Drug Development and Industrial Pharmacy, 2010; 36(2): 152–160

informa
healthcare

ORIGINAL ARTICLE

Effect of water-soluble polymers on the physical stability of aqueous polymeric dispersions and their implications on the drug release from coated pellets

Andrei Dashevsky[1], Abid Riaz Ahmed[1], J. Mota[1], Muhammad Irfan[1], Karl Kolter[2] and Roland A. Bodmeier[1]

[1]*Freie Universität Berlin, Berlin, Germany and* [2]*BASF SE, Development Pharma Ingredients, Ludwigshafen, Germany*

Abstract

Purpose: To investigate the physical stability and drug release-related properties of the aqueous polymer dispersions Kollicoat® SR 30 D and Aquacoat® ECD (an ethylcellulose-based dispersion) in the presence water-soluble polymers (pore formers) with special attention to the potential flocculation of the polymer dispersions. *Methods:* A precise characterization of the flocculation phenomena in undiluted samples was monitored with turbidimetric measurements using the Turbiscan Lab-Expert. Theophylline or propranolol HCl drug-layered pellets were coated with Kollicoat® SR 30 D and Aquacoat® ECD by the addition of water-soluble polymers polyvinyl pyrrolidone (Kollidon® 30 and 90 F), polyvinyl alcohol–polyethylene glycol graft copolymer (Kollicoat® IR), and hydroxypropyl methylcellulose (Pharmacoat® 603 or 606) in a fluidized bed coater Glatt GPCG-1 and drug release was performed according to UPS paddle method. *Results:* Stable dispersions were obtained with both Kollicoat® SR 30 D (a polyvinyl acetate-based dispersion) and Aquacoat® ECD with up to 50% hydrophilic pore formers polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat® IR) and polyvinyl pyrrolidone (Kollidon® 30). In general, Kollicoat® SR 30 D was more stable against flocculation than Aquacoat® ECD. Stable dispersions were also obtained with higher amounts of water-soluble polymer or by reducing the concentration of the polymer dispersion. Flocculated dispersions resulted in porous films and, thus, in a sharp increase in drug release. *Conclusions:* Kollicoat® SR 30 D was more resistant to flocculation upon addition of water-soluble polymers than Aquacoat® ECD. The continuous adjustment of drug release from Kollicoat® SR 30-coated pellets was possible with Kollicoat® IR amounts over a broad range.

Key words: *Aqueous polymer dispersion; coating; extended drug release; flocculation; turbidimetric measurements*

Introduction

Extended release oral dosage forms are often prepared by coating drug-containing tablets or multiparticulates with water-insoluble polymers, such as ethylcellulose, poly(vinyl acetate), or acrylate derivates. The water-insoluble polymer can be applied as organic solutions or aqueous colloidal dispersions[1–3].

Water-soluble polymers are often added to increase the permeability of the water-insoluble coatings. In previous studies, the permeability of coatings with aqueous ethylcellulose dispersions (Aquacoat® ECD or Surelease) or ammonio methacrylate copolymer dispersion (Eudragit RS 30 D) was adjusted by using blends of the water-insoluble polymer with water-soluble polymers such as hydroxypropyl methylcellulose (HPMC)[4] or hydroxy ethylcellulose (HEC)[5,6].

Both water-soluble and water-insoluble polymers are in solution when coating from organic solutions. In contrast, with aqueous polymer dispersions, the water-soluble polymer is in solution and the water-insoluble polymer is in dispersion. This could potentially affect the physical stability of the polymer dispersions.

For example, the inclusion of the water-soluble polymer polyvinyl pyrrolidone (PVP) in an aqueous polyvinyl acetate dispersion (Kollicoat SR 30 D) not only

Address for correspondence: Dr. Andrei Dashevsky, College of Pharmacy, Freie Universität Berlin, Kelchstrasse 31, 12169 Berlin, Germany. Tel: +49 308 3850708. E-mail: dashevsk@zedat.fu-berlin.de

(Received 15 Jul 2009; accepted 9 Oct 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040903410334

stabilized the dispersion but also served as an effective pore former[7]. Adding the water-soluble pore-former polyvinyl alcohol (PVA)–polyethylene glycol (PEG) graft copolymer (Kollicoat® IR) to either Kollicoat® SR 30 D or to the ethylcellulose dispersion Aquacoat® ECD resulted in physically stable dispersions[8]. The addition of Kollicoat® IR to Aquacoat® ECD coatings allowed not only the adjustment of the drug release profiles[9] but also improved the stability of the drug release upon storage at elevated temperature and humidity[10].

Flocculation of ethylcellulose dispersions has been observed above a critical HPMC concentration for Aquacoat® ECD[11]. The critical HPMC concentration decreased with increasing molecular weight of HPMC and increasing solids content of the dispersion. Compatibility problems with HPMC and HEC were also reported for ammonio methacrylate copolymer dispersion (Eudragit RS 30 D)[5,12].

The objective of this study was to investigate the influence of water-soluble polymers (pore formers) on the drug release from coated pellets as well as on the morphology, leaching, and medium uptake of films prepared from the polymer blends with a special attention to the potential flocculation of the polymer dispersions. The physical stability of the aqueous polymer dispersions Kollicoat® SR 30 D and Aquacoat® ECD was investigated by turbidimetry to identify stable formulations.

