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The distribution of plasticizers between aqueous and polymer phases in aqueous colloidal polymer dispersions

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Summary

The distribution of water-soluble (triethyl citrate and triacetin) and water-insoluble (acetyltriethyl citrate, acetyltributyl citrate, dibutyl phthalate, dibutyl sebacate, diethyl phthalate and tributyl citrate) plasticizers between the aqueous and polymer phases in an aqueous colloidal ethylcellulose dispersion, Aquacoat®, was determined. A separation scheme was developed, which allowed the determination of the amounts of plasticizers dissolved and, in the case of water-insoluble plasticizers, also emulsified in the aqueous phase, and dissolved in the colloidal polymer particles. The plasticized ethylcellulose dispersion was separated by centrifugation and/or ultracentrifugation to obtain the various plasticizer-containing fractions. The plasticizer concentration in each phase was determined by a HPLC assay. The extent of the plasticizer partitioning was investigated with respect to the type (water-soluble or water-insoluble) and concentration of the plasticizer, and the solids content of the polymer dispersion. Water-insoluble plasticizers mainly partitioned into the polymer particles due to the higher affinity towards the polymer phase, however, the amount of emulsified plasticizer droplets increased with increasing plasticizer concentration after a plasticization time of 24 h. An 'association' coefficient, which was obtained from the ratio of the plasticizer concentration in the polymer to the concentration in the aqueous phase, was used to characterize the plasticizer partitioning. The fraction of plasticizer taken up by the colloidal polymer particles increased with increasing solids content of the polymer dispersion. It is therefore recommended to add the plasticizer to the undiluted dispersions followed by dilution to the desired solids content just prior to coating, rather than first diluting the dispersion followed by addition of the plasticizer.

Introduction

Aqueous colloidal polymer dispersions (latexes or pseudolatexes) have been developed to overcome the hazards associated with organic solvent-based coating (Banker and Peck, 1979; Lehmann, 1989). The addition of plasticizers is required for polymer dispersions having a minimum film formation temperature above the coating temperature. During plasticization, the plasticizer will partition into and soften the colloidal polymeric particles thus promoting particle deformation and coalescence into a homogeneous film. The effectiveness of a plasticizer for a particular polymer or polymer dispersion will depend on the plasticizer-polymer compatibility and the perma-

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nence of the plasticizer in the film during coating, storage, and during contact with artificial or biological fluids. The plasticizer-polymer interactions have been studied by various methods including thermal analysis to measure the reductions in glass transition temperature (Hoy, 1976; Sakellariou et al., 1985; Selinger and Brine, 1988; Steuernagel, 1989), viscosity determinations (Hutchings et al., 1991), mechanical tests (Reed, 1943; Sinko and Amidon, 1989), and swelling/mass uptake measurements (Gur-Arieh et al., 1976; Sears and Darby, 1982; Storey et al., 1989).

Plasticizers are generally solvents of low volatility and are often categorized into water-soluble or -insoluble plasticizers. Water-soluble plasticizers generally dissolve, while water-insoluble plasticizers have to be emulsified in the aqueous phase of the dispersion. During plasticization, the plasticizer will partition between the aqueous and polymer phases. Plasticizer partitioning in colloidal polymer dispersions has been studied by only a few researchers. A theory of plasticization for synthetic paint latexes was developed by Dillon et al. (1953) in terms of a three-phase system comprised of the water phase, polymer particles, and plasticizer droplets. Recently, Iyer et al. (1990) determined the uptake of the water-insoluble plasticizer, dibutyl sebacate, into a commercial ethyl cellulose pseudolatex (Aquacoat®) by using an alkaline partition column to separate the unbound plasticizer, and gas chromatography for the plasticizer assay. The uptake of dibutyl sebacate was found to be complete within 30 min irrespective of the amount used and the uptake rate was faster with increasing solids content of pseudolatex or when smaller quantities of plasticizer was incorporated. However, a previous study reported the presence of visible dibutyl sebacate droplets in Aquacoat® after 1 week of mixing, indicating incomplete plasticization after such a long plasticization time (Sutter, 1987).

The objectives of this study were to develop a separation method, which allowed the characterization of the distribution of plasticizers in aqueous colloidal polymer dispersions by quantifying the plasticizer concentrations in the polymer phase and in the aqueous phase in which the plasticizer was either dissolved or emulsified. Aquacoat®, a widely used ethylcellulose pseudolatex, was investigated with various types and concentrations of plasticizers.

