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Rapid Communication

Nanocapsule formation by interfacial polymer deposition following solvent displacement

H. Fessi [1], F. Puisieux [1], J.Ph. Devissaguet [1], N. Ammoury [1], and S. Benita [2].

[1] *Laboratoire de Pharmacie Galénique et Biopharmacie, URA CNRS 1218, Université Paris XI, Paris (France).*
[2] *Pharmacy Department, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem (Israel).*

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Summary

Indomethacin-loaded nanocapsules were prepared by deposition of poly-(D,L-lactide) polymer at the o/w interface following acetone displacement from the oily nanodroplets. An attempt was made to elucidate the mechanism of formation in terms of interfacial turbulence between two unequilibrated liquid phases involving flow, diffusion and surface tension decrease (Marangoni effect).

Nanovesicular drug delivery systems varying in size from 20 to 500 nm include mainly unilamellar liposomes and nanocapsules. The former are vesicles, the membrane of which consists of phospholipids, and are widely described in the litterature (Gregoriadis, 1988). The latter comprise a tiny solid or liquid core surrounded by a thin and continuous water-insoluble membrane composed of synthetic polymer (Rollot et al., 1986). The two main factors that have limited the development of liposomes are the sensitivity of the phospholipid membranes to environmental degradation and rapid drug leakage across the phospholipidic bilayer (Grit et al., 1989). Nanocapsules, prepared using an interfacial polymerization process of alkylcyanoacrylate (Al-Khouri et al., 1986; El-Samaligy et al., 1986), were recently proposed as a new type of vesicular colloidal polymeric drug carriers (Damgé et al., 1988). But possible residues of monomers and oligomers or reagent from the polymerization process, and cross-reaction between the content of nanocapsules, especially the drug molecules, and the acrylic monomer (Gallardo et al., 1989) might limit the potential use of these nanocapsules.

The subject of this communication is the presentation of a novel and simple procedure for the preparation of nanocapsules by interfacial deposition of a preformed, well-defined, and biodegradable polymer following displacement of a semi-polar solvent miscible with water from a lipophilic solution. Nanocapsules of poly-(D,L-lactide) containing indomethacin as a drug model were prepared according to the following procedure (Fessi et al., 1988): 125 mg of poly-(D,L-lactide) polymer (PLA)

Correspondence: S. Benita, Pharmacy Department, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel.

are first dissolved in acetone (25 ml). Eventually, a mixture of phospholipids (250 mg, Epikuron 170, Lucas Meyer, Hamburg, F.R.G.) is also dissolved in acetone by increasing the temperature close to the boiling point. 0.5 ml of benzyl-benzoate containing 12.5 mg of indomethacin are then added to the acetonic solution. The resulting organic solution is poured in 50 ml of water containing 250 mg of poloxamer (Pluronic F68, Lucas Meyer, Hamburg, F.R.G.) under moderate magnetic stirring. The aqueous phase immediately turns milky with bluish opalescence as a result of the formation of nanocapsules, the wall of which is mainly constituted by the PLA polymer, and the oily core by the indomethacin benzyl-benzoate solution. The acetone, which rapidly diffused towards the aqueous phase, is then removed under reduced pressure. The colloidal suspension is concentrated to the desired final volume (10 ml) by removal of water under the same conditions.

Morphological examination of nanocapsules was performed using a transmission electron microscope (TEM) following negative staining with phosphotungstic acid solution (0.5%). Particle size distribution was measured by laser light scattering using a monochromatic laser ray diffusion counter (Supernanosizer, Coultronic, France). Free drug was determined in the clear supernatant following separation of nanocapsules from aqueous medium by a combined ultrafiltration centrifugation technique. Total indomethacin was measured following complete dissolution of the nanocapsules in acetonitrile. Indomethacin content in the nanocapsules was calculated by the difference between the total and free estimated drug concentrations in the nanocapsule suspension and the supernatant, respectively. Indomethacin was assayed according to a modified HPLC technique (Drouet et al., 1981). Long-term stability testing involving particle size measurement, drug loss and TEM examination were conducted at given time-intervals over 7 months' storage at room temperature.

The method of preparation yielded spherical vesicular nanocapsules which consisted of an oily cavity(benzyl-benzoate where indomethacin is dissolved) surrounded by a thin wall formed by interfacial deposition of PLA polymer, as confirmed by TEM examination.

Particle size distribution determinations indicated that the mean diameter size was 229 ± 29 nm. This was also confirmed by TEM examination (Fig. 1A). Furthermore, from Fig. 1B, the film coating can be clearly distinguished and is delimited by 2 arrows. The thickness of the film could be estimated at the order of 10 nm. In addition, highly solvated bilayers of phospholipids, in excess in the formulation, were formed around these nanocapsules and were easily de-

