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Pickering emulsions based on cyclodextrins: A smart solution for antifungal azole derivatives topical delivery

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ABSTRACT

Surfactants are usually used for the preparation of emulsions. Potential drawbacks on the human body or on the environment can be observed for some of them (e.g. skin irritation, hemolysis, protein denaturation, etc.). However, it is possible to use biocompatible emulsifiers such as native cyclodextrins (CDs). The mixture of oil (paraffin oil or isopropyl myristate), water and native CDs results in the formation of Pickering emulsions. The emulsion properties were investigated by ternary phase diagrams elaboration, multiple light scattering, optical and transmission microscopies. The results prove that these Pickering emulsions were very stable against coalescence due to the dense film form at the oil/water interface. The rheological behavior has shown that these emulsions remain compatible for topical applications. This kind of emulsions (biocompatibility, stability and surfactant free) has been used to obtain sustainable formulations for antifungal econazole derivatives delivery. Our results prove that these new formulations are at least as active as commercially available formulations.

1. Introduction

Candida albicans, a commensal fungus, lives in the mouth and gastrointestinal tract of 80% of the human population with no harmful effects. Under certain conditions, their overgrowth results in skin, oral and genital candidiasis (Calderone and Clancy, 2011). This kind of infections is common for patients with weak immune systems including HIV/AIDS, organ transplantation, diabetes, pregnancy, children less than one month old, the elderly people, patients in intensive care unit or after corticosteroid or antibiotic therapies. To treat superficial skin infections, such as athlete's foot, tinea, pityriasis versicolor, ringworm or jock itch, antifungal medication based on imidazole derivates is very active. One of the most widely used antifungal agents is the econazole nitrate salt (Fig. 1, Thienpont et al., 1975). In addition to its antifungal activity, econazole nitrate has also antibacterial properties especially against Gram-positive bacteria. As the aqueous solubility of econazole and its nitrate salts is very poor 2.9×10^{-8} and 1.6×10^{-3} M, respectively (Pedersen et al., 1993) and as the skin penetration of econazole nitrate is low, the most commonly used topical delivery platforms are emulsions under various commercial names, e.g., Spectazole®, Ecostatin®, Pevaryl®, etc. However, about 1 to 4% of patients treated with econazole nitrate cream or fluid emulsion reported side effects such as burning, itching, erythema (Heel et al., 1978). The clinical trials of Pevaryl® 1% cream and emulsion have shown that the most commonly reported adverse reactions were (with % incidence): pruritus (1.3%), skin burning sensation (1.3%), and pain (1.1%) (Core Safety Profile). In order to stabilize the emulsion, common surfactants are used. Nevertheless, potential drawbacks on the human body can be observed for some of them (e.g. skin irritation, hemolysis, protein denaturation, etc., Jackson et al., 2014). Here, the emulsifiers used in the formulation of Pevaryl® 1% (macrogol stearate, macrogol glycerides, or other macrogol derivates for generic drugs) are generally considered as not harmful. However, in the literature, sensitizations to macrogols, as immediate-type contact urticaria or more frequently allergic contact dermatitis are well known especially for macrogols of low molecular weight (200–400 Da, Fisher, 1978). The macrogols derivates (e.g. cetomacrogol, lauromacrogol, nonoxynol, macrogol stearate, etc.) have also a potential side effect on skin for patient with multiple allergic reactions. For instance, the possibility of contact urticaria due to macrogol stearate has been already reported (Co-Minh et al., 2007). This observation underlines that allergies to excipients even if they are rare events should be considered. In the case of Pevaryl® 1%, the presence of macrogol derivative can be seen as an aggravating factor when they are in combination with econazole nitrate. In addition, it is noteworthy that the used of common surfactants is harmful for the environment in particular for aquatic organisms and the partial biodegradability is also problematic in some cases (Karsa and Porter, 1995).

A smart solution to replace the commonly molecular surfactants is to use solid particles in order to form the so-called Pickering emulsions. In the presence of oil (O) and water (W), these particles adsorb onto the O/W interface. In addition to avoid skin irritation, sometimes linked to common surfactants, Pickering emulsions also display a high stability against coalescence (Aveyard et al., 2003). The emulsion type (O/W or W/O) depends on the wetting properties of particles (i.e. the contact angle made by stabilizing colloidal particles at the water/oil/solid

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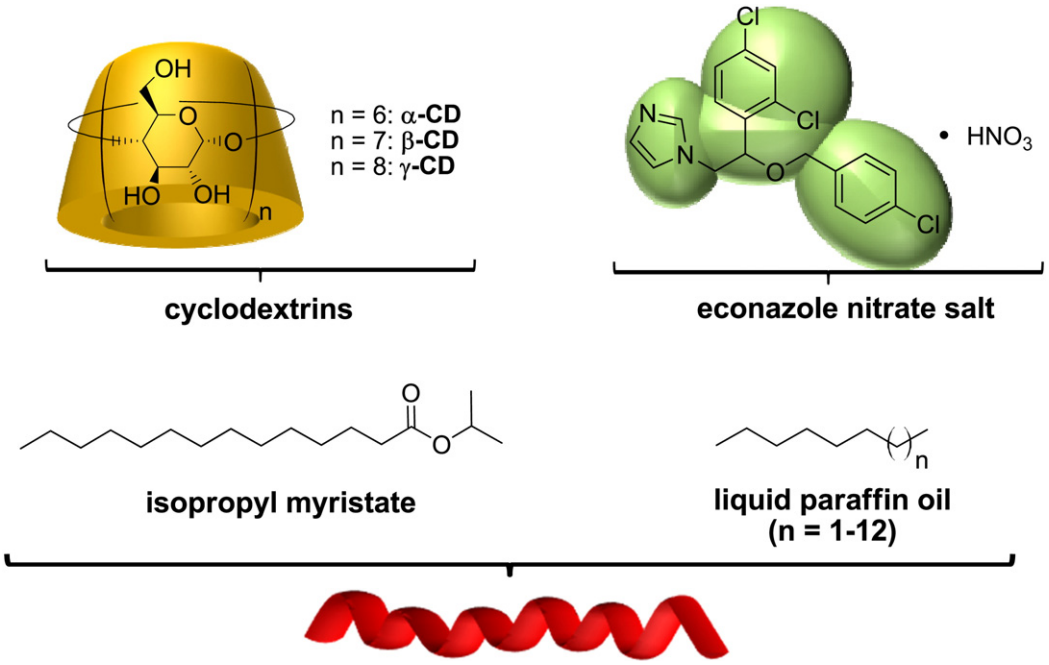

