A similar, but more pronounced difference was shown for dosage forms coated with Aquacoat® (an ethylcellulose dispersion) and was explained by the presence of the surfactant sodium dodecyl sulphate ($pK_a = 1.9$) (Bodmeier and Paeratakul, 1991; Wesseling and Bodmeier, 1999). The surfactant is fully ionized at the higher pH and therefore results in good wetting of the pellets, while at low pH, the surfactant is also nonionized, thus resulting in poorer wetting. Since sodium dodecyl sulfate is also present as stabilizer in Kollicoat® SR 30 D, the observed slight pH-dependence of the ambroxol HCl release could possibly also be attributed to the surfactant.

4. Conclusions

In summary, Kollicoat® SR 30 D is an interesting new aqueous polymer dispersion because of its physicochemical properties (e.g., low minimum film formation temperature) and its flexible extended release properties. A plasticizer addition was not required because of the low MFT. The coated pellets showed no curing or aging effects, resulting in stable drug release profiles. The drug release can be easily adjusted by the coating level or by the addition of water-soluble pore-formers.

Acknowledgement

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