ELSEVIER

International Journal of Pharmaceutics 242 (2002) 167–170

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Note

Properties of polyethylene glycol 660 12-hydroxy stearate at a triglyceride/water interface

B. Heurtault, P. Saulnier, B. Pech, J.E. Proust, J.P. Benoît *

Inserm ERIT-M 0104, Ingénierie de la Vectorisation Particulaire, Immeuble IBT, 10, rue A. Boquel, 49100 Angers, France

Received 24 December 2001; received in revised form 14 January 2002; accepted 1 February 2002

Abstract

This study proposed a method to understand the surfactant role in the first step of the formulation of a novel generation of lipidic nanocapsules. A dynamic rheological protocol was applied using a pendant drop tensiometer in order to determine the interfacial properties of the initial mixture implied in the first formulation step. The response, in terms of interfacial elasticities, described how this mixture led to monodisperse nanometer size range structures after a physico-chemical constraint. © 2002 Published by Elsevier Science B.V.

Keywords: Surface elasticity; Drop size analysis; Nanocapsule formulation

An experimental protocol has been previously described to prepare lipid nanocapsules (20–100 nm) composed by a liquid core (medium chain triglyceride) and surrounded by a solid shell (2-hydroxy-stearate of polyethylene glycol and lecithin) (Heurtault et al., submitted for publication). Briefly, in step I, all the compounds were heated at 85 °C, then cooled down to a temperature closed to the phase inversion zone of the related emulsion. In step II, a cooling-dilution of the mixture by cold water (0 °C) allowed the obtention of nanocapsules (Heurtault et al., 2000). Previous results have shown that nanocapsules were elaborated only in a well-defined zone in a ternary composition diagram (Heurtault et al., submitted for publication).

This study proposed a method to understand the surfactant role in the first step of the formulation and subsequently, to determine how the mechanical properties of the interface could allow the nanocapsule formation after the cooling-dilution step. In order to answer these questions, a dynamic rheological protocol previously described (Saulnier et al., 2001) was applied using a pendant drop tensiometer.

The organic phase, lipophilic Labrafac® WL 1349 (caprylic acid triglycerides) was kindly provided by Gattefossé S.A. (Saint-Priest, France). Solutol® HS 15 (polyethylene glycol 660 12-hydroxystearate) was a gift from BASF (Ludwigshafen, Germany). The water used was ultrapure grade from Milli Q plus system (Millipore, Paris, France). The drop tensiometer was from Tracker (IT Concept, Longessaigne, France).

* Corresponding author. Tel: +33-241735855; fax: +33-241735853

E-mail address: jean-pierre.benoit@univ-angers.fr (J.P. Benoît).

0378-5173/02/$ - see front matter © 2002 Published by Elsevier Science B.V.

PII: S0378-5173(02)00144-8

The drop tensiometer allowed the determination of the interfacial tension by analyzing the axe symmetric shape of the oily rising drop of Labrafac®, ($d = 0.945$) in an aqueous Solutol® solution (Fig. 1). The determination of surface elasticities was performed by assessing the response of the interfacial tension to several sinusoidal area variations of the oily drop (characterized by the pulsation ω). The drop surface was considered here as a model of the bicontinuous interfacial organization. These experiments were performed after the adsorption of all surfactant molecules at the oil/water interface of the drop i.e. when the surface pressure π had reached its equilibrium value. Subsequently, a complex transfer function G(ω) was calculated allowing to determine the interfacial elasticities. Thus, according to Saulnier et al. (2001), E_e (equilibrium elasticity) can describe all the lateral interactions between the various molecules at the interface and E_{ne} (non-equilibrium elasticity) characterizes the dissipation of the rheological perturbation energy, especially in relation to the expulsion of tensioactive molecules to the bulk phase. τ Represents the time necessary for the interface to reach a new equilibrium energetic state after the perturbation. Moreover the rheological model was developed so that these physico-chemical constants were not dependent on the experimental conditions (Saulnier et al., 2001). The equilibrium surface tension of a triglyceride drop in surfactant-containing water was determined for different concentrations of an hydrophilic surfactant ranging from 10^{-6} mol/l to 10^{-1} mol/l. The pseudo-critical micellar concentration (CMC) for Solutol® at the water/triglycerides interface was defined as the lowest concentration leading to the lowest value of surface tension.

