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Pseudolatex preparation using a novel emulsion–diffusion process involving direct displacement of partially water-miscible solvents by distillation

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Abstract

Pseudolatexes were obtained by a new process based on an emulsification–diffusion technique involving partially water-miscible solvents. The preparation method consisted of emulsifying an organic solution of polymer (saturated with water) in an aqueous solution of a stabilizing agent (saturated with solvent) using conventional stirrers, followed by direct solvent distillation. The technique relies on the rapid displacement of the solvent from the internal into the external phase which thereby provokes polymer aggregation. Nanoparticle formation is believed to occur because rapid solvent diffusion produces regions of local supersaturation near the interface, and nanoparticles are formed due to the ensuing interfacial phase transformations and polymer aggregation that occur in these interfacial domains. Using this method, it was possible to prepare pseudolatexes of biodegradable and non-biodegradable polymers such as poly(D,L-lactic acid) and poly(ε-caprolactone), Eudragit E, cellulose acetate phthalate, cellulose acetate trimellitate using ethyl acetate or 2-butanone as partially water-miscible solvents and poly(vinyl alcohol) or poloxamer 407 as stabilizing agent. A transition from nano- to microparticles was observed at high polymer concentrations. At concentrations above 30% w/v of Eudragit E in ethyl acetate or cellulose acetate phthalate in 2-butanone only microparticles were obtained. This behaviour was attributed to decreased transport of polymer molecules into the aqueous phase.

Keywords: Pseudolatex; Nanoparticles; Emulsion-diffusion method; Partially water-miscible solvent; Eudragit E; Cellulose acetate phthalate

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1. Introduction

In general, colloidal aqueous polymer dispersions can be prepared by emulsion polymerization of a monomer (latexes) or by emulsification of a

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water-insoluble polymer (pseudolatexes or artificial latexes). Emulsion polymerization is normally limited to liquid-insoluble precursor monomers that can polymerize in an aqueous medium in the presence of free radical initiators. After polymerization, potentially toxic by-products such as residual monomer or oligomers, and traces of initiator, are frequently present in the dispersion.

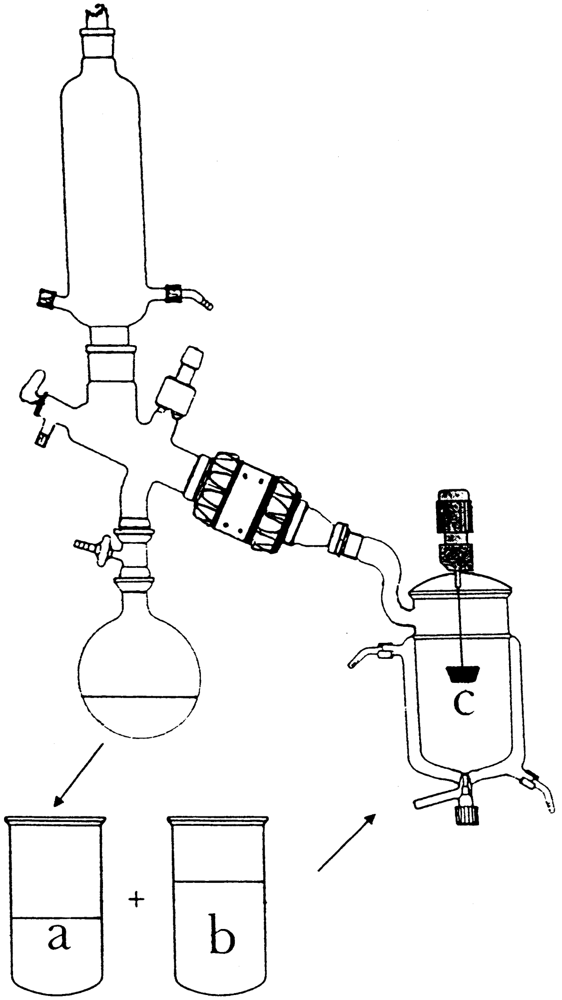

Fig. 1. Schematic representation of the pseudolatex preparation process. (a) The solution of polymer in the partially water-miscible solvent (previously saturated with water); (b) the solution of stabilizer in water (previously saturated with solvent); (c) the oil-in-water emulsion formed of the dispersion of (a) and (b). The distilled solvent is recovered and used for the preparation of other batches.

