DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(2), 229-241 (1995)

APPLICATION OF AN ORIGINAL PROCESS FOR OBTAINING COLLOIDAL DISPERSIONS OF SOME COATING POLYMERS. PREPARATION, CHARACTERIZATION, INDUSTRIAL SCALE- UP

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ABSTRACT

An original process for obtaining colloidal dispersions were used to prepare pseudolatex of coating polymers (Eudragit E 100 and Eudragit S 100). The method consists in introducing under magnetic stirring a solution of the polymers in a water-miscible solvent into an aqueous solution containing surfactant. In these conditions, polymers precipitate spontaneously in nanospheres. Investigations of some manufacturing parameters (initial polymer concentration, nature and concentration of surfactant) have allowed development of formulae for a semi-industrial scal-up. Characteristics of dispersions were also determined.

INTRODUCTION

Film-forming products are widely used in the pharmaceutical coating area. Economic and ecological considerations are encouraging industrials to replace organic polymer solutions with aqueous-based coating products (1, 2, 3) such as synthetic latexes and pseudo-latexes

(4, 5). These are colloidal aqueous dispersions of solid and spherical particles of about 0.1μm-1μm mean diameter.They are characterized by low viscosity and a high polymeric concentration (20%-30% polymer weight/dispersion weight).

Synthetic latexes are prepared with water-soluble and emulsionable monomers which can be polymerized in-situ (6). The polymeric particles of the colloidal dispersions so obtained are homogeneous and practically monodisperse, but they have to be thoroughly purified to eliminate different residues of polymerization which are potentially toxic (monomers and oligomers, catalysts, polymerization reagents, etc....).

Pseudolatexes (artificial latexes) are usually prepared by an emulsification-evaporation technique: a polymer solution in a water-immiscible organic solvent is finely emulsified in an aqueous phase containing surfactants; then the emulsion is heated to eliminate the solvent. The size of polymeric particles obtained, greater and not as homogeneous as those of a synthetic latex, depends on the fineness of the original emulsion and the concentration of polymer in the organic phase. This method has two advantages: the possibility of using various preformed polymers, natural or semi-synthetic (6), and so to avoid the presence of residues or reagants from polymerization. However, it is often necessary to use surfactants at high concentrations and instruments which require lot of energy to obtain fine emulsions.

These methods have both disadvantages. Therefore an original process has been developed using nanoprecipitaton of preformed polymers into nanospheres form without any emulsification step. It is possible to prepare nanospheres from several preformed polymers in this way.

This technique consists in introducing a polymeric phase composed of a polymer solution (liquid S 1) into a precipitating medium composed of a surfactant solution (liquid S 2) which is a non-solvent for the polymer but miscible with S1. This one and part of S 2 are then eliminated to obtain a concentrated colloidal suspension of polymeric nanoparticles (7).

The object of this work was to use the nanoprecipitation process for the preparation of coating polymer in colloidal dispersions which could be used in aqueous medium, with the following properties:

- particles with small size and narrow polydispersity
- a high polymer concentration (20 %- 30 %) and a low viscosity
- good stability of the colloidal dispersions

We first prepared dispersions in batches of about 0.5 l, followed by scale-up to 15 l. The properties of the dispersions obtained were studied.

MATERIALS AND METHODS

Two acrylic copolymers were studied: the first was composed of dimethylaminoethyl-methacrylate and neutral acid methacrylic ester, hydrosoluble at pH≤ 5 (Eudragit E, Röhm Pharma GmbH, Weiterstadt, R.F.A.) (8); the second of methacrylic acid and acid methacrylic ester, soluble in intestinal juice (pH ≥ 7)(Eudragit S, Röhm Pharma GmbH, Weiterstadt, R.F.A.)(8). Surfactants used to stabilize suspensions were: sodium dodecyl sulfate (SDS) (Texapon L 100^{R}, Henkel, France), Tween 80 (Laserson et Sabety, Etampes France), benzethonium chloride (Sigma Chemical Co., U. S. A).