The behavior of the three rheological constants is described on Fig. 1. A pronounced rheological change of the PEG stearate layer behavior in terms of elasticities is observed depending on the surfactant concentration. Three separate domains could be determined from this graph. The first one corresponds to aqueous Solutol® concentrations below 1×10^{-3} mol/l (C_1). The intermediary one is included between C_1 and 10^{-2} mol/l (C_2) and the last one is for concentrations higher than C_2.

The first domain shows that E_e was high for low aqueous Solutol® concentrations. It therefore means that the cohesion energy of the interface, represented by E_e, was important when the number of molecules at the interface was low. But E_e decreased with rising concentrations of the hydrophilic surfactant. Thus, in these conditions, the interface seemed to become more and more fluid,

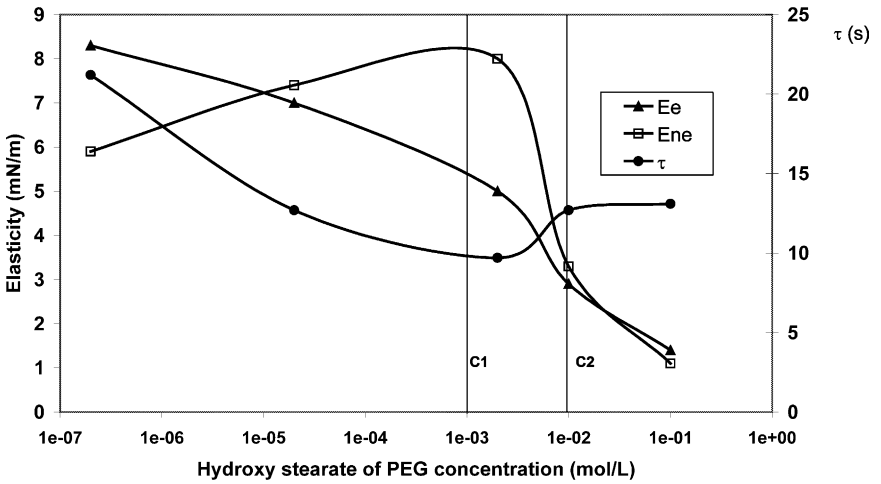

Fig. 1. Influence of the hydroxy stearate of polyethylene glycol concentrations on the elasticities of a triglycerides/water interface. E_e, equilibrium elasticity; E_{ne}, non-equilibrium elasticity; τ, relaxation time.

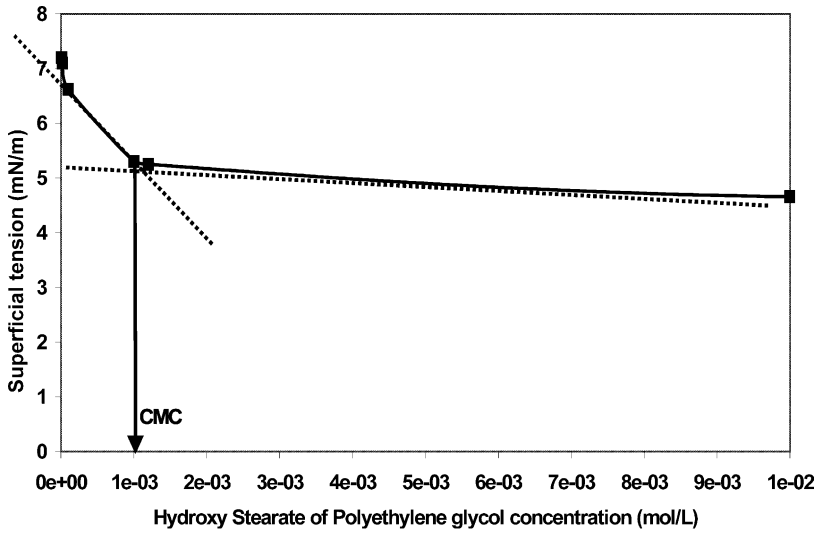

Fig. 2. Determination of the pseudo CMC of hydroxy stearate of polyethylene glycol at the triglycerides/water interface.

as well as less structured with increasing hydrophilic surfactant concentrations. This result was correlated with E_{ne} which, in the same time, increased, suggesting that, after a constraint, the molecules easily left the interface. Thus, the disorder at the Labrafac®/water interface increased with the surfactant concentration.