Materials and methods

Materials

Aqueous dispersion of poly(vinyl acetate) (Kollicoat® SR 30 D; BASF SE, Ludwigshafen, Germany), aqueous dispersion of ethylcellulose (Aquacoat® ECD; FMC BioPolymer, Brussels, Belgium), PVP (Kollidon® 30 and 90 F), PVA–PEG graft copolymer (Kollicoat® IR; BASF SE), triethyl citrate (Morflex, Greensboro, NC, USA), HPMC (Pharmacoat® 603 and 606; Shin-Etsu Chemical, Tokyo, Japan), sugar spheres (Suglets 710–850 μm; NP Pharma, Bazainville, France), sodium lauryl sulfate (Sigma-Aldrich GmbH, Taufkirchen, Germany), propranolol HCl and theophylline (BASF SE), and talc (Luzenac Europe, Toulouse, France) were used.

Physical stability of aqueous dispersions

The physical stability of the aqueous dispersions was investigated as a function of polymer dispersion concentration (7.5%, 10.0%, 12.5%, 15%, w/w) and the amount of added water-soluble polymer (2.5–50%, w/w, based on the water-insoluble polymer). Freshly prepared and undiluted samples were filled into flat bottom borosilicated glass flasks (d = 27.5 mm, h = 70 mm). The backscattering of incident light (880 nm) was measured every 3 minutes over a time period of 1 hour at 22°C using Turbiscan Lab-Expert (Formulaction, I'Union, France). Backscattering changes in the middle of the sample were plotted as a function of time. Stable samples were indicated by constant backscattering (Figure 1a). The flocculation or coalescence (particle growth without sedimentation or creaming) was reflected by a clear decrease of the backscattering through the whole height of the sample (Figure 1b). Sedimentation of flocculates resulted in the backscattering decrease/increase at the top/bottom of the sample, respectively (Figure 1c).

Alternatively, flocculation was also indicated by the appearance of sediment upon standing. The sedimentation volume (F) of the samples after standing for 24 hours in graduated glass tubes (15 mL) was calculated as the height of the sediment (mm)/height of total mixture (mm).

Preparation of Kollicoat® SR films

Kollicoat® SR films were prepared by spraying a 15% (w/w) aqueous dispersions with the corresponding water-soluble polymers using an Airbrush with a nozzle diameter of 0.75 mm (Paasche, Chicago, IL, USA) onto Teflon plates (14 × 14 cm^2) followed by oven-drying at 30°C for 48 hours. The films (100–150 μm thick) were cut into pieces (4 × 4 cm^2) and stored in a desiccator until further use.

Weight loss and medium uptake of films

The films were weighed ($weight_{initial}$), put into 80 mL prewarmed 0.1 N HCl, and shaken at 37°C, 80 rpm for up to 8 hours (GFL shaking incubator 3033; GFL mbH, Burgwedel, Germany) (n = 3). The films were removed from the medium, wiped with tissue paper to remove excess water and weighed ($weight_{wet}$). The wet films were oven-dried for 24 hours at 40°C and additionally for 48 hours in a desiccator and weighed again ($weight_{dry}$). The weight loss (leaching) and medium uptake were calculated as follows:

$$\text{Weight loss}\,(\%) = \frac{(\text{weight}_{\text{initial}} - \text{weight}_{\text{dry}})}{\text{weight}_{\text{initial}}} \times 100$$

$$\text{Medium uptake}\,(\%) = \frac{(\text{weight}_{\text{wet}} - \text{weight}_{\text{dry}})}{\text{weight}_{\text{dry}}} \times 100.$$

