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Evaluation of Physical and Chemical Stability of Nanostructured Lipid Carries Containing Ursolic Acid in Cosmetic Formulation

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ABSTRACT

The new generation of lipid nanoparticles with solid matrix are the NLC (Nanostructured lipid carriers), and these nanoparticles show increased chemical stability of drug, film formation, controlled occlusion, increased skin hydration, the bioavailability of the active skin is improved, increase the physical stability of lipid nanoparticles in topical formulations and lower toxicity. The NLC were produced by the technique of High Pressure Homogenization (HPH). The Accelerated Stability Test, also known as Normal Stability or exploratory, aims to provide data to predict product stability, shelf life and formulation compatibility with the packaging material. Therefore, this study aims: to evaluate the normal stability under varying conditions of temperature and luminosity over time as their physical and chemical characteristics in cosmetic formulation containing ursolic acid in free and nanoparticle forms. Based on the results, the ursolic acid in the nanostructured lipid carrier form achieved a better physical and chemical stability compared to ursolic acid in the free form in both variation of the viscosity and pH.

INTRODUCTION

Nanocosmetics can be defined as a cosmetic formulation that carries active ingredients or other ingredients nanostructured and presents superior properties and its performance compared with conventional products. From the scientific point of view, the advantages of using in the production of Nanobiotechnology nanocosmetics and dermatological formulations are concerned to protect the ingredients and chemical or enzymatic degradation, control of its release (especially in the case of irritants drugs at high concentrations) and a longer residence time of active cosmetics or drugs in the stratum corneum (Fronza *et al*., 2007).

In developing the cosmetic product, the study of stability is of great importance, because it assesses the amount of time in which the product maintains its physical, chemical, micro-biological and toxicological within previously established limits. In this type of study, samples of the formulations are evaluated after being submitted under certain conditions of temperature, humidity and light, which can accelerate the rate of chemical degradation of active ingredients and of physical and physico-chemical form of cosmetic and therefore interfere in the microbiological and toxicological quality (Baby *et al*., 2004). The stability study provides indications about the behavior of the formulation given period of time, compared to different environmental conditions that can be submitted, from manufacturing to the expiry date (Brasil, 2004). According to the monograph of the International Federation of Societies of Cosmetic Chemists - IFSCC, the stability test is considered as predictive procedure, based on data obtained from formulations stored in conditions designed to accelerate changes that may occur in real market conditions. As in all predictive results are not absolute, but have a probability of success (Brasil, 2004). The objectives of the research were to prepare a cosmetic formulation containing ursolic acid in free and NLC forms and evaluate the Normal Stability in various temperature and light conditions over time as its physicochemical characteristics.

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MATERIAL AND METHODS

Raw materials and apparatus

All raw materials were of pharmaceutical purity grade and water was demineralized in a Milli-Q® system (Millipore, Bedford, MA, USA). Ursolic acid was donated from HighChem, São Paulo, SP, Brazil. Olea Europaea (Olive) Fruit Oil, Cetearyl Olivate/Sorbitan Olivate, Cetyl Alcohol, Methyl Soyate, Tocopheryl Acetate, Xanthan Gum, Dissodium EDTA, Sorbitol and Phenoxyethanol/2-Methyl-4-Isothiazolin-3-one were donated from Vital Especialidades, São Paulo, SP, Brazil. Caprylic/capric Triglyceride was obtained from Mapric Produtos Fármacos e Cosméticos LT-ME, São Paulo, SP, Brazil.

All experiments were conducted using for apparatus: Magnetic stirrer microprocessor and pHmeter Quimis®, Diadema, SP, Brazil; Mechanical mixer, Kika Labortechnik® Model T25 basic, São Paulo, SP, Brazil; Analytical balance, Shimadzu®, Precision 1 mg-220 g, São Paulo, SP, Brazil; Bath with digital thermostatic incubator orbital circular motion, adjustable speed from 20 to 200 rpm and temperature gradient from 25 to 60°C (501/D) and autoclave with temperature gradient from 0 to 100°C, Nova Ética®, São Paulo, SP, Brazil; ViscoStar Viscometer (R), with adapter samples for evaluation of reduced mass and needle (spindle) TR10, Fungilab®, Bohemia, NY, United States.

Cosmetic Formulation

The following (**Table 1**) describes the components of Formulation 1 that was selected according to the stability and compatibility with the ursolic acid. The goal was to develop a simple and stable incorporation of ursolic acid in its free and NLC forms.

Preparation of the formulation

The method of preparation involved the phase inversion, given mass of 500 g. In this method, weighed components oil and water phase separately to a temperature of 75.0 ± 5.0 °C and poured over the oily to the aqueous phase slowly and with constant stirring by hand until cooling to 45 °C (Prista *et al*., 1995).

