International Journal of Pharmaceutics, 77 (1991) 211–219

IJP 02574

Concept and development of ophthalmic pseudo-latexes triggered by pH

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(Received 30 December 1990)
(Modified version received 5 June 1991)
(Accepted 3 July 1991)

Key words: Cellulose acetate phthalate; Enteric polymer; Polyacid; Solubility parameter; Phase transition system; Pseudo-latex

Summary

The apparent pK_a, acid value and maximum buffer capacity have been calculated for various polyacids generally utilized for enteric coating, in order to select a polymeric model compound for the preparation of pseudo-latexes triggered by pH for ophthalmic application. The solubility of the selected polymer (cellulose acetate phthalate) was estimated from a ternary plot of its solvents vs fractional solubility parameters. Pseudo-latexes were prepared by emulsification of various organic polymer solutions and removal of the solvents by vacuum distillation. The viscosity behaviour of 30% by weight pseudo-latexes was simulated in vitro to show the sharp and high increase of their viscosity vs pH.

Introduction

Colloidal aqueous dispersions such as latexes and pseudo-latexes have been found useful in a wide range of pharmaceutical applications such as film coating and controlled release (Vanderhoff and El-Aasser, 1988). Polymeric latexes are usually prepared from the corresponding monomers by the emulsion polymerization process. However, the presence of residual monomers as well as the residues of emulsifiers, initiators or buffers may render them unsuitable for certain pharmaceutical purposes such as drug delivery to the eye (Gurny, 1981; Gurny et al., 1985; Boye, 1986). Furthermore, polymers such as polyurethane, epoxy, polyester, polypropylene and cellulose derivatives cannot be prepared by emulsion polymerization. An alternative technique for preparing colloidal dispersions from pre-existing macromolecules relies on the emulsification of an organic solution of the polymer in water using emulsifiers, followed by the removal of the solvents by vacuum distillation, to obtain a water-based polymeric dispersion (Vanderhoff et al., 1979). These water-based systems are referred to as 'artificial latexes' or 'pseudo-latexes', as opposed to 'true latexes', made by emulsion polymerization.

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The purpose of this work was to develop a polymeric aqueous dispersion triggered by lachrymal pH. Two rapid screening techniques were used for the selection of a polymeric model compound and the organic solvents required for the preparation of a pseudo-latex made by a solution emulsification process (El-Aasser et al., 1977). The polymeric compound was selected according to parameters calculated from potentiometric titration curves and from dissolution rate data. Solvents for the polymeric compound, which have to be eliminated during the process, were selected by a chart of their three-dimensional fractional solubility parameters.

Definitions and Concepts

A pseudo-latex, like a true latex, is a water-based system characterized by a low viscosity which is independent of the molecular weight of the polymer (El-Aasser et al., 1977). An ophthalmic pseudo-latex triggered by pH is an aqueous polymeric dispersion of low viscosity which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac to form a highly viscous gel (Ibrahim, 1989). This system must not be compared to the Piloplex® preparation (Ticho et al., 1979) which is a true latex of a low polymer content that is retained in the conjunctival cul-de-sac by bioadhesive bonds due to changes in the ionic environment (Plazonnet et al., 1987).

The alkali-thickening phenomenon of anionic latexes was considered for the development of ophthalmic pseudo-latexes triggered by pH. Wesslau (1963) described this effect as an 'inner thickening', which is due to the swelling of the particles by neutralization of the acid groups contained on the polymer chain and the absorption of water. The lachrymal pH values are normally 7.2–7.4, but may rise to pH 9, according to the interval of time between two blinks (Fischer and Wiederholt, 1982). Thus, only colloidal dispersions of anionic polymers will stay under a coagulation value at an acceptable physiological pH to form a gel in the lachrymal pH range (Ibrahim et al., 1988). Ophthalmic dispersions will be obtained by dispersing a high amount (30% w/w) of an anionic polymer in water (pH 4–5). The colloidal dispersion is maintained by keeping the pH below the coagulation threshold (Banker, 1978) and a gel of high viscosity will be obtained above it (Fig. 1).

