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A polysiloxane surfactant dissolves a poorly soluble drug (nystatin) in water

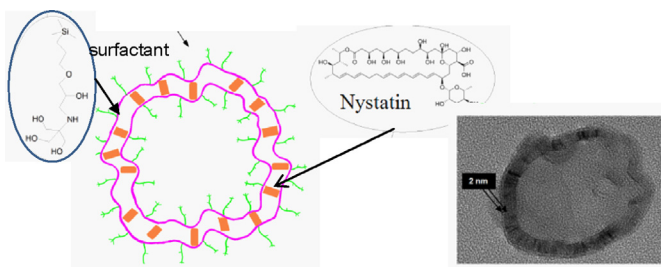
Carmen Racles[a,b,*], Mihai Mares[c], Liviu Sacarescu[a]

[a] "Petru Poni" Institute of Macromolecular Chemistry, Aleea Gr. Ghica Voda 41A, 700487 Iasi, Romania
[b] "Gh. Asachi" Technical University, Department of Natural and Synthetic Polymers, Str. Prof. Dr. Docent Dimitrie Mangeron, nr. 73, Iasi 700050, Romania
[c] Ion Ionescu de la Brad University, Laboratory of Antimicrobial Chemotherapy, 8 Aleea Sadoveanu, P4, 1st Floor, 700489 Iasi, Romania

HIGHLIGHTS

- A tromethamol-modified polysiloxane surfactant is investigated.
- A method to dissolve nystatin in water is proposed using this surfactant.
- The drug is physically encapsulated within the surfactant aggregates.
- The in vitro antifungal activity was seriously improved.

GRAPHICAL ABSTRACT



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ABSTRACT

The aqueous dissolution of a poorly soluble drug nystatin (Nys) was achieved by a simple, excipient-free procedure using a tromethamol-modified polysiloxane (ST) as surfactant. Long-term stable Nys aqueous formulation was prepared and investigated by different methods, in order to understand the mechanism of drug solubilization. The cryo-TEM analysis revealed the presence of soft vesicles in the Nyst_ST solution. According to TEM measurements, the drug is contained in the hydrophobic layer of the surfactant vesicles. The dynamic light scattering (DLS) measurements on Nys_ST showed a main population around 134 nm having the Zeta potential of 33.3 mV. FT-IR, UV–vis, and thermogravimetric (TG-DTG-DTA) data point toward physical encapsulation, accompanied by a decrease of H-bonding between the drug molecules. The antifungal activity tested in vitro toward four yeast strains was seriously improved compared to the aqueous dispersion of the native drug, although the availability was diminished compared to DMSO solution.

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1. Introduction

The aqueous solubility of drugs is a serious problem that affects, based on some estimation, almost half of the potentially useful drug candidates [1]. To overcome this problem, many types of colloidal delivery systems have been investigated.

Micellar solubilization is generally regarded as a powerful tool for enhancement of the solubility of active compounds in water which is the preferred solvent for medical applications [2–4]. This effect is due to the hydrophobic core of the direct micelles, which represents a more suitable microenvironment for the solubilizate. In this context, as a consequence of their ability to associate in water, new perspectives are opened by using micellar systems based on amphiphilic compounds.

Colloidal lipid emulsions and solid lipid nanoparticles, as well as lipid and surfactant based drug delivery systems (LSBDDS) are largely used for the delivery of poorly water-soluble drugs [5,6].

One class of drugs whose efficacy is drastically reduced because of poor water solubility is represented by polyene antibiotics. This

* Corresponding author at: "Petru Poni" Institute of Macromolecular Chemistry, Aleea Gr. Ghica Voda 41A, 700487 Iasi, Romania. Tel.: +40 232217454; fax: +40 232211299.
E-mail address: raclesc@icmpp.ro (C. Racles).

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fact affects particularly amphotericin B and nystatin (Nys) which are well known as the most effective and extensively used drugs in the treatment of systemic and mucosal fungal infections respectively. Therefore, intensive research is still ongoing in view of improving the aqueous formulations. These are needed for parenteral administration, which sometimes induce toxicity, including due to excipients.

There are rather few studies on water solubilization of polyene antibiotics. Two main methods are used: one is based on micellar solubilization [7] and the other is based on chemical modification of the drug molecules, using their functional groups [8].

The first method usually uses liposomes or other types of vesicles which are first formed (for example by sonication) and then interact with the drug. Egg PC or (egg PC and sterol) was used in an early study [7a] to prepare vesicles, then amphotericin B, candicidin or mediocidin were introduced and the dissociation of the formed complexes was studied.

