

**MINIMALIST SKIN CREAM CONTAINING UREA AND LAMELLAR PHASE: SKIN
BIOPHYSICAL *IN VIVO* AND *IN VITRO* EVALUATION**

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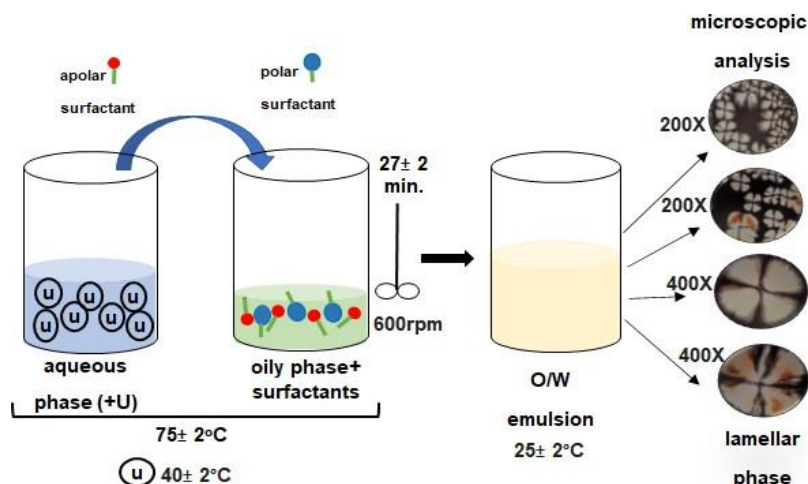
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ABSTRACT

The combination of efficacy and minimalism encourages formulators to seek stable and safe creams with a differentiated sensory experience and, of course, the minimum number of components in the formulation. The components can promote the formation of an ordered arrangement of surfactant and oil molecules, with microscopic structures called lamellar crystalline phases. These structures differentiate the emulsion from traditional ones, in addition to promoting stability, controlled release and skin hydration. These systems exhibit biomimicry with the skin due to their similarity with the lipid-protein organization of the skin barrier, which facilitates interaction with the skin in addition to the differentiated sensory aspect, promoting repair and lasting hydration of the skin. It was developed an O/W emulsion for skin care that presents a lamellar crystalline phase. It was composed by a blend of surfactant (lanolin derivative+ fatty alcohol) + oily phase+ purified water. Urea was employed as hydration agent. The occlusive power of O/W was determined *in vitro* onto gelatin support cells (noninvasive method) and *in vivo* method skin biophysical properties evaluation. The developed formulation significantly increased the occlusive power of emulsion. Skin hydration was studied by using an *in vitro* non-invasive methodology and it was found that the presence of liquid crystal in the emulsion increases the skin hydration level. This was attributed to the fact that it formed the same self-organizing structure as natural stratum corneum lipids.

KEYWORDS: O/W emulsion; liquid crystal; lamellar liquid phase; urea; skin properties (hydration, oiliness and pH values).**Graphical Abstract**

INTRODUCTION

The skin's function is to act as a physical barrier, preventing moisture loss and protecting the body from the external environment while maintaining elasticity and firmness. Changes in the barrier function make the skin dry and rough, sometimes associated with diseases such as xerosis, atopic dermatitis and psoriasis.

The skin is composed of three main layers: epidermis, dermis and hypodermis, with the horny layer or stratum corneum being the outermost layer of the epidermis. The stratum corneum is formed by corneocytes, flattened, densely packed and metabolically inactive cells that form an impermeable barrier. The horny layer is formed by the process of epidermal differentiation and the lipid layer has a neutral character. This continuous lipid layer formed by lipids occupies about 20% of the total volume of the horny layer and is organized into multiple lamellar structures. The skin's protective barrier is composed of corneocytes intertwined in a complex lipid-protein mixture called lamellar lipids.^[1,2]

The intercellular lamellar lipids in the stratum corneum form a single, coherent membrane stabilized by lipid components and the length distribution of these components in the intercellular spaces of the stratum corneum.

The healthy appearance of the skin can be attributed to the intercellular lipids of the stratum corneum that contribute to hydration, cell adhesion and reduction of TEWL. This occurs due to the structural organization of the amphiphilic molecules of the lipids of the stratum corneum.^[3,4,5]

A properly hydrated stratum corneum is capable of (a) maintaining the plasticity of the skin, protecting it from damage; (b) allowing hydrolytic enzymes to act adequately in the desquamation process and (c) contributing to the ideal functioning of the stratum corneum barrier.