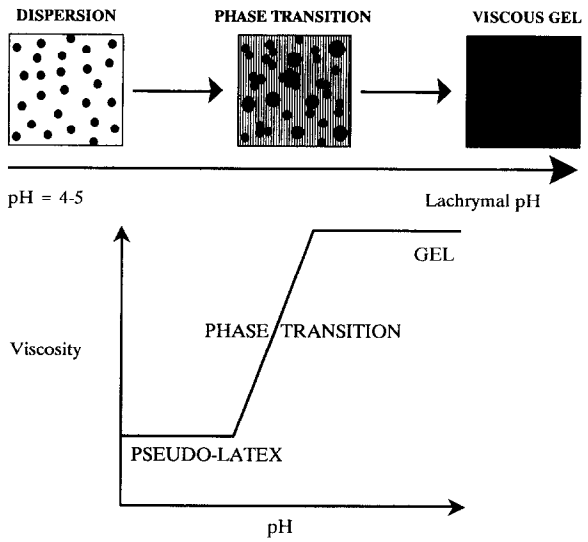

Fig. 1. Schematic representation of the concept of the in situ gel forming system from a pseudo-latex triggered by pH. (□) Aqueous phase; (●) insoluble polymer particle; (▥) gel.

Materials and Methods

Potentiometric titrations of polymers

Eight commercially available polymers were selected for our study: (1) polyvinyl acetate phthalate (PVAP, Colorcon, Orpington, U.K.), (2) a copolymer of vinyl acetate and crotonic acid (Coating CE 5142, BASF, Ludwigshafen, Germany), (3) a copolymer of vinyl acetate and crotonic acid (Mowilith CT5, Hoechst, Frankfurt, Germany), (4) a butyl monoester of poly(methyl vinyl ether/maleic acid) (Gantrez ES-425, GAF, New York, U.S.A.), (5) a copolymer of methacrylic acid and methylmethacrylate (Eudragit S, Röhm Pharma, Darmstadt, Germany), (6) carboxymethylethylcellulose (Duodcel, Freund, Tokyo, Japan), (7) hydroxypropyl methylcellulose phthalate (HPMCP HP-55, Shinetsu, Tokyo, Japan), (8) cel-

lulose acetate phthalate (CAP, Eastman, Kingsport, U.S.A.).

The acid group content of the polymers was determined by dissolving the samples in a mixture of acetone and water (Malm et al., 1953; Hayashi et al., 1970). 1 g of each polymer was added to a titration medium composed of 30 ml of deionized water, 70 ml of acetone (Pro analysis, Merck, Darmstadt, Germany) and 1 g of sodium chloride (Pro analysis, Merck, Darmstadt, Germany). As the resulting pH values are shifted in organo-aqueous solvents, reference pH values were obtained by using a citrate buffer/acetone mixture, to establish the correlation between the chosen medium and an aqueous medium. The titrations were performed by successive additions of 1 ml of 0.1 N sodium hydroxide solution and the pH values were recorded after an equilibration time of 1 min. A pH-meter (CG 822, Schott-Geräte, Feldbach, Switzerland) equipped with a combined micro-electrode (N 600, Schott-Geräte, Feldbach, Switzerland) and calibrated with standard buffers (pH = 2.00 ± 0.01 and pH = 7.00 ± 0.01, at 25 °C) was used for the pH measurements.

Since the apparent pK_a, pK_{app}, depends on the degree of ionization α of the polymer, the apparent pK_a values were determined for $\alpha = 0.50$ (Davis et al., 1986a). The acid value indicates how many mg of potassium hydroxide are necessary for the neutralization of the acid groups contained in 1 g of dry substance (Eur. Ph.). The maximum buffer capacity of a polymer, β_{max}, was calculated analogously from the formula for the maximum buffer capacity of a solution (Martin et al., 1983). The maximum buffer capacity occurs when pH = apparent pK_a, i.e. when $\alpha = 0.50$. β_{max} is calculated using Eqn 1:

$$\beta_{max} = \frac{\Delta B}{\Delta pH} \qquad (1)$$

where β_{max} is the maximum buffer capacity of a polymer, ΔB represents the small increment in g equiv. per l of strong base added to the solution to produce a pH change of ΔpH and ΔpH is the change of pH.

The titration of anionic polymers can be described by Eqn 2 (Bardet and Alain, 1980; Nesbitt et al., 1985):

$$pH = pK_0 + \log\frac{\alpha}{(1-\alpha)} + \Delta pK$$

$$= pK_{app} + \log\frac{\alpha}{(1-\alpha)} \qquad (2)$$

where pK_0 denotes the negative logarithm of the intrinsic ionization constant characteristic of the single ionizable group on the polymer at zero degree of ionization, α is the degree of ionization, ΔpK represents the increase in the electrical free energy of the polyion and its atmosphere on increasing the polyion charge by one unit and pK_{app} is the apparent $pK_a = pK_0 + \Delta pK$.