The organic solvents were acetone and isopropyl alcohol (Rectapur, Prolabo, France).

Preparation of suspensions

Two techniques were developed. The only difference between them is the mode of introduction of the organic phase into the aqueous phase (9).

- Technique A

The organic phase was introduced by the means of a funnel into the precipitating medium which was stirred magnetically (figure 1).

- Technique B

The organic phase was introduced by an air-spray gun type Kremlin J3 used without compressed air, connected to a peristaltic

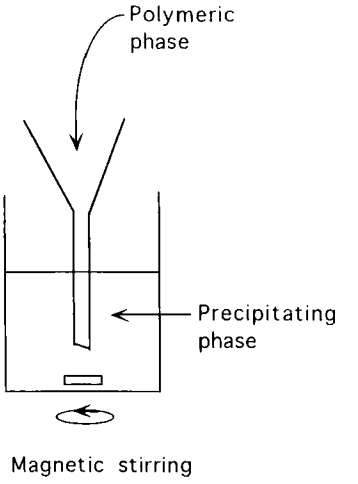

FIGURE 1
Technique A

pump working at maximum speed. It was immersed in the aqueous phase under stirring (Figure 2).

In these two techniques, nanoparticles formation was spontaneous. The suspension obtained was then concentrated and filtered on n°2 sintered glass to eliminate possible aggregates.

Semi-industrial scale-up.

Batchs of 15l volume were prepared using two peristaltic pumps with variable output and two air-spray guns. A turbine stirrer was used for this step. Several batchs were put together after being concentrated. Two different apparatus could be used for concentration:

-Rotavapor 150 (Büchi Laboratoriums-technik AG, Flawil, Suisse) with a 10 l round-bottomed flask which allowed evaporation of 1- 2 liters per hour used with a water-bath at 50°C

-Evaporator LUWA type N(Luwa S.A., Zurich, Suisse). This allowed continuous solvent evaporation under vacuum(Figure 3).

The suspension was introduced into the evaporator at the top of a tube surrounded by a heating element and it was uniformely dispersed

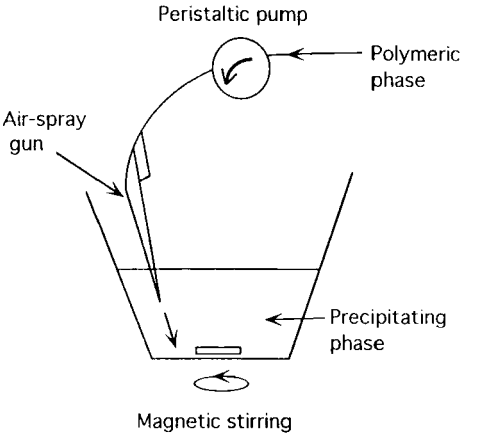

FIGURE 2
Technique B

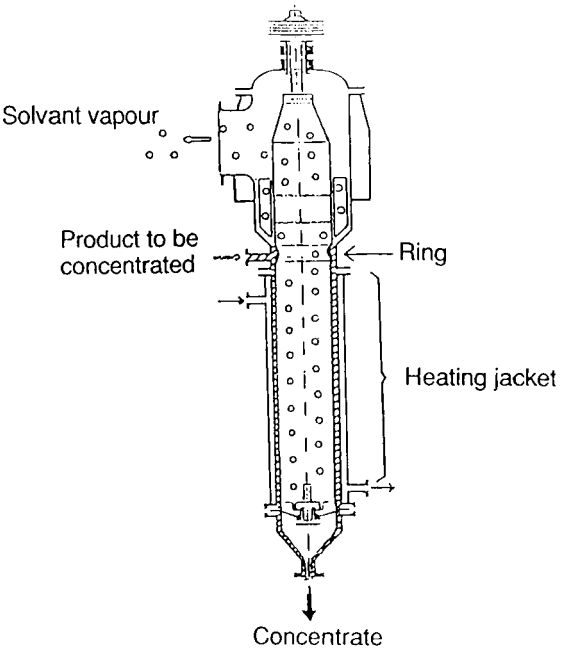

FIGURE 3
Luwa Thin Film Evaporator

by a ring. The rotor blades (not represented in the figure) spread it over the heating surface as a thin mobile film. The dispersions flowed down under the influence of the gravity and at the same time was concentrated by rapid evaporation.

