Novel Delivery System for Insoluble Active Ingredients in Cosmetics

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Abstract

Clean beauty, currently a major trend in cosmetics, advocates the use of cleaner, greener, more natural, and safer cosmetic ingredients. PEG- and silicone-free surfactants are the most popular, as they are the main building blocks of thickeners and emulsifiers for cosmetics. The applications of conventional insoluble ingredient stabilization, which is based on liposome technology, are limited in the cosmetic field due to low solubility, short half-life, and high production cost. Herein, we introduce a system that can stabilize a large amount of insoluble ingredients, such as pseudo-ceramide, and provide clean beauty. We focused on the preparation and characterization of lipid carriers that serve as colloidal carriers for pseudo-ceramide. Surfactant screening showed that the most suitable surfactants are polyglyceryl-10 stearate, a PEG and PPG-free surfactant, which is suitable for clean beauty trend. We also developed an optimized lipid carrier that enables the formation of a multilayer structure; this carrier contains disteardimonium hectorite, polyglyceryl-10 stearate, caprylic/capric triglycerides, phytosterol, stearic acid, and pseudo-ceramide. For the structural analysis of the emulsion containing the lipid carrier, microscopy and cryo-SEM were conducted. Furthermore, Turbiscan analysis showed that emulsions containing lipid carriers were more stable than those containing liposomes. Our results also indicated that the emulsion surface contains disteardimonium hectorite, which might be a contributor to its increasing stability. Furthermore, we examined the

moisturizing effect of a cream containing pseudo-ceramide and found it to be more effective than general commercial ceramide cream. Based on these findings, disteardimonium hectorite–based lipid carriers are expected to play an important role as stable insoluble ingredient delivery systems in cosmetics.

Keywords: clean beauty; pseudo-ceramide; multilayer structure; disteardimonium hectorite; insoluble ingredients, hectorite-based lipid carrier

Introduction

Clean beauty, which advocates the use of cleaner, greener, more natural, and safer cosmetic ingredients, is currently a major trend in cosmetics. Among the surfactants used to realize clean beauty, PEG- and silicone-free ingredients have garnered the most attention, as they are the main building blocks of thickeners and emulsifiers for cosmetics [1]. Naturally abundant clay particles such as hectorite and laponite have been widely used in various fields. Recently, the use of hectorite has increased, owing to its beneficial properties such as null toxicity, chemical inertness, specific surface area, and cation exchange capacity [2]. However, research on the use of surface-modified hectorite as a stabilizer for insoluble active ingredients in cosmetics is lacking.

Ceramides are the major components of intercellular lipids in the stratum corneum and play a crucial role in the barrier function and moisture retention ability of the skin, which, when damaged or aged, exhibits low ceramide levels in the stratum corneum [3, 4]. Hydroxypropyl bispalmitamide MEA is a synthetic pseudo-ceramide, which has been found to display functions similar to those of natural ceramides when applied to damaged or dried skin [5, 6]. The barrier properties of this MEA can be enhanced by adding components such as fatty acids and cholesterol. Despite their contribution to skin barrier function, pseudo-ceramides are difficult to apply in cosmetic formulations with high concentrations due to their high crystallization [7]. Therefore, recent research on the skin delivery system has been aimed at the effective stabilization and delivery of the insoluble ingredients through the skin barrier into the skin, with emphasis on the role of liposomes

[8-10]. Liposomes are double phospholipid structures comprising phospholipids that can support both hydrophilic and lipophilic active ingredients. However, liposomes have several disadvantages, such as low active ingredient loading efficiency, physicochemical instability, and complicated manufacturing processes [11]. Therefore, further research on a novel active ingredient delivery system is required.

Herein, we focus on the preparation and characterization of a disteardimonium hectorite–based lipid carrier, which serves as a colloidal carrier for pseudo-ceramide. The most stable composition was selected and applied to the O/W formulation to analyze its structural properties, and comparative studies on its stability and moisturizing effect were conducted.

