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Pharmaceutical Nanotechnology

The effect of monomers on the formulation of polymeric nanocapsules based on polyureas and polyamides

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Abstract

Formulation of nanocapsules based on polyureas and polyamides have been tested using a patented process. This method based on polycondensation reaction of two complementary monomers and spontaneous formation of oil in water emulsion, is an alternative concept to the known technique based on the same type of reaction used for the formulation of microcapsules, and in which the lipophilic monomer was emulsified in the organic phase before the formation of the polymeric membrane. Nanocapsules can be prepared from different monomers. Wall based on cross-linked polymer contributes to the stability of nanocapsules during and after formulation. The permeability of the polymeric wall is related to its crystallinity and contributes to the growth of nanocapsule membrane by the diffusion of the hydrophilic monomers to get stable colloidal suspensions.

Keywords: Nanocapsules; Spontaneous emulsification; Interfacial polycondensation; Polymers

1. Introduction

In recent years, an increasing interest has developed on the nanoencapsulation of active ingredients (Mayer, 2005; Chang et al., 2000). Polymeric nanocapsules are described in the literature as oil, aqueous or solid core, surrounded by a thin polymeric wall with different roles of protection, permeability and controlled release. Different technologies can be used for the formulation of these polymeric nanocapsules such as a physicochemical process in which a preformed polymer can be used (Fessi et al., 1989; Calvo et al., 1997; Quintanar-Guerrero et al., 1998). Interfacial polycondensation is a chemical process based on a polymerization reaction often used for the preparation of microcapsules (Yadav et al., 1997; El-Gibaly and Anwar, 2004; Mathiowitz and Cohen, 1989a,b). Interfacial polycondensation coupled to spontaneous emulsification of oil in water emulsion is a new patented process for the encapsulation of lipophilic material in the form of nanocapsules (Montasser et al., 2003a,b). In the present work this technique has been used to produce nanocapsules based on polyureas and polyamides. Different monomers were used to obtain these nanocapsules. The chemical structure of the monomers played an important role to obtain different polymeric walls. The physicochemical properties and in particular the crystallinity and the cross-linked structure of polymeric walls played an important role for the formation, the stability and the size of the nanocapsules.

2. Materials and methods

2.1. Materials

The monomers: phtaloylchloride "PTC", Sebacoyl chloride "SC", hexamethyle-1,6 diisocyanate "HMDI", 2,4-toluene-diisocyanate "TDI", ethylenediamine "EDA", 1,6-hexamethyl-enediamine "HMDA" and diethylenetriamine "DETA" were purchased from Fluka. The surfactants: Lipoids® S75 was supplied by Lipoids GmbH. PLuronic ®F68 was purchased from Sigma. Oil: Miglyol ®812 was supplied by Condea Chemie GmbH. Solvent: pure acetone was purchased from Prolabo.

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2.2. Methods

2.2.1. Preparation of nanocapsules

Polymeric nanocapsules were obtained using the patented method of Montasser et al. (2003a,b). Homogeneous organic phase, composed of 20 ml of water miscible solvent (acetone), 200 mg of oil (miglyol ®812), 40 mg of lipophilic surfactant (lipoid ®S75) and 100 mg of lipophilic monomer (PTC, SC, HMDI or TDI) was added under magnetic stirring (500rpm) to an aqueous phase, composed of 40 ml of distilled water, 60 mg of hydrophilic surfactant (Pluronic ®F68) and 500 mg of hydrophilic monomer (HMDA, EDA or DETA). Agitation was maintained under 500 rpm during 3 h to obtain colloidal suspension of nanocapsules and completely polymerized monomer. Acetone in the final mixture was eliminated by evaporation under reduced pressure at 40 °C.

2.2.2. Size of nanocapsules

The mean diameter of the nanocapsules was measured using Laser granulometer (Coulter® LS230). All measurements were done in triplicate, the nanocapsules suspensions were dispersed in distilled water at room temperature before measurement.

2.2.3. Stability and formation of nanocapsules

Basically, the formation of the nanocapsule suspensions was estimated by the tyndall effect characterised by a blue reflection of the different batches. This phenomenon indicated that the colloidal suspension was formed. However when the nanocapsules formulation failed we could not get any tyndall effect and a precipitation at the bottom of the beaker was observed.

The phenomenon was then confirmed by the determination of the particle size of the colloidal preparation using laser granulometer.

