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New approach of the Preparation of Nanocapsules by an Interfacial Polycondensation Reaction

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Summary

Nanocapsules were prepared by interfacial polycondensation of an oil-soluble monomer (phthaloylchloride) and a hydrophilic monomer (diethylentriamine). Upon addition of the oil phase to the aqueous phase, interfacial reaction takes place at the interface of an oil in water submicronic emulsion. After the initial formation of the wall, the polycondensation is diffusion controlled. The influence of different variables on nanocapsules size was evaluated. Oil (Miglyol® 812) concentration played an important role by controlling the size of the emulsified droplets (precursor of nanocapsules). Ratio of lipohilic to hydrophilic monomer showed a significant effect on the size, indicating that polymeric walls of difference thicknesses can be obtained. The introduction of a lipohilic surfactant (Lipoid® S75) and a hydrophilic surfactant (Pluronic®F68) in the formulation is important for the stability of nanocapsules after their preparation.

Introduction

Nanocapsules consist of a thin membrane surronding a core (liquid, solid). Their size ranging from 10 nm to 1000 nm [1]. The membrane may be composed of natural or synthetic polymers with varying physico-chemical and morphological properties.
The nanometric size of nanocapsules can be interesting for many applications, like cosmetics, perfumes or pharmaceutics industries.
Contrary to nanospheres, in which active substances are entrapped or dissolved in matrix type structures, in nanocapsules active substances are usually dissolved in the inner core surrounded by a polymeric wall. Therefore, the knowledge of the polymeric properties and the wall thickness can be used for a control release of active substances.

Several methods can be used for the preparation of nanocapsules [2-3]. They can be classified in tow main categories, according to whether the formation of the nanocapsules requires a interfacial polymerization reaction like polyalcylcanoacrylate nanocapsules [4-5] or whether it is achieved directly from a performed polymer [6].

Nevertheless, the use of preformed polymer is favorable to formation of nanospheres, because the polymer aggregation can result in individual matrix type structures.
Polycondensation reaction of two complementary monomers is a simple technique to obtain capsule wall. It consists in making an emulsion of two immiscible phases, each one containing dissolved monomer(s) able to react with other monomer(s) present in the other phases. After the initial formation of the wall, the polycondensation reaction is diffusion controlled. So the polymer formation is the result of an interfacial reaction between the monomers, leading to the formation of capsules-like particles, the size of which depending on the initial emulsion.
The work reported here describes a new process of manufacture of nanocapsules, we present some major achievements concerning synthesis of oil-containing nanocapsules. In our process no emulsification step is required prior to polycondensation, as a nanometric emulsion is spontaneously obtaines by mixing the two phases (see experimental part).The influence of several synthesis parameters (eg monomer and oil concentration) on nanocapsules size has been studied. The nature and the concentration of different surfactants were also investigated to evaluate the stability of the preparations.

Experimental

Materials

Monomers: Phthaloylchloride (PTC) and diethylene triamine (DETA) were obtained from Fluka Chemical company. Emulsifiers/surfactants: Lipoid GmbH (Ludwigshafen, Germany) supplied Phospholipide mixture (Lipoid® S 75 with purity of 70%). Pluronic® F68 was from Sigma. Oil: Miglyol® 812 was obtained from Condea Chemie GmbH. Solvent: pure acetone from Prolabo company.

Preparation of nanocapsules.

The concept of the preparation method was based on the polycondensation reaction of hydrophilic and lipohilic monomer at the interface of an oil in water submicronic emulsion [7]. The method was the following: Miglyol® 812 (0 - 400 mg), Lipoïd® S75 (0- 140 mg) and lipohilic monomers (PTC) (20-180 mg) were dissolved in 20 ml of acetone. 60 mg of Pluronic® F68 and 500 mg of hydrophilic monomers (DETA) were dissolved in 40 ml of distilled water. The acetonic phase is then slowly poured into the aqueous phase under magnetic stirring (500 rpm). The nanocapsules were formed by progressive interfacial polycondensation reaction between DETA and PTC at the interface of Miglyol® in water submicronic emulsion. After 3 hours, the colloidal solution is then concentrated by evaporation under reduced pressure at 40 °C to about 20 ml. For comparison data, miglyol® in water submicronic emulsions was prepared by the same formulation without monomers.
Nanocapsules size was determined by using Zetasizer® S (Malvern, France). The stability of different lots was evaluated by the measurement of Zeta potential (Malvern, France) and Tyndall effect. Morphological observations of nanocapsules and emulsion was performed using a transmission electron microscope (TEM) following negative staining with phosphotungstic acid solution (0,1%).