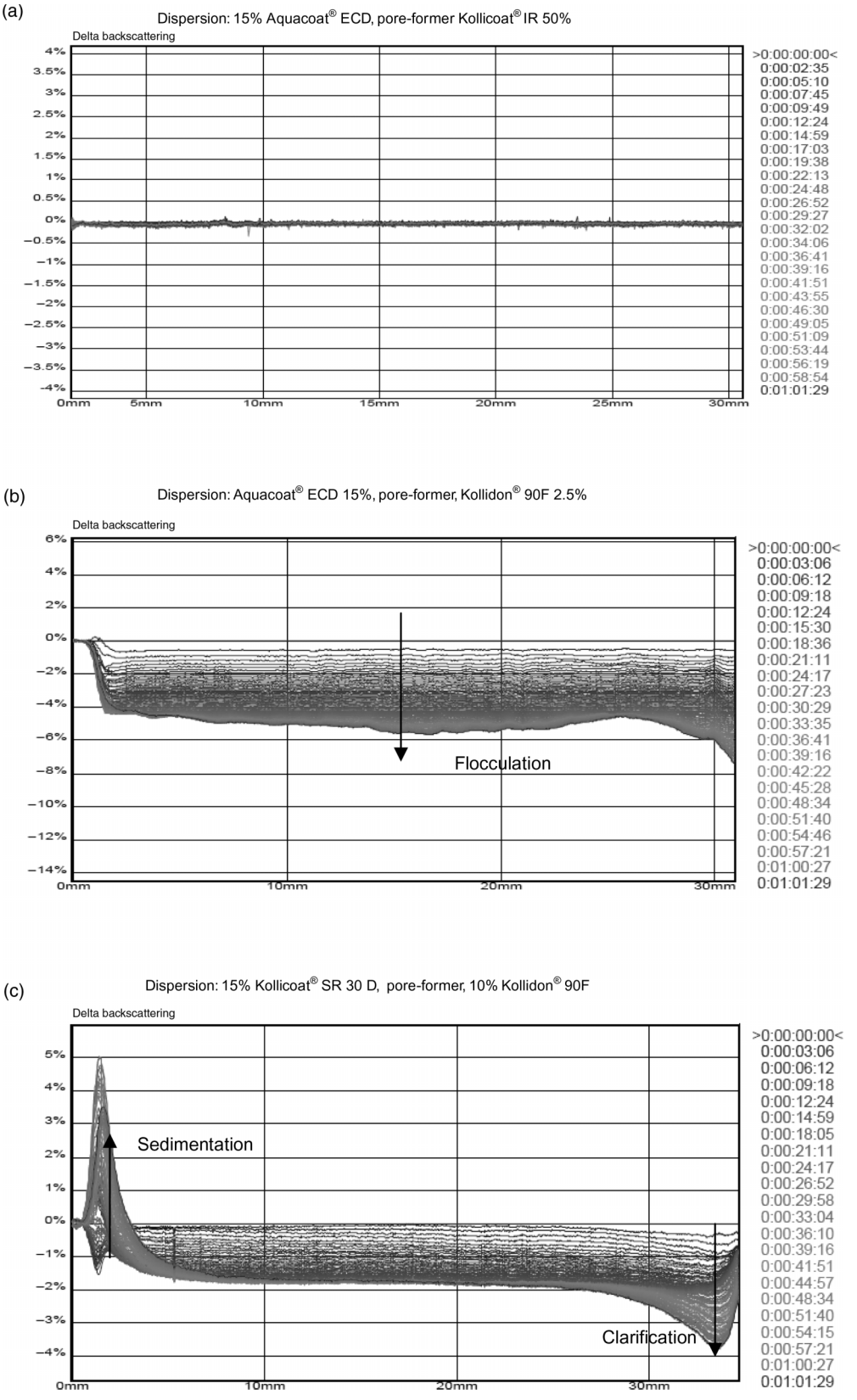

Figure 1. Example of the backscattering profiles. (a) stable dispersion, (b) flocculation without sedimentation and (c) flocculation with sedimentation.

Scanning electron microscopy

Polymer films were sputtered with gold palladium for 230 seconds and then observed with a scanning electron microscope (Philips SEM 515, Typ PW6703; Philips Optical Electronics, Endhoven, the Netherlands).

Drug layering onto sugar pellets

Theophylline or propranolol HCl was layered on sugar pellets from a suspension or solution, respectively, in ethanol:water (60:40, v/v) with a solids content of 21% (w/w) and Pharmacoat® 606 as a binder (5%, w/w, based on drug) in a fluidized bed coater Glatt GPCG-1 (Glatt Process Technology GmbH, Binzen, Germany) to achieve a 10% drug content based on the initial pellet weight. The layering conditions were batch size = 800 g, inlet temperature = 42–44°C, product temperature = 38–40°C, air flow = 130 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 7.5 g/min, and final drying at 40°C for 15 minutes.

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 a predetermined weight gain. Coating conditions were batch size = 800 g, inlet temperature = 30–34°C, product temperature = 28–32°C, air flow = 130 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 2.0 bar, spray rate = 8.5 g/min, and final drying at 30°C for 15 minutes.

Drug release

The coated pellets were released in a paddle apparatus (Vankel VK 300, 900 mL, 0.01 N HCl, 100 rpm, 37°C, $n = 3$). Samples were withdrawn at predetermined time points and measured by UV spectrophotometer:propranolol HCl, $\lambda = 290$ nm; theophylline, $\lambda = 270$ nm.

Results and discussion

Two commonly used aqueous polymer dispersions, Kollicoat® SR 30 D and Aquacoat® ECD, in combination with three water-soluble polymers, Kollicoat® IR, Kollidon® 30 or 90 F, and Pharmacoat® 603 or 606, were investigated with respect to the physical stability of the dispersions and its possible implications on the drug release from coated pellets.

Sedimentation in polymer dispersions containing water-soluble polymers can be observed visually after standing or centrifugation of flocculated samples[11]. However, small flocculates or highly viscous systems are difficult to analyze visually. Monitoring the particle size by laser diffractometry was also not possible because of deagglomeration of the flocculates upon the required aqueous dilution.

In this study, flocculation was characterized by using backscattering profiles recorded by turbidimetric measurements with the Turbiscan Lab-Expert (Figure 1).