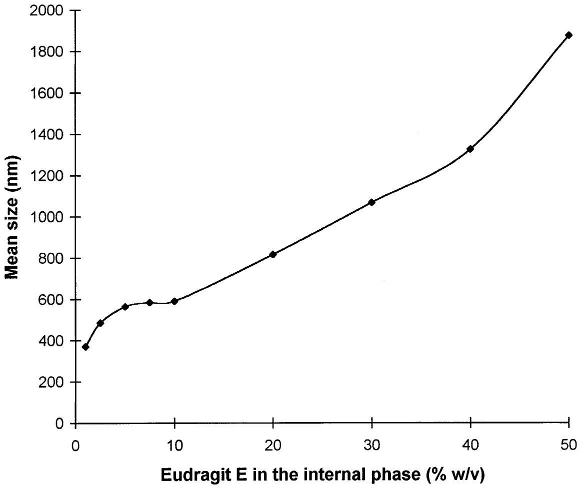

Fig. 2. Influence of the percentage of Eudragit E in the internal phase (ethyl acetate) on the mean particle size. All batches were prepared with 5% w/v of PVAL as stabilizer in the external phase and a stirring rate of 1500 rev./min.

For this reason the processes starting with preformed polymer are preferred for pharmaceutical use (El-Aasser et al., 1977; Banker, 1982; Bindschaedler et al., 1983; Hogan, 1995; Wheatley and Steuernagel, 1997).

Pseudolatexes are typically prepared by the emulsification–evaporation technique patented by Vanderhoff et al. (1979): a polymer solution in a water-immiscible organic solvent is emulsified in an aqueous phase containing emulsifiers. This crude emulsion is then submitted to a high energy source, e.g. ultrasound radiation, or is passed through homogenizers, high pressure dispersers, colloid mills, etc. The polymer emulsion resulting from such treatment is very stable and contains very small droplets (below 0.5 μm diameter). This emulsification procedure is followed by the removal of the solvent by vacuum steam distillation, producing a fine aqueous dispersion of polymeric particles averaging less than 0.5 μm (generally 0.1–0.3 μm). Commercially, pseudolatex products of ethylcellulose, cellulose acetate phthalate and other cellulosics are prepared by this technique. Stabilizers play an important role in the preparation and stability of colloidal polymer dispersions. They facilitate the formation of the emulsion and prevent agglomeration and coalescence of the dispersed polymer particles during solvent evaporation and storage (Wheatley and Steuernagel, 1997; Banker and Peck, 1981; Bindschaedler et al., 1983).

Recently, a new method, the emulsification–diffusion, has been proposed to prepare nanoparticles from preformed polymers (Quintanar-Guerrero et al., 1996). This process involves the emulsification of a partially water-miscible solvent (previously saturated with water), containing the polymer, in an aqueous phase (previously saturated with the solvent), containing a stabilizer. The subsequent addition of water to the system causes the solvent to diffuse into the external phase, resulting in the aggregation of polymer in nanoparticles. This process is of interest from a technological standpoint, since it does not need comminuting forces (as in Vanderhoff's technique), it is highly efficient, reproducible and easy to scale up (Quintanar-Guerrero et al., 1998). However, to obtain a high polymer concentration in the final dispersion, it is necessary to remove the solvent and a considerable amount of water.

The aim of the present study was to investigate the possibility of developing a technique to obtain pseudolatexes with high polymer concentration based on the emulsification–diffusion process. In light of recent experimental evidence suggesting that the mechanism of formation of