Eudragit E 100 dispersions were concentrated with Rotavapor 150 because they were not stable at the temperatures encountered in the LUWA.

Batchs of Eudragit S 100 suspensions were pooled and concentrated in the LUWA. If necessary, a second evaporation in the Rotavapor 150 was carried out to obtain the desired polymer concentration.

Dispersion characteristics

These were studied with reference to the Röhm Pharma monographs for aqueous dispersions.

The aspect of the dispersions was estimated with the naked eye.

The polymer concentration was determined by gravimetry (a precise amount of the dispersion was dried in oven at 50° C for 12 h).

N. B : The concentration of commercially available organic solutions of Eudragit E 100 and S is about 12.5%.

The pH of the dispersions was determined using a pH meter M 64 (Radiometer, Paris, France) and their viscosity was measured with a Brookfield viscosimeter (Prolabo, Paris) at 20° C.

The specific gravity was measured according to the method described in European Pharmacopia I.

The residual solvent levels were determined by gas chromatography.

Particle size was measured by analytical ultracentifugation. This method has the advantage of giving information on particle size distribution. It also allows a granulometric analysis of dispersions containing nanoparticles of about 10 to 100 nm in diameter.

Dispersion stability

Since an increase in the particle size destabilizes dispersions by causing sedimentation, the evolution of the dispersions was followed for

six months of storage at ambient temperature or at 4°, 35° and 50°C. Eudragit S 100suspensions were followed for two years. Particle size was measured using a "Nanosizer" Coulter N 4 (Coultronics, Andilly, France).

RESULTS AND DISCUSSIONS

Optimization of the process

One disadvantage of the process described by Fessi et al. (7) is the low concentration of polymer in the dispersion after solvent evaporation (5% w/v) . To obtain a higher final concentration (20 % w / v), it is necessary to remove a considerable amount of water. The use of a more concentrated polymer solution seemed to be the best way to obtain a more concentrated final dispersion. However, in practice, this was not the case. The mixing of polymer solution S1 in non solvent S2 resulted in polymer precipitation as large aggregates of various sizes (several nm to a few μm). Nanoparticles were formed in a low yield compared with the initial amount of polymer.

Therefore, we searched for the best experimental conditions for obtaining colloidal suspensions as concentrated as possible in polymer with a yield of particle formation as close as possible to 100%.

Several preparation parameters were studied:

- the choice of the initial polymer concentration
- the nature and concentration of the surfactants

Polymer concentration

Two steps were necessary to determine the optimal polymer concentration:

a) We prepared a series of dispersions to study the relationship between polymer precipitation and the polymer concentration in phase S1.

b) The formulae which gave a level of precipitation lower than 25% were then prepared by technique B to optimize the yield.

Technique A was used for this study because it was very simple and easy to apply to small volumes (≤ 500 ml).

TABLE 1

Percentage Loss of Polymer as Aggregates as a Function of Initial Polymer Concentration.

	%Polymer	% Loss
Eudragit E 100	2	0.05
	2.5	5
	3	25
	6	88
Eudragit S 100	1	0
	1.5	22
	2	57
	2.5	71

The results are shown in Table 1. The yield was inversely related to the polymer concentration.

Dispersions containing Eudragit E 100 at 2.5% or Eudragit S 100 at 1.5% were prepared by technique B without any loss by precipitation. These polymer concentrations were chosen for further studies.

