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Short communication

Design of skin-simulating nanoformulations for ceramide replacement in the skin: a preliminary study

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Introduction

Ceramides are lipid components, which contribute for unique barrier property to outermost layer (*stratum corneum*) of the skin. They exist in intercellular lipid domain of *stratum corneum*, at approximately equimolar concentrations of free fatty acids, cholesterol, and ceramides (Coderch et al., 2003). Furthermore, ceramides play a crucial role in structuring and maintaining of barrier function of the skin. Dermatologists also revealed that total levels of ceramides decrease with some differences in ceramide pattern of *stratum corneum* for certain skin disorders such as psoriasis, atopic dermatitis with compromised skin barrier function, then trans-epidermal water loss (TEWL) and pH of the skin increase. Then, redness and itching are observed in the patients (Kahraman et al., 2019).

In the light of this information, it has considered that the formulations consisting of ceramide could improve impaired skin disorders. Additionally, it is well known that replacement of endogenous *stratum corneum* lipids accelerates skin barrier recovery (Coderch et al., 2003). Recently, Ishida et al. (2020) reported that synthetic *pseudoceramide* significantly decreased skin symptoms, reducing in TEWL and raising in water content, as a result clinically provided to transport ceramide profile from an atopic dermatitis to a healthy skin phenotype. Thus, a numerous of commercial lotions, creams, and moisturizers (Eucerin Smoothing Repair Dry Skin Lotion, Eucerin Eczema Relief Body Creme, CeraVe Moisturizing Lotion) consisting of ceramide I and III have been formulated in the market (Spada et al., 2018). However, high lipophilicity of ceramides may impede their penetration to *stratum corneum* and reach into lipid lamellae when applied conventional topical formulations (Deli et al., 2009). To overcome this issue, some researchers studied ceramide loaded nano-carriers (Deli et al., 2009; Tessema et al., 2018), although not enough.

In this study, we aimed to develop skin-simulating nanoformulations for ceramide replacement in the skin. In this context, ceramide loaded liposomes, ultra-deformable vesicular systems (transethosomes) and micelles were prepared and optimized in terms of particle size and polydispersity index (PDI, size distribution).

Materials and methods

Preparation of liposomes, transethosomes and transferomes

In preparation of the liposomes, Phospholipon 90G (Lipoid GmbH, Germany), cholesterol (Sigma-Aldrich, USA), and ceramide III (Evonik Ind. AG, Germany) were dissolved in a mixture of methanol and chloroform (1:1, v/v). Then, residual solvents were removed by a vacuum evaporator and a thin film layer generated in a round-bottom flask. The film layer was hydrated with ultrapure water. The formulation was sonicated for diverse times at 20

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MHz of frequency. The same procedure was applied for the transethosomes and transfersomes. Just only, Tween 80 was facilitated instead of cholesterol for the transethosome and transfersome formulations. Also, a mixture of ethanol and ultrapure water (3:7, v/v) was used as dispersion medium in the transethosome formulations.

Preparation of micelles

D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) (BASF, Germany) super refined oleic acid (Croda, UK), cholesterol and ceramide III were dissolved in methanol. A thin film layer was obtained in a round-bottom flask after evaporating of organic solvent. Afterwards, the film layer was hydrated with ultrapure water.

Particle size and PDI

The particle size and PDI of vesicular systems and micelles were measured using dynamic light scattering by NanoZS ZetaSizer (Malvern Instruments, UK) at 25.0±0.1 °C.

Results and discussion

The particle size and PDI value are importance keys for optimization of nano-carriers (Kahraman et al., 2016). Thus, these parameters were examined to optimize a feasible nanoformulation simulating the skin. In all of the liposome formulations, micro-scale size and high PDI value were determined. Assessing the transethosomes formulations, it was demonstrated that Tween 80 improved size and PDI of nanocarriers in comparison with cholesterol. The formulation containing of ceramide III, Phospholipon 90G and Tween 80, which sonicated for 3 min, exhibited the smallest size (approximately 100 nm) and the narrowest size distribution (0.086). The particle size and PDIs of transfersomes, which were prepared at similar constituent ratios, were measured about 60 nm and approximately 0.4, respectively. In the transfersome formulations, this case may be explained absence of ethanol, reducing polarity of dispersion medium and increasing ceramide solubility.

When the micellar formulations were evaluated, it was revealed that formation of TPGS micelles was negatively affected in presence of oleic acid, cholesterol and ceramide in the dispersion medium, separately. Thus, ceramide loaded micelles could not be prepared and visible aggregates were viewed in the formulations.

Conclusion

As a result, transethosomes consisted of Phospholipon 90G, Tween 80 and ceramide III, could be a feasible formulation for ceramide replacement in the skin, because of small size and narrow size distribution. However, more characterization studies and *in vivo* experiments are required to assess conformity of this formulation.

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