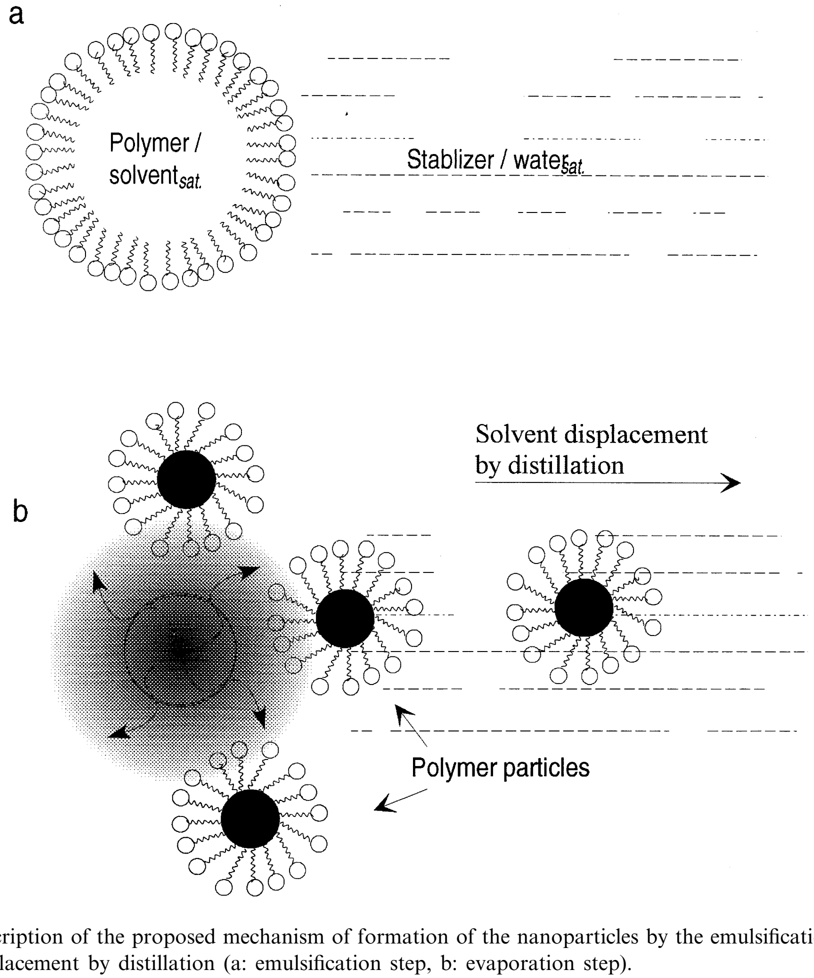

Fig. 3. Schematic description of the proposed mechanism of formation of the nanoparticles by the emulsification–diffusion method based on solvent displacement by distillation (a: emulsification step, b: evaporation step).

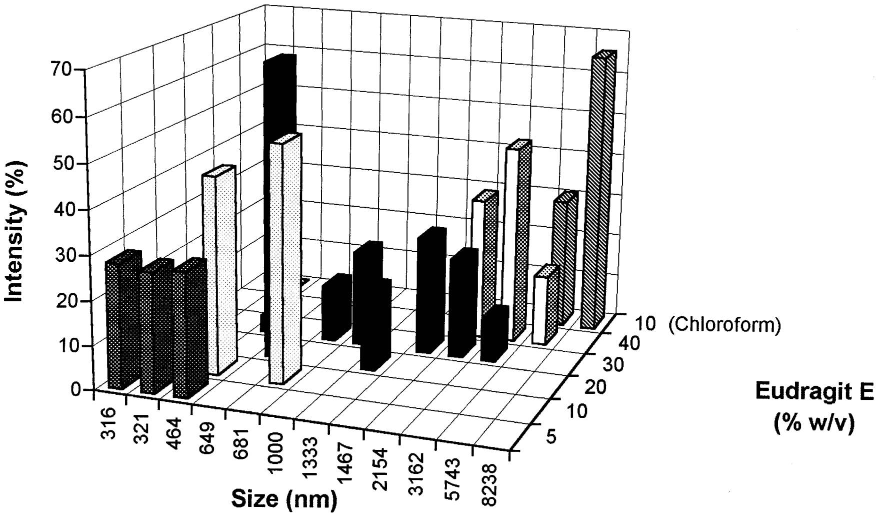

Fig. 4. Particle size distribution of batches prepared with different concentrations of Eudragit E in ethyl acetate and at 10% w/v in chloroform.

colloidal particles by this method is due to diffusion alone (Quintanar-Guerrero et al., 1997), we now propose a new technique based on the displacement of partially water-soluble solvent of the internal phase into the external phase, by direct vacuum steam distillation of the oil-in-water emulsion. Ethyl acetate and 2-butanone were used as partially water-miscible solvents because of their widely recognized low toxicity, good solubilizing properties and low boiling points (Opdyke, 1974; ICH, 1996). Poly(vinyl alcohol) and poloxamer 407 were selected as stabilizer agents for the emulsification and to stabilize the final dispersion, because of their water solubility, suitability for ingestion and compatibility with the system. Furthermore, they can act as annealing agents in the dosage coating formulation (Banker, 1982; Koller and Buri, 1987; Yamaoka et al., 1995). Several polymers were tested, in particular Eudragit® E-100 which is not yet available as a commercial colloidal dispersion.

The influence of some preparative variables on nanoparticle size, such as polymer and stabilizer concentration, stirring rate and internal/external phase ratio, was investigated in order to control and to optimize the process.

2. Materials and methods

2.1. Materials

Eudragit® E was a generous gift from Röhm (Darmstadt, Germany). Cellulose acetate trimellitate (CAT) was obtained from Eastman (Kingsport, USA). Cellulose acetate phthalate (CAP) ethylene vinyl acetate copolymer (EVAC, vinyl acetate content 40%) and ethyl cellulose (EC, η^{25} (toluene/ethanol 80:20) = 45 mPa s) were purchased from Fluka (Buchs, Switzerland). Poly(D,L-lactic acid) (PLA) (Medisorb®, 100 D,L) was supplied by Medisorb (Cincinnati, OH). Poly(ε-caprolactone) (Tone® 767) was obtained from Union Carbide (Danbury, USA). The stabilizing agents were poly(vinyl alcohol) (PVAL) (Mw 26 000) (Mowiol® 4-88, Hoechst, Frankfurt-am-Main, Germany) and poloxamer 407 (Pluronic® F-127, BASF, Ludwigshafen, Germany). The partially water-soluble solvents, ethyl acetate ($\eta^{20} = 1.372$; water solubility = 10 mg/ml) and 2-butanone ($\eta^{20} = 1.378$; water solubility = 275 mg/ml), were of HPLC and of analytical grade, respectively (Fluka). Distilled water was purified using a Milli-Q system (Millipore, Bedford, MO). All other chemicals were of analytical grade and used without further purification.