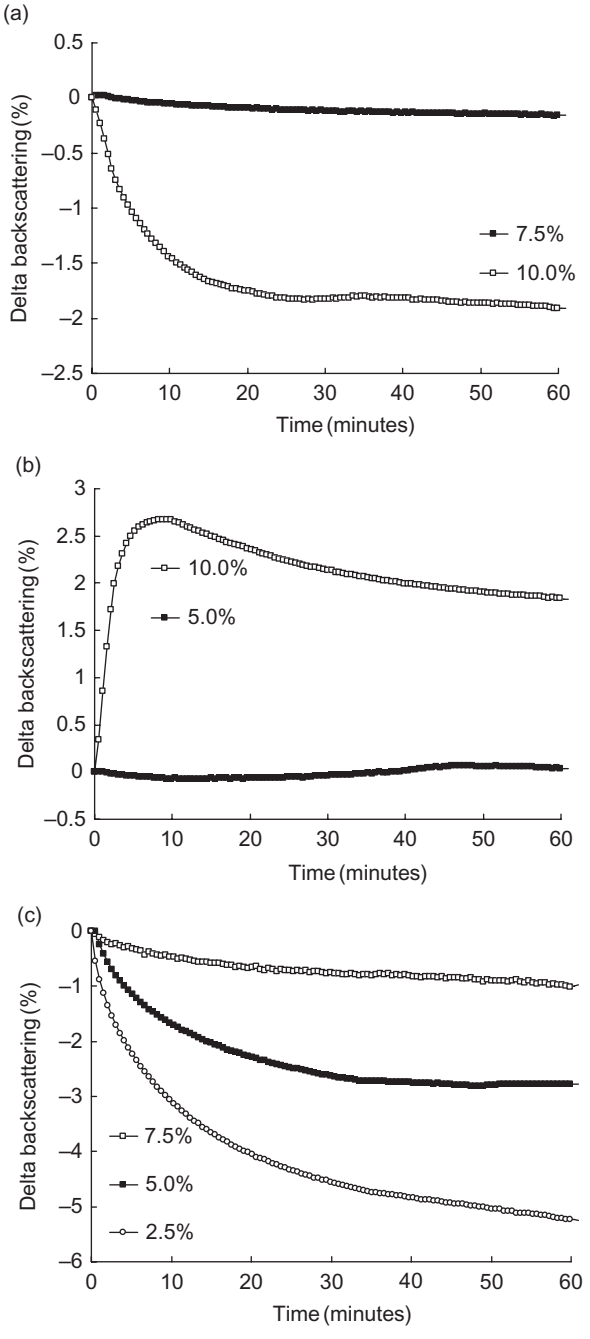

Figure 2. Backscattering/time profiles of 15% w/w dispersions with different amount of water-soluble polymers: (a) Kollicoat® SR 30 D + Kollidon® 90F, (b) Aquacoat® ECD + Pharmacoat® 603, (c) Aquacoat® ECD + Kollidon® 90 F.

The flocculation behavior of the dispersion with corresponding backscattering/time profiles was as follows:

1. No flocculation: stable backscattering/time profiles [e.g., 15%, w/w, Kollicoat® SR 30 D with 7.5%, w/w, Kollidon® 90 F (Figure 2a) or Aquacoat® ECD with 5%, w/w, Pharmacoat® 603 (Figure 2b)].
2. Formation of fine flocculates (<0.6 μm): increase in backscattering. This is because of the flocculates being smaller than the wavelength of incident light[13]. A further growth of flocculates over a critical size (0.6 μm) resulted in a decrease in backscattering (e.g., 15%, w/w, Aquacoat® ECD with 10%, w/w, Pharmacoat® 603, Figure 2b).
3. Formation of coarse flocculates (>0.6 μm): decrease in backscattering [e.g., 15% w/w, Kollicoat® SR 30 D with 10%, w/w, Kollidon® 90F (Figure 2a) and 15% w/w, Aquacoat® ECD with 2.5–7.5%, w/w, Kollidon® 90 F (Figure 2c)].

Summarizing the turbidimetric studies (Table 1), stable systems were obtained with both Kollicoat® SR 30 D and Aquacoat® ECD with the hydrophilic pore formers: Kollicoat® IR and Kollidon® 30 up to at least 50% (w/w) pore-former concentration. With the other pore formers, Kollidon® 90 F and Pharmacoat® 603 or 606, Kollicoat® SR 30 D was more stable than Aquacoat® ECD, as indicated by a higher flocculation concentration. This could be because of the smaller particle size of Kollicoat® SR 30 D (d = 140 versus 270 nm for Aquacoat® ECD). The physical stability (higher critical flocculation concentration) also increased with decreasing molecular weight of the water-soluble polymer (Kollidon® 30 versus Kollidon®90 F or Pharmacoat® 603 versus Pharmacoat® 606) and also decreasing concentration of the polymer dispersion.

Interestingly, the rate of flocculation also decreased with increasing amount of water-soluble polymer (Figure 2c). Upon visual observation of flocculated systems, the sedimentation volume first decreased and then increased with increasing amount of water-soluble polymer (Figure 3). The increase of the sedimentation volume was caused by the higher viscosity of the dispersion and delayed sedimentation. This was the reason for the overestimation of the critical flocculation concentration measured by visual observation versus turbidimetric measurements (Table 1). This effect was more pronounced with Aquacoat® ECD than with Kollicoat® SR 30 D. This is because of the formation of a three-dimensional network in the case of Aquacoat ECD dispersion indicated by shear-thinning flow in contrast to Kollicoat® SR 30 D with almost Newtonian flow behavior (Figure 4). Thus, the identification of flocculated samples was difficult by visual observation and more accurate by turbidimetric measurements.

Next, the drug release from pellets coated with combinations of Kollicoat® SR 30 D and various water-soluble polymers at different polymer concentrations was investigated.

As described above, physically stable Kollicoat® SR 30 D dispersions were obtained with the water-soluble polymers Kollidon® 30 and Kollicoat® IR up to 50% (w/w) of the water-soluble polymers (Table 1). The drug release increased proportionally to the amount of water-soluble polymer within the broad range of 15–50% (w/w) (Figures 5a and 6a, c). With flocculated dispersions (e.g.,

Table 1. Flocculation summary.

			Critical flocculation concentration (%)			
			Kollicoat® SR		Aquacoat® ECD	
Pore former		Concentration of dispersion	Turbidimetry	Visual observation	Turbidimetry	Visual observation
Polyvinyl alcohol–polyethylene glycol graft copolymer	Kollicoat® IR	7.5–15	≥50.0	≥50.0	≥50.0	≥50.0
Polyvinyl pyrrolidine	Kollidon® 30	7.5–15	≥50.0	≥50.0	≥50.0	≥50.0
	Kollidon® 90 F	7.5	25.0	30.0	7.5	10.0
		10.0	15.0	17.5	<2.5	12.5
		12.5	10.0	12.5	<2.5	5.0
		15.0	7.5	7.5	<2.5	2.5
Hydroxypropyl methylcellulose	Pharmacoat® 603	7.5	45.0	45.0	25.0	35.0
		10.0	45.0	45.0	5.0	15.0
		12.5	30.0	30.0	5.0	12.5
		15.0	10.0	20.0	5.0	7.5
	Pharmacoat® 606	7.5	30.0	30.0	7.5	12.5
		10.0	20.0	20.0	5.0	7.5
		12.5	15.0	15.0	<2.5	5.0
		15.0	7.5	7.5	<2.5	2.5