The discovery of the NMF^[5] in the stratum corneum reveals the presence of water-soluble compounds involved in the water retention process, the removal of which reduces epidermal hydration. The function of NMF is to maintain adequate skin hydration, and its components are highly efficient humectants that attract and retain water from the atmosphere, promoting corneocyte cohesion.^[6]

Components of NMF such as lactic acid, sugars, amino acids and urea are essential for the skin's ability to retain water. Reduced hydration of the stratum corneum results in dry, rough-feeling skin that is prone to flaking, tightness, cracking, and itching that results in bleeding.^[7] This may be caused by changes in the composition of the natural moisturizing factor.

Among the components of the skin's natural moisturizing factor, urea plays an important role in the integrity and consequent maintenance of skin hydration.^[5,6,7]

Due to its moisturizing capacity, urea is used to treat dry skin. It can be easily incorporated into skin care products such as creams, lotions, emulsions, ointments, gels and even shampoos and nail polishes.^[8,9,10] Used in low concentrations ($\leq 5\%$), it is very safe and effective and recommended for body products applied once or twice a day for a long period of time. A decrease in the content of NMF and especially urea can cause a reduction in the hygroscopic capacity of the skin and increase TEWL, in addition to unbalancing the epidermal reproduction process, inhibiting skin desquamation and causing hyperkeratosis and pruritus.^[10,11]

Skin care emulsions showing the presence of lamellar liquid crystals are structurally like the intercellular lipids of the epidermis, act as smart structures and interact positively with the stratum corneum, stimulating the skin's natural regenerative functions and accelerating epidermal renewal.^[12]

We therefore developed a skin care cream whose structure is similar to that found in the lipids of the stratum corneum, that is, with a lamellar crystalline phase.

MATERIALS AND METHODS

Materials (INCI nomenclature)

Oil phase- Paraffinum liquidum

Aqueous phase- Purified water

Surfactants

Hydrophilic- PEG- 75 lanolin (Croda Brasil)

Lipophilic- PEG lauryl alcohol (Cognis Brasil). HLB value= 6.2 ± 0.2

Active- moisturizing agent – urea (Nuclear Brasil)

Methods

Development of the Emulsion

1. Ternary Diagram

To obtain the formulations it was employed the ternary diagram method. The diagram was obtained using initial concentrations that increased in 10.0% w/w in order to obtain O/W emulsions.^[13]

2. O/W emulsions preparation

The emulsions were prepared by the Emulsion Phase Inversion (EPI) method. The aqueous and oil phases were heated separately at $75 \pm 2^\circ\text{C}$. Then, the aqueous phase was slowly poured over to the oily phases containing surfactants and keeping under stirring (600 rpm) (Ika RW 20 digital) at room temperature ($25 \pm 2^\circ\text{C}$) until complete cooling (27 ± 2 minutes). Urea aqueous solution was added at ($40 \pm 2^\circ\text{C}$).^[14]

3. Macroscopic Analysis

The intrinsic stability was performed twenty-four hours after preparation and organoleptic properties and homogeneity of the formulations were observed, identifying possible signs of instability such as coalescence and creaming.^[15]

4. Microscopic Analysis

The microscopy analysis samples were performed using the microscope with normal and polarized light (BX 50 microscope, Olympus, Melville, NY, USA). Only emulsions with anisotropy were selected for further study.^[16]

5. Preliminary Stability

Macroscopically stable emulsions after twenty-four hours of preparation were subjected to the following preliminary stability tests: centrifugation, thermal stress and pH analysis.^[17] All tests were performed in triplicate.

5.1. Centrifugation Test

It was performed under the following conditions: room temperature ($24 \pm 2^\circ\text{C}$). The samples were submitted to 3000rpm in the centrifuge (Centrilab, model CE80).^[18,19]

5.2. Thermal Stress

The samples were subjected to thermal stress in a thermostated bath in the temperature range of 40 ± 2 to $80 \pm 2^\circ\text{C}$, increasing the temperature by 5°C at each 30-minute interval and subsequently evaluated macroscopically (19). For this test, the nomenclature proposed by Ribeiro *et al.* (20) was used to classify the samples: N = Normal; without change; LM = Slightly Modified; M = Modified; IM = Heavily Modified.