2.2. Methods

2.2.1. Pseudolatex preparation

Ethyl acetate (or 2-butanone) and water were mutually saturated for 1 min before use in order to ensure initial thermodynamic equilibrium of both liquids. Typically, 4 g of Eudragit E were dissolved in 40 ml of water-saturated ethyl acetate

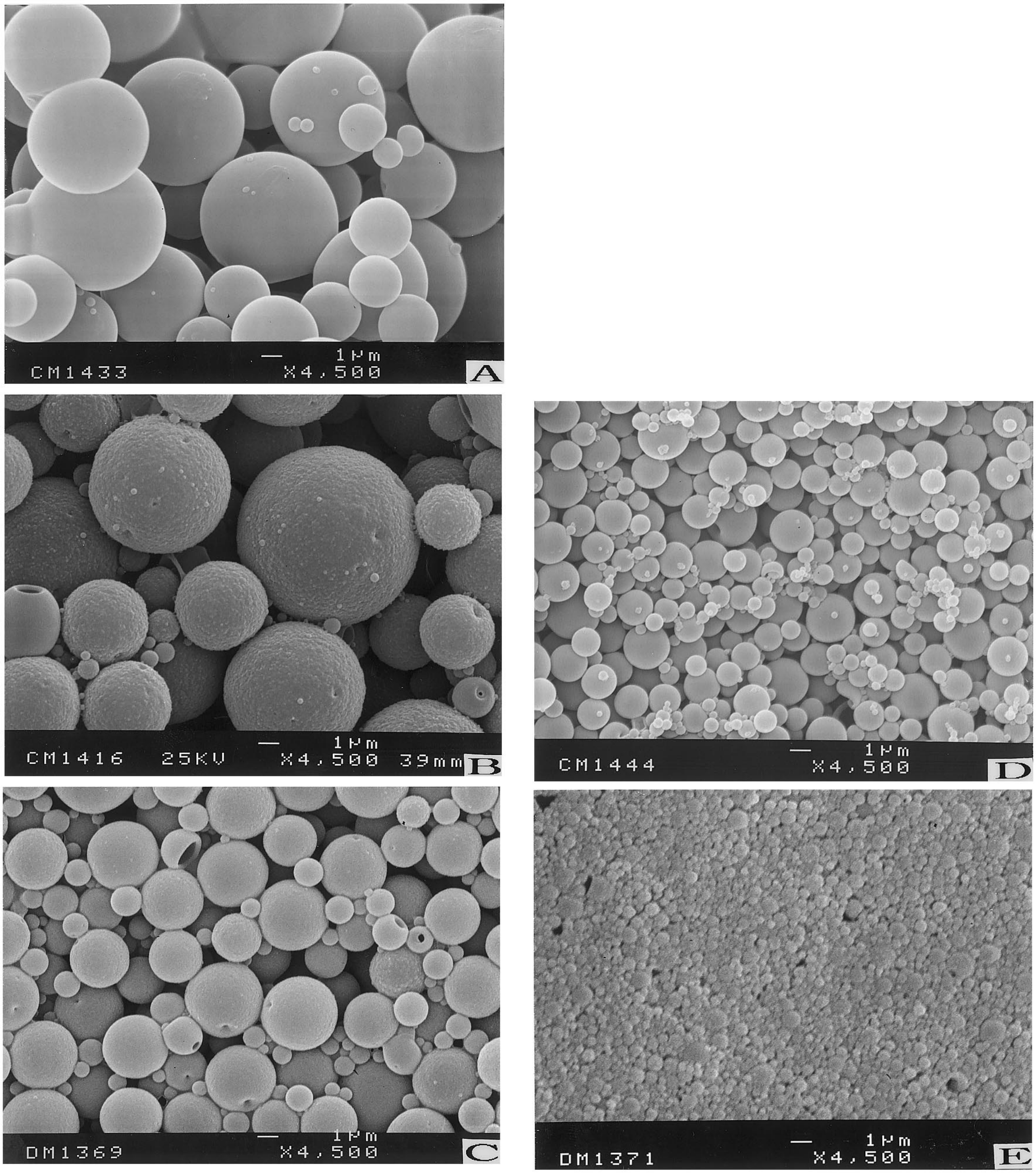

Fig. 5. Scanning electron micrographs of Eudragit E particles prepared at different concentrations in the internal phase (× 4500): (A) 10% w/v in chloroform; (B) 40% w/v in ethyl acetate; (C) 30% w/v in ethyl acetate; (D) 20% w/v in ethyl acetate; (E) 10% w/v in ethyl acetate.

