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Water-dispersible non-aqueous emulsions stabilized by a poly(butadiene)-*b*-poly(2-vinylpyridine) block copolymer

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ABSTRACT

Submicron non-aqueous emulsions, of interest for biomedical and cosmetic formulations, were developed for the system comprising poly(ethylene glycol) (PEG) 400 and Miglyol 812, an enzymatic degradable liquid glycerine ester. These emulsions, with PEG 400 as continuous phase and Miglyol 812 droplets, in the size range of 200 nm, were stabilized by a poly(butadiene)-*b*-poly(2-vinylpyridine) (PBut-*b*-P2VP) block copolymer with a composition close to 50/50 wt%. The droplet size, stability and the rheological characteristics were examined as a function of the copolymer concentration. An original aspect of these anhydrous emulsions, with a water miscible continuous phase, is their water dispersibility without additional surfactant. In fact, the initial anhydrous emulsion is sterically stabilized and after water addition at low pH, the protonated P2VP sequence of the copolymer provides the electro-steric stabilization. This oil-in-water emulsion is characterized by sub micron sized Miglyol 812 droplets in an aqueous phase of PEG 400 and water at pH 1.

RÉSUMÉ

Des émulsions submicroniques non aqueuses, ayant des applications biomédicales et cosmétiques, ont été préparées pour le système poly(éthylène glycol) (PEG) 400/Miglyol 812, un triglycéride biocompatible. Ces émulsions, avec une phase continue PEG 400 et des gouttes dispersées de Miglyol 812 de 200 nm, sont stabilisées par un copolymère à blocs poly(butadiène)-*b*-poly(2vinylepyridine) (PBut-*b*-P2VP) ayant une composition massique proche de 50/50 wt%. La taille des gouttelettes, la stabilité et les caractéristiques viscoélastiques de ces émulsions ont été déterminées en fonction du taux en copolymère. Un aspect original de ces émulsions anhydres, ayant une phase continue miscible à l'eau, est de pouvoir les diluer, sans émulsifiant supplémentaire, par adjonction d'eau à pH 1. L'émulsion non aqueuse initiale est stabilisée stériquement par le copolymère, lequel, par protonation de la séquence P2VP à pH 1, assure la stabilisation électro-stérique de l'émulsion aqueuse comportant des gouttes submicroniques de Miglyol 812 dispersées dans une phase PEG 400/eau.

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1. Introduction

Anhydrous emulsions, also known as non-aqueous or oil-in-oil emulsions, started to be developed in the early 1960s [1–4] and have since gained great interest as outlined in several recent review articles [5–7].

It was shown for the first time, by our group, that block copolymers are efficient steric stabilizers for non-aqueous emulsions formed by two non-miscible organic solvents, such as hexane/dimethylformamide (DMF) or cyclohexane/acetonitrile [8]. It could be demonstrated that, in contrast to aqueous emulsions where the stability is in general provided by low molecular weight ionic or non-ionic surfactants, anhydrous emulsions require preferably polymeric surfactants, such as block- or graft-copolymers.

As outlined by Crespy and Landfester [7], one of the most interesting features of anhydrous emulsions is the fact that they allow to perform any kinds of water-sensitive chemical reactions. Moreover, this type of emulsions has a broad application range in pharmaceutical and cosmetic formulations for handling of unstable or scarcely soluble drugs in controlled release systems and transdermal preparations. Of particular interest are therefore those emulsions comprising biocompatible oil components, as for instance, paraffin oil, ethylene glycols, silicon and triglyceride oils [9–12].

In this context, we recently became interested in block copolymers stabilized anhydrous emulsions based on poly(ethylene glycol) 400 (PEG 400) and Miglyol 812, a typical biocompatible and enzyme degradable medium chain triglyceride (MCT) [12]. Such drug loaded emulsions, with PEG 400 as dispersed phase stabilized by poly(butadiene)-*b*-poly(2-vinylpyridine) (PBut-*b*-P2VP) copolymers were developed in view of their topical application possibilities.