For higher concentrations included between C_1 and C_2, in the second domain of the graph, E_e decreased in a faster way with increasing surfactant concentrations, indicating an increase in the interface fluidity. This interpretation led to assume a structure formation around the surface due to the high concentration of surfactant. Moreover an important energy dissipation occurred (E_e decreased) when a constraint was applied. This hypothesis was confirmed by the rapid decrease of E_{ne}; indeed these formations prevented the departure of surfactant molecules from the surface. Once the expulsion happened, the molecules took a long time to come back because of the obstruction and so τ was significantly increased.

Fig. 2 enabled to define the pseudo-CMC for Solutol in water versus triglycerides at 2×10^{-3} mol/l. The CMC was consequently comprised in the second domain of Fig. 1 Around the CMC, the previously hypothetised interface structures were probably micellar-like organizations.

In the last part of the graph, the Solutol® concentrations corresponded to the range of concentrations used during the first step of the particle formulation ($> 10^{-3}$ mol/l). Unexpectedly, E_e and E_{ne} values were still decreasing with the increase of Solutol® concentration and were characterized, when a sinusoidal volume constraint was applied, by low and close equilibrium and non-equilibrium elasticities at the same time ($E_e = 1.4 \pm$ mN/m and $E_{ne} = 1.1 \pm$ mN/m). The interactions in-between the surfactant molecules were minimal (low E_e), corresponding to a low interface rigidity while surfactant molecules remained at the interface after a constraint (low E_{ne}). Usually, for classical emulsions, a high value of E_{ne} can be forecasted when E_e is low because of the lowered lateral interactions facilitating the departure of molecules to the surrounding bulk phase. In our case, this mechanical ability to be slightly cohesive, whilst keeping the initial structure, was interesting because such a system could support its own break (low E_e) without generating a coalescence phenomenon due to the surfactant departure (low E_{ne}). The strong hydrophilic interactions in-between the ethylene oxide units of the Solutol® at the interface should explain this result. Consequently, such elasticity properties, characterising the initial mixture during the formulation,

should favour the regular breaking into nanostructures following a physical shock. In the solid–lipid nanoparticle formulation, alcohols with a potential toxicity were often used (Witschi and Doelker, 1994). One of the corollary to the use of such a molecule was probably to decrease E_{ne}. In our case, nanoparticles can thus be expected to form without using alcohol because of the Solutol® molecule properties at the triglycerides/water interface.

This study enabled to describe the mechanical properties of the interface of an initial mixture through the use of an interfacial rheological technique (drop tensiometer). This mixture consisted in a bicontinuous phase and led to stable nanocapsules. The interfacial characteristics of the appropriate mixture were described by low equilibrium and non-equilibrium elasticities. Such properties confered a suitable fluidity with a sufficiently stable interface to support a constraint which gave rise to regular nanostructures. This was the base for the development of a new concept ending in the formulation of solvent-free lipidic nanocapsules.

References

Heurtault, B., Saulnier, P., Pech, B., Proust, J.E., Richard, J., Benoit, J.P., 2000. A novel phase inversion-based process for the preparation of lipidic nanocarriers. Patent FR 0002688.

Heurtault, B., Saulnier, P., Pech, B., Venier-Julienne, M.C., Sergent, M., Proust, J.E., Benoit, J.P. Response surface methodology to modelise the influence of the composition of lipidic nanocapsules on their size characteristics, submitted for publication.

Saulnier, P., Boury, F., Malzert, A., Heurtault, B., Ivanova, T., Cagna, A., Panaïotov, I., Proust, J.E., 2001. Rheological model for the study of dilational properties of monolayers. Comportment of dipalmitoylphosphatidylcholine (DPPC) at the dichloromethane/water interface under ramp type or sinusoidal perturbations. Langmuir 17 (26), 8104–8111.

Witschi, C., Doelker, E., 1994. Residual solvents in pharmaceutical products: acceptable limits, influences on physicochemical properties, analytical methods and documented values. Eur. J. Pharm. Biopharm. 43, 215–242.