Materials and Methods

2.1. Materials

Polyglyceryl-10 stearate was procured from Nikkol Chemicals Co., Ltd. (Japan). Coco-caprylate/caprate was procured from BASF (Germany). Hydroxypropyl bispalmitamide MEA was procured from Daebong LS Co., Ltd. (Republic of Korea). Stearic acid was procured from IOI Acidchem, Sdn. Bhd. (Malaysia). Phytosterols were procured from Shaanxi Healthful Bioengineering Co. Ltd. (China). All other raw materials used in this study were of cosmetic grade.

2.2. Equipment

An agi-mixer unit (PL-SS11D, Republic of Korea) was used as a general emulsifier, and crystallinity confirmation was observed using a Nikon Optophoto 2-POL polarizing microscope (Japan).

2.3. Computational calculations

Biovia Materials Studio was used to simulate the molecular modeling of synthetic ceramide (hydroxypropyl bispalmitamide MEA), and several emulsifiers. As shown in Fig. 2, geometry optimization and cell construction were conducted using Forcite and Amorphous Cell modules, respectively. The proposed structures were geometrically optimized and equilibrated before simulating mechanical tests. Geometry optimization was

conducted by the Forcite module using the atom-based summation method and smart algorithms at medium convergence tolerance and universal forcefield with an energy of 0.001 kcal/mol and force of 0.5 kcal/mol/A°. The Forcite module performs molecular mechanics calculations for a wide range of systems. Molecular dynamics simulations were performed using a sequence of canonical ensemble (NVT) and Berendsen barostat calculations at 298 K and 1 atm with a time step of 1 fs and a velocity scale thermostat for system temperature and pressure conversion. These simulations were also conducted using an NVE system at the same conditions.

2.4. Preparation of the O/W emulsion containing the hectorite-lipid carrier

A cream containing 5% of the lipid carrier was prepared to confirm the stability and efficacy of the lipid carrier in cosmetics; the composition of this cream is summarized in Table 1. The cream containing no lipid carriers was used as a buffer. To ensure skin safety, some of the ingredients listed in Table 1, namely, PEG, PPG surfactants, and silicone oils, were not used; furthermore, only EWG green-grade raw materials were carefully selected to develop a formulation. The cream was prepared by emulsifying and mixing for 5 min at 1200 rpm and room temperature.

During the preparation of this cream, the organic and aqueous phases were weighed, heated to 80 ℃, and then completely dispersed. Using a homomixer, the organic phase was slowly introduced into the aqueous phase and emulsified in the range of 3500–4000 rpm for 5 min. TMA was then added and stirred at 3500 rpm for 3 min to neutralize the reaction. After cooling to 50 ℃, phase D was added, stirred, cooled to room temperature, and deformed to prepare a cream. The buffer cream was prepared under the same conditions and methods. The prepared cream was left for 24 h, and the following experiments were performed.

Table 1. Ingredients of the O/W emulsions

Ingredient		Formulation (w/w, %)			
		O/W cream	O/W cream with the hectorite-lipid carrier	O/W cream with liposome	O/W cream with pseudo-ceramide
A	Water	Up to 100	Up to 100	Up to 100	Up to 100
	Carbomer	0.15	0.15	0.15	0.15
	1,3-Butylene glycol	5	5	5	5
	Glycerin	2	2	2	2
B	Hydroxypropyl bispalmitamide MEA	-	-	-	0.5
	Phytosterols	-	-	-	0.25
	Stearic acid	-	-	-	0.25
	Hydrogenated lauryl olive esters	4	4	4	4
	Medofoam seed oil	2	2	2	2
	Hydrogenated polydecene	3	3	3	3
	Arachidyl alcohol/behenyl alcohol/arachidylglucoside	1	1	1	1
	Polyglyceryl-10 oleate	4	4	4	4
	Cetyl alcohol	1	1	1	1
	Squalane	3	3	3	3
	Butyrospermum parkii (shea) butter	1	1	1	1
	Dipentaerythrityl hexahydroxystearate/hexastearate/hexarosinate	3	3	3	3
C	Water	5	5	5	5
	Trimethylamine	0.15	0.15	0.15	0.15
	1,2-Hexanediol	1	1	1	1
	Ethylhexylglycerin	0.1	0.1	0.1	0.1
D	Hectorite-lipid carrier	-	5	-	-
	Liposome	-	-	5	-