Materials and Methods

Materials

The following chemicals were obtained from commercial suppliers and used as received: Aquacoat® (30% w/w aqueous dispersion of ethyl cellulose) (FMC Corp., Newark, DE), dibutyl sebacate (DBS), diethyl phthalate (DEP), dibutyl phthalate (DBP), glyceryl triacetate (triacetin) (Eastman Kodak Co., Rochester, NY), triethyl citrate (TEC; Citroflex-2), acetyltriethyl citrate (ATEC; Citroflex A-2), tributyl citrate (TBC; Citroflex-4), acetyltributyl citrate (ATBC; Citroflex A-4) (Morflex Chemical Co., Greensboro, NC), and methanol (HPLC grade, Mallinckrodt Specialty Chemicals Co., Paris, KY).

Methods

The plasticizer (600 mg) was mixed with the diluted colloidal polymer dispersion (solids content = 15% w/w, 20 g) by either shaking the sample vials on a horizontal shaker (90 strokes/min; Eberbach Corp., Ann Arbor, MI) or by stirring the plasticized dispersion in a beaker using a magnetic stir bar (plasticization time = 24 h; $T = 22°C$; $n = 2$). Unless otherwise indicated, the solids content of the latex was 15% w/w and the plasticizer concentration was 20% w/w (based on polymer solids). The actual solids contents of the commercial latexes were found to be within $\pm 0.5\%$ w/w of the labelled values provided by the manufacturer. The following variables affecting the distribution of the plasticizers in the ethylcellulose pseudolatex were investigated: type of plasticizer, water-soluble (TEC and triacetin) and water-insoluble (ATEC, ATBC, DBP, DBS, DEP, and TBC); plasticizer (TEC and DBS) concentration, 10–30% w/w of polymer solids, 5% increments; solids content of polymeric dispersion, 5–30% w/w, 5 or 10% increments.

In order to determine the plasticizer concentrations in the different phases, the separation

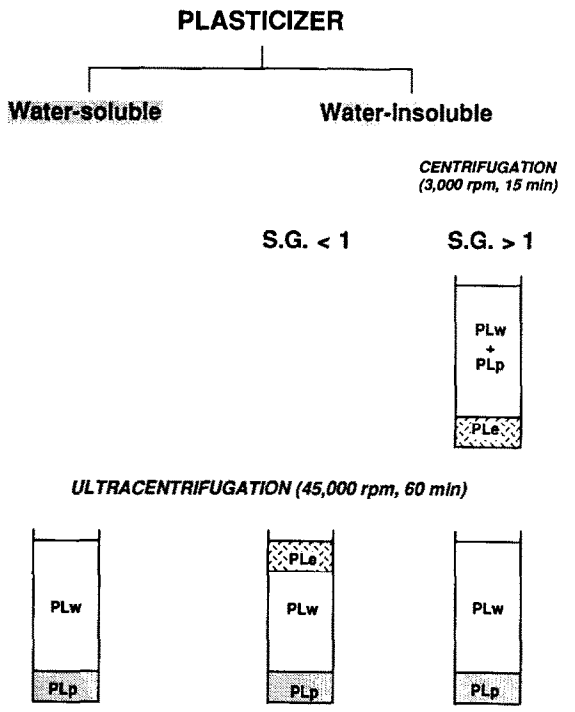

Fig. 1. Separation scheme for the quantification of plasticizer present in different phases (PLw, plasticizer dissoved in aqueous phase; PLe, plasticizer emulsified in aqueous phase; PLp, plasticizer in the polymer phase; S.G., specific gravity).

