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Liquid crystal applications and benefits

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1. Introduction

Liquid crystals have been increasingly utilized in various cosmetic and pharmaceutical areas. Liquid crystals were capable of enhancing their own stability, prolonged moisturization and improving the solubility of substances with low water solubility or those present in the oily phase. They can also regulate the release of drugs encapsulated within their structure and facilitate the hydration of the skin surface [1-4]. Liquid crystals (LC) possess a unique state of matter, combining the fluidity of liquids with the ordered structural features of crystalline solids. Depending on their formation mechanisms, LC can be categorized into two main types: thermotropic LC and lyotropic LC. Thermotropic LC arise from changes in temperature within the liquid state, whereas lyotropic LC were created by dissolving specific compounds in suitable solvents [2]. In order to generate stable and enhanced LC format, D. Terescenco et. al. investigated the interactions between the surfactant (alkyl polyglucoside/fatty alcohol) and different kinds of emollients, to form lamellar LC [5]. The emollient studied was widely used in the cosmetic field, with different hydrophobicity. For the emollients with high hydrophobicity, the formation of the lamellar liquid phase was less present or totally absent; For the emollient with less hydrophobicity, lamellar LC formation around the droplets was observed. Different emollients will affect the droplet size, shape and distribution, viscoelastic characteristics and spreading properties. In cosmetic area, LC also has a lot of applications, due to its unique characteristic properties such as prolonged moisture retention, superior rheological properties and controlled release of actives. Li et. al studied the application of 3-O-ethyl-ascorbic acid (EA) and potassium 4-methoxysalicylate (4-MSK) formulated into lamellar liquid crystalline (LLC) cream via topical administration for effective skin-whitening [6]. They made a comparison analysis of the skin retention of the two drugs between the LLC cream and the common o/w (COW) cream, with result showed that the LLC cream significantly increased the skin retention of EA and 4-MSK both in vitro and in vivo. In addition, Lee et al. studied the LC emulsions with fatty alcohol to stabilize high ceramide content in cosmetics, by incorporating fatty alcohol and surfactants which contributing to forming higher-order structures. Their result showed that up to 3% ceramide can be incorporated into the formulation, maintaining stability for 12 weeks at room temperature and avoiding recrystallization due to the high order structure. They showed that LC emulsions also significantly improved skin barrier recovery.

This paper focused on the applications and benefits of LC in skincare. We investigated various factors affecting the liquid crystal effect, including the effect of emulsifiers, the polyols, the fatty alcohol and the emollients. In addition, we studied the characteristics of LC emulsion, through the polarization microscopic observation, the rheological approach and sensory evaluation. Furthermore, we studied the benefits of LC formation on the controlled release of actives through Franz cell transdermal tests. Finally, we found the synergistic effect of cermaides with LC format, proving LC as a promising carrier for ceramide, while enhancing skin barrier function.

2. Materials and Methods

2.1 Materials

Emulsifiers such as Sorbitan Stearate (and) Sucrose Cocoate, Glyceryl Stearate (and) PEG 100 Stearate), Glyceryl Stearate, were used. Fatty alcohols such as Stearyl alcohol, Cetyl alcohol, Cetearyl Alcohol and emollients such as Caprylic/capric triglyceride (GTCC), Triethylhexanoin, Pentaerythrityl Tetraisostearate, Avocado oil, Olive fruit oil and Tomato seed oil were chosen for the oil phase. Thickeners, preservative and actives were from different suppliers on market. All other chemicals were of the highest reagent grade available.

2.2 Formulation preparation methods:

The O/W LC cream were prepared by hot process emulsification. The formulation in Table1 was taken for example. The ingredients in part A in the main beaker were dissolved in a hot bath at 75 °C for 30 minutes; and then the ingredients in Part B were heated, mixed and added into the main beaker; and then the mixture was homogenized at 5000 rpm for 5 minutes. The mixture was then stirred at 200 rpm for cooling down and adding phase C.