2.5. Turbiscan analysis

Existing particle stability evaluation methods require dilution, rendering accurate particle analysis impossible. However, as cosmetic stock can be measured without dilution by Turbiscan analysis, the correlation between the emulsified particles in the cosmetic can

be derived with an accurate numerical value. In this study, the experimental temperature was kept constant at 50 ± 3 ℃, and the stability of the emulsion was measured for three days. The sample (20 mL) was placed in a glass container for Turbiscan analysis using a syringe, such that no air bubbles were generated. The backscattering (BS %) level of the emulsified particles was evaluated after labeling. The measurement principle is schematically represented in Fig. 1.

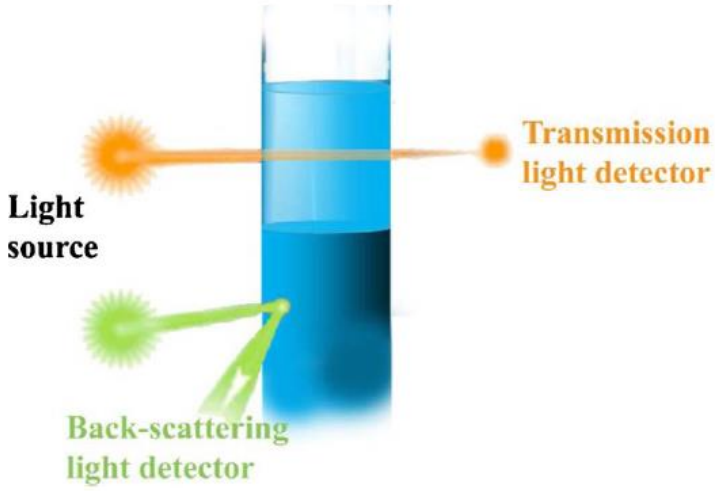

Fig. 1 Schematic principle of Turbiscan analysis.

2.6. Measurement of TEWL

O/W cream was applied once evenly to the volar forearm of the participants in a double-blind manner. The opposing volar forearm served as an untreated buffer. Before every set of measurements, participants were required to equilibrate in a closed environment at a constant temperature (20 ± 2 ℃) and humidity (45%–55% RH). TEWL was measured using GPSkin Barrier® (GPOWER Inc., Republic of Korea) at t = 0 (pre-application) and at 0.5, 1, 3, 5, and 7 h (post-application). Any adverse effects observed during the entire study period were documented by the investigator.

2.7. Statistical analysis

All experiments were replicated three times, and the values are expressed as mean ± standard deviation. Statistical comparisons were performed using one-way ANOVA (SPSS 17.0, USA). Differences in means were considered statistically significant at $p < 0.05$.

Results and Discussion

3.1. Optimization of the hectorite-lipid carrier

In physics and chemistry, binding energy is defined as the minimum amount of energy required to remove a particle from a system of particles or to disassemble a system of particles into individual parts [12]. The binding energy between the pseudo-ceramide and emulsifier should be sufficiently high to encapsulate a sufficient amount of pseudo-ceramide. Therefore, this study aimed to determine the optimal composition of the hectorite-lipid carrier that can inhibit the crystallization of pseudo-ceramide, such that the final cosmetic formulation contains at least 5000 ppm of pseudo-ceramide. Several emulsifiers have been tested for this purpose. As shown in Fig. 2, polyglyceryl-10 distearate exhibits the highest binding energy among the tested emulsifiers.

Experiments showed that polyglyceryl-10 distearate was the best at inhibiting the crystallization of pseudo-ceramide in the O/W emulsion (data not shown), in agreement with the simulation results. Based on these findings, an optimized hectorite-lipid carrier was developed and used in further experiments, which contained disteardimonium hectorite, polyglyceryl-10 stearate, caprylic/capric triglyceride, phytosterol, stearic acid, and pseudo-ceramide.