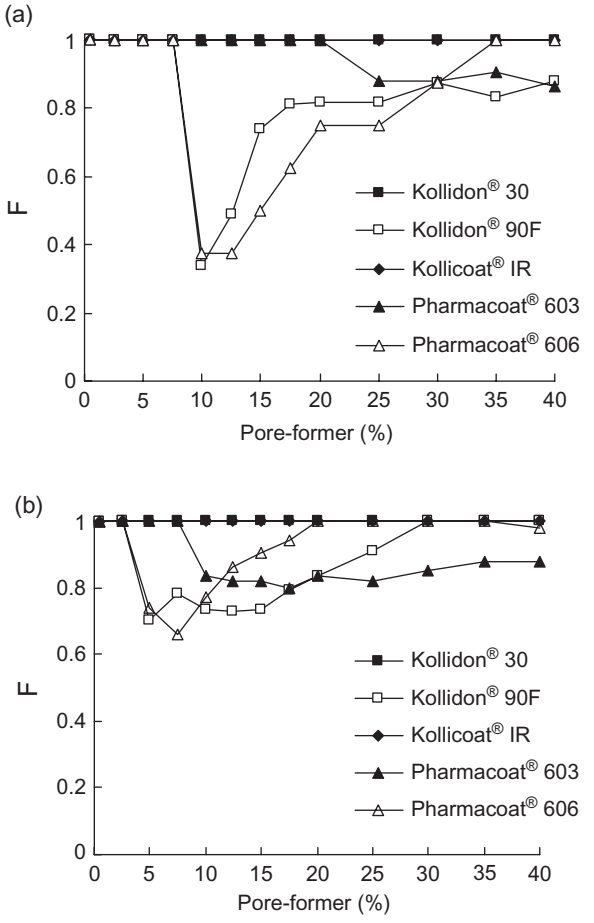

Figure 3. Effect of pore-former concentration on the sedimentation volume (F) of (a) Kollicoat® SR 30D, (b) Aquacoat® ECD (15% w/w solid content, standing for 24 h).

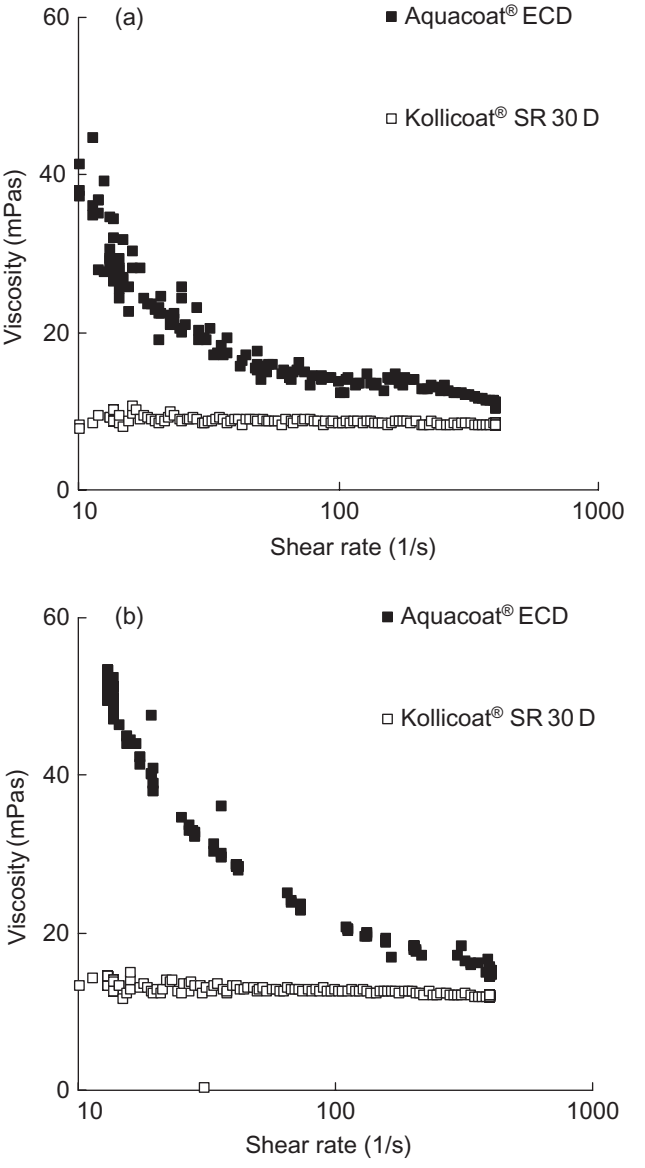

Figure 4. Viscosity–shear rate profiles of 15% w/w Kollicoat® SR 30 D and Aquacoat ECD dispersions by addition of (a) 15% w/w and (b) 20% w/w Pharmacoat® 603.

15%, w/w, Kollicoat® SR 30 D with Kollidon® 90 F or Pharmacoat® 606), the drug release increased sharply (Figures 5b and 6b, c) above the critical flocculation concentration (7.5%, w/w, water-soluble polymer, Table 1).