RESULT AND DISCUSSION

The following are graphs of variation of the viscosity versus time (**Figures 1** and **2**) and variation of pH versus time (**Figures 3** and **4**) of Formulation 1, selected in a Normal Stability Test evaluating 4 conditions: fridge at 5.0 ± 2.0 °C, room temperature to 25.0 ± 2.0 °C, autoclave at 45.0 ± 2.0 °C and exposure to indirect sunlight 25.0 ± 2.0 °C. It was compared the ursolic acid in the free form with ursolic acid in the NLC form.

The Solid lipid nanoparticles (SLN) may be prepared from safe raw materials, and the term "green chemistry" can be applied therefore due to not use organic solvent such as the polymeric nanoparticles, which deal with the presence of their residues in the final product, which gives the SLN increased safety. However, there are some difficulties as limited ability to load drugs; expulsion during storage and high water content in the aqueous dispersion (Muller *et al*., 2002).

These difficulties have thus provided a new and improved generation of lipid nanoparticles as the nanostructured lipid carrier (NLC). In contrast the SLN, produced from solid lipids, the NLC are prepared using mixture of solid lipids (saturated fatty acids) and liquid lipids (unsaturated fatty acids). These have the following advantages when compared to the SLN: high rate of active membership, greater control of their release, lower release of the same product during storage and lower water concentration in the formulation (Fang *et al*., 2008; Pardeike *et al*., 2009).

Table. 1: Components of Formulation 1.

	INCI	% p/p	Critical Analysis
OP	*Olea Europaea* (Olive) Fruit Oil	2,50	emolient
	Cetearyl Olivate/Sorbitan Olivate	7,00	surfactant
	Cetyl Alcohol	5,00	emolient
	Caprylic/capric Triglyceride	2,50	emolient
	Methyl Soyate	6,30	surfactant
	Tocopheryl Acetate	0,05	antioxidant
	Ursolic Acid	1,00	antioxidant and antimicrobial
WP	Xanthan Gum	0,25	thickener
	Dissodium EDTA	0,10	antioxidant/chelate
	Sorbitol	10,30	humectant
	Phenoxyethanol/ 2-Methyl-4-Isothiazolin-3-one	0,30	preservative
	Aqua	q.s.p. 100,0	vehicle

Legend: **OP** – Oil phase/ **WP** - Water phase/ **INCI** – *International Nomeclature of Cosmetic Ingredient*

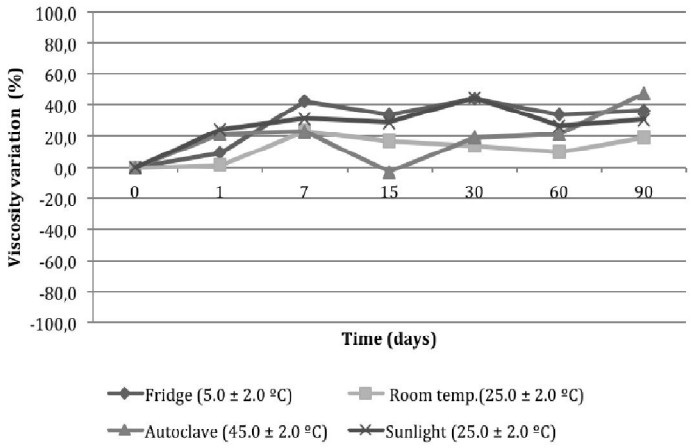

Fig. 1: Graph of Formulation 1 with 1% ursolic acid in free form (AUL) and its Normal Stability Test conditions: fridge at 5.0 ± 2.0 °C, room temperature to 25.0 ± 2.0 °C, autoclave at 45.0 ± 2.0 °C and exposure to indirect sunlight 25.0 ± 2.0 °C.

The first compound formulated in NLC was retinol. The load capacity of retinol in SLN produced from Compritol® was only about 1%. The NLC produced from a mixture of Compritol® and Miglyol®812 increased to 5% (Jenning, 1999). The NLC is considered the most intelligent, and most recent generation of lipid nanoparticles that have improved properties for loading drugs modulating the release profile and stable incorporation of active ingredients during storage (Muller *et al*., 2007).

As may be observed in **Figure 1** and **2** concerning the variation of viscosity versus time, it is observed that in all the conditions of the stability test with the formulation containing 1% ursolic acid in NLC form had less then 40% viscosity variation. This improvement brought by the NLC in the formulation can be seen even more clearly in **Figure 3** and **4** that show the variation of pH versus time. **Figure 4** that contains formulation with 1% of ursolic in NLC form kept less than 20% variation of the pH during the 90-day stability test.

Thus, these nanocarriers have been employed in the preparation of cosmetics intended to reach the effectiveness of these products, while reducing their cytotoxicity and increasing the physical and chemical stability (Schmaltz *et al*., 2005).