Fig. 1. Structure of different molecules used in this work: emulsifier (cyclodextrins and their schematic representation), antifungal agent (econazole nitrate salts) and oils (liquid paraffin and isopropyl myristate).

contact surface, Binks, 2002). Contact angles less than 90° give rise to O/W emulsions while contact angles greater than 90° favors W/O emulsions (Miller et al., 2006). The most commonly studied particles used to stabilize emulsion systems are based on silica, clays, calcium carbonate, titanium dioxide or latex. However, other "particles", biocompatible and derived from biomass feedstocks, can be used to stabilize Pickering emulsions such as starch (Marku et al., 2012). On the same way, we propose to use native cyclodextrins (CDs, see Fig. 1) obtained by the treatment of ordinary starch by enzymatic degradation in the presence of cyclodextrin glycosyl transferase (EC 2.4.1.19). Native CDs are six, seven or eight-membered-1,4-linked cyclic oligomers of α-D-glucopyranose, named, respectively, α-, β- and γ-CDs (Szejtli, 1988). These cyclic oligosaccharides have a shallow truncated cone shape with hydrophilic annulus due to the primary and the secondary hydroxyl groups of the glucoses that face the exterior ends of the molecule. In contrast, CDs also present a largely hydrophobic cavity that can be used to form highly water-soluble complexes (Szejtli, 1988). In addition to their technological properties, in some antifungal formulations cyclodextrins have also been shown to contribute to antifungal activity of the main compounds through different mechanisms (Macaev et al., 2013). For instance, miconazole or econazole nitrate can be encapsulated in CDs (Pedersen et al., 1993; Jacobsen et al., 1999; Tenjarla et al., 1998). However, the most commonly used topical delivery platforms are emulsions due to their better compatibility with the skin than other platforms. Since 1991, it is known that native CDs could be used as emulsifiers (Shimada et al., 1991). More recently, the formation of emulsions using native CDs instead of surfactants have been reported (Hashizaki et al., 2007; Inoue et al., 2008a, 2008b; Hashizaki et al., 2009; Inoue et al., 2009, 2010). The results have clearly highlighted that in the presence of various oil phases (e.g. *n*-alkane, *n*-alkanol, etc.) leading to the formation of oil/CD insoluble complexes at relatively high CD concentration. In 2013, Mathapa and Paunov have reported the mechanism of these kinds of emulsions. Molecularly dissolved CDs from the continuous aqueous phase are self-assembled into colloid particles (partially wettable by water and oil) directly onto the emulsion drop surface leading to effective Pickering stabilization (Mathapa and Paunov, 2013). These kinds of Pickering emulsions are very promising in a range of surfactant-free formulations with possible applications in cosmetics, home and personal care. Moreover, native CDs are biodegradable and biocompatible contrary to the archetypal surfactants or nanoparticles (Mitra et al., 2015). In addition, it is noteworthy that CDs have already been used in a wide range of applications including biocidal formulations (Nardello-Rataj and Leclercq, 2014; Leclercq et al., 2010, 2012a). Despite the possibilities to formulate surfactant free emulsions for pharmaceutical applications, this kind of emulsifiers remain unexplored: only two publications use these Pickering emulsions based on CDs to perform catalytic reactions (Leclercq et al., 2013; Potier et al., 2013). In this article, we report on the application of the three natives CDs (α-, β- and γ-CD) as emulsifiers for water/paraffin or water/isopropyl myristate systems (Fig. 1). The ternary phase diagrams, the droplets size distributions and the stabilities of these emulsions have been investigated with and without econazole nitrate salt as antifungal drug. Finally, antifungal and antibacterial activities of these emulsions, charged with econazole nitrate, against *C. albicans* and *Staphylococcus aureus* have been also reported and compared to commercial emulsion using colloidal silica and surfactants.

2. Experimental

2.1. General information

All chemicals (econazole nitrate, paraffin oil, isopropyl myristate and cyclodextrins) were purchased from Sigma-Aldrich Chemical Company at the highest purity available. Sterile water for injection was used in all experiments (Fresenius-Kabi, France). Petri dishes and sterile disks were also purchased from Sigma-Aldrich Chemical Company.

2.2. Molecular modeling

Semi-empirical quantum calculations were performed using the PM7-DH2X method with COSMO (conductor-like screening model) water solvation parameters as implemented in MOPAC2012™ 15.089W (©Stewart Computational Chemistry). The geometries were fully optimized with the PM7-DH2X semi-empirical SCF-MO method without restriction to know dispersion and H-bond energy contribution (Stewart, 2013). Relative permittivities of 78.4, 3.20 and 1.90 were