To explain the rapid increase in drug release with flocculated systems, weight loss, medium uptake, and SEM photographs of sprayed polymer films of same compositions were investigated. The weight loss of the Kollicoat® SR 30 films upon incubation in 0.1 N HCl was rapid and complete with all hydrophilic pore formers at all concentrations [Kollidon® 30 and Kollidon® 90 F as well as for Kollicoat® IR (Figure 7a–c)], indicating a rapid release/leaching of the water-soluble polymer in the release medium[14]. Differences between flocculated and unflocculated systems were seen on SEM photographs and with medium uptake data of the resulting films. Homogeneous films were obtained from physically stable Kollicoat® SR 30 D dispersions (e.g., with 30%, w/w, Kollidon® 30 or Kollidon® IR), whereas flocculated dispersions (e.g., with 15% or 30%, w/w, Kollidon® 90 F) resulted in porous films (Figure 8). The formation of porous films from flocculated dispersions can be explained by the 'tail-loop-train' adsorption of water-soluble polymers on the particle surface and therefore steric hindrance for particles coalescence. Consequently, the medium uptake of porous films increased with increasing amount of water-soluble polymer (Kollidon® 90 F) to a higher extent when compared to the homogeneous films containing Kollidon® 30 or Kollicoat® IR (Figure 7d–f).

In summary, the adjustment of drug release profiles of coated pellets via controlling the permeability of extended release coatings prepared from aqueous polymer dispersions with the addition water-soluble polymers (pore formers) should take into account the physical state of the dispersion (flocculated versus

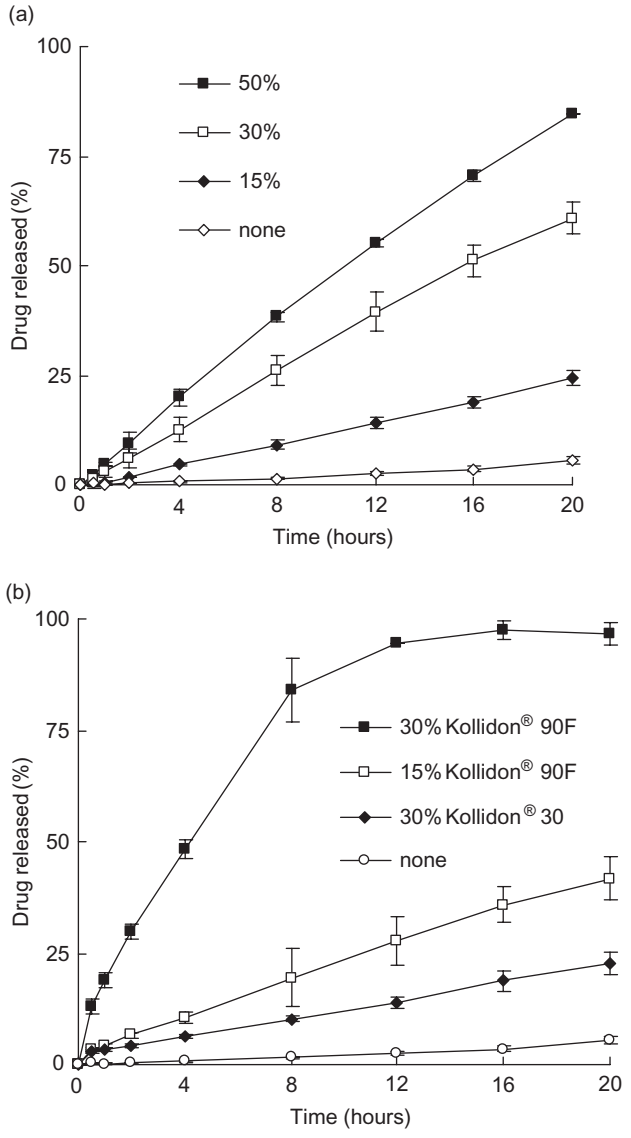

Figure 5. Effect of (a) Kollicoat® IR and (b) Kollidon® 30 or Kollidon® 90F on the theophylline release from Kollicoat® SR 30 D-coated pellets (15% w/w coating level, 0.1N HCl).

unflocculated) to explain possible irregularities in the magnitude of release enhancement.

Conclusions

Flocculation phenomena of aqueous colloidal dispersions in the presence of water-soluble polymers could be precisely characterized using turbidimetric measurement. Kollicoat® SR 30 D was more resistant to flocculation upon addition of water-soluble polymers than Aquacoat® ECD. The continuous adjustment of drug release from Kollicoat® SR 30-coated pellets was possible with Kollicoat® IR amounts over a broad range.