Solubility determinations

All solvents were purchased either from Merck (Darmstadt, Germany) or Fluka (Buchs, Switzerland). Weighed amounts of polymers were combined with a given volume of solvent in a glass flask at a concentration of 10%. The flasks were shaken continuously over a period of 24 h at 25 °C in a platform incubator shaker (GFL, Hahling, Aigle, Switzerland), after which they were allowed to stand undisturbed for 24 h (Crowley et al., 1966). Then, an inspection of the samples was made and solution behavior recorded as follows:

Soluble:	Occurrence of a homogenous solution.
Partially soluble:	Incomplete solubilization of the polymer by the solvent, as demonstrated by gelation or graininess.
Insoluble:	No apparent action of the solvent on the polymer, as demonstrated by the absence of gelation or swelling.

The solubility parameters (Eqn 3) of the solvents were calculated as fractional parameters (Gardon and Teas, 1976), where x represents the dispersion (d), the polar (p) or the hydrogen-

bonding (h) component of the solvent solubility parameter, δ.

$$F_x = \frac{\delta_x}{\delta_d + \delta_p + \delta_h} \times 100 \qquad (3)$$

Pseudo-latex preparation

An o/w emulsion was formed after phase inversion had occurred and the resulting emulsion was homogenized by a double pass through a high-pressure homogenizer (Büchi 196, Flawill, Switzerland). The organic solvents were removed by vacuum distillation. The temperature was maintained between 30 and 45 °C and vacuum was set between 200 and 300 hPa. The process was stopped after concentration of the dispersion to a polyacid content of 30% by weight.

Particle size determination

Samples of pseudo-latex were diluted with distilled water and particle size was measured with a Nano-Sizer® analyser (Coulter, Coultronics, Andilly, France).

Viscosity determination

All rheological studies were performed at 25 °C with a rotational cup and bob viscosimeter (Rheomat 15T-FC, Contraves, Zürich, Switzerland). Although ascending and descending rheograms were run, only the ascending curves were considered. A shear rate of 35.5 s^{-1}, to cover the largest number of samples to be tested, was taken for the calculation of the apparent viscosity.

Results and Discussion

Titration profiles of polymers

The pH of the aqueous medium to which a polyacid is exposed and the pK_a value(s) of its acidic groups determine the degree of dissociation of the acidic groups, and therefore determine the solubility of the polymer (Schroeter, 1965). Potentiometric titration curves of the polymers which were studied are given in Fig. 2. It

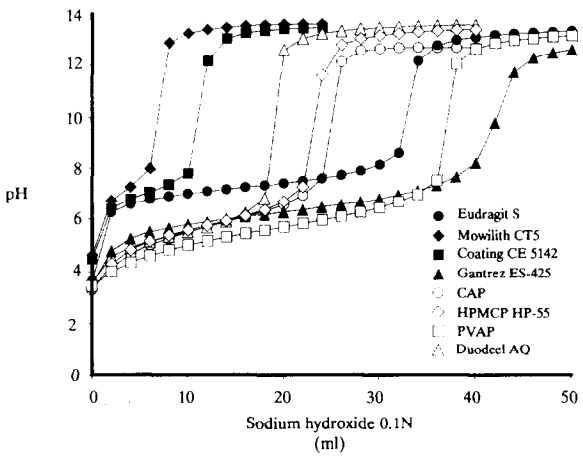

Fig. 2. Potentiometric titration curves of the polyacids.

was assumed that small quantities of free acid from polymer samples did not affect the titration curves. All the polymers tested were soluble in water when completely neutralized. The titration curves in Fig. 2 had the same profiles as the titration curves obtained from acid-containing latex polymers (Verbrugge, 1970).

The equivalence point of titration was obtained from the differential plots of the titration curve for each polymer. Eudragit S had the highest apparent pK_a (7.3) while Duodcel AQ had the lowest (5.5). The apparent pK_a value determined in the acetone-water mixture (70:30 v/v) is 1 unit higher than it would have been in water. According to Delporte (1970), the apparent pK_a value of the model compound should be 2 units lower than the pH of tears (7.2–7.4) to avoid solubilization. Thus, the apparent pK_a value determined in the acetone-water system, should be equal to or lower than 6.2 (Table 1). The acid value above the dissolution point in water should be as low as possible to minimize neutralization time. The maximum buffer capacity, β_{max}, was calculated for a pH change of $\Delta pH = 1$. This value should be as low as possible, to ensure a rapid pH increase of the preparation in the preconeal area to neutral value, for optimal tolerance. Both parameters can be reduced by partial neutralization of the polymer to such an extent that the dissolution point of the macromolecule will just not be reached.