scheme shown in Fig. 1 was developed. During plasticization, the plasticizer will partition between the polymer and aqueous phase. While water-soluble plasticizers will be completely dissolved in the aqueous phase, water-insoluble plasticizers could be present in the aqueous phase in dissolved and emulsified forms. Water-soluble plasticizers (triethyl citrate and triacetin) were determined in the aqueous, clear supernatant (plasticizer dissolved in the aqueous phase) and the polymer sediment (plasticizer dissolved in the colloidal polymer particles) after ultracentrifugation of the plasticized polymer dispersions (45 000 rpm, 60 min, 22°C; Beckman Ultracentrifuge L5-50). With the exception of dibutyl sebacate (specific gravity = 0.94), all other water-insoluble plasticizers investigated had specific gravities higher than that of water. With these plasticizers, the undissolved, emulsified plasticizer droplets were first separated from the polymer dispersion by centrifugation at 3000 rpm for 15 min (Beckman centrifuge TJ-6). The emulsified plasticizer accumulated at the bottom of the vials, while the colloidal polymer particles did not settle under these conditions. No concentration gradient of the plasticizer was observed in the remaining portion of the centrifuged polymer dispersions indicating that the emulsified portion of the plasticizer settled to the bottom of the vial. The amounts of plasticizer dissolved in the aqueous and polymer phase were then obtained after ultracentrifugation (45 000 rpm, 60 min, 22°C) of the supernatant (colloidal polymer dispersion excluding the emulsified plasticizer) and analysis of the resulting supernatant and polymer sediment. The first centrifugation step was not necessary with dibutyl sebacate because of its lower specific gravity. The emulsified dibutyl sebacate droplets floated on the surface of the pseudolatexes after ultracentrifugation and thus could be separated from the remaining clear aqueous phase and the polymer sediment.

A previously developed HPLC assay was used for the analysis of plasticizers (Bodmeier and Paeratakul, 1991). The chromatographic system consisted of a solvent delivery module (LC-9A), a UV spectrophotometric detector (SPD-6A), an automatic sample injector (SIL-9A), an integrator (Chromatopac CR601) (Shimadzu, Kyoto, Japan), and an analytical column (Beckman-Ultrasphere, C-18, 5 μm particle size, 25 cm $\times$ 4.6 cm i.d.). The mobile phases consisted of methanol:water of varying ratios depending on the hydrophobicity of the plasticizer (methanol:water, % v/v: 90:10 for TBC, ATBC, DBP; 70:30 for TEC, ATEC, DBS, DBP and 50:50 for triacetin). The aqueous phase of the polymer dispersion was assayed for the plasticizer content after appropriate dilution with the respective mobile phase. The polymer sediment was freeze-dried for 24 h and was further vacuum-dried for 4 h, to obtain the dried polymer powder. The dried polymer (200–500 mg) was dissolved in methanol (10–18 ml) followed by addition of water (2–10 ml) to precipitate the polymer. The extraction samples were ultracentrifuged, if necessary, prior to appropriate dilution with the mobile phase and injection into the HPLC. The emulsified portion of plasticizer was dissolved in methanol (20–50 ml) fol-

lowed by dilution with appropriate mobile phase prior to injection. The plasticizer standards were prepared in the mobile phase and the calculation for plasticizer concentration was based on peak area measurements.

To determine the solubilities of plasticizers, excess amount of the plasticizers were placed in contact with the sodium lauryl sulfate solutions corresponding to the supernatant of the diluted ethyl cellulose dispersion, Aquacoat®. The samples ($n = 2$) were shaken for 48 h at 22°C. The mixture was centrifuged at 3000 rpm for 15 min and the aqueous layer analyzed for plasticizer content, after appropriate dilution with mobile phase, by HPLC.

Results and Discussion

Various pharmaceutically acceptable and widely used plasticizers were evaluated with respect to their partitioning behaviour between the aqueous and polymer phases in colloidal polymer dispersions. The plasticizers were classified into water-soluble (triethyl citrate and triacetin) and water-insoluble plasticizers (acetyltriethyl citrate, acetyltributyl citrate, dibutyl phthalate, dibutyl sebacate, diethyl phthalate and tributyl citrate). Depending on the solubility of the plasticizer in the aqueous phase, it could be either dissolved or emulsified into the colloidal polymer dispersion prior to the coating process. During plasticization, the plasticizer will partition into the colloidal polymer particles, the rate and extent of partitioning being dependent on its water solubility and affinity towards the polymer phase. The plasticizer will be distributed between the polymer and aqueous phases. Water-soluble plasticizers will be dissolved in the polymer and aqueous phase, while a water-insoluble plasticizer could additionally be present in the aqueous phase in an emulsified form.

We determined the extent of plasticizer distribution by developing a separation scheme, which allowed the quantification of the amount of plasticizer in the aqueous and polymer phases (Fig. 1). The plasticizer present in the different phases could be separated because of differences in the specific gravities of the plasticizers, water, and polymer particles. The amount of plasticizer in each phase was determined after centrifugation and/or ultracentrifugation steps by a HPLC method.