Table 1 Formulation sheet of LC emulsion

INIC name	wt%
Phase A	
Wate	81.0
Glycerine	1.5
Xanthan gum	0.15
Sorbitan Stearate (and) Sucrose Cocoate	5.0
Phase B	
Stearyl Alcohol	1.5
Caprylic/Capric Triglyceride	10.0
Phase B	
Citric Acid	0.05
Phenoxyethanol (and) Ethylhexylglycerin	0.8

2.3 Physiochemical Characterization

2.3.1 Microscopy

The microstructure of the emulsion was investigated by polarized light microscope (Olympus, BX53), with a 40X objective and 10X ocular. Firstly, the sample was observed under the bright field and secondly, under the polarized light (using cross-polarizers) in order to

investigate the presence of the LC state in each sample. Software VistarImage was used to analyze the obtained micrographs.

2.3.2 Rheological measurements

The rheological study of the samples was conducted by the strain sweep method in the oscillatory mode at constant frequency of 1Hz, through the rheometer MCR 92 from Aton Paar. In addition, viscosity over a range of shear rate was investigated through steady shear mode for study of the shear shinning behavior of the samples. The rheological geometry applied was CP 50 with gap size 0.106 mm. The samples were trimmed during the measurement to make sure the repeatability of the data.

2.3.3 Sensory evaluation

Sensory evaluation of the samples was performed by internal volunteers, who were given the training of sensory attributes of benchmarks. They were asked to evaluate the samples and provide the score of each individual sensory attributes during application and after application based on the internal sensory evaluation protocol.

2.3.4 Transdermal experiments.

The skin penetration study of actives was modelled with the Franz Cell experimental set up. The mimicked skin membrane, the Strat-M was purchased from Merck Millipore, it was a polymeric membrane to replicate skin-like permeation process. About 2 mL of the emulsion containing the active substance was placed above the membrane in top chamber of the Franz cell. The lower part of the cell was placed in the water bath of the Franz cell equipment from YuLin at temperature of 36 ° C and a flow speed of 200 rpm, to mimic the skin permeation process. Samples from the receiver of the Franz cell below was collected at time intervals of 6, 24, 48 hours. The collected samples were then filtered through a 0.22 μm filter, and stored at 4° C for later HPLC analysis.

3. Results

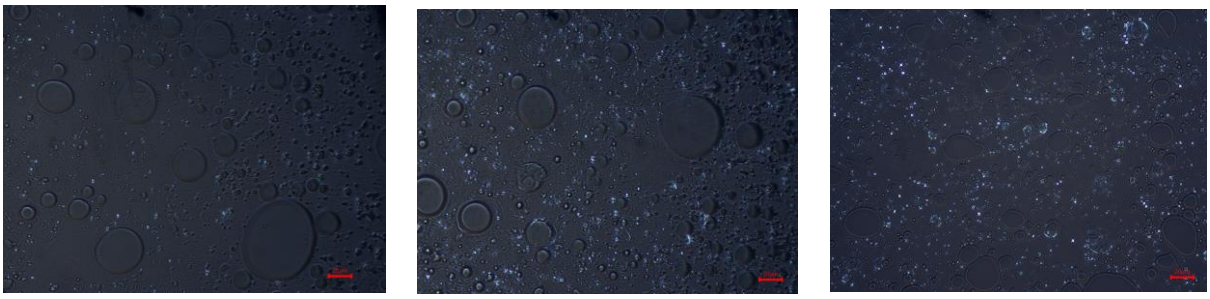
3.1 Factors affecting the liquid crystal effect

The LC emulsifier studied in this part was Sorbitan Stearate (and) Sucrose Cocoate. It was an optimised emulsifier, with critical packing parameter (CPP) approximately 1, which maximises the benefits of generating LC format and lamellar crystalline gel network formation. The formulation sheets applied in this part were derived from Table 1.