TABLE 1

Titration parameters calculated from potentiometric titration curves

Polymer	Apparent pK_a	Acid value (mg KOH)	Maximum buffer capacity
Duodcel AQ	5.5	107	0.0093
PVAP	5.7	213	0.0130
HPMCP HP-55	5.8	135	0.0097
CAP	5.8	146	0.0089
Gantrez ES-425	6.4	241	0.0168
Coating CE 5142	7.1	67	0.0059
Mowilith CT5	7.1	39	0.0032
Eudragit S	7.3	191	0.0181

Carboxylic polymers are weak acids. Their dissolution which will induce coagulation, when they are in a colloidal form, depends on the pH of the dissolution medium, on their pK_a and on the amount of free acid groups present in each molecule. The rate of dissolution of a polymeric model compound is at least as important as its solubility. On seven anionic polymers, Spitael and Kinget (1979) showed that they could be divided into two groups: polymers with a phthalic acid carboxylic group and those with an acrylic acid group (Fig. 3). The former dissolved at a lower pH value and their dissolution rate increased considerably with a small increase in pH. The latter needed a higher pH for dissolution and the dissolution rate remained rather low.

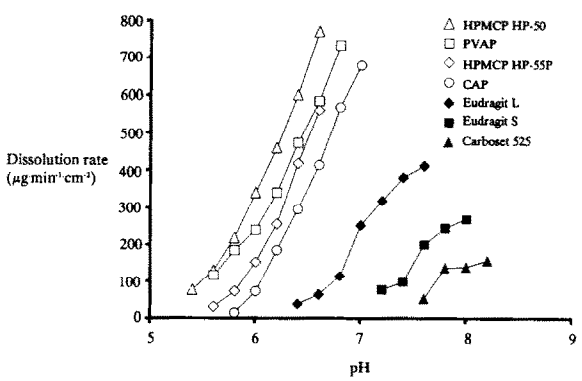

Fig. 3. Dissolution rate of polymer films as a function of pH (Spitael and Kinget, 1979).

Two polymers were selected, CAP and HPMCP. Duodcel AQ has too low a pK_{app} and PVAP has too great an acid value. The dissolution of CAP begins at a higher pH than that of HPMCP (Gurny et al., 1985) and its dissolution rate is lower than that of HPMCP. These two characteristics designated hypothetically CAP as the model compound for the development of ophthalmic pseudo-latexes.

Determination of solvents for CAP

To predict the solubility of CAP, a three-dimensional fractional parameter concept was used (Teas, 1968). By this method, the solubility area of CAP can be determined indirectly by studying polymer-solvent interactions which are assumed to be strongest when the solubility parameter of the polymer is equal to the solubility parameter of the solvent. The positioning of the solvent fractional solubility parameters on a triangular chart according to the relative contribution of its subparameters F_d, F_p and F_h to the total solubility parameter, δ, as calculated by Hansen and Beerbower (1971), enabled us to define an 'area of solubility'.

Published solubility parameter data were used for the calculation of fractional solubility parameters (Crowley et al., 1966; Hansen and Beerbower, 1971; Gardon and Teas, 1976). 82 solvents were tested and the results were plotted on a triangular chart (Ibrahim et al., 1986). A boundary line which separates good solvents from poor solvents and nonsolvents was drawn (Fig. 4). Primary candidate solvents with appropriate evaporation and low water miscibility properties were selected from the area of solubility. It was also possible to use nonsolvents, so that the effective parameter value of the solvent mixture falls within the area of solubility, or to reduce the miscibility of a solvent blended with water.

