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Research paper

Interactions and release of two palmitoyl peptides from phytantriol cubosomes

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ABSTRACT

Phytantriol cubosomes loaded with two palmitoyl peptides (Palpepcubes), namely GHKcube and GQPRcube, were prepared using an ultrasonication protocol. The Palpepcubes dimensions were characterized by dynamic light scattering (DLS) and cryo-transmission electron microscopy (cryo-TEM). Small-angle X-ray scattering (SAXS) analyses revealed that the bicontinuous cubic structure remained even at palmitoyl peptide contents as high as 5 wt.%, with an increase in the cell parameter from approximately 6.5 to 7.2 nm. Isothermal titration calorimetry (ITC) was used to elucidate the interactions between the blank cubosomes and the palmitoyl peptides, revealing an exothermic process of interaction. Moreover, the *in vitro* release of the palmitoyl peptides from the Palpepcubes was studied using a dialysis method coupled with liquid chromatography–mass spectrometry (LC/MS) technique, in which a sustained release of up to a few days was observed. Finally, the stability of the aqueous solutions of the palmitoyl peptides and the Palpepcubes kept at room temperature and at low temperature (4 °C) was studied by LC/MS method, indicating that incorporation into cubosomes increases the peptide stability significantly.

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1. Introduction

Cubosomes are nanoparticles formed by the colloidal dispersion of the inverse bicontinuous cubic phases (BCP) in water using proper surfactants [1]. Cubosomes are stable to high heat, have low viscosity and large surface area, and can be found in almost any dilution level [2]. There are a limited number of biocompatible molecules capable of forming viscous reverse phases in excess water under physiological conditions and temperature. Currently, the most investigated liquid crystal structures for biomedical applications are prepared by cubic mesophases of unsaturated glyceryl monoglycerides (GMO) and phytantriol (3,7,11,15-tetramethyl-1,2,3-hexadecanetriol) shown in Fig. 1A. Phytantriol has gained more interest compared to GMO in the biomedical industry due to several reasons such as, enhanced skin penetration properties [3], improved moisture retention [4], superior chemical stability due to the absence of the ester group [5], and higher purity [6]. Cubosomes require the addition of a surfactant to kinetically stabilize these colloidal dispersions. Pluronic®F127 is a nonionic linear triblock copolymer that contains a polypropylene oxide block (PPO) between two polyethylene oxide blocks (PEO) and is widely used for topical applications (Fig. 1B) [7]. In our previous study we established a robust method to prepare phytantriol cubosomes stabilized with Pluronic®F127 using a top-down method [8].

Peptides are a rapidly expanding category of cosmeceuticals. The purpose of cosmeceutical peptides is mainly anti-aging and to improve the appearance of skin. Most of the research on the anti-aging role of peptides is a secondary benefit of research on wound healing [9]. Lipopeptides are amphiphilic molecules that consist of a peptide head group linked to lipid chains [10]. Lipopeptides have some advantages over peptides for potential biomedical applications due to their amphiphilicity and compatibility with the lipids in the cell membranes [10]. Matrikines are small peptides derived from the surrounding extracellular matrix and participate in cell activity regulation by emitting signals [11]. They are also effective in stimulating collagen production *in vitro* [12]. It has been claimed by the pioneering company in producing Matrikines (Sederma, France) that one of their palmitoyl peptide formulations (palmitoyl pentapeptide-3, Matrixyl®) has improved anti-wrinkle effects compared to retinol based on visual changes in "half-face" studies [13]. Matrixyl®3000 (Sederma, France) is a newer generation formulation of Matrixyl® that contains a lipotripeptide (Palmitoyl-GHK, N-palmitoyl-Gly-His-Lys, Biopeptide-cl, Fig. 1C)

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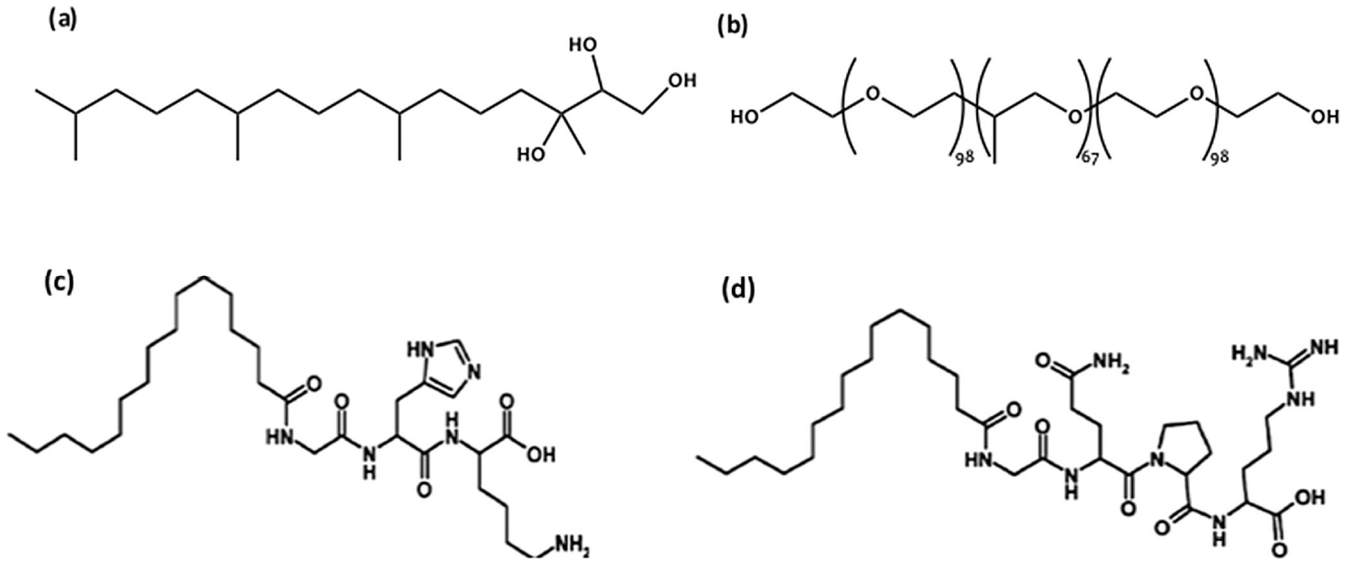

