

Preparation of pseudolatex by nanoprecipitation: influence of the solvent nature on intrinsic viscosity and interaction constant

O. Thioune^a, H. Fessi^{b,*}, J.P. Devissaguet^a, F. Puisieux^a

^aUniversité de Paris-Sud, Laboratoire de Pharmacotechnie et Biopharmacie, URA CNRS 1218, 92290 Chatenay-Malabry, France

^bLaboratoire de Galénique, I.S.P.B. Lyon 1, Av. Rockefeller 69373 Lyon Cedex 08, France

Received 25 July 1996; revised 3 December 1996; accepted 5 December 1996

Abstract

The importance of the nature of two solvents used in a patented method for obtaining aqueous dispersions of polymers is discussed. The principle of the method resides in the fact that a preformed polymer can precipitate as nanospheres when a solution in a water-miscible organic solvent (organic phase) is mixed with water containing surfactants (aqueous phase). To obtain HP55 (hydroxypropyl methyl cellulose phthalate) pseudolatex suitable for coating by this method, i.e. with a high polymer concentration, the amount of polymer in the organic phase was increased, but this caused considerable precipitation of the polymer in large aggregates when the two phases were mixed. Changing the nature of the organic solvent by replacing acetone with a mixture of acetone and water resulted in reducing aggregation. To explain this phenomenon, hypothesis based on viscosity parameters of dilute polymer solutions i.e. the intrinsic viscosity $[\eta]$, and the interaction constant k' , were advanced. The influence of the dielectric constant (ϵ) of the final dispersant medium (a mixture of acetone and water after dispersion of organic phase with aqueous phase) is also discussed. © 1997 Elsevier Science B.V.

Keywords: Intrinsic viscosity; Interaction constant; Hydroxypropylmethyl cellulose phthalate (HP55); Pseudolatex; Nanoprecipitation

1. Introduction

The methodology for obtaining polymeric nanoparticles developed in our laboratory (Fessi

et al., 1992) comprises two main steps: dissolution of the polymer in a water-miscible solvent S1 and dispersion of the obtained solution (polymeric phase) in an aqueous phase (S2) consisting of water with or without surfactant. The polymer then precipitates as nanoparticles and the result-

* Corresponding author.

ing dispersion is filtered on no. 2 sintered glass to eliminate possible aggregates. Finally, it is concentrated by rotary evaporation.

It has been suggested (Stainmesse, 1990) that the mechanism of nanoparticle formation is comparable to the 'diffusion and stranding' mechanism which occurs during spontaneous emulsification (Davies and Rideal, 1963).

According to this mechanism, during the dispersion of the organic phase in the aqueous phase, acetone diffuses rapidly carrying with it the polymer which is still in solution, forming a three-component phase in the immediate vicinity of the interface. As acetone diffuses further into the water, the associated polymer 'stranded' in the water in several possible forms (particles whose size could range from some nm to several mm or large aggregates). These differences, as demonstrated in other studies (Ammoury et al., 1991; Guterres et al., 1995), are related to the polymer concentration in the organic phase. When this is low, dispersions with small particle size can be obtained easily by this method. In contrast, when it is necessary to increase the amount of polymer in the organic phase in order to obtain a final dispersion with a high concentration in polymer, large aggregates appear. This is the main difficulty encountered when this method is used to prepare pseudolatexes for coating (De Labouret, 1987, De Labouret et al., 1995).

It has been shown that, by increasing the polarity (represented by the dielectric constant) of the final dispersant medium, it was possible to reduce aggregation when this method was used to obtain a pseudolatex of poly- ϵ -caprolactone (Stainmesse, 1990).

Thus, one of the objectives of this study was to verify whether increasing the dielectric constant of the final dispersant medium would have similar effects on the preparation of a pseudolatex of hydroxypropyl methylcellulose phthalate (HP55).