5.3. pH Evaluation

The pH value was measured by inserting the electrode (Analion-Mod. PM608 pH meter, Analion, Ribeirão Preto, SP, Brazil) in the sample solution.^[18,19]

6. Accelerated Stability Test

The samples considered stable were placed in clear plastic vials and kept under different storage conditions: ($25 \pm 2^\circ\text{C}$); ($4 \pm 2^\circ\text{C}$); ($40 \pm 2^\circ\text{C}$).^[20,21,22] The samples were analyzed on the 1st (24 h), 7th, 15th, 30th, 60th and 90th days. The tests used to evaluate the prolonged stability was: macroscopic observation, polarized light microscopy and determination of pH values.

7. In vitro and in vivo evaluation

7.1. In vitro hydration emulsion evaluation on gelatin support cells

Water loss was determined gravimetrically and occlusivity values were determined by the same method employed by Rocha-Filho, P.A.^[23]

7.2. In vivo assessment of skin hydration, oiliness and pH (Corneometer CM 820, a Sebumeter SM 810 and a Skin-pH-meter PH 900 instruments (Courage & Khazaka, Köln, Germany))

The biophysical properties of skin (the skin hydration evaluation, the skin oiliness evaluation and the skin pH evaluation) were evaluated by the method employed by Rocha-Filho, P.A.^[24]

Environmental conditions were standardized by maintaining the temperature at $21 \pm 1^\circ\text{C}$ and relative humidity at $60 \pm 3\%$ (ARSEC dehumidifier). Ten healthy volunteers of both sexes aged between 20 and 40 years, without medication, free of any dermal changes in the forearm region, were part of the studies. All readings were taken in triplicate. The tests were performed on the right forearm, divided into four regions. The region identified as number 1 is kept as control (figure 1). The products were applied ($10 \pm 1\text{g}/\text{cm}^2$) and measures (triplicate). were performed at the standardized times at 0, 30, 90 and 150 minutes after application.

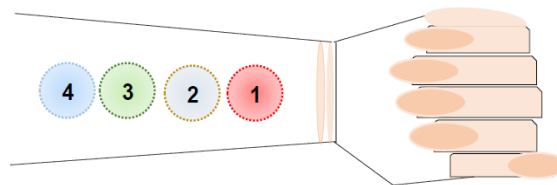


Figure 1: Sites for assessment of skin hydration, oiliness and pH values.

RESULTS AND DISCUSSION

Development of the Emulsion

1. Ternary Diagram

Table 1 shows the emulsions chosen from the ternary diagram.

The emulsions had a white or slightly yellowish appearance due to the absence or presence of the lanolin derivative.

The formulations showed lamellar crystalline phase (figures 2 and 3) and had pH values between 5.91 -sample 82 without urea and 7.63-sample 14 with urea (Table 2) and were considered suitable for skin topical application.

Liquid crystals are anisotropic and are visible in the form of Maltese crosses under an optical microscope with polarized light.

They promote emulsion stability against coalescence and creaming.

They are highly valued for their ability to mimic the skin's own structure, which makes them particularly useful for skincare formulations that aim to hydrate, protect and repair the skin barrier and are here considered as "smart cosmetics". They retain water and active ingredients from the formulation and integrate

easily into the skin and provide longer-lasting effects.

Table 1: O/W emulsions compositions.

Sample n ^r	water (% w/w)	oil (% w/w)	surfactant (% w/w)
4	60.0	30.0	10.0
7	50.0	40.0	10.0
14	40.0	20.0	40.0
37	45.0	20.0	35.0
58	25.0	20.0	55.0
82	60.0	20.0	20.0

Table 2: pH values of O/W emulsions.

Sample n ^r ↓	pH value		
	Without urea	With urea	difference
4	6.64	7.27	0.63
7	6.36	6.70	0.34
14	6.79	7.63	0.84
37	6.33	6.57	0.24
58	6.37	-	-
82	5.91	7.37	1.46

The centrifugation test was performed as an additional test to predict any possible instability of the

emulsions.^[17] After centrifugation, all formulations in table 1 were stable and considered for studies. After 3 months of evaluation according to the accelerated stability test, no macroscopic changes and appearance were observed in the emulsions. It was found that the storage temperature can alter or eliminate the microscopic appearance and formation of liquid crystals as well as alter the pH values of all formulations.