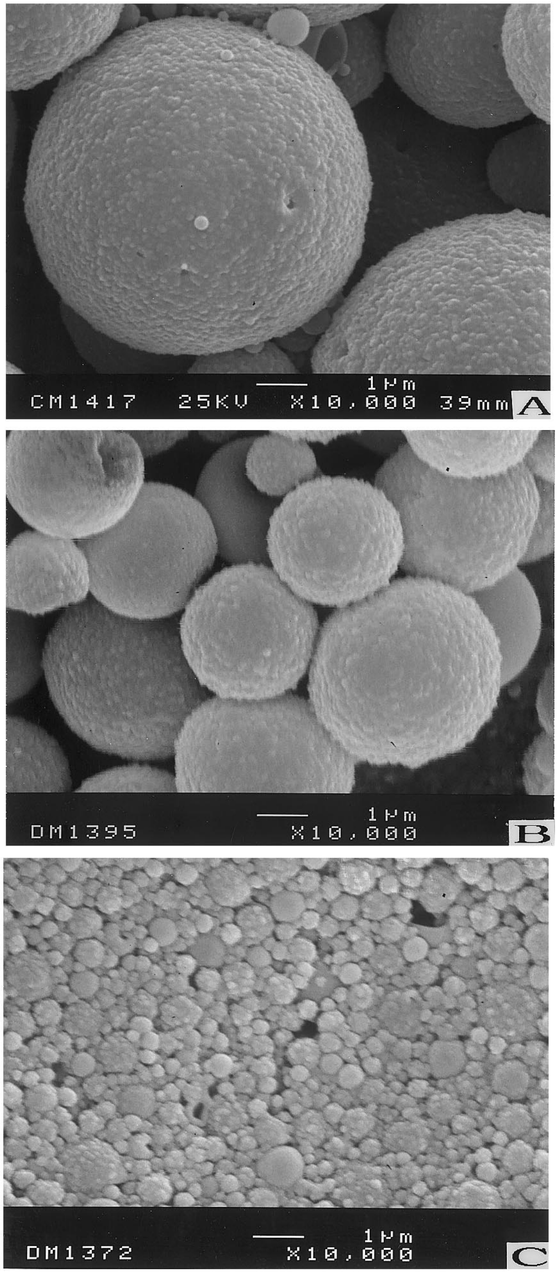

Fig. 6. Scanning electron micrographs showing the surface morphology of Eudragit E particles prepared with ethyl acetate at different concentrations (× 10 000): (A) 40% w/v; (B) 30% w/v; (C) 10% w/v.

and this organic solution was emulsified with 80 ml of a 5% w/v PVAL ethyl acetate-saturated aqueous solution, using a propeller stirrer (Heidolph-Elektro, KG type E-60, propeller: IKA 1381, Germany) at 1500 rev./min for 10 min. The oil-in-water emulsion formed was subjected to vacuum steam distillation at 35°C and 70 mmHg until

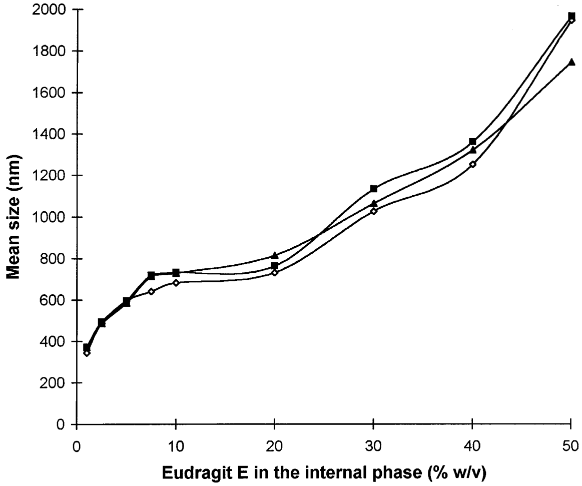

Fig. 7. Influence of the internal/external volume ratio on the mean particle size for batches prepared at different Eudragit E concentrations. ▲, ratio 1:2; ◇, ratio 1:3; ■, ratio 1:4.