In other respects, it is well known that the chains of a dissolved polymer are in different states according to the solvent used. In a good solvent, polymer solutions are characterised by a high intrinsic viscosity $[\eta]$ and a low interaction constant k' . In a study dealing with selection of a suitable solvent for polymers derived from cellu-

lose, it was shown that mixtures of water and different organic solvents were more suitable for dissolving the polymers than organic solvents alone (Arwidsson and Nicklasson, 1990).

In this study, a mixture of acetone and water (solvent B) was used as the solvent for the organic phase in order to determine whether it was a more suitable solvent for HP55 than acetone alone (solvent A). In other words, the question of whether the interactions between polymer chains in the organic phase (which are influenced by the solvents nature) would be related to the particle size was addressed.

2. Materials and methods

2.1. Materials

Solvents: Acetone (Rectapur, Prolabo, France) and different mixtures of Acetone/water. Polymer: Hydroxypropyl Methylcellulose Phthalate (HP55, SEPPIC, France). Surfactant: Sodium dodecyl sulfate (SDS) (texapon L100R, Henkel, France).

2.2. Pseudolatex preparation

Several formulations were developed using the methodology described previously. Solvents for the organic phase were either acetone alone (solvent A) or mixtures of acetone with water in the following proportions: 10%, 20%, 28.5% (solvent B). The initial polymer concentration in the organic phase was varied from 1 to 4%. No surfactant was used in this series of preparations; so, the variation of the yield was influenced only by the nature of the solvents.

Preparations using solvent A and solvent B were called, respectively, formulation I and formulation II.

2.3. Pseudolatex characterization

The followed characteristics were determined for a pseudolatex obtained with a good yield, i.e. which formula could be used for an industrial scale-up. The pH was determined by using a pH meter M64 (Radiometer, Paris, France). The vis-

cosity was measured with a Rheometer type CSL 100 (RHEO 99, Champlan, France) at 20°C. The specific gravity was measured according to the method described in European Pharmacopoeia (1980). Particle size was measured with a Nano-sizer Coulter N 4 (Coultronic, Andilly, France).

2.4. Intrinsic viscosity

The intrinsic viscosity of polymers was measured from solutions in acetone alone or in a mixture of acetone and water. Solution concentrations ranged from 0.1 to 1%. A Ubbelohde viscosimeter (Schott-Geräte GmbH, Germany) was used to perform measurements. With this apparatus, the efflux time of a defined volume of solution is determined and this allows different viscosity parameters to be deduced.

Using the dynamic viscosity of the solution η and that of the solvent η_0 , the specific viscosity η_{sp} could be determined according to Eq. (1)

$$\eta_{sp} = \frac{\eta - \eta_0}{\eta_0} \quad (1)$$

which can be written:

$$\eta_{sp} = \frac{\rho k t - \rho_0 k t_0}{\rho_0 k t_0} \quad (2)$$

where t and t_0 are the efflux times for the solution and for the solvent respectively; ρ and ρ_0 their densities. It is admitted that in cases of dilute solutions, ρ and ρ_0 can be considered as equivalent. Thus Eq. (2) becomes

$$\eta_{sp} = \frac{t - t_0}{t_0}$$

Intrinsic viscosity $[\eta]$ and interaction constant k' were determined by linear regression analysis from the plot of η_{sp}/c vs. c according to Eq. (3) (Alfrey, 1947)

$$\eta_{sp}/c = [\eta] + k'[\eta]^2 c \quad (3)$$

$[\eta]$ and k' were obtained from the intercept and the slope, respectively.

2.5. Dielectric constant (ϵ)

The dielectric constants of different mixtures of acetone and water were determined in a Q meter (Type M 803 A, Ferisol France). These correspond to the final dispersant phases of the pseudolatexes. The percentages of water in the samples tested were varied from 58.3 to 76%.