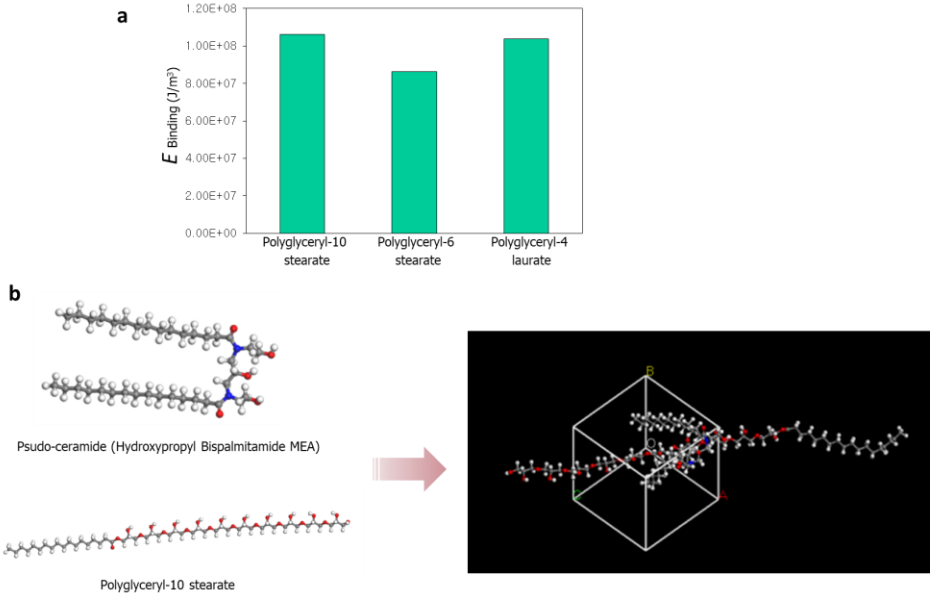

Fig. 2 Binding energy of pseudo-ceramide molecule with emulsifiers (a). Model of the pseudo-ceramide molecule and polyglyceryl-10 stearate (b). The gray, white, red, and blue spheres represent C, H, O, and N atoms, respectively.

3.2. Morphology characterization of the emulsion containing the hectorite-lipid carrier

To determine the shape and surface morphology of the optimized O/W emulsion containing the hectorite-lipid carrier, bright field, crossed polarizing microscopy, and cryo-SEM were conducted. Fig. 3a and b show that the emulsion that contains the hectorite-lipid carrier gradually forms a Maltese cross pattern after 2 weeks at 50 ℃. This indicates that a multilayer structure was formed in the emulsion. Cryo-SEM was used to observe the multilayers of the frozen emulsion (Fig. 3c and d); clearly, the emulsion is spherical with a multilayer structure on its surface, while the lipid carrier is well dispersed in the formulation and does not form crystalline pseudo-ceramide.

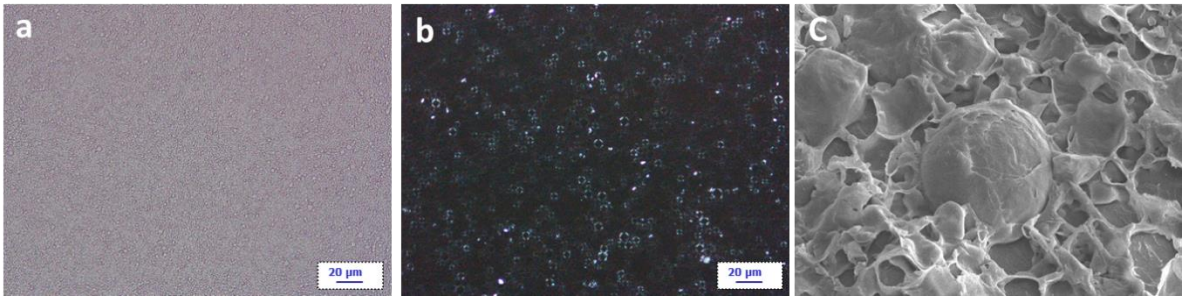

Fig. 3 Morphology of O/W emulsion with hectorite-lipid carrier was characterized by bright field(a), crossed polarized (b), and Cryo-SEM microscopes.