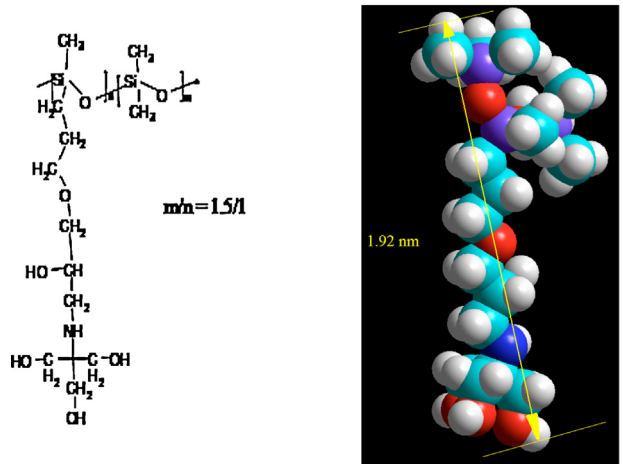
The method based on pH sensitive Egg-PC liposomes was also used for nystatin solubilization [7b]. This approach was reported to minimize the toxic manifestations of the drug. Other examples of liposome-based approach are discussed in a review article [7c], focusing on clinical studies, pharmacokinetics, tissue distribution and pharmacological activity. Formulations based on oil-in-water emulsions were described [7d], which are often very complex, containing many components and high amounts of additives; for example, the amount of oil or fat can range from about 5 to about 40%.

Good solubilization results were reported recently for pro-drug complexes (imine adducts) obtained with pyridoxal phosphate (vitamin B_6) via primary amine groups of amphotericin B and nystatin [8a]. However, these adducts were found to exhibit attenuated antifungal potency. Water soluble amide derivatives of aureofungin were reported [8b], in which the antifungal activity was preserved, while the improvement of selective toxicity was put in relation with the absence of a free carboxyl group.

Although less investigated and used than the poly(alkylene-oxide) surfactants, the siloxane-based surfactants are known for their ability to decrease the surface tension of liquids in such extent that is comparable only with some fluorinated compounds, which are thought to exhibit potential toxicological problems. Due to the versatile chemistry of siloxanes, a very broad range of siloxane-organic compounds has been synthesized, including amphiphilic macromers or polymers [9]. The siloxane-containing surfactants may exhibit both hydrophobic and oleophobic properties, while their low CMC values make possible their use in small amounts [10–15]. The high flexibility and low cohesive energy of the siloxane bond are the main reasons for the unique behavior of the siloxane-based surfactants [16,17]. In addition, polydimethylsiloxanes (PDMS) exhibit transparency to visible and UV light, high permeability to oxygen and other gases, physiological inertness, excellent compatibility with blood (low interaction with plasma proteins) [18].

We reported a new class of siloxane-based surfactants, easy to synthesize, and biocompatible by structure [19]. Within these surfactants, tris(hydroxymethyl)amino-methane (known as tromethamol, tris buffer or THAM) was used as partner for polysiloxanes and the resulting compounds exhibited very good surface properties.

In this paper we show an example of highly effective dissolution of a non-soluble drug using a very simple procedure, which involves a diluted solution of such a surfactant, without any other excipients. Through this approach an aqueous formulation of Nys, containing 4/1 wt. ratio of Nys/surfactant was prepared. The drug-surfactant mixture was analyzed by different methods (FT-IR, TG-DTG-DTA, UV, MS, TEM, cryo-TEM, AFM and DLS), in order to understand the nature of the solubilization process. In vitro antifungal susceptibility was tested in comparison with DMSO solution and water dispersion of Nys.



Scheme 1. Chemical structure and Hyperchem [21] molecular model of surfactant ST.

2. Experimental

2.1. Materials

The surfactant (ST), (Scheme 1) was previously synthesized and characterized [19].

Nys powder was obtained from Antibiotice SA (Iasi, Romania). Methanol (Chimopar) and DMSO (Sigma–Aldrich) were used as received. Double distilled water was used for preparing the surfactant solution.

2.2. Methods

For the characterization of the surfactant, surface tension, critical micelle concentration (CMC) and dynamic contact angle were measured with an automatic tensiometer, Sigma700 from KSV, using the Wilhelmy plate method, adequate software and external dosing for CMC detection.

The infrared spectra were registered on a Bruker Vertex 70 FT-IR instrument, in transmission mode, in the 300–4000 cm^{-1} range (resolution 2 cm^{-1}, 32 scans), at ambient temperature.

TEM investigations were made with Hitachi High-Tech HT7700 Transmission Electron Microscope, operated in high contrast mode at 100 kV accelerating voltage. Samples were cast from diluted solution (1 g/L) on 300 mesh carbon coated copper grids and vacuum dried. Cryo-TEM samples were prepared using an EMS-002 Cryo rapid freezing Workstation. Thin films of sample were prepared by placing a 3 μL drop of solution on a carbon coated copper grid of 300 mesh. The drop was blotted with filter paper so that thin films remained on the TEM grid. The sample was further frozen using the ESM-002 Cryo Workstation by plunging in liquid propane. Transfer of the sample to the TEM was done using a Single Tilt Nitrogen Cryo Transfer Holder, Gatan 626. Temperature control of the cryo holder was done with a Smart Cold Stage Controller, Gatan 900.

The thermogravimetric analyses (TG-DTG-DTA) were performed on an STA 449F1 Jupiter NETZSCH (Germany) equipment. The measurements were made in the temperature range 20–700 °C under a nitrogen flow (50 mL/min) using a heating rate of 10 °C/min. Alumina crucible was used as sample holder.

The AFM measurements were made on a SPM Solver Pro-M platform (NT-MDT, Russia), in air, in semi-contact mode, using a

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