As an extension of this study, it was of interest to examine the colloidal characteristics of Miglyol 812-in-PEG 400 emulsions stabilized by a PBut-*b*-P2VP copolymer. Up to now, and to the best of our knowledge, only Amemiya et al. [13,14] have prepared this type of anhydrous emulsions of rather limited stability by using low molecular weight non-ionic surfactants.

An original aspect of the present study is that Miglyol 812/PEG 400 anhydrous emulsions, with PEG 400 as a water miscible continuous phase, opens the way to the design of water dispersible non-aqueous submicron sized emulsions, with the major advantage that no further addition of a stabilizer would be necessary.

In fact, the anhydrous emulsion is sterically stabilized by the PBut-*b*-P2VP copolymer and after water addition at low pH, the protonated P2VP sequence of the copolymer provides the electro-steric stabilization of the aqueous emulsion.

This concept of stimuli-responsive stabilization mechanism of emulsions could be of interest for drug release applications. Thus, a hydrolytically instable and/or scarcely water-soluble drug could be loaded in the anhydrous emulsions in order to provide its storage stability. Then just before administration, its dispersion would be possible in an aqueous medium at a pH around 1–2, for instance, like that existing in the stomach.

Therefore, the objective of this study was to examine in a first step the particle size, the stability and the rheological characteristics of the anhydrous Miglyol 812/PEG 400 emulsions as a function of the PBut-*b*-P2VP copolymer concentration. In a second step, the dispersion of these non-aqueous systems in water and the characteristics of the final aqueous emulsions will be investigated.

2. Materials and methods

2.1. Materials

The poly(butadiene)-*b*-poly(2-vinylpyridine) (PBut-*b*-P2VP) copolymer was synthesized by living anionic polymerization in THF according to the technique developed by Fontanille and Sigwalt [15]. The copolymer used in this study has the following characteristics: $Mn_{(PBut)}$ = 6900 g/mol; $Mn_{(P2VP)}$ = 5300 g/mol; and an polydispersity index Mw/Mn of 1.06. The configuration of the PBut sequence corresponds to 90 mol% 1,2 and 10 mol% 1,4 *trans*. In this study, the block copolymer will be designated as $PBut_{0.55}$-*b*-$P2VP_{0.45}$, where 0.55 and 0.45 are the PBut and the P2VP weight fractions.

Medium chain triglyceride (Miglyol 812), which is a blend of caprylic and capric triglyceride, was purchased from Axo Industry (Belgium) and it is characterised by a viscosity of 30 mPa·s, a refractive index of 1.45 and a specific mass of 0.95 g/cm^3 at 20 °C. PEG 400, purchased from Fluka, has a refractive index of 1.47, a specific mass of 1.128 g/cm^3 and a viscosity of 120 mPa·s.

2.2. Emulsion preparation

Non-aqueous emulsions, with PEG 400 as continuous phase and Miglyol 812 as dispersed phase, were prepared by varying the copolymer concentrations from 1 to 5 wt% with respect to the total emulsion volume, which has been fixed at 100 mL. The composition of the Miglyol 812/PEG 400 emulsions was 30/70 vol. The PBut-*b*-P2VP copolymer, used as polymeric stabilizer, was dissolved at 70 °C in PEG 400 at the desired concentrations. After complete dissolution, the Miglyol 812, also kept at 70 °C, was dispersed in the continuous PEG 400 phase with an addition rate of 2 mL/min under agitation at 20 000 rpm provided by an Ultra-Turrax T18 (IKA, Germany) homogenizer. In order to obtain submicron droplet sizes, this emulsion was further homogenized, at the same speed, for 10 min. At this stage, the emulsion temperature was around 60 °C and then, the temperature was slowly decreased to room temperature.

For the preparation of oil-in-water emulsions, two methods were used. In the first one, 10 mL of a non-aqueous emulsion were added to 10 mL H_2O at pH 1 and the emulsification was carried out by gentle shaking. In the second one, the water was added to the non-aqueous emulsion and then agitated also by gentle shaking. Since, within the experimental error limits, identical droplets diameters were obtained for both methods, only the second one was used in the present study. After dispersion in acidic medium, the emulsion composition was 15/85 vol. with Miglyol 815 dispersed in a continuous phase formed by the mixture of PEG 400 and H_2O at pH 1.