The surfactants tested were those commonly used for the preparation of aqueous polymer dispersions:

- anionic surfactant: Sodium dodecyl sulfate (SDS).
- non ionic surfactant: Tween 80
- cationic surfactant: Benzethonium chloride

SDS was used in all the precedent experiments. The others were tested with the aim of obtaining a better yield. A series of preparations using technique A allowed us compare the percentage of polymer lost with different surfactants.

Table 2 shows that SDS gave the lowest percentage loss and for this reason it was retained.

TABLE 2

Percentage Loss of Polymer as a Function of Surfactant Type.

	% of polymer lost	
	Eudragit E 100	Eudragit S 100
SDS	5	3
Tween 80	53	16.5
Benzethonium chloride	9.9	96.5

As far as Eudragit S 100 dispersions were concerned, our experiments showed that surfactant was not necessary for their preparation; but to ensure stability during long-term storage, 2% of SDS was used. In contrast, surfactant (5% of SDS) was necessary for the preparation of Eudragit E 100 dispersions.

Scale-up

The formulation studies of two polymers described above allowed us to select dispersion formulae which were used for scale-up studies. Dispersions of about 15l were prepared by technique B. Table 3 shows the two compositions used.

Several batchs are put together and first concentrated by the LUWA to a polymer concentration of about 3%. A second evaporation was carried out in a 10l Rotavapor.

Dispersions characteristics.

These are represented in Table 4.

Dispersion stability

- Eudragit E 100dispersions.

The suspensions were translucid with a yellowish color. No sedimentation was observed after six months at either ambiant

TABLE 3

Formulae of Dispersions used for Scale-up studies.

	Eudragit E 100	Eudragit S 100
polymeric phase		
- solvent	100 ml acetone	100ml(acet./isopro.)(4/6)
- polymer	2.5 g	1.5 g
precipitant phase		
- water	200 ml	200 ml
- surfactant (SDS)	200 mg	30 mg

TABLE 4

Summery of dispersions characeriristics

	Eudragit E 100	Eudragit S 100
aspect	fluid translucid yellowish colour	very fluid whitis blue reflection
polymer concentration	18 - 20 %	25 %
pH	10.2	5.2
viscosity	24 mPa.s	4 mPa.s
specific gravity	$d_4^{20} = 1.022$	$d_4^{20} = 1.049$
residual solvents	acetone =74 ppm	acetone < 10 ppm isopropanol < 10 ppm
size	40 nm ± 20	100 nm ± 30

temperature, 4°C or 35°C. Although the dispersions appear limpid, particle size determinations (ultracentrifugation, Nanosizer) show the presence of particles and refute the hypothesis of solubilization.

Storage at about 50°C or in the presence of some plastisizers such as Citroflex or triacetine caused the appearence of a non redispersible and compact solid which filled the entire volume of the dispersion. With time, water was released from this solid which became extremely dense. The system was then composed of two phases. This kind of instability is irreversible.

Table 5

Effect of Storage on Dispersion Particule Size of Eudragit S 100.

Conservation time	Size
0	100 nm ± 30
2 years	150 nm ± 30

- Eudragit S 100dispersions

During storage, their aspect remained very fluid. Some particles and small aggregates sedimented at the bottom of the recipient; these were easily redispersed by mechanical stirring. This phenomena was observed when dispersions were stored for six months at ambient temperature, 4°C and 35°C or two years at ambient temperature.

Particle size measured after two years proved that these dispersions were extremely stable (Table 5).

CONCLUSION

An original process has allowed the preparation of aqueous dispersions of two acrylic derivatives: Eudragit E 100and Eudragit S. The industrial scale-up of the process is very easy and only requires the use of classical industrial equipment. From test batchs of 500 ml volume, we succeeded in preparing dispersions of about 100 l.

The properties of these dispersions, coupled with their stability, suggest that they could be used in coating processes. This process could be applied to several polymers. At the moment, the possibility of producing colloidal dispersions from some cellulose derivatives is being studied.

ACKNOWLEDGEMENTS

The authors thank Laboratories Röhm-Pharma for their help and particulary Dr. LEHMAN and PETEREIT for their invaluable advice.

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