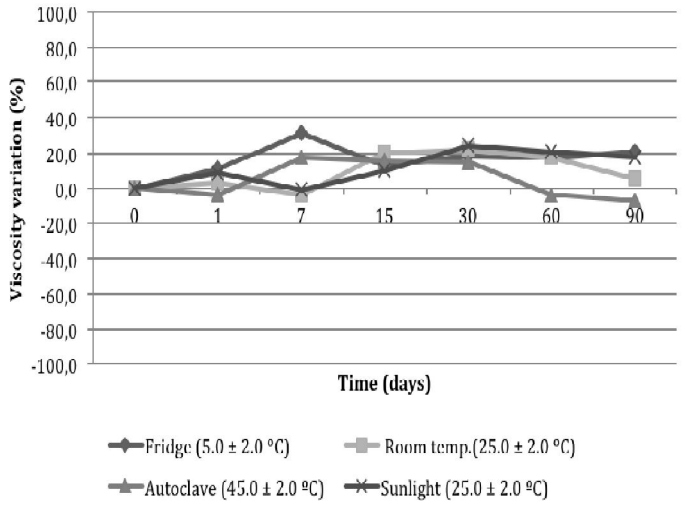

Fig. **2:** Graph of Formulation 1 with 1% ursolic acid in NLC form (AUE) and its Normal Stability Test conditions: fridge at 5.0 ± 2.0 °C, room temperature to 25.0 ± 2.0 °C, autoclave at 45.0 ± 2.0 °C and exposure to indirect sunlight 25.0 ± 2.0 °C

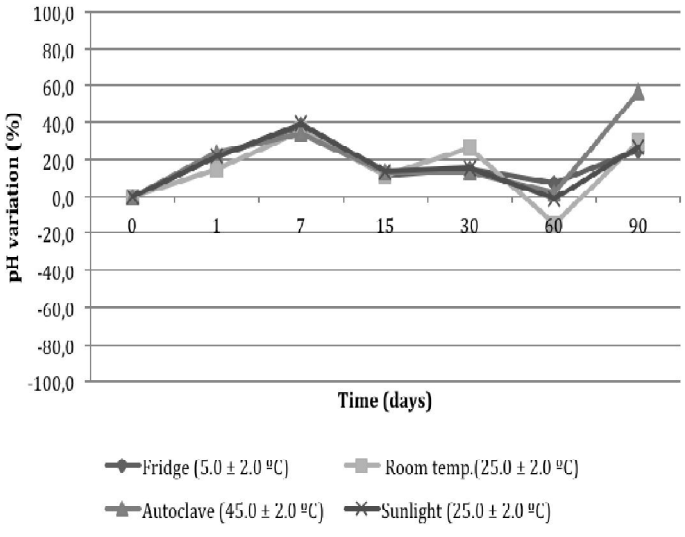

Fig. 3: Graph of Formulation 1 with 1% ursolic acid in free form (AUL) and its Normal Stability Test conditions: fridge at 5.0 ± 2.0 °C, room temperature to 25.0 ± 2.0 °C, autoclave at 45.0 ± 2.0 °C and exposure to indirect sunlight 25.0 ± 2.0 °C.

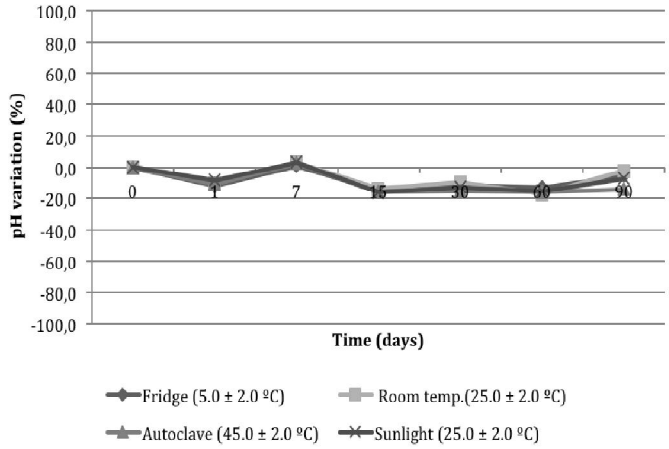

Fig. 4: Graph of Formulation 1 with 1% ursolic acid in NLC form (AUE) and its Normal Stability Test conditions: fridge at 5.0 ± 2.0 °C, room temperature to 25.0 ± 2.0 °C, autoclave at 45.0 ± 2.0 °C and exposure to indirect sunlight 25.0 ± 2.0 °C.

CONCLUSION

We can conlude that the ursolic acid in the form of nanostructured lipid carriers obtained better physical and chemical stability against the ursolic acid in free form in both variation of the viscosity and pH.

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