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Influence of the preparation conditions on poly(ethylcyanoacrylate) nanocapsule formation

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Abstract

Poly(ethylcyanoacrylate) (PECA) nanocapsules suitable for use as drug delivery systems were prepared by in situ polymerization, adding the monomer to an organic phase and subsequent mixing of the latter to an aqueous phase containing a nonionic surfactant. Different preparation conditions have been able to influence the final PECA nanocapsule colloidal suspension. In particular, the kind of organic solvent caused the formation of either simple PECA nanocapsule suspensions (aprotic fully water-miscible solvents) or PECA nanoparticle colloidal suspensions consisting of nanospheres and nanocapsules (protic water-miscible solvent). Both mechanisms, the interfacial precipitation of a pre-formed polymer and the interfacial polymerization, could play a significant role in nanocapsule formation. Also other variables, such as the kind of the nonionic surfactant and the monomer concentration, affected in different ways the nanocapsule formation process.

Keywords: PECA; Nanosphere; Nanocapsule; Morphology; Mechanism of formation

1. Introduction

Drug delivery systems have been used to target biologically active molecules to various organs, due to the physicochemical properties of the carrier systems in determining the destination and biological fate of the drug contained in the delivery devices. An important requisite in drug delivery design is the drug leakage from the system at a suitably controlled rate. In this way, rather than freely diffusing through the body, drugs can be localized in a specific body site by passive and active mechanisms. For this purpose, different colloidal systems have recently been developed (Chasin and Langer, 1990)

Poly(alkylcyanoacrylate) (PECA) nanoparticles have been thoroughly studied proposing different applications ranging from ophthalmic delivery to carriers in cancer chemotherapy (Couvreur and Vauthier, 1991). Following an emulsion (Couvreur et al., 1979) or an interfacial polymerization process (Al Khoury Fallouh et al., 1986), poly(alkylcyanoacrylate) nanospheres or nanocapsules have been obtained, respectively. Transmission

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electron microscopy studies (Rollot et al., 1986) have shown nanospheres to be made up of a dense polymeric matrix with a high surface area (finely dispersed colloidal system) and porosity, which allow the entrapment of significant amounts of a wide variety of drugs, sufficiently water soluble to be dissolved in the aqueous medium where the nanospheres are formed. The architecture of nanocapsules is different, being constituted by an oil core surrounded by a polymeric shell (Rollot et al., 1986). Therefore, nanocapsules may behave as a reservoir system for a lipid-soluble drug. In principle, the difference between these two systems is also in the drug release behaviour: a first-order and a zero-order release for nanospheres and nanocapsules, respectively (Tice et al., 1989).

Recently, we have studied the influence both of the formulation conditions on poly(alkylcyanoacrylate) nanospheres (Puglisi et al., 1993) and of the nonionic surfactant on the release process (Vandelli et al., 1994). In this paper, we would like to establish the most suitable preparation conditions to achieve high-quality poly(alkylcyanoacrylate) nanocapsules, evaluating the effects of variables, such as organic solvent, concentration and type of surfactant, and amount of monomer employed in the preparation.

2. Materials and methods

In this study ethyl-2-cyanoacrylate (Sigma, St. Louis, USA) was used as the polymerizing monomer. The nanocapsule preparation was carried out by adding 50 ml of an organic solution, consisting of Miglyol 812 (1 ml) and an amount of monomer dissolved in an organic solvent, to 100 ml of an aqueous phase containing a nonionic surfactant (Pluronic F-68, Tween-80 or Triton X-100) at different concentrations. This system was thoroughly stirred at room temperature for 3 h. Finally, the colloidal suspension was concentrated under vacuum up to 25 ml. The characterization of the various nanocapsule colloidal suspensions was carried out by freeze-fracture electron microscopy (Müller et al., 1980) and laser light scattering (Fresta et al., 1994), using both the standard cumulant analysis and the inverse laplace transformation for data fitting (Chu, 1974; Provencher et al., 1978).

3. Results and discussion

The influence of the organic solvent used during the preparation process on the nanocapsule mean size is reported in Table 1. The concentration of the nanocapsule suspensions allowed not only the complete evaporation of the organic solvent but also the formation of colloidal suspensions more homogeneous in size (see polydispersity index values) and a reduction of the mean size of nanocapsules. These findings could probably be due to a concentration of the nonionic surfactant which is able to form a resistant film coating, avoiding nanoparticle agglomeration and, hence, conferring colloidal stability. The electron microscopy analysis showed the formation of both nanospheres and nanocapsules, when protic water-miscible organic solvents, i.e. ethanol, n-butanol and *iso*-propanol, were used during the preparation; whereas the use of aprotic fully water-miscible organic solvents, i.e. acetone and acetonitrile, achieved the formation of nanocapsules.