Initial studies on the rate of plasticizer uptake (to be presented in a future publication) indicated that the equilibrium in plasticizer distribution was rapidly obtained with water-soluble plasticizers, however, plasticization times in excess of 24 h were required to obtain equilibrium with water-insoluble plasticizers. For practical reasons

TABLE 1

Distribution of plasticizers between aqueous and polymer phases in Aquacoat (plasticization time, 24 h; pseudolatex solids, 15% w/w; level of plasticizer, 20% w/w of polymer)

Plasticizer	Plasticizer concentration (%)			Recovery (%)
	Aqueous phase		Polymer phase	
	Dissolved	Emulsified		
Water-soluble				
Triethyl citrate	49.87 ± 0.01	–	50.10 ± 0.18	99.97 ± 0.16
Triacetin	63.96 ± 1.12	–	35.41 ± 1.67	99.36 ± 0.55
Water-insoluble				
Acetyl triethyl citrate	7.63 ± 0.27	7.25 ± 0.37	84.72 ± 1.33	99.60 ± 0.69
Acetyl tributyl citrate	0.44 ± 0.01	12.19 ± 0.58	86.37 ± 1.98	98.99 ± 1.39
Dibutyl sebacate	10.77 ± 0.03	1.51 ± 0.01	87.43 ± 0.25	99.73 ± 0.25
Diethyl phthalate	2.46 ± 0.15	10.59 ± 1.23	87.41 ± 1.02	100.46 ± 0.37
Dibutyl phthalate	0.37 ± 0.01	13.74 ± 1.46	85.92 ± 0.88	100.03 ± 0.89
Tributyl citrate	0.81 ± 0.01	9.88 ± 0.69	89.22 ± 0.75	99.91 ± 0.06

relating to plasticization times used in the pharmaceutical industry, a plasticization time of 24 hours was selected to characterize the distribution of plasticizers. The following data therefore do not represent values obtained under equilibrium conditions. The extent of the distribution of both water-soluble and -insoluble plasticizers in a commercial ethyl cellulose pseudolatex, Aquacoat®, after a plasticization time of 24 h is shown in Table 1. The recovery of the plasticizers was close to 100% in all cases. The water-soluble plasticizers, triethyl citrate and triacetin, were dissolved in both the aqueous and polymer phase. The higher amount of triacetin in the aqueous phase, when compared to triethyl citrate, could be explained with its higher solubility in the supernatant (triacetin, 84.88 ± 0.07 mg/ml; triethyl citrate, 62.80 ± 1.52 mg/ml). With water-insoluble plasticizers, between 85 and 90% of the incorporated plasticizer partitioned into the colloidal polymer particles or polymer phase. The remaining plasticizer was present in the aqueous phase in predominantly emulsified form (between 7 and 14% of the total amount of plasticizer added). This clearly showed that water-insoluble plasticizers were not completely taken up by the colloidal polymer particles within a 24 h period, a result also found by Sutter (1987) with dibutyl sebacate. This may have important implications for the coating with polymer dispersions when compared to organic polymer solutions in which the plasticizer is completely dissolved. During the coating process, in addition to the plasticized polymer particles, the emulsified plasticizer droplets will be sprayed onto the substrates. This could result in an uneven plasticizer distribution within the film, potentially causing changes in the mechanical and especially release properties upon aging. A thermal treatment following the coating (curing step) (Goodhart et al., 1984; Lippold et al., 1989; Bodmeier and Paeratakul, 1991), which is now widely used to promote further coalescence of the colloidal polymer particles and to overcome stability problems, might also result in a more homogeneous distribution of the plasticizer.

The concentration of the plasticizer and the solids content of the polymer dispersion are often varied in coating experiments. The distribution of

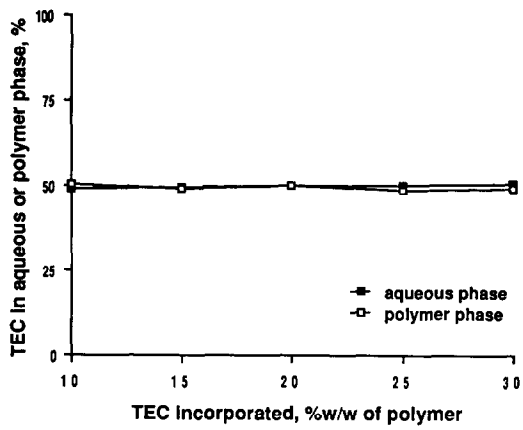

Fig. 2. Effect of triethyl citrate concentration (% w/w of polymer) on TEC concentration in aqueous or polymer phase (% w/w of total plasticizer incorporated) (plasticization time = 24 h; solids content of pseudolatex = 15% w/w).

triethyl citrate (TEC) and dibutyl sebacate (DBS) in the ethyl cellulose pseudolatex was investigated as a function of these two variables.