3. Results and discussion

Fig. 1 shows that there was a correlation between the polymer concentration in the organic phase and the amount of polymer precipitation as aggregates. The latter increased when the amount of polymer in the organic phase was increased. However, there was a significant difference in the results obtained when the solvent for the organic phase was pure acetone (solvent A) or a mixture of acetone and water (solvent B). A maximum of 28–28.5% water could be included in solvent B, because beyond this limit, HP55 precipitated.

These preparations were made with a ratio of S2/S1 of 2 as indicated in the original description of the method (Fessi et al., 1992). It should be noted that the replacement of a part of acetone by water resulted in a greater proportion of water in the final dispersion in formulation II than in formulation I. Under these conditions, the dielectric constant of the final dispersant medium was

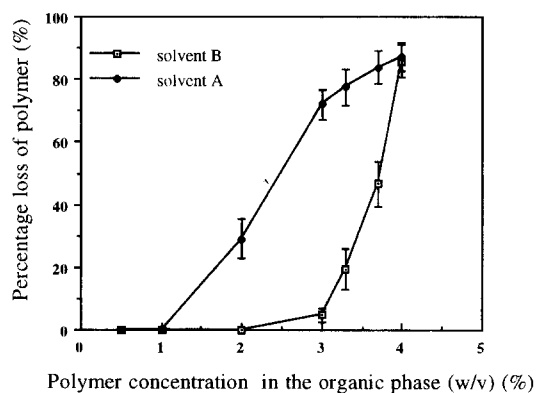


Fig. 1. Percentage loss of polymer as aggregates as a function of polymer concentration in the organic phase and solvent nature.

Table 1
Water amount in the organic phase (%)

	Formulation I	Formulation II		
Water amount in the organic phase (%)	0	10	20	28.5

not the same for the two formulations and it was not possible to determine which parameter (solvent nature or dielectric constant) was responsible for the differences in the results.

So, another series of preparations in which the only difference between the two formulations was the solvent nature were made. The formulations used are represented in Table 1. The polymer concentration in the organic phase was 3% and the dielectric was 66.5 for both formulations. The results obtained are given in Fig. 2.

When solvent A was used, more than 70% of HP55 precipitated as aggregates. Increasing the amount of the water in the organic phase resulted in a reduced proportion of aggregates (from about 70% to less than 7%), i.e. an improvement in the yield of the preparation. In addition, it was possible to reduce the amount of acetone used of about 29%. These are two main advantages to be considered in the case of an industrial scale-up of the method.

Fig. 3 represents the linear regression lines for HP55 in the two solvent systems. Values of $[\eta]$ and k' are shown in Table 2.

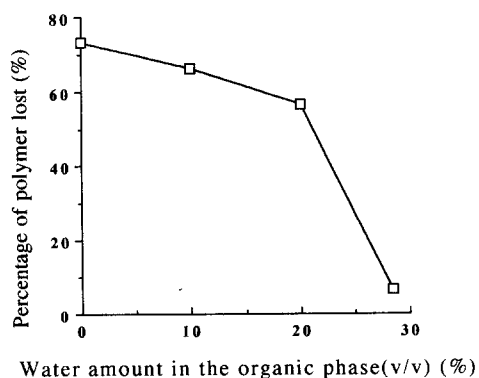


Fig. 2. Percentage loss of polymer as aggregates as a function of the water amount in the organic phase.

According to the values of k' , it seemed that the polymer chains interactions were weaker in solvent B than in solvent A. When $[\eta]$ was considered, the results obtained suggested that the polymer chains were organized in such a way that their hydrodynamic volume was greater in solvent B than in solvent A. Moreover, the polymer in solvent B was close to precipitation, so when the organic phase was introduced in the aqueous phase, the diffusion of a little amount of acetone in water (and/or water in acetone) caused the precipitation of the polymer. Thus, it was advanced the hypothesis according which, when the polymer precipitated from its solution in solvent B, less aggregation occurred. In contrast, since the polymer chains were much more associated in solvent A, the polymer precipitated as larger particles. This phenomenon was not observed in the case of low polymer concentrations in the organic phase (up to 1%), when the interactions between polymer molecules were less because of the high dilution.