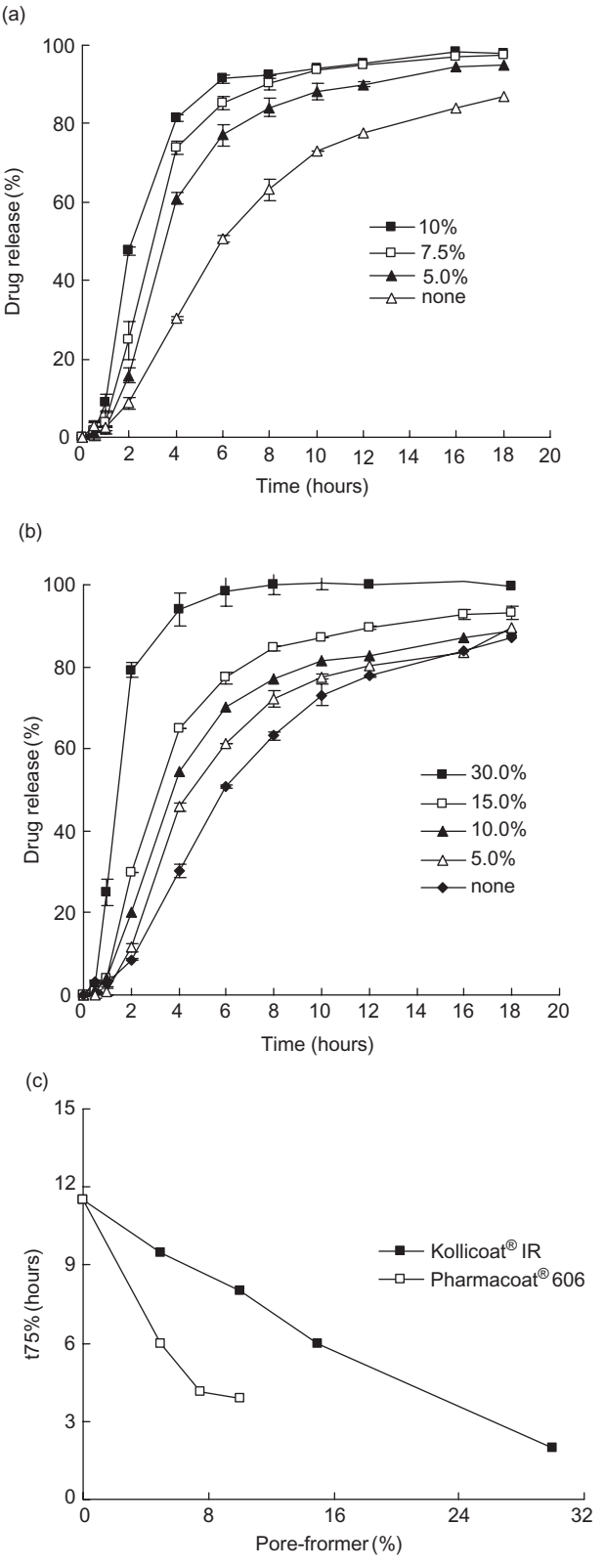

Figure 6. Effect of type and amount of pore-former on the propranolol HCl release from Kollicoat® SR 30 D-coated pellets (15% w/w coating level, in 0.1N HCl): (a) Kollicoat® IR, (b) Pharmacoat® 606 and (c) T75% (time for 75% drug released) vs. pore-former concentration.

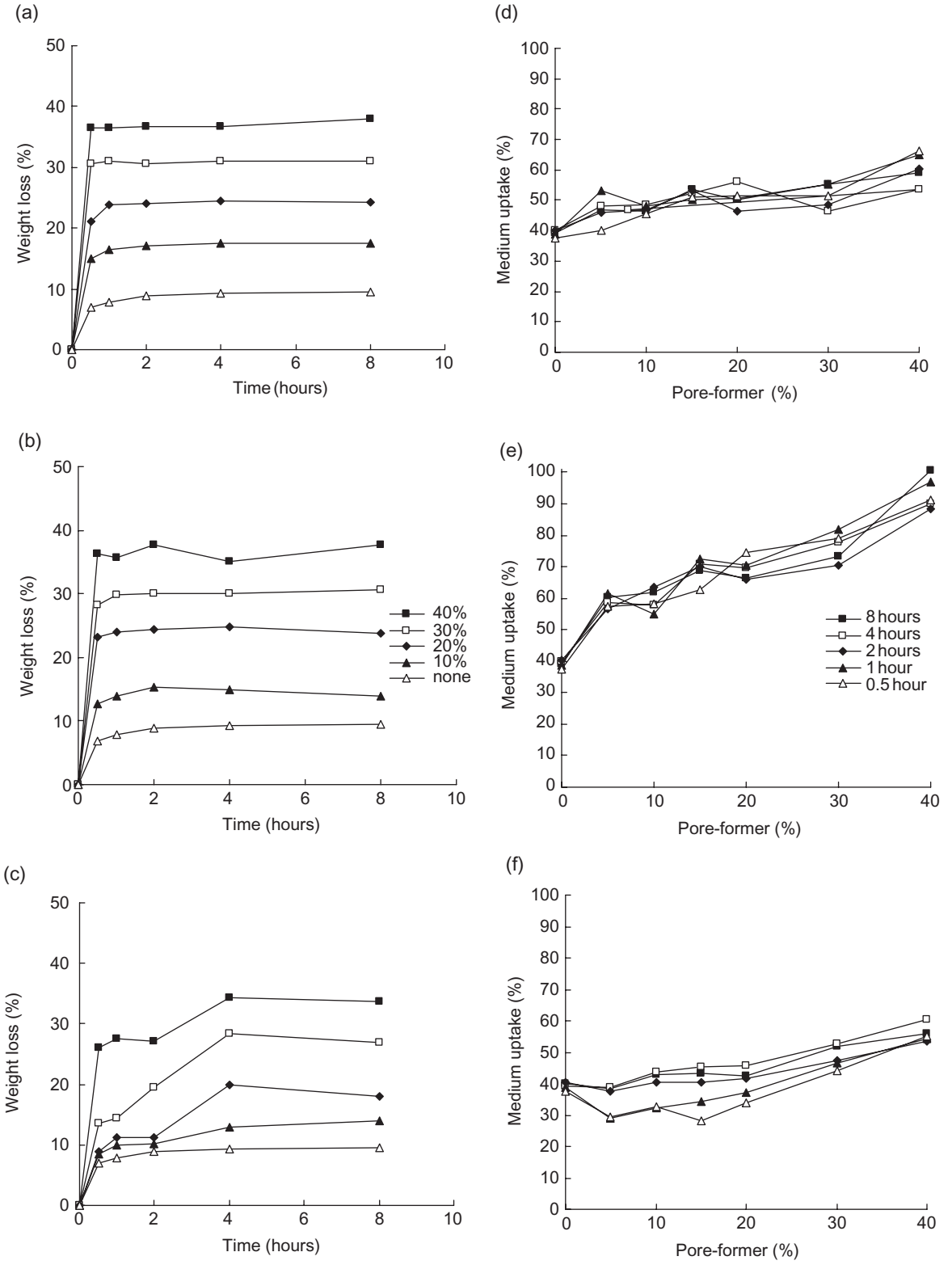

Figure 7. Weight loss and medium uptake during incubation of Kollicoat® SR 30D films in 0.1 N HCl with different amounts of (a), (b) Kollidon® 30, (b), (e) Kollidon® 90 F and (c), (f) Kollicoat® IR.