3.1.1 Effect of liquid crystal emulsifier

Different dosages of emulsifier were studied, with the purpose to verify the minimum dosage of LC emulsifier that can stabilize the emulsion and maintain a certain LC effect. The results showed that, for the chassis shown in Table 1, when the dosage of the emulsifier was reduced to 3% or less, the viscosity was very low and the system cannot be stabilized after 3 freeze-thaw cycles. The investigation of polarized microscope images was applied with LC emulsifier above 3%. Compared with the 5% and 6% LC emulsifier, for the formulation with

4% emulsifier, the LC effect was less obvious (Figure 1). In addition, the LC effect of the formulation with 6% LC emulsifier was not significantly enhanced, compared with the one with 5%. As a result, 5% of LC emulsifier was used for further investigation.

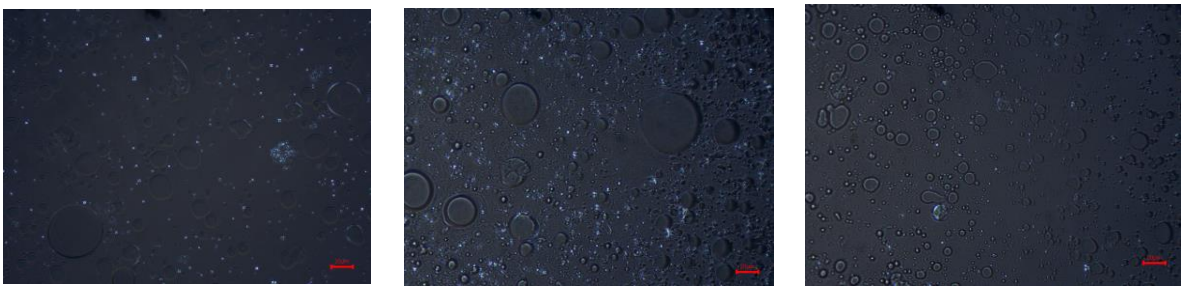


(a) **(b)** **(c)**

Figure.1 Polarization microscope image of LC cream. (a) with 4% LC emulsifier; (b) with 5% LC emulsifier; (c) with 6% LC emulsifier.

3.1.2 Effect of Polyols

Polyols, such as glycerin, were widely used in cosmetic formulations for their moisturizing benefits. In this part, the addition of different amount of glycerin was investigated for the effect of LC formation. For the chassis with 1.5% glycerin, the dispersion of thickener was insufficient, and the system was not uniform enough, hence less LC formation in the system (Figure 2 a). After doubling the amount of glycerin addition (Figure 2 c), the LC effect was also reduced, which may be due to the interaction of excess glycerin with the hydrophilic part of the emulsifier, causing reduced the regularity and less arrangement of the LC. Finally, the concentration of glycerin of 2.25% was applied, with concentration in between for the benefits of both dispersion and LC effect (Figure 2 b).



(a) **(b)** **(c)**

Figure.2 Polarization microscope image of LC cream. (a) with1.5% glycerin; (b) with 2.25% glycerin; (c) with 3% glycerin.

3.1.3 Effect of Fatty alcohols

In this part, different fatty alcohols with various chain length were investigated, namely cetyl alcohol, cetearyl alcohol and stearyl alcohol. The amount of fatty alcohol was chosen with 3% to enhance stability of the formulation. Polarized light microscopy was applied to observe the LC effect. The results were shown in Figure 3, indicating that the strong LC effect from the