As far as the dielectric constant (ϵ) was concerned, the values of this parameter for the final dispersant medium were varied in formulation I

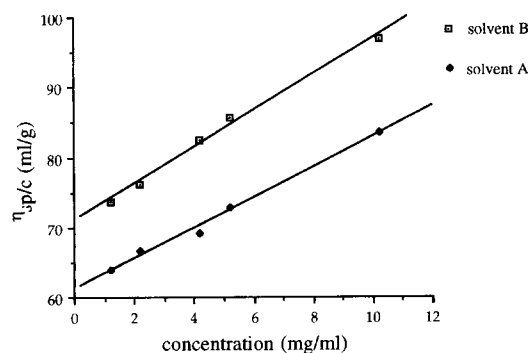


Fig. 3. Specific viscosity/concentration, η_{sp}/c versus concentration for HP55 in acetone and a mixture of acetone and water (28.5% water amount).

Table 2

Values of intrinsic viscosity $[\eta]$ and interaction constant k' for HP55 in acetone and a mixture of acetone and water (28.5% water amount).

Solvent	$[\eta]$ (ml/g)	k'
Solvent A	60.72	0.60
Solvent B	70.89	0.52

and all formulations II by adding different amounts of water in the aqueous phase. According to the results obtained, as shown in Fig. 4, it is not possible to conclude that an improvement in the yield is only due to an increase in ϵ value. When the dielectric constant for formulation I was higher or equal to those of formulations II, the yield obtained with the latter was better. The decrease in aggregation was observed in both formulations, but it was more important when solvent B was used. This seemed to indicate that it was the nature of the solvent of the polymeric phase which was the more important, and in particular its influence on the polymer in solution, reflected by the values of the intrinsic viscosity and the interaction constant.

The characteristics of the dispersion obtained when solvent B (with 28.5% water amount) was used are shown in Table 3. These characteristics are comparable with those of the latex which are used for coating. The viscosity is low, despite the

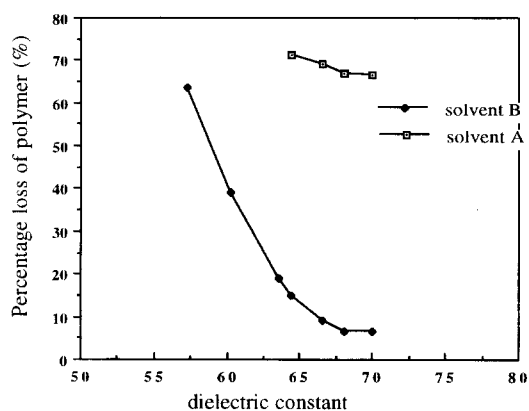


Fig. 4. Percentage loss of polymer as aggregates as a function of the dielectric constant of the final dispersant medium. (n.d.: not done).

Table 3

Summary of the characteristics of the dispersion obtained with formulation II (solvent B with 28.5% water amount)

Characteristics	Values	
	t_0	$t_0 + 2$ years
pH	3.5	2.3
Viscosity (mPas)	2.44	3.72
Final polymer concentration (%)	17	17
Relative density (d_4^{20})	1.01	1.01
Particle size (nm)	300 ± 58	330 ± 69

high polymer concentration and this facilitates the spraying and prevents the blockage of the nozzle of the coating apparatus

Another interesting characteristic is the particle size of the latex. It has been demonstrated that a small particle size is of a great advantage with regard to sedimentation (Lehmann, 1988) and film formation process (Dillon et al., 1951; Brown, 1956; Nagakami et al., 1991).