3.3. Stability analysis of the emulsion containing the hectorite-lipid carrier

The stability of emulsified particles in cosmetic formulations containing a hectorite-lipid carrier was analyzed by Turbiscan analysis at 50 ℃ for 3 d. A low Turbiscan stability index (TSI) indicates high stability. The O/W cream without pseudo-ceramide, O/W cream with liposomes containing the same amount of ceramide, and O/W cream prepared by adding pseudo-ceramide in the organic phase were set as control groups. Fig. 4 shows the following values of TSI: O/W cream (TSI = 1) ≈ O/W cream with a hectorite-lipid carrier (TSI = 1.2) < O/W cream with liposomes (TSI = 1.9) < O/W cream with pseudo-ceramide (TSI = 3.1). This implies that the O/W cream with a hectorite-lipid carrier is the most stable with a level similar to that of the O/W placebo cream. Furthermore, the backscattering intensity of the O/W cream with the hectorite-lipid carrier is very similar to that of the O/W cream, while the change of backscattering intensity is the least. This is because DDAC-hectorite, a component of the hectorite-lipid carrier, increases the hardness of the interfacial

film of the emulsion and stabilizes the formulation containing pseudo-ceramide [13]. These results are consistent with those of previous studies that suggested that ceramide is difficult to apply to formulations because of its high crystallinity [14], and that liposomes are unstable when applied to cosmetics because of their short half-life [15].

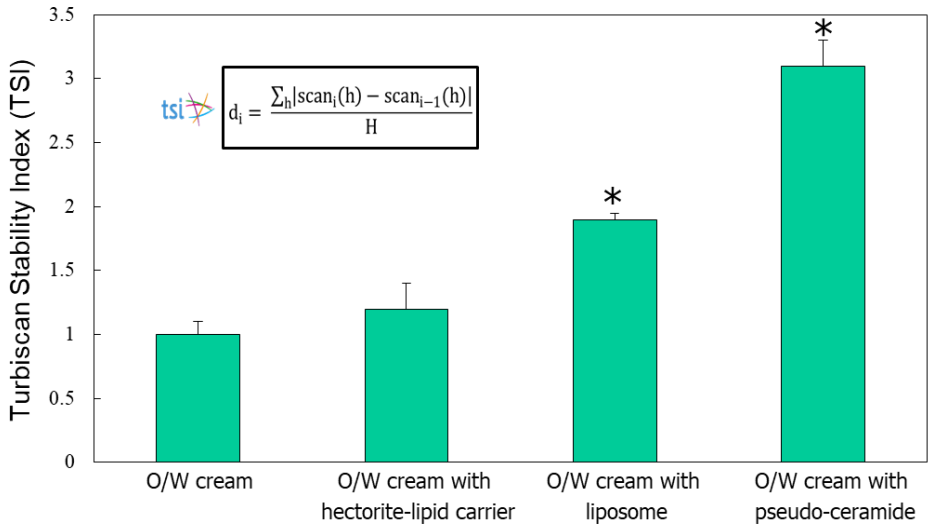

Fig. 4 Stability analysis of O/W cream, O/W cream with Hectorite-lipid carrier, O/W cream with Liposome, and O/W cream with pseudo-ceramide by Turbiscan for 3days at 50 ℃. All data represented mean ± SD of three replicates, as compared with the O/W cream (*$p < 0.05$).