***In vitro* emulsion evaluation on gelatin support cells^[23]**

The O/W emulsions spread easily when applied to the cells on the gelatin surface and it was observed that the water content in the emulsion progressively evaporates. This can cause the emulsion to break and therefore increase the proportion of oils and emulsifiers on the gelatin surface. According with Teeranachaideekul, V. et al.^[25] this evaporation of a certain volume of water in the formulation can cause occlusion by the oil and emulsifier on the gelatin surface (Figure 4A. For O/W emulsion with lamellar phase with a structure similar to the lamellar phase, imitating the natural lipids of the stratum corneum, occlusion can reduce the evaporation of water from the skin surface due to entrapped water onto lamellar liquid crystal structures (Figure 4 B.^[12,26,27,28,29]

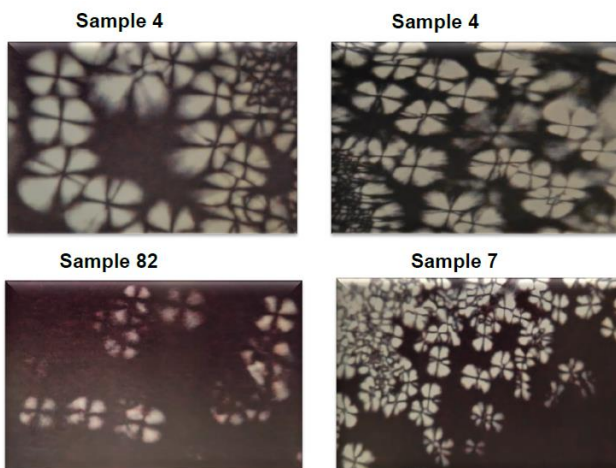


Figure 2: Microscopic analysis (200X) of O/W emulsions samples.

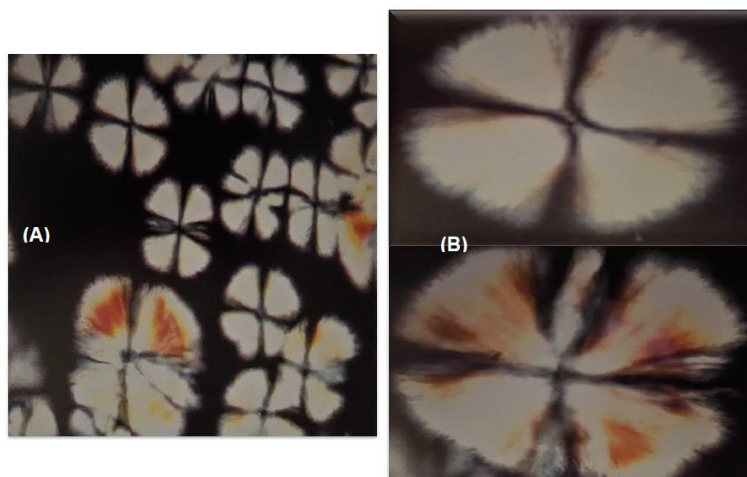


Figure 3: Microscopic analysis of O/W emulsions sample 7 (A) 200X and (B) 400X.