The TEC and DBS concentration based on the polymer content was varied between 10 and 30%, a plasticizer concentration range frequently used in coating experiments; its effect on the plasticizer partitioning between the aqueous and polymer phase at a constant pseudolatex solids content (15% w/w) is shown in Figs 2 and 3. The fraction of the TEC in the polymer and aqueous

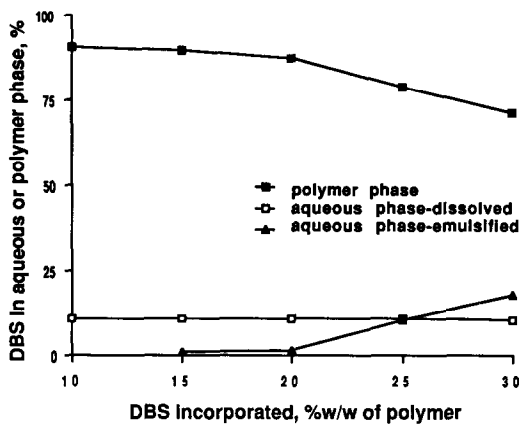

Fig. 3. Effect of dibutyl sebacate concentration (% w/w of polymer) on DBS concentration in aqueous or polymer phase (% w/w of total plasticizer incorporated) (plasticization time = 24 h; solids content of pseudolatex = 15% w/w).

phase did not change over the concentration range investigated. The plasticizer was evenly distributed between the aqueous and polymer phase. With DBS, the fraction of DBS dissolved was independent of the plasticizer concentration, however, the fraction of DBS dissolved in the polymer phase decreased and the fraction emulsified in the aqueous phase increased with increasing DBS level, especially at DBS concentrations in excess of 20%. As the incorporated plasticizer concentration increased, increasing amounts of DBS were not completely absorbed by the polymer particles. The polymer probably became saturated with the plasticizer, and plasticizer added in excess of the amount soluble in the polymer phase thus remained in the aqueous phase as emulsified droplets. The results on the extent of the plasticizer partitioning were obtained after a plasticization time of 24 h. The plasticization time in most coating experiments is generally less than 2 h; the attainment of an equilibrium in the distribution of the plasticizer in such cases is questionable.

The effect of pseudolatex polymer content on the plasticizer concentrations (% w/w of total plasticizer added) in the polymer and the aqueous phases at a constant plasticizer level (20% w/w of polymer) is shown in Figs 4 and 5 for TEC and DBS, representing a water-soluble and-insoluble plasticizer. The TEC uptake into

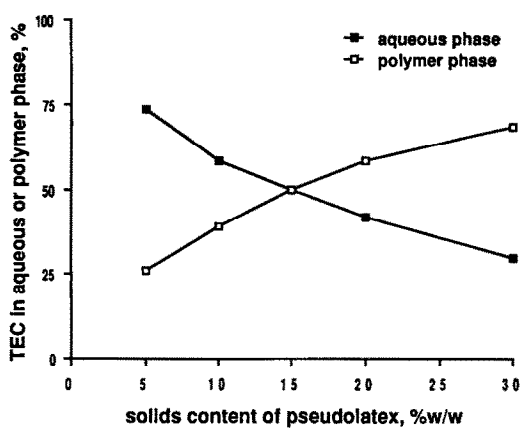

Fig. 4. Effect of solids content of pseudolatex on TEC concentration in aqueous or polymer phase (plasticization time = 24 h; plasticizer concentration = 20% w/w of polymer).