3. Results and discussion

3.1. Polymeric nanocapsules based on polyamides

3.1.1. Formulation using phtaloylchloride "PTC" as lipophilic monomer and ethylenediamine "EDA", 1,6-hexamethylenediamine "HMDA" or diethylenetriamine "DETA" as hydrophilic monomers

The use of an aromatic monomer (PTC) and different aliphatic diamines (EDA, HMDA or DETA) was a successful formulation for the production of colloidal suspensions based on polymeric nanocapsules. In fact, no sedimentation phenomenon was observed during or after the preparations. Furthermore, using HMDA we obtained nanocapsules with mean diameter larger than that of the nanocapsules based on EDA or DETA (Fig. 1). This result was also obtained by Alexandridou et al. (1995) during the preparation of microcapsules by interfacial polycondensation. In that study, the authors observed that the use of HMDA yielded to microcapsules with a smooth and dense membrane wall. In our case we suppose that the larger size obtained with this monomer is maybe due to this morphologic propriety, as it could be the result of a fusion of small vesicles. On the contrary, the mechanical properties of the polymeric

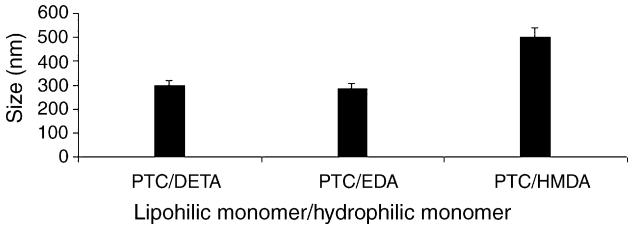

Fig. 1. Influence of the hydrophilic monomer on the size of nanocapsules based on polyamide.

membrane wall in case of EDA and DETA nanocapsules cause them to resist to fusion and hence smaller nanocapsules are produced. In order to study the role of wall permeability on the size of the nanocapsules, we prepared nanocapsules based on PTC and DETA with different amounts of the lipophilic monomer (PTC). The results (Fig. 2) reveal that as the monomer amount is increased, the size of the nanocapsules also increases. This phenomenon is due to the permeability of the polyamide wall to the hydrophilic monomer (Poncelet de Smet et al., 1990; Kioshi et al., 1969).

3.1.2. Formulation using sebacoyl chloride "SC" as lipophilic monomer and ethylenediamine "EDA", 1,6-hexamethylenediamine "HMDA" or diethylenetriamine "DETA" hydrophilic monomers

With DETA, a stable nanocapsules suspension was obtained. Using EDA and HMDA, sedimentation of the preparation and loss of the tyndall effect were observed. In order to increase the rate of the interfacial polycondensation and to avoid the hydrolysis of the lipophilic monomer in the aqueous medium, we tried to increase the concentration of the hydrophilic monomers. No improvement was obtained regarding the stability of the preparation. We observed a loss of the tyndall effect and a separation of the aqueous and organic phases with sedimentation of the polymer in the bottom of the beaker. This result suggests that using EDA and HMDA, we formed a pre-membrane wall based on linear polyamide. This polymer structure has a relatively high degree of crystallinity (Peppas and Gurny, 1983) and this physicochemical propriety decreases the diffusion of the hydrophilic monomer through the pre-membrane and delays the growth of the nanocapsules wall. The agitation breaks this thin pre-membrane and the lipophilic monomer diffuses into the

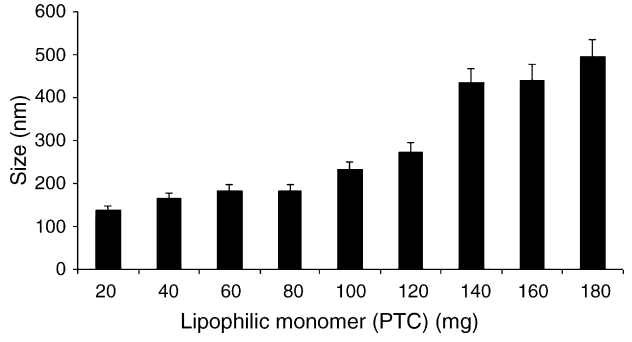

Fig. 2. Influence of the amount of lipophilic monomer on the size of nanocapsules based on polyamide.