This method of display possesses a predictive accuracy of 90% (Gardon and Teas, 1976), which was also observed in this study. Four solvent mixtures, with a low water miscibility, forming azeotrope systems and dissolving CAP, were selected by this method (Table 2). A good solvent mixture should have low miscibility with water, a low azeotrope boiling point and a favorable

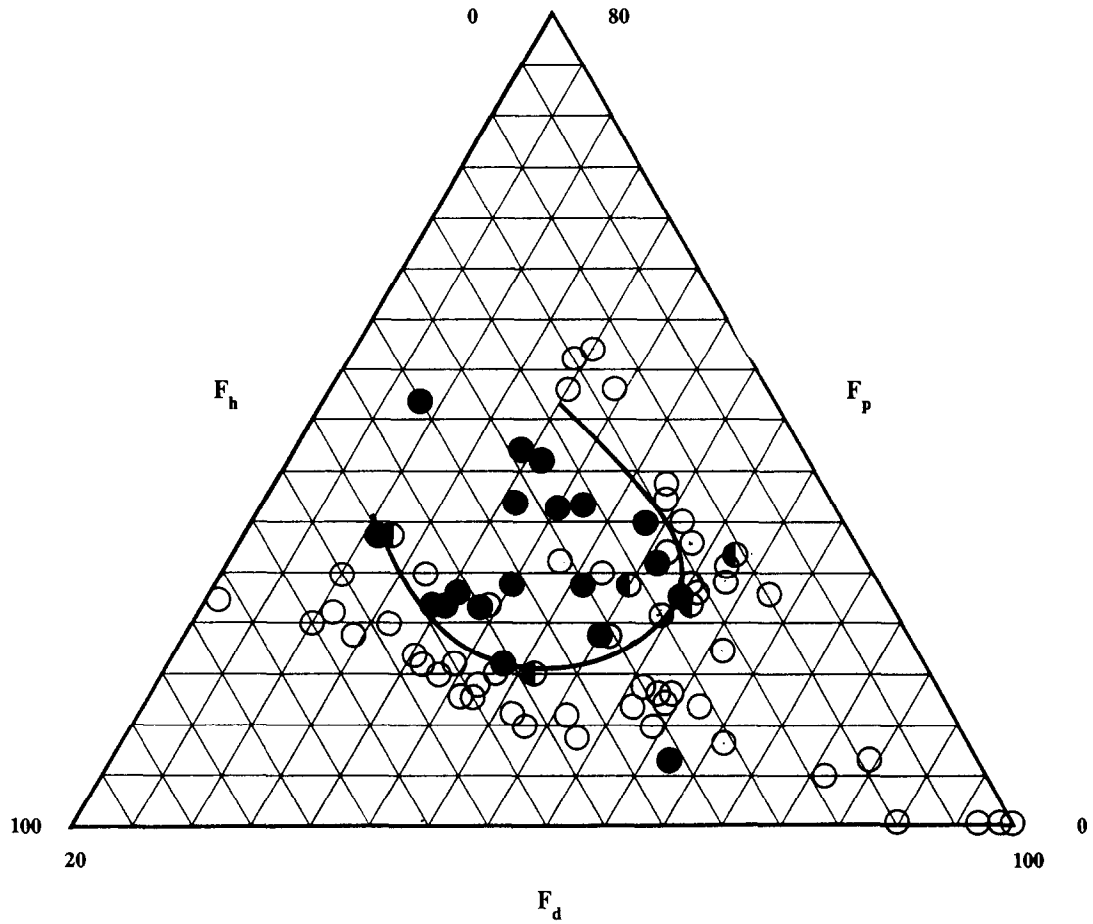

Fig. 4. Solubility of CAP; solubility efficiency of 82 solvents vs the relative intensity of dispersion (F_d), dipolar (F_p) and hydrogen (F_h) interaction forces. (●) Solvents which dissolve the polymer; (◐) solvents which partially dissolve or swell the polymer and (○) solvents which have no apparent interaction with the polymer.

TABLE 2

Solvent blends selected from solubility area

Solvent composition	Solvent proportion (%)	Azeotropic boiling point (°C)	Proportion in azeotrope (wt. %)	Solubility in water (%)
Cyclopentanone	60	93.5	58.0	(low)
Methyl isobutyl ketone	40	87.9	76.0	1.9
Mesityle oxide	80	91.8	65.3	3.3
Ethyl acetate	20	70.4	91.9	10
Cyclohexanone	50	95.0	38.4	5–10
Methyl ethyl ketone	50	73.4	88.0	27.5
Methyl isobutyl ketone	10	87.9	76.0	1.9
Methyl ethyl ketone	90	73.4	88.0	27.5

azeotropic composition. All the solvent mixtures listed in Table 2 were used for the preparation of CAP pseudo-latexes.

A mixture of ethyl acetate and isopropanol (80:20) was used by Davis et al. (1986b). This solvent combination also falls within the solubility area on the triangular chart (Fig. 4), but was not selected because of the miscibility of isopropanol with water. This solvent combination was used for the production of CAP pseudo-latexes (20% of polymer by weight) prepared with emulsifiers which render them unsuitable for an ophthalmic use.