Fig. 1. Chemical structure of (a) phytantriol and (b) Pluronic®F-127, (c) pal-GHK and (d) pal-GQPR.

and a lipotetrapeptide (Palmitoyl-GQPR, palmitoyl-Gly-Gln-Pro-Arg, Rigin™, Fig. 1D) and is known to have anti-wrinkle properties when topically applied to the skin [14].

Cubosomes have the potential to be used as carriers for the delivery of active compounds due to their sustained release profiles of the active compounds as well as their assistance in solubilizing poorly water-soluble drugs [15]. Moreover, their inexpensive raw materials and enhanced payload make them suitable candidates for delivery [16]. Larsson et al. first applied cubosomes as controlled delivery systems [17,18] and ever since they have been used to deliver a variety of active compounds [19]. The most promising applications of cubosomes is in the delivery of proteins and peptides [15]. The importance of applying cubosomes as a potential carrier for the delivery of peptides arises from the fact that compared to other structures (i.e. liposomes, transfersomes, and ethosomes), cubosomes have shown better skin retention and greater peptide penetration [3].

Several studies have been performed on the topical applications of cubosomes. In one study, Kim et al. prepared GMO cubosomes loaded with a hydroxypropyl-cyclodextrin (HPCD)–minoxidil (MXD) complex [20]. Their results showed that the *in vitro* skin permeation of the cubosomes loaded with MXD was increased compared to a solution of MXD in water-ethanol-propylene glycol. In another study, cubosomes were loaded with silver sulfadiazine (SSD) and were tested for the topical treatment of infected burns [21]. The SSD-loaded cubosomes demonstrated promising results compared to the commercially available product in *in vivo* studies in the treatment of deep infected burns. Finally, for vaccine delivery cubosomes loaded with the vaccine were used in conjunction to microneedles. Their results showed that the cubosomes were present in the skin at suitable concentrations after application [22].

In this study we aim to prepare and characterize phytantriol cubosomes loaded with palmitoyl peptides (Palpepcubes). The effects of loading the palmitoyl peptides on the size, zeta potential, morphology and internal crystalline structure of the cubosomes as well the thermodynamics of the interactions between the palmitoyl peptides and the cubosomes are investigated. Moreover, the *in vitro* release profile of the palmitoyl peptides from the Palpepcubes and their stability is studied. The results obtained in this study could shed light on the potentials of the Palpepcubes in the development of anti-aging formulations aiming at the topical delivery of the palmitoyl peptides.

2. Experimental section

2.1. Materials

Phytantriol (3,7,11,15-tetramethyl-1,2,3-hexadecanetriol) was purchased from SARFAM (São Paulo, Brazil) and used as received. Pluronic®F127 (PEO_{98}-PPO_{67}-PEO_{98}) with an average molar mass of 12,600 g mol^{-1} was acquired from Sigma-Aldrich (St. Louis, USA). The palmitoyl peptides namely palmitoyl-GHK and palmitoyl-GQPR were kindly donated by Sederma (Le Peray-en-Yvelines, France). Acetonitrile and formic acid were purchased from Sigma-Aldrich. Deionized water (18.2 MΩ cm^{-1}) (Milli-Q, Millipore Corp., Bedford, MA) was used to prepare all aqueous samples.

2.2. Methods

2.2.1. Cubosome preparation

Approximately 200 mg of phytantriol was weighed into a glass vial and heated at 40 °C until melted. Then, 2.5 mL of an F127 stock solution (2.0 wt%) containing 0.05 g F127 at the same temperature was added to the vial containing phytantriol. To prepare the Palpepcubes with lower palmitoyl peptide content, a solution containing various amounts of palmitoyl peptides (prepared from 10 ppm stock solutions) was added to the vial up to a volume of 10 mL. In order to prepare the Palpepcubes with higher palmitoyl peptide content (above the solubility of the palmitoyl peptides in water), different amounts of palmitoyl peptides were weighed and directly added to the phytantriol and F127 solution followed by addition of 10 mL water. Subsequently, the mixtures were homogenized by ultrasonication (Hielscher UP100H equipment, Germany, using a MS3 sonication probe) at 40 °C, amplitude 80%, and pulse cycle 1 for 30 min until a milky dispersion was formed.

2.2.2. Dynamic light scattering (DLS) and zeta potential measurements

Particle size (Z-average), polydispersity index (PDI), and zeta potential values of the samples were determined using a dynamic light scattering (DLS) instrument (Malvern Zetasizer 3600, Malvern, UK) operating at the wavelength of 632.8 nm and an angle of 173°. Measurements were performed at 25 °C and the data were the mean of three successive analyses (100 s) for at least

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