3.4. Evaluation of moisturizing efficacy

Four participants (one male and three females) aged 21–35 y participated in the study. All participants completed the study, and no adverse effects were observed. The mean difference in the TEWL measurements ($g/m^2/h$) for each sample that was tested for over 7 h is shown in Fig. 5. There were no significant differences in TEWL at any point. A single topical application of either the O/W cream with a hectorite-lipid carrier or the O/W reference product significantly reduced TEWL over time. The O/W cream with a hectorite-lipid carrier showed the largest decrease in TEWL compared to the O/W reference product from 30 min to 7 h post-application. Furthermore, 7 h after the application, the O/W cream with the hectorite-lipid carrier continued to exhibit a significantly greater decrease in TEWL compared to the O/W reference product.

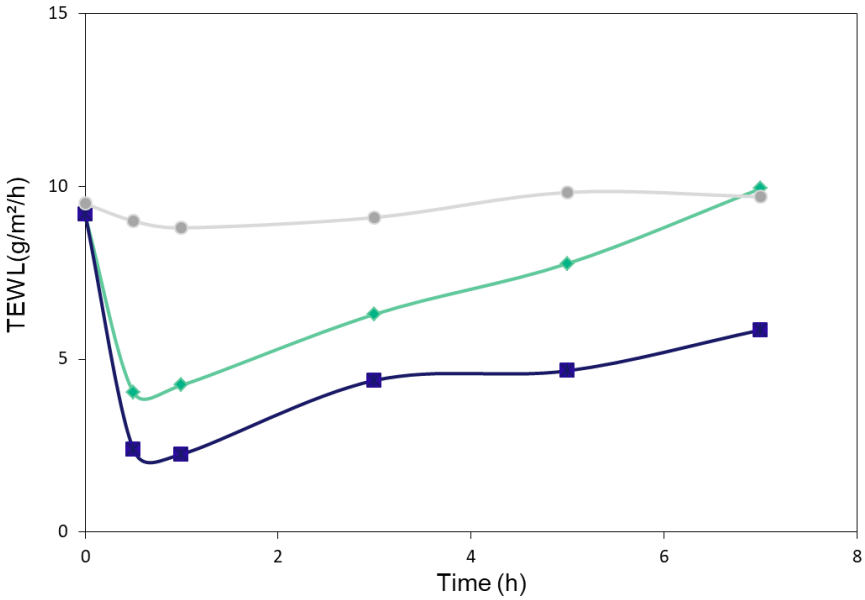

Fig. 5 TEWL measurements (g/m²/h) over time following the single application of (■) O/W cream with the hectorite-lipid carrier, (♦) O/W reference product, and (●) bare skin.

Conclusion

In this study, hectorite technology, which is applied in pharmaceuticals, was introduced into the stabilization system of insoluble ingredients in cosmetics. A lipid carrier comprising hectorite-DDAC, surfactant, oil, and pseudo-ceramide was applied to the O/W-type emulsion, and the formation of a multilayer structure was confirmed by cryo-SEM. In addition, Turbiscan analysis confirmed that the emulsion containing the hectorite-lipid carrier had better stability than that of the emulsion containing the liposome. As shown in Fig. 6, the surface-modified hectorite was arranged at the interface of the emulsified particles, which may be a contributor to the improvement in stability. In addition, when an emulsion containing the hectorite-lipid carrier was applied to the skin, it showed an excellent moisturizing effect. Based on these findings, disteardimonium hectorite–based lipid carriers are expected to play an important role as stable insoluble ingredient delivery systems in cosmetics.