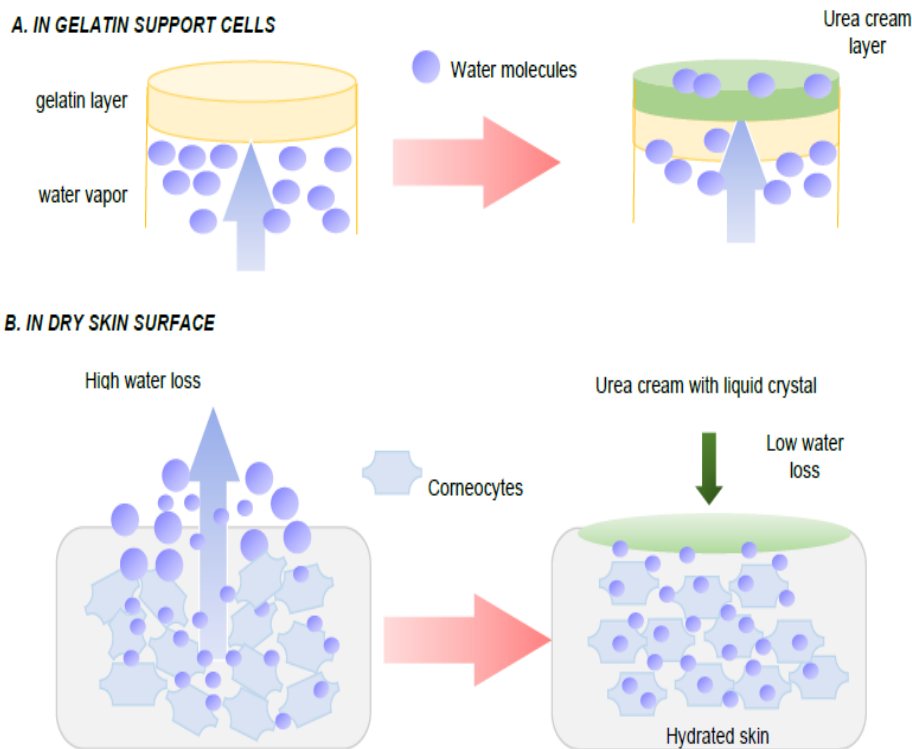


Figure 4: Water content evaporation scheme: A. from gelatin support cell;B. from dry.

Table 3 presents the values of the angular coefficients of the lines obtained before application (25 and 50 minutes) and after application (25, 50, 100 and 150 minutes) of O/W emulsions. Comparing for example for sample 4 without urea and with urea, values of angular coefficients were minor after product application. So, the lines had

minor inclinations in relation to X axis, and this show that the loss of water in gelatin support cells, was minor and the applied product avoid the water loss. In table 4 were show the great values of occlusive power of O/W emulsions, mainly for the presence of lamellar crystalline phase.

Table 3: Angular coefficients of the lines before and after application of O/W emulsions.

Formula n ^r	Before (B)	After (A) application 300± 4mg	Angular Coefficient Difference (B- A)
4	0.99774	0.99677	0.0009
4U	0.99892	0.97555	0.0233
7	0.99990	0.99981	0.0009
7U	0.99866	0.99327	0.0053
14	0.99753	0.99981	-0.0022
14U	0.99158	0.99778	-0.0062
37	0.99999	0.99961	0.0004
37U	0.99792	0.99950	0.0015
82	0.99958	0.99986	-0.0002
82U	0.99585	0.99924	0.0033

Table 4: Occlusive power of O/W emulsions.

Sample n ^r	Occlusive power (%)		
	Without urea (C)	With urea (D)	Difference (D-C)
↓			
4	26.85	77.57	50.72
7	31.49	57.77	26.28
14	3.81	23.85	20.04
37	14.94	18.38	3.44
82	25.11	43.40	18.29

In vivo emulsion evaluation- skin application

From figure 4 the results obtained for the hydration values it was observed an increase in hydration values as a function of time. In formulations containing urea, the hydration values at the final time of 150 minutes were higher than the control. These values can be explained not only by the formation of the crystalline lamellar phase, but by the presence of urea, the water retention capacity of urea and also by the formation of the lamellar crystalline phase. For formulation 37 where there was no formation of the lamellar phase, the hydration values are attributed to the presence of urea. By applying skin care products containing lamellar liquid crystal, which has a water reserve, it is possible to change the resistance to

transepidermal water loss and maintain and/or increase skin hydration.^[27,28,29]

Bianchini JM et al^[30] used oil and emulsifiers that mimic the lipids of the skin barrier in cosmetic formulations that increase hydration and greater efficacy due to the presence of lamellar crystalline structures.

Cosmetic products containing urea for skin care are safe and effective and are among the most popular moisturizers and keratolytic agents for topical application.^[31] These cosmetic creams containing lamellar crystalline phase provide superior skin hydration by reducing TEWL and are also indicated for maintaining healthy skin.

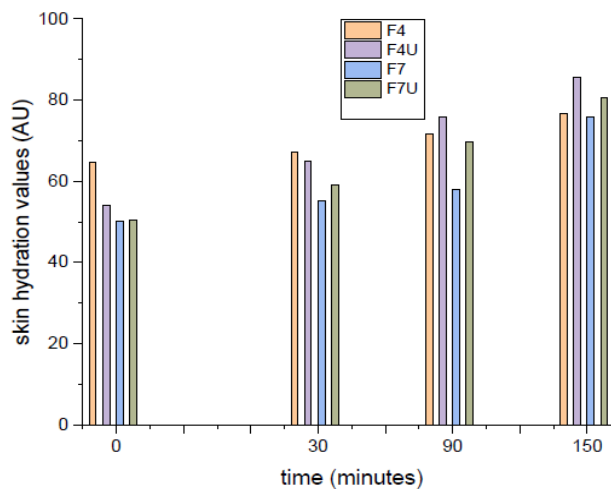


Figure 4: Skin hydration values for formulas 4 and 7 (U= urea).