Results and Discussion.

Morphological examination.

The feasibility of nanocapsules by this technique was evaluated by TEM microphotograph as shown on Figure 1. Simple observation shows a clearly difference between the submicronic emulsion (Fig 1A) and nanocapsules (Fig 1B) allowing us to conclude that solid nanoparticles were formed. The average mean size of the particle varied between 100 and 600 nm with good homogeneity, depending on the materials amount used.

Influence the amount of Miglyol® 812 on the size of nanocapsules.

The effect of the amount of Miglyol® 812 on nanocapsules size was investigated. Acetonic phase consisted of lipophilic monomer (100 mg), lipoid® S75 (40 mg). Figure 2 shows that increasing Miglyol® 812 amount, significantly increased the nanocapsules mean size. This result indicates that nanocapsules size is mostly determined by the size of initial emulsion (precursor of nanocapsules).

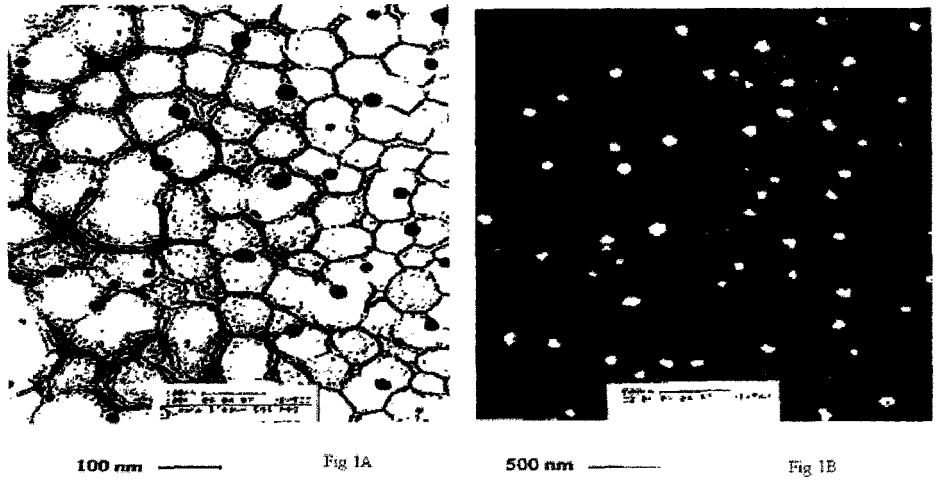

Figure 1: TEM photographs of emulsions and nanocapsules

Furthermore, the rapid polycondensation reaction between DETA and PTC takes place at the interface of the oil in water emulsion formed by spontaneous process. In that case, the diameters of nanocapsules result from the diameter of nano-emulsion and the thickness of polymeric membrane. Above 400 mg of miglyol 812, the suspension appeared without any Tyndall effect and the final nanocapsules tend to cluster together.