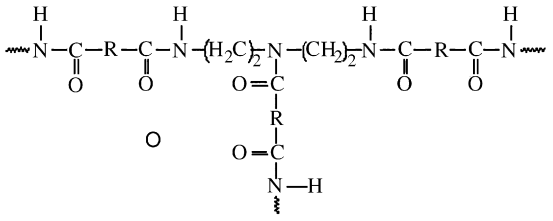

Fig. 3. Chemical structure of a cross linked polymeric membrane based on DETA and SC (R = –$(CH_2)_8$–).

aqueous phase to change the pH and the stability of the initial oil in water emulsion. In the case of the formulation using DETA as the hydrophilic monomer and CS as the lipophilic monomer, the pre-membrane is based on a cross linked polymer. This gives stable nanocapsules with strong mechanical properties during and after preparation (Fig. 3).

3.2. Polymeric nanocapsules based on polyureas

3.2.1. Formulation using 2,4-tolyenediisocyanate "TDI" as lipophilic monomer and ethylenediamine "EDA", 1,6-hexamethylenediamine "HMDA" or diethylenetriamine "DETA" as hydrophilic monomers

The study of these different combinations showed again the importance of the physicochemical properties of the polymeric walls for the stability of nanocapsules during the preparation. In fact, when DETA was used as hydrophilic monomer, a stable colloidal suspension was obtained. With EDA and HMDA, the emulsion formed upon the addition of the oil phase to aqueous phase destabilized during agitation and after a few minutes the polymer collected at the bottom of the beaker. DETA and TDI yield a branched polymer that enhances the stability of the nanocapsules (El-Gibaly and Anwar, 2004). With EDA and HMDA, the polymeric pre-membrane is not cross linked. Based on the difference in hydrogen bonding (Fig. 4) between the polyamide and the polyurea (Stuart, 1995), it could be inferred that the increased crystallinity of the polyurea reduces the diffusion of the hydrophilic monomer and the growth of the polymeric walls surrounding the nanoemulsion. The walls are therefore destroyed during agitation.

3.2.2. Formulation using hexamethyle-1,6 diisocyanate "HMDI" as lipophilic monomer and ethylenediamine "EDA", 1,6-hexamethylenediamine "HMDA" or diethylenetriamine "DETA" as hydrophilic monomers

The formulation using HMDI and DETA was successful in producing a stable colloidal suspension. With formulations using

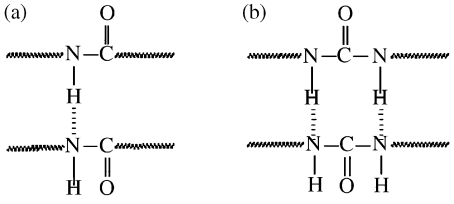

Fig. 4. Hydrogen bonding in polyamide (a) and in polyurea (b).

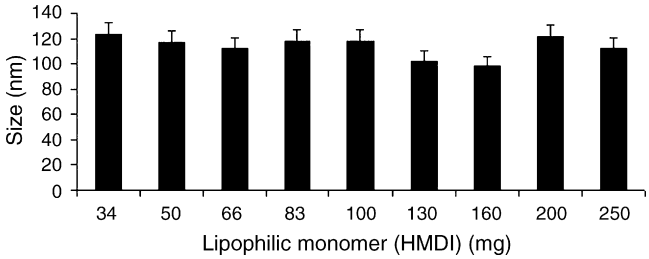

Fig. 5. Influence of the amount of lipophilic monomer (HMDI) on the size of nanocapsules based on polyurea.

EDA and HMDA, a phase separation was observed a few minutes after the introduction of the organic phase to the aqueous phase. This result is related as the above example to the strength of the wall due to cross linking of the polymer. To confirm this opinion and eliminate the possibility that it could be due to the growth of the pre-membrane by monomer diffusion as in the case of the polyamides, we tried to vary the amount of the lipophilic monomers in the organic phase (Fig. 5). The results showed no significant variation of the nanocapsule sizes and confirm that the polymeric wall is not changed during the agitation step.

4. Conclusion

The colloidal suspensions of nanocapsules were most stable when trifunctional monomer (DETA) was used. This result is attributed to the strong mechanical properties of the cross-linked polymeric walls. Low crystallinity of the wall is favourable to the growth of the nanocapsules, and to the stability of final suspension. The knowledge of these physico-chemical properties can be used to modulate the release kinetic of different active ingredients incorporated in the oil core of these nanocapsules and of course the development of other nanocapsules based on different polymeric walls.

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