4. Conclusion

The nanoprecipitation method for obtaining aqueous dispersions of HP55 seems to be interesting owing to its simplicity and ease to use. This study has shown the importance of the choice of solvent for the polymeric phase, using intrinsic viscosity $[\eta]$ and interaction constant k' measurements. In particular, it was demonstrated that a mixture of acetone and water was more suitable than acetone alone for obtaining an optimal yield of the preparation. Moreover, when industrial scale-up of this method is considered, replacing a part of the acetone by water would represent a considerable advantage.

Acknowledgements

Acknowledgement The authors thank Dr G. Barratt (Laboratoire de Pharmaceutique et Biopharmacie URA CNRS 1218, Chatenay-Malabry, France), Prof. J.L. Grossiord and Prof. G. Couaraze (Laboratoire de Physique URA CNRS 1218,

Chatenay-Malabry, France) for their invaluable help.

References

- Alfrey, T., The influence of solvent composition on the specific viscosities of polymer solutions. *J. Coll. Sci.*, 2 (1947) 99–114.
- Ammoury, N., Fessi, H., Devissaguet, J.P., Dubrasquet, M. and Benita, S., Jejunal absorption, pharmacological activity and pharmacokinetic evaluation of Indomethacin loaded poly(D,L-lactide) and poly(isobutyl-cyanoacrylate) nanocapsules in rats. *Pharm. Res.*, 8 (1991) 101–105.
- Arwidsson, H. and Nicklasson, M., Application of intrinsic viscosity and interaction constant as a formulation tool for film coating. 1. Studies on ethylcellulose 10 cps in organic solvent systems. *Int. J. Pharm.*, 58 (1990) 73–75.
- Brown, G.L., Formation of films from polymer dispersions. *J. Polym. Sci.*, 22 (1956) 423–434.
- Davies, J.T. and Rideal, E.K., (Eds.), Disperse systems and adhesion. In *Interfacial Phenomena*, 2nd edn., Academic Press, New York, 1963, pp. 343–450.
- Dillon, R.E., Matheson, L.A. and Bradford, E.B., Sintering of synthetic latex particles. *J. Coll. Sci.*, 6 (1951) 108–117.
- De Labouret, A., *Mise au point de pseudolatex acryliques et transposition semi-industrielle de leur fabrication. Etude de leurs propriétés filmogènes et application à l'enrobage*. D. E. A de Pharmaceuterie industrielle et Biopharmacie, Paris–Sud, 1987.
- De Labouret, A., Thioune, O., Fessi, H., Devissaguet, J.P. and Puisieux, F., Application of an original process for obtaining colloidal dispersions of some coating polymers. Preparation, characterization, industrial scale-up. *Drug Dev. Ind. Pharm.*, 21 (1995) 229–241.
- European Pharmacopoeia*, 2nd edn. part 1–V. 6.4. Maisonneuve Ed, Paris, 1980.
- Fessi, H., Devissaguet, J.P., Puisieux, F. and Thies, C., Process for the preparation of dispersible colloidal systems of a substance in the form of nanoparticles. *US. Pat.* 5, 118, 528, 1992.
- Guterres, S.S., Fessi, H., Barrat, G., Devissaguet, J.P. and Puisieux, F., Poly(D,L-lactide) nanocapsules containing Diclofenac: formulation and stability study. *Int. J. Pharm.*, 113 (1995) 57–63.
- Lehmann, K.O.R., Chemistry and application properties of polymethacrylate coating systems. In McGinity, J.W. (Ed.), *Drugs and the Pharmaceutical Sciences*, Vol. 36, Marcel Dekker, New York, 1988, pp. 163–245.
- Nagakami, H., Keshikawa, T., Matsumura, M. and Tsukamoto, H., Application of aqueous suspensions and latex dispersions of water-insoluble polymers for tablets and granule coatings. *Chem. Pharm. Bull.*, 39 (1991) 1837–1842.
- Stainmesse, S., Etude galénique d'un nouveau procédé d'obtention de vecteurs colloïdaux submicroniques à partir d'une protéine ou d'un polymère synthétique. *Thèse de Pharmacie no. 129*, Paris-Sud, 1990.