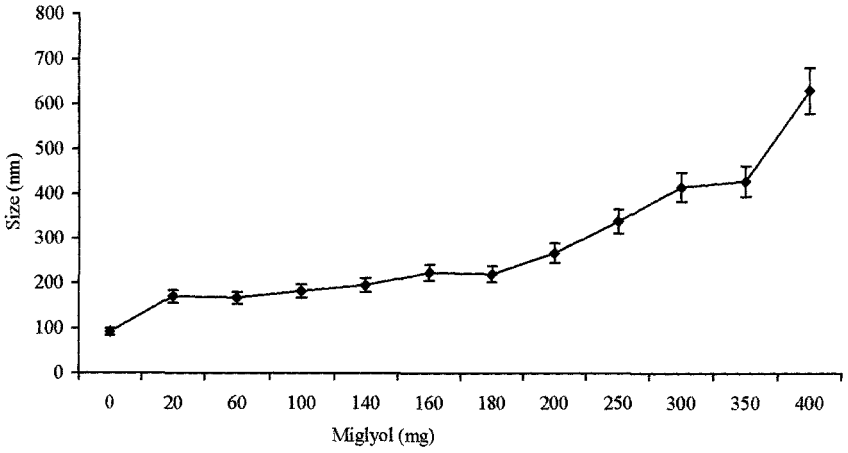

Figure 2 : Influence of the amount of miglyol 812 on the size of nanocapsules

Influence the amount of Lipoid® S 75 on the size and the stability of nanocapsules.

The preparation of nanocapsules with different amounts of lipoid S75 in the acetonic phase containing 100 mg of PTC and 200 mg of miglyol, showed no significant difference in size (Fig 3). Nevertheless, the presence of lipoid S75 in formulation is necessary for the stability of the suspension, nanocapsules could sediment and form a cake difficult to redisperse in absence of Lipoid S75. In this case, the same observation is confirmed by AMMOURY et al in the study of polyisobutylcyanoacrylate nanocapsules preparation [8]. For more affirmation, evaluation of the Zeta potential was investigated (Fig 4). The results show that an increase of lipoid® S75 amount in organic phase produced an increase in the negative zeta potentials, probably due to the increase of the charge on the surface of nanocapsules. Nevertheless, lipoid® S75 plays the role of an antifloculant agent by electrostatic stabilization [9]. This role is valid only in the presence of Pluronic F68 in aqueous phase, this later can played in our case the role of steric stabilization [9].
However, the increase of the lipoid® S 75 quantity in organic phase above 40 mg can also lead to the formation of liposome structures and the final system can consist of tow colloidal structures (nanocapsules and liposomes). We didn't check this assumption.

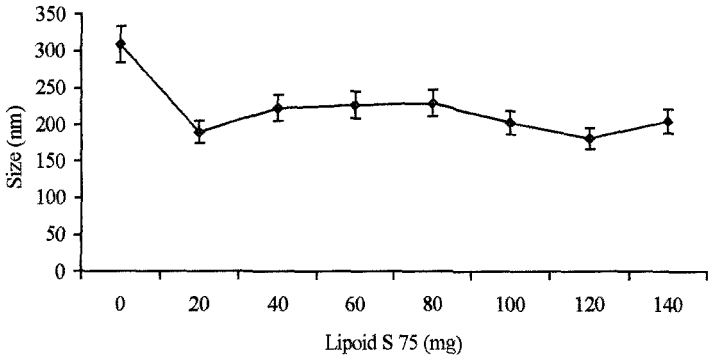

Figure 3 : Influence the amount of Lipoid S75 on the size of nanocapsules.

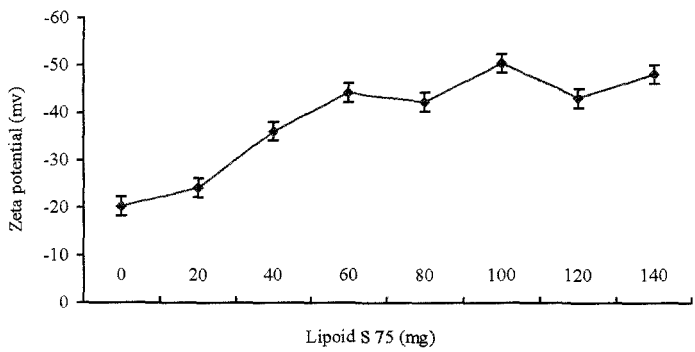

Figure 4 : Relation between zeta potential and the amount of lipoid S75

The preparation of nanocapsules with organic phase containing 200 mg of miglyol, 40 mg of Lipoid S75 and amounts of PTC ranging from 0 to 180 mg, showed significant difference in size of nanocapsules (Fig 5). This result can be attributed to the increasing of the wall thickness [11]. Furthermore, after the formation of the 'pre-membrane' during the introduction of the organic phase in the aqueous phase, the polycondensation proceeds via diffusion of the diamine through the membrane, and reaction whith the dicloride at the inner face of the nanocapsules wall [12]. Thus, in this process the crystallinity of the membrane plays a principal role, diffusion is assumed to take place exclusively through the amorphous region of the polymer.
Specifically, in our system, the choice of the chemical natures of hydrophilic and lipophilic monomers will determine the formation and the stability of nanocapsules. Therefore, according to many other tests the formation of nanocapsules is not possible with some monomer [13].