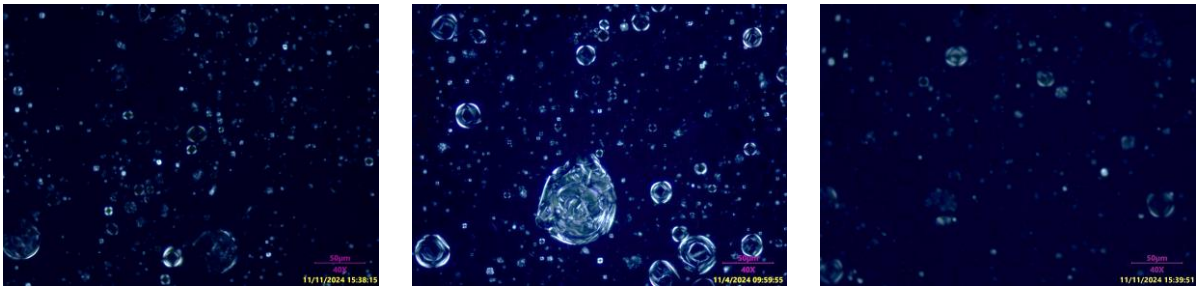
formulation with cetyl alcohol. The reason for that was probably due to the source of the emulsifier with the presence of fatty acids with multiple carbon chain lengths in cocoic acid; and the relatively short chain of cetyl alcohol in the mosaic of emulsifier and fatty alcohols could better strengthen the LC system.

(a) **(b)** **(c)**

Figure.3 Polarization microscope image of LC cream. (a) with 3% stearyl alcohol ; (b) with 3% cetearyl alcohol; (c) with 3% cetyl alcohol.

3.1.4 Effect of emollients

Liquid crystal emulsifiers such as Sorbitan Stearate (and) Sucrose Cocoate exhibit a strong ability to hold oils and fats in formulations. The emollient applied was GTCC, in the formulation with dosage from 8% to 12%. The results showed in Figure 4 indicating that the reduction of emollient did not significantly improve the LC effect; However, the increase of emollient led to the decrease of LC effect. This was probably due to the reason that the increase of oil relatively reduced the proportion of LC emulsifier per oil, and less multilayer formation during the formulation process. A single layer of emulsifier will not show the LC effect. In addition, various emollients with 10% content in the formulation were studied. Since the emulsifier was not HLB-dependent, it can emulsify a wide range and concentrations of oils. The oils studied here included different polarity, origins and chemical compositions, namely Caprylic/capric triglyceride (GTCC), Triethylhexanoin, Pentaerythrityl Tetraisostearate, Avocado oil, Olive fruit oil and Tomato seed oil. The samples with different oils in the formulation all showed the LC benefits; however the droplet sizes and LC effect varied for different oils in the formulation. As a result, combination of oils for optimized sensory and LC effect was applied in the further study.



(a) **(b)** **(c)**

Figure.4 Polarization microscope image of LC cream. (a) with 8 % GTCC; (b) with 10 % GTCC; (c) with 12 % GTCC.

3.2 Characteristics of liquid crystal formation

There were significant differences between LC and ordinary emulsions in both microscopic and macroscopic characteristics. These differences bring many benefits for LC emulsion, for example, superior sensory and sustained release of actives. The following discussion will include the microstructure of LC, rheological data, skin sensory assessment, and the application of LC in the sustained release of active substances.

The formulations of the samples were S-LC and S-control. Other ingredients and the dosage of the emulsifier were kept the same, only changing the type of the emulsifiers, which were LC emulsifier Sorbitan Stearate (and) Sucrose Cocoate and control emulsifier Glyceryl Stearate (and) PEG 100 Stearate, as shown in Table 2.