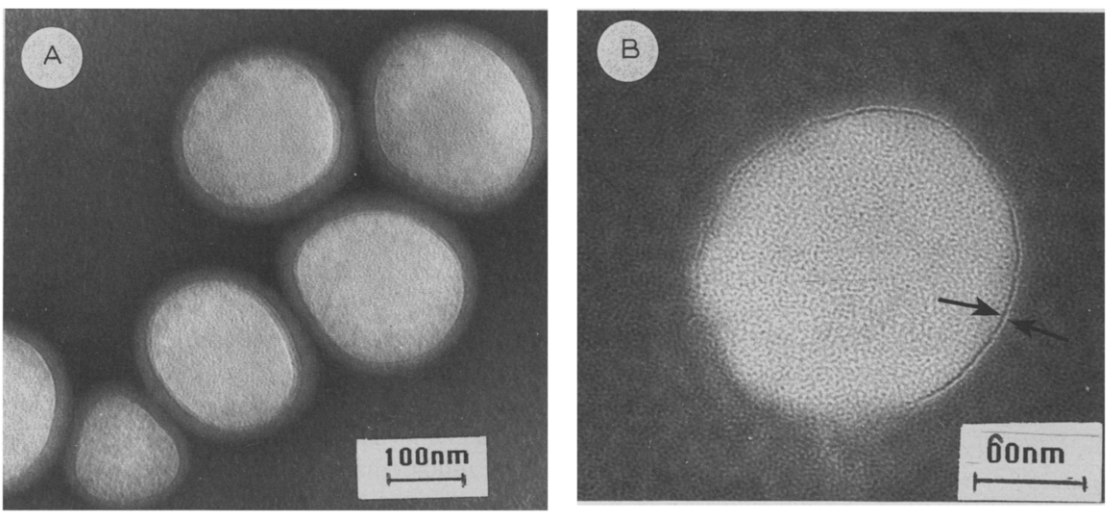

Fig. 1. TEM photographs of PLA nanocapsules prepared following standard conditions.

tected during TEM examination. Nevertheless, the excess of phospholipids in the final nanocapsule preparation could be controlled by variation of initial phospholipid concentration in the original composition. It should be pointed out that the mean particle size of PLA nanocapsules was not clearly dependent on the surfactants' concentration or on various ratios of phospholipid to poloxamer. It is noteworthy that the presence of at least one of the emulsifiers was needed for wall coating formation and for suspension stabilization. Maximum stability of suspensions was achieved with a combination of both emulsifiers since, when prepared with only one emulsifier, nanocapsules would sediment and form a cake difficult to redisperse.

The amount of indomethacin incorporated into the nanocapsules was gradually increased from 0.06 to 0.25% w/v in an attempt to evaluate drug incorporation efficiency. No increase above 0.25% could be studied owing to solubility limitation of indomethacin in benzyl-benzoate (0.25% w/v in the aqueous suspension corresponded to a concentration of 5% of indomethacin in benzyl-benzoate). Above this concentration, indomethacin precipitated as evidenced by the presence of drug crystals in the bottom of the vial and HPLC assay. Thus, a high encapsulation efficiency (100%) was achieved in the tested range of indomethacin concentrations which did not alter the particle size distribution of the drug-loaded nanocapsules formed.

Seven months of stability studies indicated that no marked differences were observed in the mean particle size of the nanocapsules. This was also confirmed by TEM examination. Furthermore, drug content remained constant, indicating that no leakage or release occurred in the final concentrated suspension, where acidic conditions limited markedly the solubility of the drug in the aqueous phase.

In addition, other polymers and drug models were tested for the purpose of confirming that this simple method can be applied to a wide range of polymers and drugs. A non-exhaustive list of different types of nanocapsules is presented in Table 1. It should be emphasized that other polymers, such as polyvinylacetate, polyvinylchloride, poly-

TABLE 1

Characterization of various nanocapsules prepared using interfacial polymer deposition following solvent displacement

Polymer	Drug	Nanocapsule mean diameter (nm), mean ± S.D.	Incorporation efficiency, (% of initial conc.)	Drug content (% w/w) [3]
PLA	Taxol	260 ± 20	100	2.40
PLA	Dexamethasone	300 ± 25	40	0.96
PLA	Vit. K	270 ± 30	100	75 [4]
HP 55 [1]	Progesterone	250 ± 25	100	2.40
Eudragit L100 [2]	Indomethacin	240 ± 32	100	2.00

[1] Hydroxy-propyl-methyl-cellulose phtalate. SEPPIC, Paris, France.
[2] Roehm Pharma, Darmstadt, F.R.G.
[3] Drug/total weight of nanocapsules.
[4] Vit K being an oily solvent was directly encapsulated.

ϵ-caprolactone, ethylcellulose, were successfully used as coating materials for the incorporation of drugs such as ciclosporin, taxol, betaxolol, essential oils, contrast agent (lipiodol), reflecting the extended potential of the nanocapsule preparation method proposed.

The nanocapsule preparation process, apparently simple, may involve complex interfacial hydrodynamic phenomena. Addition of the acetonic-oily solution resulted in spontaneous emulsification of the oily solution in the form of nanodroplets, due probably to some kind of interface instability arising from rapid diffusion of the acetone across the interface and marked decrease in the interfacial tension. The origin of the mechanism of nanocapsule formation could be then explained in terms of interfacial turbulence or spontaneous agitation of the interface between two unequilibrated liquid phases, involving flow, diffusion and surface processes. The process would then be governed by the well-known Marangoni effect, wherein movement in an interface is caused by longitudinal variations of interfacial tension (Sternling and Scriven, 1959). Interfacial turbulence may be promoted by various factors exten-

sively described in the literature (Sternling and Scriven, 1959; Berg, 1982; Wasan, 1968). Among them, solute transfer out of the phase of higher viscosity, steep concentration gradients near the interface and interfacial tension sensitive to solute concentration, are the most important factors. Furthermore, the presence of surfactants may markedly complicate the situation since they act to suppress interfacial flow (Berg, 1982). Thus, it can be deduced from the overall results that the rapid diffusion of acetone from the organic phase to the aqueous phase led to the formation of oily nanodroplets as result of interfacial tension decrease and migration of the insoluble PLA towards the o/w interface where it is deposited, forming the nanocapsule membrane. This interpretation of the observed phenomenon apparently agrees with the observations made during this study regarding the influence of surfactants on the nanocapsule properties. It was possible to prepare nanocapsules in the absence of any surfactant, but the poloxamer, a highly aqueous soluble surfactant, was needed for physical stability of the nanocapsule suspension.

The main advantage of this one-step manufacturing process is the instantaneous and reproducible formation of nanometric, monodisperse nanocapsules exhibiting a high drug loading capacity.

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