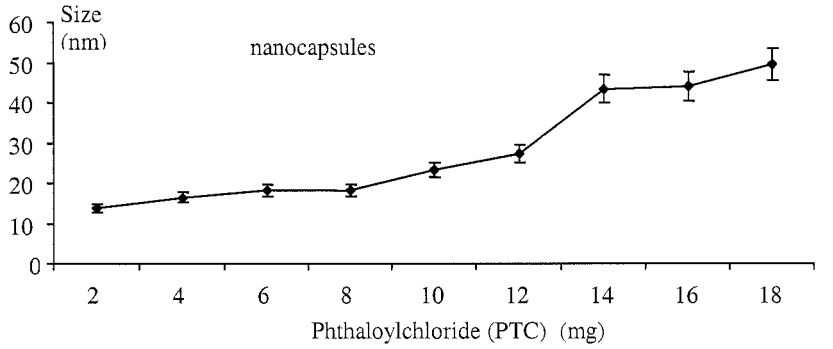

Figure 5: Influence of the amount of lipophilic monomer (PTC) on the size of nanocapsules

Conclusion

A new technique was developed for the preparation of nanocapsules by interfacial polycondensation of tow complementary monomers. This reaction takes place exclusively at the interface of oil in water submicroscopic emulsions. Nanocapsules size is mainly influenced by factors acting on the droplet size, such as Miglyol® 812 concentration and ratio of lipophilic monomer to hydrophilic monomer. The presence of minimal amount of lipophilic surfactant (Lipoïd® S75) in formulation is necessary to ensure the stability of the suspension. During the nanocapsules preparation the wall grows and the diffusion rate of the monomer decrease, thus decreasing the reaction rate. Contrary to the other techniques, this possibility could be of interest for the study of nanocapsule walls and the drugs release kinetics. More work is now necessary to investigate the final structure of the nanoparticles and the polymeric wall, in relation with the polycondensation conditions.

References

1 Kreuter J., (1983). Pharma. Acta Helva, 58 (7), 196-208.
2 Montasser I., Briançon S., Lieto J., Fessi., (2000). J. Pharm. Belg, 55 (6), 155- 167.
3 Allémann E., Gurny R., Doelker E., (1993). Eur. J. Pharm. Biopharm, 39 (5), 173-191.
4 Al khouri Fallouh N., Roblot-Treupel L., Fessi H., Devissaguet J Ph., Puisieux F., (1986).Int.J. Pharm, 28,125-132.
5 Vranck H., Demostier M., Delleers M., (1996). US Patent N° 5, 500, 224.
6 Fessi H., Puisieux F., Devissaguet J Ph., (1988). Eur. Pat. Appl, 0274961 Al, July 20 th.
7 Montasser I., Fessi H., Briançon S., Lieto J., (2001). PCT/FR00/03133.
8 Ammoury N., Fessi H., J Ph., Puisieux F., Benita S., (1989). S.T. P. Pharma, 5 (10), 647-651.
9 Lucks J S., Müller B W., Müller R H., (1990). Int. J. Pharm, 63,183-188.
10 Stolnik S., Davies MC., Illum L., Davis SS., Boustta M., Vert M., (1994). J.Contr.Rel, 30,57-67
11 Janssen L J J M., Boersma A., (1993). J. Membrane. Sci, 79,11-26.
12 Mathiowitz E., Cohen M D., (1989). J. Membrane. Sci, 40,1-26.
13 Montasser I., (1999). Préparation et caractérisation de vecteurs colloïdaux submicroniques par une nouvelle technique de polycondensation interfaciale. Ph D thesis, n° 289 Université Lyon I, France.