CAP pseudo-latex preparation

The method involves the emulsification of an organic solvent solution of the polymer with an aqueous solution of the surfactant, followed by the removal of the organic solvent and of a fraction of the water (Fig. 5). Poloxamer 407 (Pluronic F127, BASF, Wyandotte, U.S.A.) was used as surfactant and stabilizer. CAP was dissolved in a solvent mixture to form an organic phase of low viscosity suitable for emulsification (Table 2). The

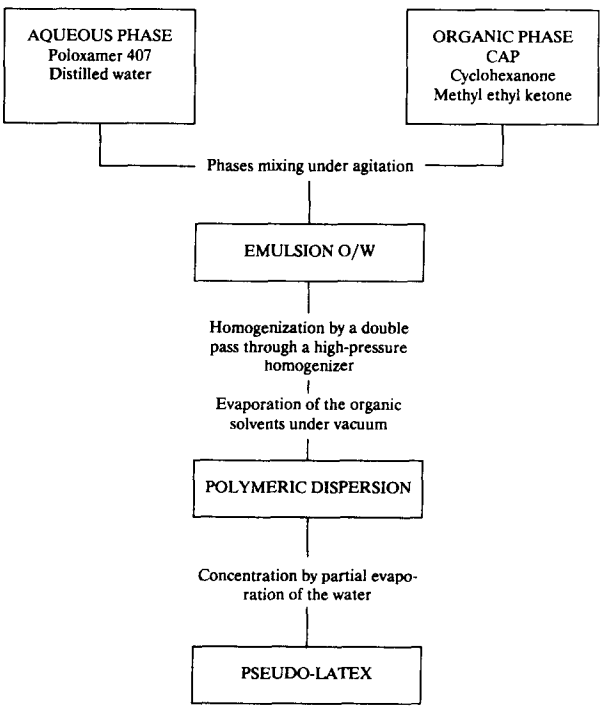

Fig. 5. Diagram for the preparation of a CAP pseudo-latex.

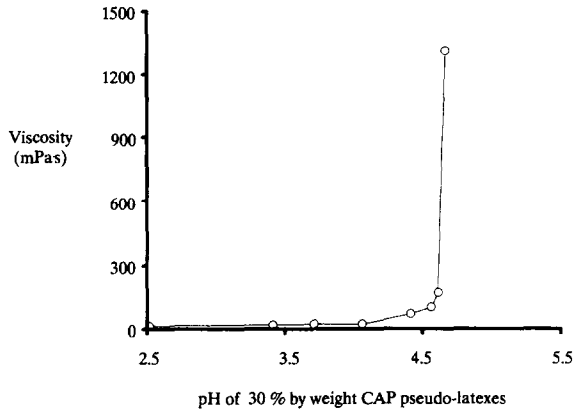

Fig. 6. Viscosity behavior of pseudo-latexes containing 30% of CAP at $D = 35.5\ s^{-1}$.

organic-aqueous volume ratios in the emulsion were determined by the azeotrope systems formed by the solvents with water.

A typical preparation procedure is shown in Fig. 5. CAP (15.0 g) was dissolved in 130 ml of cyclohexanone:methyl ethyl ketone (50:50) and poloxamer 407 (4.5 g) was dissolved in 200 g of distilled water. Both phases were mixed and the resulting emulsion was homogenized before the organic solvents were removed. The final product contained 30% CAP and 9% poloxamer 407 by weight. Without any partial neutralization of the polymer, the final dispersions made from the four solvent systems had average particle sizes between 150 and 200 nm. The pH of the polymeric dispersions was 2.4 ± 0.1 and the viscosities were 20–30 mPa s at a shear rate (D) of $35.5\ s^{-1}$. The large increase in pseudo-latex viscosity, simulated in vitro by increasing the partial neutralization of the polymer before emulsification, was measured for dispersions made from the cyclohexanone:methyl ethyl ketone solvent mixture (Fig. 6).

No significant increase in viscosity was observed below pH 4.4 but a highly viscous gel was already observed at pH 4.8. At pH 4.4 the viscosity of the preparation was approx. 80 mPa s at $D = 35.5\ s^{-1}$ and the degree of neutralization of the polymer $\alpha = 0.10$. Raising the pH by 0.25 units changed the viscosity of the preparation from 80 to 1320 mPa s ($\alpha = 0.18$). This phenomenon shows the sharp increase of the viscos-

ity and the narrow pH range which induces the coagulation of the dispersions.