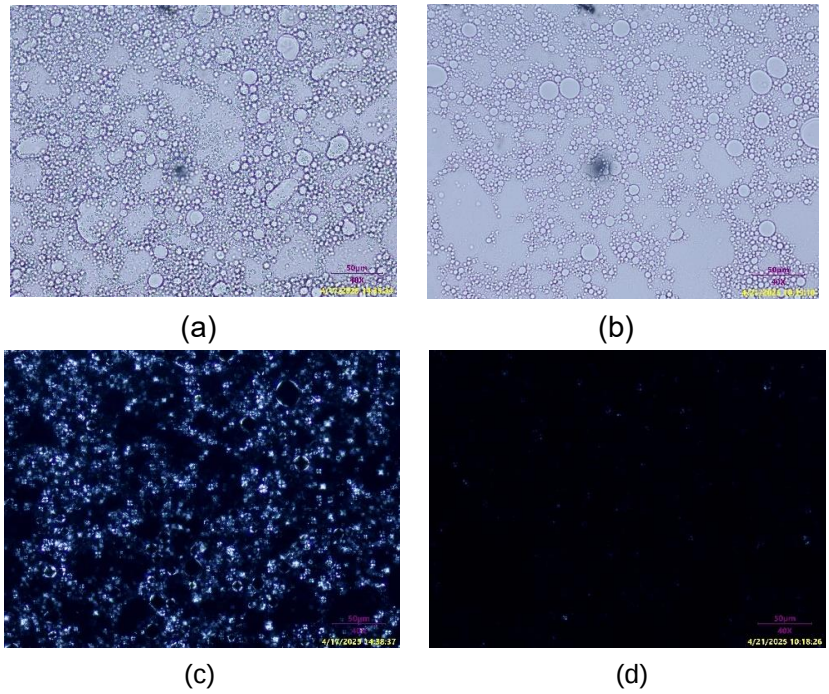
Table 2 Formulation sheet of LC emulsion (Sample S-LC and S-Control)

	S-LC	**S-Control**
Ingredient/INCI Name	**% w/w**	**% w/w**
Part A		
Deionized Water	To 100	To 100
Glycerin	10.0	10.0
Xanthan Gum	0.1	0.1
Disodium Edta	0.05	0.05
Allantoin	0.2	0.2
Acrylates/Beheneth-25 Methacrylate Copolymer	0.5	0.5
Carbomer	0.1	0.1
Sorbitan Stearate (and) Sucrose Cocoate	4.0	-
Glyceryl Stearate (and) PEG 100 Stearate	-	4.0
Part B		
Cetearyl Alcohol	2.0	2.0
Cyclopentasiloxane	8.0	8.0
Pentaerythrityl Tetraisostearate	1.0	1.0
Diethylhexyl Succinate	4.0	4.0
Triethylhexanoin	1.0	1.0
Olea Europaea (Olive) Fruit Oil	1.5	1.5
Squalane	1.5	1.5
Tocopheryl Acetate	0.5	0.5
Dimethicone	2.0	2.0
Part C		
20% NaOH	0.06	0.06
Part D		
Imperata Cylindrica Root Extract (and) Water (and) Glycerin (and) PEG- 8 (and) Carbomer	3.0	3.0
Butylene Glycol (and) Propanediol (and) Mirabilis Jalapa Extract	3.0	3.0

Water (Aqua) (and) Caprylic/Capric Triglyceride (and) Cetyl Palmitate (and) Sorbitan Stearate (and) Polysorbate 80 (and) Hydrogenated Lecithin (and) Palmitoyl Tetrapeptide-10	3.0	3.0
Part E		
Phenoxyethanol (and) Ethylhexylglycerin	0.8	0.8

3.2.1 Microscopic observations

The microstructure of the emulsion was investigated by a polarized light microscopy method (Olympus, BX53), with a 40X objective and 10X ocular. Firstly, the samples were observed under the bright field; and then, the samples were investigated under the polarized light (using cross-polarizers). The microscopic images of sample S-LC and S-control were shown in Figure 5. Under the bright field, the droplets of the internal phase were relatively similar compared with the two samples, indicating similar emulsifying capabilities. However, under polarized light, the sample S-LC showed strong LC effect and the sample S-control showed almost no LC effect. This was due to the formation of layered LC in the presence of the LC emulsifier, which had an anisotropic structure, and was orderly arranged. When it was observed between two crossed polarizers, it showed a birefringent phenomenon; and that it appeared bright through the images. For the control sample, there was no such phenomenon observed.



(a) (b)

(c) (d)

Figure 5. Microscopic images of sample S-LC and S-control. (a): bright light S-LC; (b): bright light S-control; (c): polarized light S-LC; (d): polarized light S-control.