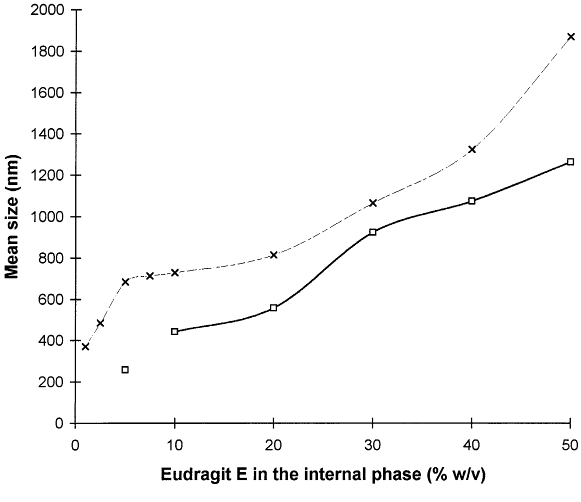

Fig. 8. Effect of stirring type on mean particle size for batches prepared at different concentrations of Eudragit E with high speed stirrer (Ultra turrax) at 8000 rev./min. The dashed line corresponds to the data obtained with the propeller stirrer at 1500 rev./min.

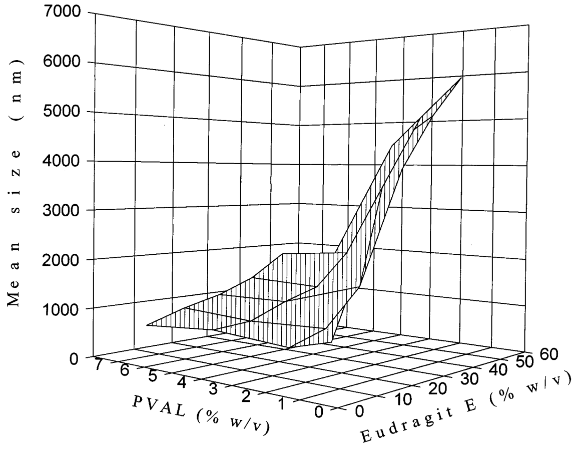

Fig. 9. Three-dimensional graph representing the effect of PVAL concentration in the external phase and Eudragit E concentration in the internal phase on mean particle size.

complete solvent evaporation. Generally, the solvent was recovered and used to prepare new batches. A schematic description of the nanoparticle preparation process is shown in Fig. 1. Several formulations were prepared using the above-mentioned method by varying the stirring type, the polymer and stabilizer concentration and the internal/external phase volume ratio. Some batches were prepared using chloroform as solvent in order to compare the particle size obtained with this poorly water-soluble solvent ($\eta^{20} = 1.447$; water solubility = 0.007 g/ml).

2.2.2. Particle size analysis

The average particle size and polydispersity index (scale from 0 to 9) were determined using a Coulter® Nanosizer (Coulter Electronics, Harpenden, UK). Measurements were made in triplicate for all the batches prepared. In some cases, the particle size distribution was analyzed with a Model N4 submicrometer particle sizer (Coulter Electronics).

2.2.3. Scanning electron microscopy (SEM)

A concentrated aqueous dispersion of nanoparticles was finely spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with a gold layer (~ 20 nm thick). The surface morphology of the nanoparticles was observed by SEM using a JSM-6400 scanning electron microscope (JEOL, Tokyo, Japan).

3. Results and discussion

The proposed technique enabled preparation of submicron particles of Eudragit E at concentrations up to 30% w/v in ethyl acetate using 5% w/v of PVAL in the external phase (Fig. 2). These data suggest that it is possible to form pseudolatexes from a conventional oil-in-water emulsion by simple solvent displacement during distillation

Table 1
Examples of nanoparticles produced by the emulsification–diffusion process[a]

Batch no.	Polymer	Solvent	Stabilizer (% w/v)	Stirring rate (rev./min)	Mean size (nm ± C.V.)	Pd
1	Eudr. E	EtAc	PVAL (2.50)	1500	573 ± 3.0	4
2	Eudr. E	EtAc	PVAL (1.25)	1500	590 ± 2.8	4
3	Eudr. E	EtAc	PVAL (2.50)	8000	345 ± 1.9	4
4	Eudr. E	EtAc	PVAL (1.25)	8000	409 ± 2.3	4
5	PCL	EtAc	PVAL (5.00)	1500	543 ± 2.1	3
6	EVAC	EtAc	PVAL (5.00)	1500	435 ± 2.0	5
7	PLA	EtAc	PVAL (5.00)	1500	472 ± 1.1	2
8	EC	EtAc	PVAL (5.00)	1500	2470 ± 6.9	6
9	EC	2-Butanone	Poloxamer 407 (5.00)	1500	1670 ± 7.8	5
10	CAP	2-Butanone	Poloxamer 407 (5.00)	1500	260 ± 1.1	2
11	CAP	2-Butanone	Poloxamer 407 (1.25)	1500	308 ± 1.3	4
12	CAT	2-Butanone	Poloxamer 407 (5.00)	1500	811 ± 2.7	7

[a] Internal phase: 40 ml (polymer, 10% w/v); external phase: 80 ml; C.V., coefficient of variation (%) ($n = 3$); Pd, polydispersity (index expressed from 0 to 9).