Conclusion

In this study, the characterization of enteric polymers was carried out using potentiometric titration in an acetone-water medium. Three titration parameters were calculated (pK_{app}, acid value and maximum buffer capacity) to select a model polymeric compound for the preparation of ophthalmic pseudo-latexes triggered by pH. These three parameters allowed us to eliminate a great number of candidates among the commercially available compounds which were tested, but were not sufficient to make a final decision between CAP and HPMCP. A lower dissolution rate and a higher dissolution pH were hypothetically chosen as criteria to finally select CAP rather than HPMCP.

Once the polymeric compound had been selected, its solubility in organic solvents was determined using a triangular chart display of fractional solubility parameters of solvents. Solvent mixtures were used, because no single solvent had all the characteristics of solubilizing CAP, non-miscibility with water and low azeotrope boiling point, which are essential for the process involved. Four solvent mixtures were tested and gave final dispersions of comparable particle size and pH. This screening technique gave more rapid information for the preparation process and will be useful, when the dispersed polymer will be changed in the development of new formulations.

Pseudo-latexes with a CAP content of 30% and a total solid content of 39% (w/w) were prepared. The dispersions exhibited a low viscosity and it was shown, in vitro, that the dispersions form highly viscous gels. The change in viscosity on raising the pH of the medium occurs in a narrow pH range and thus will allow the formation of a gel onto the eye. Therefore, these CAP pseudo-latexes are classified among the ophthalmic phase transition systems as well as thermosetting gels (Miller and Donovan, 1982) and ion-activated gelling polymer vehicles (Rozier et al., 1989).

Although the pK_{app} value in water of CAP was 4.8, coagulation of the dispersion began at pH 4.4, which is 3 pH units below the lachrymal pH. Further investigations would be needed to determine to which pK_{app} value of the polymer, that is closer to the lachrymal pH values coagulation, will still occur. Polymers with a higher pK_{app} value than CAP, such as poly(methyl vinyl ether/maleic anhydride) derivatives, should be interesting candidates for this approach.

References

Banker, G.S., Controlled release of effectors from polymers and microcapsules. In Kostelnik, R.J. (Ed.), *Polymeric Delivery Systems*, Gordon and Breach, New York, 1978, pp. 25–58.

Bardet, L. and Alain, M., Etude conformationnelle par titration potentiométrique d'un haut polymère d'acide acrylique utilisé en pharmacie. *Int. J. Pharm.*, 5 (1980) 91–100.

Boye, T., Développement de nouvelles formes ophtalmiques à libération prolongée et évaluation de la durée de leur activité pharmacologique, Ph.D. Thesis, no. 2176, University of Geneva (1986).

Crowley, J.D., Teague, G.S. and Lowe, J.W., A three-dimensional approach to solubility. *J. Paint Technol.*, 38 (1966) 269–280.

Davis M.B., Ichikawa, I., Williams, E.J. and Banker, G.S., Comparison and evaluation of enteric polymer properties in aqueous solutions. *Int. J. Pharm.*, 28 (1986a) 157–166.

Davis M.B., Garnet, E.P. and Banker, G.S., Preparation and stability of aqueous-based enteric polymer dispersions. *Drug Dev. Ind. Pharm.*, 12 (1986b) 1419–1448.

Delporte, J.-P., Les enrobages entériques. *Pharm. Acta Helv.*, 45 (1970) 525–552.

El-Aasser, M.S., Vanderhoff, J.W. and Poehlein, G.W., Preparation of polymer latexes with mixed emulsifier systems by emulsion polymerization and direct emulsification of polymer solutions. *Coatings Plastics Prep.*, 37 (1977) 92–95.

Fischer, F.H. and Wiederholt, M., Human precorneal tear film pH measured by microelectrodes. *Graef's Arch. Clin. Exp. Ophthalmol.*, 218 (1982) 168–170.

Gardon, J.L. and Teas, J.P., Solubility parameters. In Myers, R.R. and Long, J.S. (Eds), *Treatise on Coatings*, Vol. 2, Part II, Dekker, New York, 1976, pp. 413–471.

Gurny, R., Preliminary study of prolonged acting drug delivery system for the treatment of glaucoma. *Pharm. Acta Helv.*, 56 (1981) 130–132.

Gurny, R., Boye, T. and Ibrahim, H., Ocular therapy with nanoparticulate systems for controlled drug delivery. *J. Contr. Rel.*, 2 (1985) 353–361.