3.2.2 Rheological approach

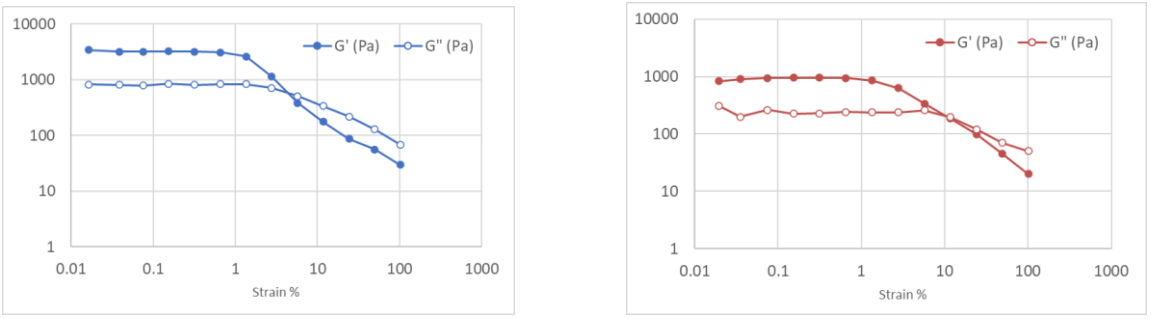
The rheological behavior of liquid crystal and the control was investigated by the strain sweep method with strain from 0.01 to 100 % at constant frequency of 1Hz and steady shear

method with shear rate from 0.1-1000 1/s. The results were shown in Figure 6. From the strain sweep results, the storage modulus G' for the LC form was almost three times higher than the one for the control, which indicating more interactions between networks on microscopic scale. The lamellar formation of LC and more bound water formed brought more connections and interactions between networks, which also helped to improve the stability of the sample. The results about shear thinning behavior for both of the samples was indicated in Figure 7, from shear rate 0.01 to 1000 1/s. Compared with control, the LC emulsion shows higher viscosity over the applied shear rate. The Herschel-Bulkley model was applied to describe the shear thinning behavior, with the equation shown in eqn. (1) and the fitting data was also shown in Figure 8. The parameters from the model were shown in Table 3, with yield stress σ_0 and the shear thinning index n. The results showed that for LC structure holds higher yield stress, indicating LC emulsion with improved product stability, while had similar shear thinning behavior with the control sample. The rheological behavior indicates the superior sensory of the LC format, high stability and high spreadability.

$$\boldsymbol{\sigma = \sigma_0 + k\dot{\gamma}^n} \quad (1)$$

Table 3 Parameters from the modelling of the shear viscosity profile

Sample	$\boldsymbol{\sigma_0}$ (Pa)	$\boldsymbol{n}$
S-LC	24.4	0.38
S-Control	10.5	0.38



(a) (b)

Figure 6. Strain sweep of sample (a) S-LC and (b) S-control.

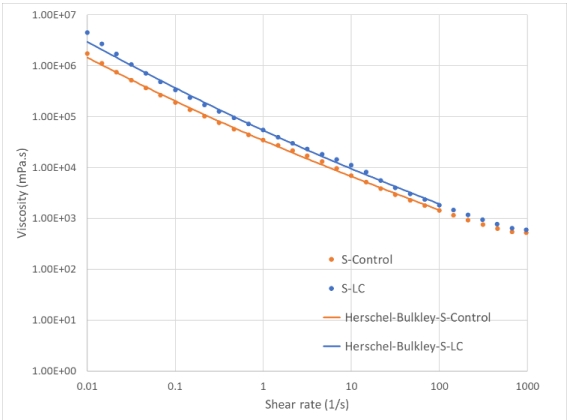


Figure 7. The profile of viscosity versus shear rate of sample S-LC and S-control

3.2.3 Sensory evaluation

The sensory evaluation of the sample S-LC and S-control was performed according to the internal sensory evaluation form with attributes scaling from 0-10. The results were compared with the internal benchmarks with fixed scores on attributes and analyzed with subtraction of the scores from benchmarks. The results were shown in Figure 8. Figure 8a) showed the comparison of sensory during application, between sample S-LC and S-control. The LC form showed better spreadability, absorption, freshness and softness and less greasiness during application. In addition, the sensory was evaluated 10 minutes after application (Figure 8 b)), on the attributes of Stickiness and greasiness, the scores were almost same for the two samples. However, the LC form showed higher performance on attributes of softness and moisturization after application, indicating LC emulsion as a superior sensory format for cosmetic applications.