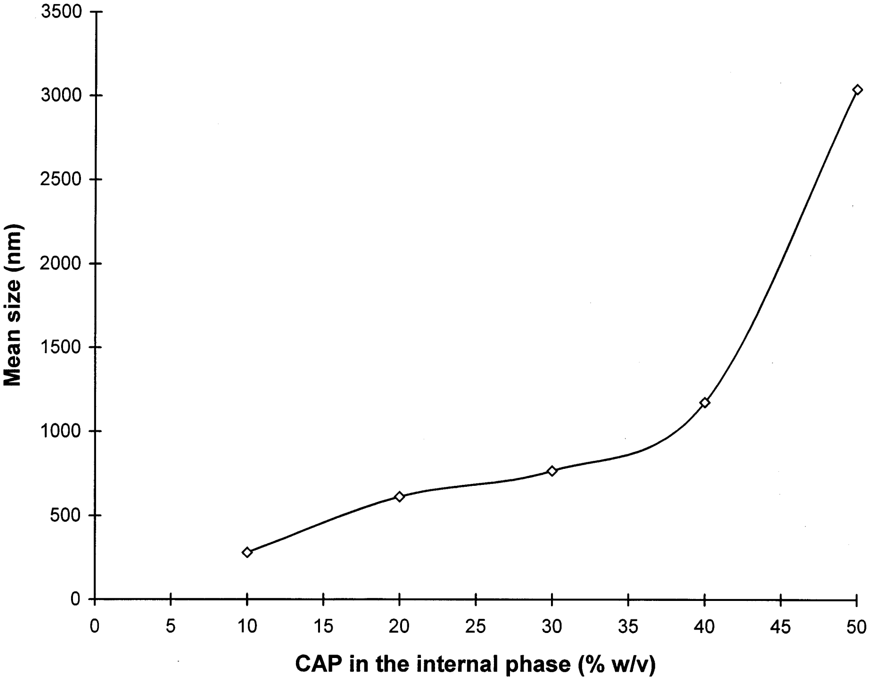

Fig. 10. Influence of the percentage of cellulose acetate phthalate in the internal phase (2-butanone) on mean particle size. Batches prepared with 5% w/v of poloxamer 407 in the external phase. Propeller stirrer rate at 1500 rev./min.

without requiring a homogenization step. Thus, Bodmeier and McGinity (1988) have established that the rate of polymer precipitation is significantly affected by the rate of diffusion of the organic solvent into the aqueous phase. This diffusional motion is closely related to the solvent/non-solvent/polymer interactions. Organic solvents of low water solubility, e.g. chloroform, result in slow precipitation and microparticles particles will be formed by the solvent loss from the surface of the droplet. Once the limiting concentration for polymer precipitation is reached, phase separation will occur from the interface and each droplet will form a particle. In earlier work, we established that, using the emulsion–diffusion technique, each emulsion droplet will form several nanoparticles (Quintanar-Guerrero et al., 1997). Since the solvent is partially water-miscible and both internal and external phases are mutually saturated, solvent diffusion is thought to be rapid during distillation. We propose that nanoparticle formation occurs since this high solvent flux produces regions of local supersaturation near the interface, and nanoparticles are formed due to the phase transformation and polymer aggregation that take place in these regions. A schematic representation of this chemical instability mechanism is shown in Fig. 3.

The formation of nanoparticles is highly dependent on the polymer concentration in the internal phase, when high concentrations of Eudragit E in the ethyl acetate were used (above 30% w/v), only microparticles were obtained. The particle size was similar to those prepared using chloroform as polymer solvent (Figs. 4 and 5A,B). When the Eudragit concentration was reduced, the presence of particles of colloidal size was observed. The particle distribution shown in Fig. 4 indicates an apparent transition between micro- and nanoparticles. With a Eudragit concentration of 30% w/v, two populations were present, with the microparticle form being predominant; at 20% w/v, the proportion of nanoparticles was higher, and finally when the concentration was $\leq 10\%$ w/v, only nanoparticles were formed. The micrographs in Fig. 5C–E seem to confirm this transition. The most likely explanation of this behaviour is the tendency of the ‘protonanoparticles’ generated during diffusion to coalesce at high polymer concentrations. They are more abundant and are highly concentrated at the interface. The probability that they can collide and coalesce among themselves, or with the interfaces, is greater than at low concentrations. Furthermore, the high viscosity and low limiting concentration for polymer precipitation at the interface will provoke a decrease of solvent diffusion and hence fewer polymer molecules will be carried into the aqueous phase. Therefore, the formation and stabilization of individual ‘protonanoparticles’ at these concentrations is reduced. An argument in favour of these assumptions is the morphological surface of the particles (Fig. 6A–C) which is very rough and is apparently formed by the overlapping of small polymer aggregates, produced, presumably, during solvent diffusion.