Hansen, C. and Beerbower, A., Solubility parameters. In Standen, A. (Ed.), *Kirk-Othmer Encyclopedia of Chemical Technology*, Suppl. Vol., Wiley, New York, 1971, pp. 889–910.

Hayashi, M., Nagai, T. and Nogami, H., Factors affecting dissolution rate of cellulose acetate phthalate in aqueous solution. *Chem. Pharm. Bull.*, 18 (1970) 2350–2353.

Ibrahim, H., Gurny, R. and Buri, P., Méthodologie pour le choix de solvants dans la fabrication de pseudo-latex à base d'acétophtalate de cellulose. *Proc. 4th Int. Congr. Technol. Pharm.*, Paris, Vol. IV, 1986, pp. 282–290.

Ibrahim, H., Buri, P. and Gurny, R., Composition, structure et paramètres physiologiques du système lacrymal impliqués dans la conception de formes ophtalmiques. *Pharm. Acta Helv.*, 63 (1988) 146–154.

Ibrahim, H., Concept et évaluation de systèmes polymériques dispersés (Pseudo-latex) à usage ophtalmique. Ph.D. Thesis, no. 2369, University of Geneva (1989).

Malm, C.J., Genung, L.B. and Kuchmy, W., Analysis of phthalic acid esters of cellulose and polyvinyl alcohol. *Anal. Chem.*, 25 (1953) 245–249.

Martin, A., Swarbrick, J., Cammarata, A. and Chun, A.H.C., Buffered and isotonic solutions. In Martin, A., Swarbrick, J., Cammarata, A. (Eds.), *Physical Pharmacy*, Lea & Febiger, Philadelphia, 3rd Edn, 1983, pp. 222–244.

Miller, S.C. and Donovan, M.D., Effect of Poloxamer 407 gel in the miotic activity of pilocarpine nitrate in rabbits. *Int. J. Pharm.*, 12 (1982) 147–152.

Nesbitt, R.U., Goodhart, F.W. and Gordon, R.H., Evaluation of polyvinyl acetate phthalate as an enteric coating material. *Int. J. Pharm.*, 26 (1985) 215–226.

Plazonnet, B., Grove, J., Durr, M., Mazuel, C., Quint, M. and Rozier, A., Pharmacokinetics and biopharmaceutical aspects of some anti-glaucoma drugs. In Saettone M.F., Bucci, M. and Speiser, P. (Eds), *Ophthalmic Drug Delivery*, Fidia Research Series, Vol. 11, Liviana Press, Padova, Springer, New York, 1987, pp. 117–139.

Rozier, A., Mazuel, C., Grove, J. and Plazonnet, B., Gelrite®: A novel, ion-activated, in-situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. *Int. J. Pharm.*, 57 (1989) 163–168.

Schroeter, L.C., Coating of tablets, capsules and pills. In Martin, E.W. (Ed.), *Remington's Pharmaceutical Sciences*, Mack, Easton, 1965, pp. 601–602.

Spitael, J. and Kinget, R., Solubility and dissolution, rate of enteric polymers. *Acta Pharm. Technol., Suppl.*, 7 (1979) 163–168.

Teas, J.P., Graphic analysis of resin solubilities. *J. Paint Technol.*, 40 (1968) 19–25.

Ticho, U., Blumenthal, M., Zonis, S., Gal, A., Blank, I. and Mazor, Z., A clinical trial with Piloplex. A new long-acting pilocarpine compound. Preliminary report. *Ann. Ophthalmol.*, 11 (1979) 555–561.

Vanderhoff, J.W. and El-Aasser, M.S., Theory of colloids. In Liebermann, H.A., Rieger, M.M. and Banker, G.S. (Eds), *Pharmaceutical Dosage Forms: Disperse Systems*, Vol. 1, Dekker, New York, 1988, pp. 93–149.

Vanderhoff, J.W., El-Aasser, M.S. and Ugelstad, J., Polymer emulsification process. US Patent 4,177,177 (1979).

Verbrugge, C.J., Mechanism of alkali thickening of acid-containing emulsion polymers. I. Examination of latexes by means of viscosity. *J. Appl. Polym. Sci.*, 14 (1970) 897–909.

Wesslau, H., Zur Kenntnis von Acrylsäure enthaltenden Copolymerdispersionen II. Die Verdickbarkeit Acrylsäure enthaltender Dispersionen. *Makromol. Chem.*, 69 (1963) 220–240.