Regarding the oiliness of the formulations figure 5 the sensorial of sample was like the application of oily formulations to the skin: the application of an O/W emulsion showed initially an increase in oiliness values. There was a gradual increase in oiliness value until the time of 90 minutes, with a decrease occurring until the final time of 150 minutes. This fact was observed for emulsions containing or not containing urea, however,

the decrease in these values was smaller in relation to the values control.

The application of simple emulsion O/W showed an increase in oiliness, mainly in the initial time, despite the emulsion having low oil content. It can be observed that the presence of the urea does not present alterations to oiliness and at the end of the test, the values correspond to those of the simple O/W emulsion.

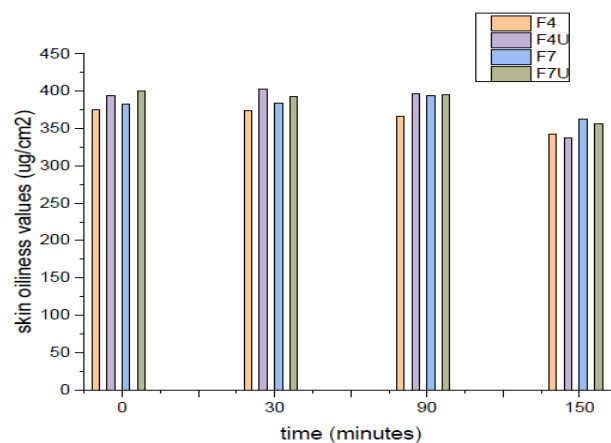


Figure 5: Skin oiliness values for formulas 4 and 7 (U= urea).

From figure 6 it was observed that pH values measurements were between 4.5. and 7.0. With the application of O/W without urea, a slight decrease in these values was observed. When applying O/W containing urea, it was observed that the pH values were in the acidic range, which shows that there was no change in the skin's pH values. The statistical analysis carried

out at a significant level of 5% allow to conclude that the O/W showing lamellar crystalline liquid phase and urea markedly improve the hydration, maintain the oiliness the skin and do not alter skin pH values and must be indicated to individuals with dehydrated skin.

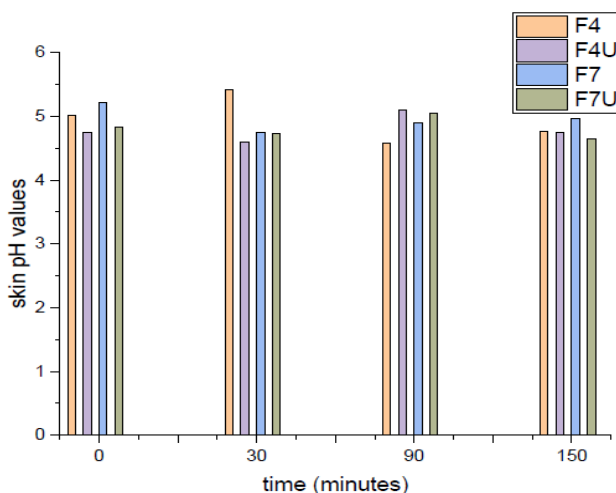


Figure 6: Skin pH values for formulas 4 and 7 (U= urea).

CONCLUSION

Microscopic analyses had identified lamellar crystalline phase in some formulations obtained from ternary diagram method. Lamellar phase liquid crystal formulations mimic the lipid-protein layer of the skin and optimize the interaction of active ingredients in the stratum corneum, providing longer-lasting effects of efficacy and hydration. Thus, they were called smart cosmetics in this research, since the hydration levels obtained with the identification of the lamellar phase with urea are considered excellent during the study period.

The hydration formulation power was studied by using an *in vitro* non-invasive methodology and it was observed that hydration power was increased by the presence of liquid crystal. Same results were obtained with *in vivo* methods and no alterations on oiliness values and no alterations on skin pH values. The efficacy of these formulations was due to the presence of lamellar crystalline phase.

Ethical aspects

This study was designed in accordance with good clinical practice. All patients kindly agreed to participate in the assessments.

Author Contributions

Conceptualization, methodology, writing - review and editing P.A.R.F.

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Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The author declare no conflict of interest.

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