This behaviour may be explained by the possibility of starting the polymerization process in protic solvents with a certain nucleophilic character. In this case, the polymerization takes place initially in the organic mixture. Therefore, the

Table 1
Light scattering analysis of PECA nanoparticle colloidal suspensions before and after the evaporation process [a]

Solvent	Before concentration		After concentration	
	Size (nm)	PI [b]	Size (nm)	PI [b]
Ethanol	560	0.35	267	0.14
n-butanol	450	0.50	200	0.10
iso-propanol	410	0.71	188	0.27
Acetone	500	0.62	215	0.03
Acetonitrile	240	0.93	275	0.19

[a] The nanocapsules were prepared in the presence of Pluronic F68 (0.5% w/v) with various organic solvents. Each value is the average of three different experiments.
[b] Polydispersity index value.

nanocapsule mechanism of formation seems to be the precipitation of the pre-formed polymer in a large excess of non-solvent at the oil/water interface (Chouinard et al., 1994). In any case, a certain contribution in the formation of the nanocapsule polymeric shell is given by the interfacial polymerization process. The presence of poly(ethylcyanoacrylate) (PECA) nanospheres is due to the polymerization nuclei, already formed in the organic solvent, which assume their final shape in the aqueous medium, rather than to a fragmentation process of the polymeric interfacial film which does not contain any oil droplets, as proposed by Gallardo and co-workers (Gallardo et al., 1993).

Only the interfacial polymerization process (Gallardo et al., 1993) could be considered as a possible mechanism of nanocapsule formation when an aprotic water-miscible solvent is used, i.e. acetone or acetonitrile. In fact, no evidence of polymerization process in the organic solvent was obtained, the solution being perfectly clear (a cloudy suspension was obtained in ethanol, n-butanol and *iso*-propanol). A colloidal milky suspension was achieved only after the addition of the organic phase to the aqueous phase. In these cases (acetone and acetonitrile), a nanocapsule colloidal suspension was formed. Particularly, the presence of acetone ensured high-quality nanocapsule systems (Fig. 1), presenting a homogeneous size distribution (Fig. 2).

Changing the amount of monomer to be added during the preparation process had no particular influence on size and size distribution, only an

Fig. 1. Freeze-fracture electron micrograph of a PECA nanocapsule prepared with 260 μl of monomer in the presence of acetone and Pluronic F68 (0.5% w/v). The black arrow indicates the oil core of Miglyol 812 surrounded by the polymeric shell. Magnification $\times 300\,000$.

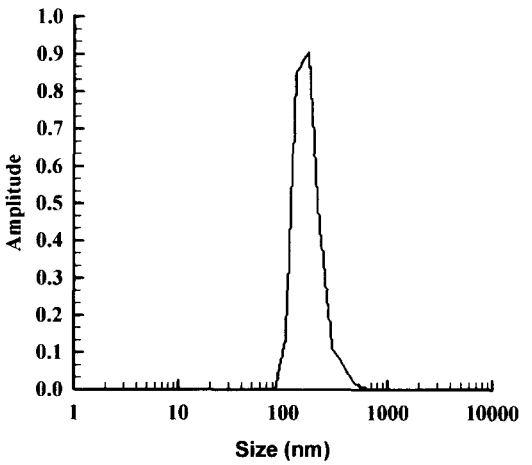

Fig. 2. Size distribution of PECA nanocapsules prepared with acetone in the presence of Pluronic F68 (0.5% w/v). The sample was diluted to achieve the most suitable optical density for light scattering analysis. The distribution function was determined by the inverse laplace transform.

increase of the nanocapsule wall thickness occurred as shown by the freeze-fracture electron microscopy analysis (data not reported).

The kind of nonionic surfactant employed in the PECA nanocapsule preparation was able to affect the parameters of the colloidal suspensions (Table 2). In fact, the different physicochemical characteristics of the various noionic surfactants and, hence, the different emulsifying properties could influence the interfacial polymerization process, resulting in PECA nanocapsule colloidal suspensions with different sizes and size distributions. In particular, Tween-80 achieved the highest values of nanocapsule size with a contemporaneous increase in PECA nanocapsule wall thickness.

Table 2
Light scattering analysis of PECA nanoparticle colloidal suspensions before and after the evaporation process [a]

Surfactant	Before concentration		After concentration	
	Size (nm)	PI [b]	Size (nm)	PI [b]
Triton X-100	622	0.53	228	0.24
Pluronic F-68	500	0.62	215	0.03
Tween-80	597	0.81	336	0.41

[a] The nanocapsules were prepared with acetone as organic solvent in the presence of different nonionic surfactants (0.5% w/v). Each value is the average of three different experiments.
[b] Polydispersity index value.

The results reported in this communication led to the consideration that a single mechanism of PECA nanocapsule formation is not easy to hypothesize; in fact, it is a function of the organic solvent used in the nanocapsule preparation. Although the mechanism proposed by Chouinard et al. (1994) may explain the events taking place in the presence of ethanol or other protic organic solvents, the most acceptable hypothesis about the formation of nanocapsules in the presence of aprotic water-miscible organic solvent is the interfacial polymerization mechanism, which is in agreement with Gallardo et al. (1993). Probably, both mechanisms, as a function of the organic solvent, play an important role, though in different ways, in the formation of polyalkylcyanoacrylate nanocapsules. As reported, other parameters should also be taken into account for the realization of high-quality nanocapsule colloidal suspensions.

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