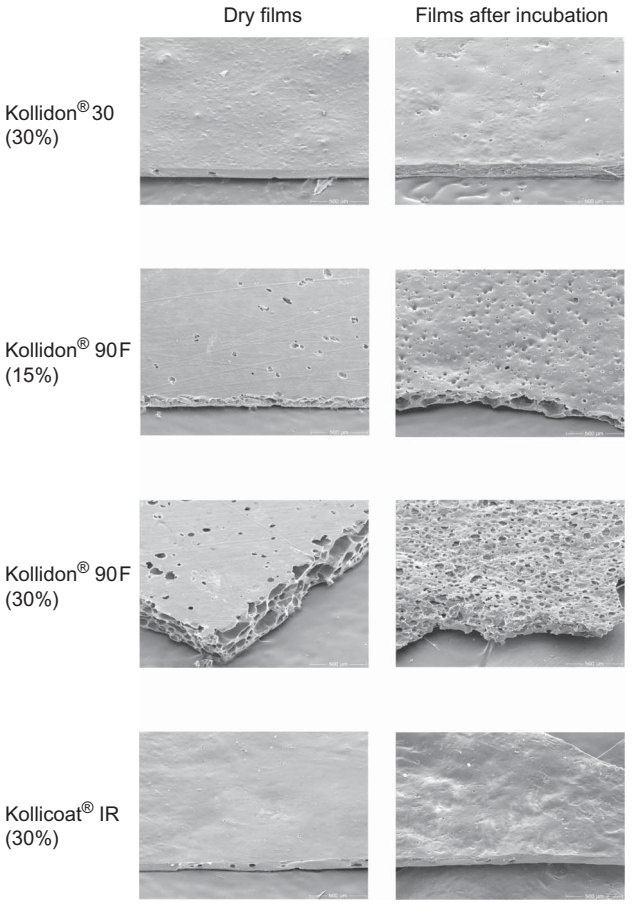

Figure 8. SEM photographs of Kollicoat® SR films with different pore-formers in the dry state and after incubation 0.1 N HCl for 2h.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Cole G, Hogan G, Aulton ME. (1995). Pharmaceutical coating technology. London: Taylor & Francis.
2. McGinity JW, Felton LA. (2008). Aqueous polymeric coatings for pharmaceutical dosage forms. 3rd ed. New York: Informa Healthcare.
3. Wesseling M, Bodmeier R. (1999). Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, aquacoat, or an organic ethylcellulose solution. Eur J Pharm Biopharm, 47:33–8.
4. Frohoff-Hülsmann MA, Schmitz A, Lippold BC. (1999). Aqueous ethylcellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets: I. Drug release rates from coated pellets. Int J Pharm, 177:69–82.
5. Lippold BC, Pagés RM. (2001). Control and stability of drug release from diffusion pellets coated with the aqueous quaternary polymethacrylate dispersion Eudragit® RS 30D. Pharmazie, 56:477–83.
6. Zheng W, Sauer D, McGinity JW. (2005). Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D. Eur J Pharm Biopharm, 59:147–54.
7. Dashevsky A, Wagner K, Kolter K, Bodmeier R. (2005). Physicochemical and release properties of pellets coated with Kollicoat SR 30 D, a new aqueous polyvinyl acetate dispersion for extended release. Int J Pharm, 290:15–23.
8. Dashevsky A, Kolter K, Bodmeier R. (2004). Water soluble pore-formers for the controlled release aqueous dispersions Kollicoat® SR 30 D and Aquacoat® ECD. 2004 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, Baltimore, MD, Vol. 6, Abstract T3200.
9. Siepmann F, Hoffmann A, Leclercq B, Carlinc B, Siepmann J. (2007). How to adjust desired drug release patterns from ethylcellulose-coated dosage forms. J Control Release, 119(2):182–9.
10. Siepmann F, Muschert S, Leclercq B, Carlin B, Siepmann J. (2008). How to improve the storage stability of aqueous polymeric film coatings. J Control Release, 126(1):26–33.
11. Wong D, Bodmeier R. (1996). Flocculation of an aqueous colloidal ethyl cellulose dispersion (Aquacoat®) with a water-soluble polymer, hydroxypropyl methylcellulose. Eur J Pharm Biopharm, 42:12–5.
12. Wong D. (1994). Water-soluble polymers in pharmaceutical aqueous colloidal polymer dispersions. Ph.D. thesis, University of Texas at Austin, Austin, USA.
13. Mengual O, Meunier G, Cayre I, Puech K, Snabre P. (1999). Turbiscan MA 2000: Multiple light scattering measurement for concentrated emulsion and suspension instability analysis. Talanta, 50:445–56.
14. Wagner K. (2002). Aqueous polymer dispersions for extended release dosage forms. PhD thesis, Freie Universität Berlin, Germany.