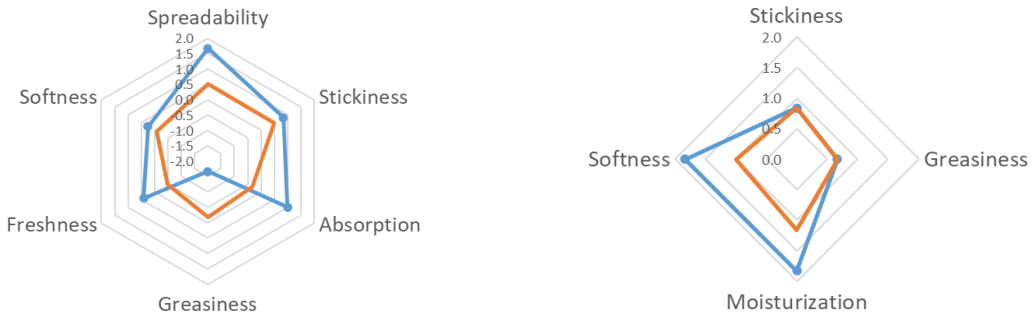


Figure 8 The sensory evaluation of sample S-LC and S-control; (a) During application; (b) After application.

3.2.5 Controlled release of actives

Theoretically LC emulsion can control the slow release of active substances and achieve a mild and safe approach, while effectively utilizing the active substances. In order to study the benefits of LC emulsion, the active applied was vitamin C derivative with 10% added into during the final part of the formulation process. The method studied was described in 2.3.5. The results were shown in Figure 9. At time interval of 6 hours, no active was detected for neither the control nor the LC emulsion. At time interval of 24 and 48 hours, the active was detected by HPLC for both formulations. Compared with control, the concentration of active in the receiver was lower for the cell when the upper charmer was loaded with the LC emulsion. In addition, the concentration difference of active from the receivers between LC and control became closer as the penetration time increased, indicating the capability of LC format for a sustained release of actives.

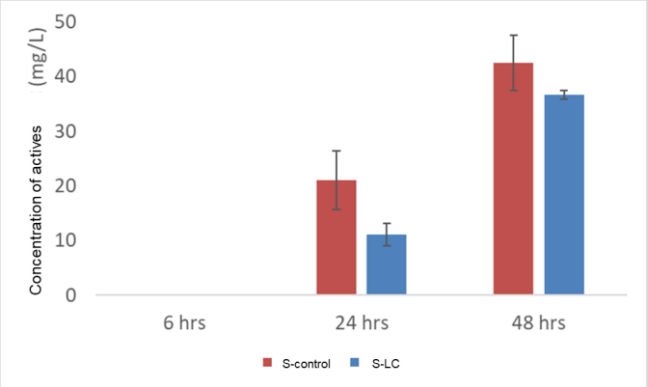


Figure 9 Concentration of vitamin C derivative from the Franz Cell receiver from both LC and control chamber at different time intervals of 6, 24, 48 hours.

4. Discussion

LC has a wide application in pharmaceutical and cosmetic area for its benefits such as prolonged moisturization, controlled release of actives and targeted drug delivery. We investigated in this paper, different factors in the formulation that affect the LC effect. In addition, we showed the superior rheological properties and sensory benefits of the LC emulsion compared with the control. Then we studied the benefits of LC emulsion in terms of controlled release of actives. Our further work also showed the synergistic effect of LC emulsion with ceramides, which are the most abundant lipids in the stratum corneum and part of skin barrier. We found that ceramides can be incorporated into the LC form to form stable formulation to avoid recrystallization of ceramides and enhanced the liquid crystal effect to optimize the utilization of ceramides to protect the skin.

5. References

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