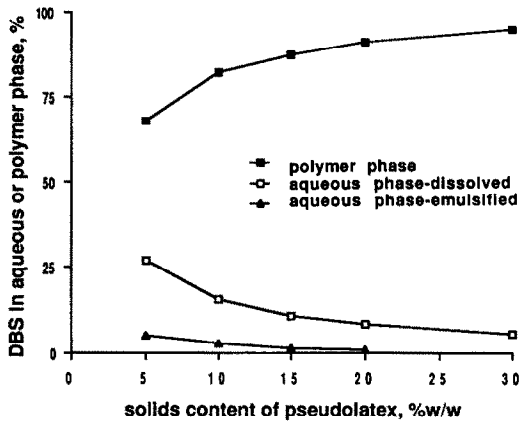

Fig. 5. Effect of solids content of pseudolatex on DBS concentration in aqueous or polymer phase (plasticization time = 24 h; plasticizer concentration = 20% w/w of polymer).

the polymer phase increased with increasing solids content, while the fraction dissolved in the aqueous phase decreased (Fig. 4). At a solids content of 5%, approx. 75% of the TEC were dissolved in the aqueous phase and only 25% in the polymer phase, while these numbers were almost reversed at a solids content of 30%. Similar trends were also seen with the water-insoluble plasticizer, DBS, with the amounts of plasticizer dissolved or emulsified into the aqueous phase decreasing with increasing pseudolatex solids content (Fig. 5). Although most commercial polymer dispersions for pharmaceutical coatings are available with a solids content of 30%, the coating is generally performed after diluting the dispersions to a solids content between 10 and 15%. It is common practice to dilute the polymer dispersion with water prior to the addition of the plasticizer or to add a diluted plasticizer solution or emulsion to the dispersion. In order to have most of the plasticizer present in the polymer particles, it is therefore recommended to add pure plasticizer to the concentrated dispersions followed by dilution to the desired solids content just prior to coating, rather than first diluting the dispersion followed by addition of the plasticizer.

In analogy to partitioning experiments with drugs, an 'association coefficient' was calculated to characterize the plasticizer distribution in the colloidal polymer dispersions after a plasticiza-

tion time of 24 h. The association coefficient, K, was calculated as the ratio of the concentration of the plasticizer in the polymer phase to the concentration of plasticizer in the aqueous phase (K = [plasticizer (g)/ polymer (g)]/[plasticizer (g)/ aqueous phase (g)]). The concentration of the plasticizer in the aqueous phase included the dissolved and emulsified portion with the water-insoluble plasticizer, DBS.

The association coefficient as a function of solids content and plasticizer concentration is shown in Figs 6 and 7. It was higher for DBS than for TEC reflecting the higher uptake of DBS by the polymer phase. The association coefficient could be used to reflect the affinity of a polymer for a particular plasticizer within a colloidal polymer dispersion. The solids content of the polymer dispersion did not affect the association coefficient, indicating a constant distribution of the plasticizer between the two phases. Although the fraction of plasticizer in the polymer phase increased with increasing solids content (as shown in Figs 4 and 5), the concentration in both the polymer and aqueous phases did not change. Higher solids contents resulted in a proportional decrease in the volume of the aqueous phase. Adding varying amounts of plasticizer to the polymer dispersion did not influence the association coefficient with TEC but with DBS (Fig. 7). The association coefficient decreased with increasing

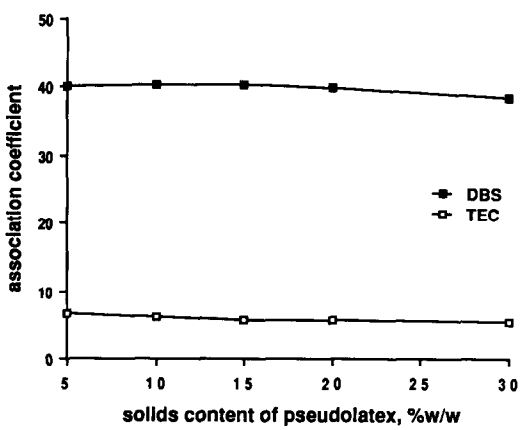

Fig. 6. The association coefficient as a function of solids content of pseudolatex (plasticization time = 24 h; plasticizer concentration = 20% w/w of polymer).

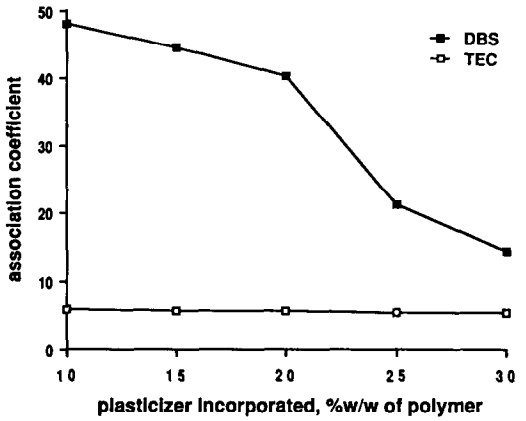

Fig. 7. The association coefficient as a function of plasticizer concentration (plasticization time = 24 h; solids content of pseudolatex = 15% w/w).