Fig. 7 shows the relationship between particle size and % w/v of Eudragit E in the ethyl acetate for batches prepared with different internal/external volume ratios (1:2, 1:3, 1:4) at a fixed concentration of stabilizer (PVAL 5% w/v). No difference was observed between the slopes, suggesting that the particle formation is not affected by (1) globule packing in the emulsion, (2) nonsolvent volume and (3) initial volume of solvent (arising from the saturation) in the external phase. On the other hand, a decrease of the particle size (Fig. 8) was observed when the Ultra-Turrax® stirrer was used at 8000 rev./min. This stirring effect has been attributed to the formation of a finer and more homogeneous emulsion that permits a decrease of the thickness of the polymer-saturated region and allows, to a certain extent, the formation and stabilization of smaller particles (Quintanar-Guerrero et al., 1996).

The influence of PVAL concentration in the external phase on particle size at different Eudragit concentrations in the internal phase was also evaluated. Experiments were planned using a simple Latin square design ($n=20$). The results are shown in Fig. 9. At concentrations $\leq 30\%$ w/v of Eudragit, there was no significant difference of particle size for any PVAL concentration. Nanoparticles were always obtained at concentrations $\leq 20\%$ w/v of Eudragit including the lowest PVAL concentrations (1.25% w/v). When the Eudragit concentration was above 30% w/v, the particle size was drastically increased for the batches prepared with PVAL concentrations $\leq 2.5\%$ w/v revealing aggregation by an insufficient protective effect at these concentrations. It is important to point out that some of these pseudolatexes (batches 1–4 in Table 1) were concentrated (12.5% of total solids) and used in pilot coating processes using a Hi-Coater HCT 20 Mini (Lödige, Paderbun, Germany). Coated tablets shown a transparent glossy continuous film which was firmly attached to the tablet. These preliminary results seem to indicate that PVAL can serve as an annealing agent to the Eudragit E pseudolatexes.

A series of batches were prepared in order to evaluate the feasibility of the proposed method for other polymers. Some illustrative data are summarized in Table 1. As shown, nanoparticles were obtained with most of the polymers tested, showing that the method can be applied to several non-biodegradable polymers commonly used in pharmaceutical coating and to biodegradable polymers. In contrast, it was not possible to prepare nanoparticles with ethylcellulose, this polymer formed solutions of high viscosity which, as indicated above, tend to form large particles by decreasing the transport of polymer molecules into the aqueous phase. It should be noted that the method is not restrictive to ethyl acetate and PVAL. Other partially water-soluble solvents such as 2-butanone and stabilizers such as poloxamers can also be used. The key requirement is that the stabilizing agent allows the formation of stable emulsions with the partially water-soluble solvent and that it does not avoid coalescence during solvent displacement. Of particular interest is the preparation of nanoparticles of cellulose acetate phthalate (CAP) using 2-butanone and poloxamer 407. Fig. 10 shows that at concentrations $\leq 30\%$ w/v of CAP in the butanone and using 5% of poloxamer 407 in the external phase, it was possible to obtain nanoparticles of this polymer.

4. Conclusions

The present study has shown that it is possible to prepare pseudolatexes from a conventional oil-in-water emulsion without requiring homogenization, by direct displacement of a partially water-miscible solvent during distillation. This approach has clear advantages over the existing methods, namely: (a) the use of pharmaceutically acceptable organic solvents, e.g. ethyl acetate or butanone; (b) the possibility of solvent reuse; (c) it may be adaptable to several coatings polymers, e.g. Eudragit E, cellulose acetate phthalate, etc.; (d) simple implementation and easy scaling up (no need for high energy sources); (e) high reproducibility.

The formation mechanism is attributed to an inherent chemical instability of the system. The diffusion of solvent from the internal to the external phase during distillation causes the appearance of regions of local polymer supersaturation near the interface, and nanoparticles are then formed due to the phase transformation and aggregation that occur in these regions. A transition between micro- and nanoparticles was observed for the Eudragit E/ethyl acetate/PVAL and the cellulose acetate phthalate/2-butanone/poloxamer 407 systems, which was dependent on the polymer concentration in the internal phase. Therefore, an optimization step would be required for each polymer/solvent/stabilizer system in order to find the component ratio necessary to produce only nanoparticles.

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