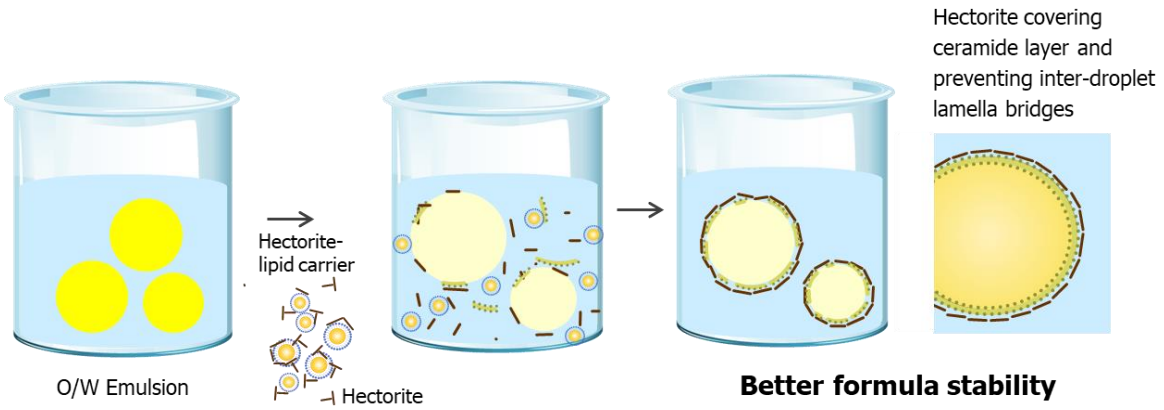

Fig. 6 Brief paragraph that summarizes the major achievements of the research.

Acknowledgments.

NONE.

Conflict of Interest Statement.

NONE.

References

1. Lee J, Kwon KH (2022) Sustainable changes in beauty market trends focused on the perspective of safety in the post-coronavirus disease-19 period. J. Cosmet. Dermatol. 00:1-8.

2. Zhang J, Zhou CH, Petit S, et al (2019) Hectorite: Synthesis, modification, assembly and applications. Appl. Clay Sci. 177:114-138.

3. Cha HJ, He C, Zhao H, et al (2016) Intercellular and intracellular functions of ceramides and their metabolites in skin (Review). Int. J. Mol. Med. 38(1):16-22.

4. Harrison IP, Spada F (2019) Breaking the Itch-Scratch Cycle: Topical Options for the Management of Chronic Cutaneous Itch in Atopic Dermatitis. Medicines. 6(3):1-14.

5. Kim DH, An EJ, Kim J, et al. (2009) Fabrication and characterization of pseudo-ceramide-based liposomal membranes. Colloids Surf. B. 73(2):207-211.

6. Kim AR, Lee NH, Park YM, et al (2019) Preparation and characterization of novel pseudo ceramide liposomes for the transdermal delivery of baicalein. J Drug Deliv Sci Technol. 52:150-156.

7. Yoon J, Noh M, Lee JB, et al (2020) Highly Sustainable and Completely Amorphous Hierarchical Ceramide Microcapsules for Potential Epidermal Barrier. Polymers. 12(9):1-12.
8. Allen TM, Cullis PR (2013) Liposomal drug delivery systems: from concept to clinical applications. Adv. Drug Deliv. Rev. 65(1):36-48.
9. Rayamajhi S, Marchitto J, Nguyen TDT, et al (2020) pH-responsive cationic liposome for endosomal escape mediated drug delivery. Colloids Surf. B. 188:110804.
10. Huang M, Su E, Zheng F, et al (2017) Encapsulation of flavonoids in liposomal delivery systems: the case of quercetin, kaempferol and luteolin. Food & function. 8(9):3198-3208.
11. Li W, Yu L, Liu G, et al (2012) Oil-in-water emulsions stabilized by Laponite particles modified with short-chain aliphatic amines. Colloids Surf. A: Physicochem. Eng. Asp. 400:44-51.
12. Rohlf JW (1994) Modern Physics from α to Z°. John Wiley & Sons. p.20.
13. Cho YS, Lee SH, Seo HM, et al. (2021) Structuring Pickering Emulsion Interfaces with Bilayered Coacervates of Cellulose Nanofibers and Hectorite Nanoplatelets. Langmuir. 37(13):3828-3835.
14. Vovesna A, Zhigunov A, Balouch M, et al (2021) Ceramide liposomes for skin barrier recovery: A novel formulation based on natural skin lipids. Int. J. Pharm. 596:120264.
15. Manaia EB, Abucafy MP, Chiari-Andreo BG, et al (2017) Physicochemical characterization of drug nanocarriers. Int. J. Nanomed. 12:4991-5011.