DBS concentration, reflecting the increased fraction of DBS in the aqueous phase.

In conclusion, a separation scheme was developed, which allowed the determination of the extent of plasticizer partitioning between aqueous and polymer phases in colloidal polymer dispersions. Future studies will include the characterization of plasticizer-polymer interactions with several pharmaceutically acceptable colloidal polymer dispersions and the determination of the rate of plasticizer partitioning into the colloidal particles and its impact on the film formation of and coating with aqueous colloidal dispersions.

References

Banker, G.S. and Peck, G.E., The new, water-based colloidal dispersions. *Pharm. Technol.*, 5 (1981) 55–61.

Bodmeier, R. and Paeratakul, O., Determination of plasticizers commonly used in pharmaceutical dosage forms by high performance liquid chromatography. *J. Liq. Chromatogr.*, 14 (1991) 365–375.

Bodmeier, R. and Paeratakul, O., Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes. *Int. J. Pharm.*, 70 (1991) 59–68.

Dillon, R.E., Bradford, E.B. and Andrews, R.D., Jr, Plasticizing synthetic latexes. *Ind. Eng. Chem.*, 45 (1953) 728–735.

Goodhart, F.W., Harris, M.R., Murthy, K.S. and Nesbitt, R.U., An evaluation of aqueous film-forming dispersions for controlled release. *Pharm. Technol.* 8 (1984) 64–71.

Gur-Arieh, Z., Ingamells, W. and Peters, R.H., The effect of plasticizing compounds on acrylic fibers. *J. Appl. Polym. Sci.*, 20 (1976) 41–54.

Hoy, K.L., Estimating the effectiveness of latex coalescing aids. *J. Paint Technol.*, 45 (1973) 51–56.

Hutchings, D., Nicklasson, M., Singh, S. and Sakr, A., Intrinsic viscosity and interaction constant as indices for evaluating ethyl cellulose-plasticizer interactions. *Pharm. Res.*, 8 (1991) S-116.

Iyer, U., Hong, W.-H., Das, N. and Ghebre-Sellassie, I., Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations. *Pharm. Technol.*, 14 (1990) 68–86.

Lehmann, K.O.R., Chemistry and application properties of polymethacrylate coating systems. In McGinity, J.W. (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Dekker, New York, 1989, pp. 153–245.

Lippold, B.H., Sutter, B.K. and Lippold, B.C., Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersions. *Int. J. Pharm.*, 54 (1989) 15–25.

Reed, M.C., Behavior of plasticizers in vinyl chloride-acetate resins. *Ind. Eng. Chem.*, 35 (1943) 896–904.

Sakellariou, P., Rowe, R.C. and White, E.F.T., The thermo-mechanical properties and glass transition temperatures of some cellulose derivatives used in film coating. *Int. J. Pharm.*, 27 (1985) 267–277.

Sears, J.K. and Darby, J.R., *The Technology of Plasticizers*, Wiley, New York, 1982, pp.1–150.

Selinger, E. and Brine, C.J., Use of thermal analysis in the optimization of polymeric diffusion barriers in controlled release delivery systems. *Thermochim. Acta*, 134 (1988) 275–282.

Sinko, C.M. and Amidon, G.L., Plasticizer-induced changes in the mechanical rate of response of film coatings: an approach to quantitating plasticizer effectiveness. *Int. J. Pharm.*, 55 (1989) 247–256.

Steuernagel, C.R., Latex emulsions for controlled drug delivery. In McGinity, J.W. (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Applications*, Dekker, New York, 1989, pp. 1–61.

Storey, R.F., Mauritz, K.A. and Dwain Cox, B., Diffusion of various dialkyl phthalate plasticizers in PVC. *Macromolecules*, 22 (1989) 289–294.

Sutter, B., Aqueous Ethyl Cellulose Dispersions for Preparing Microcapsules with Controlled Drug Release. Ph.D. Thesis, University of Düsseldorf, Germany, 1987.