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NLC delivery systems for alpha lipoic acid: Physicochemical characteristics and release study

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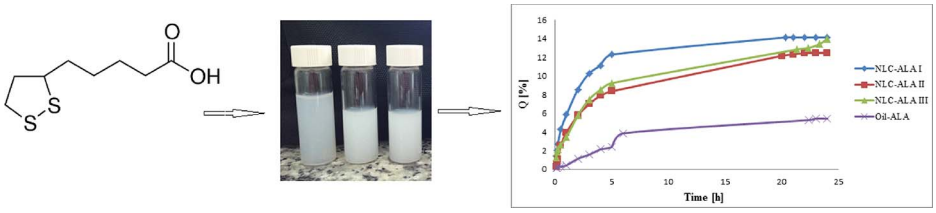
GRAPHICAL ABSTRACT



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ABSTRACT

The main objective of this study was to prepare nanostructured lipid carriers as long term stable carrier systems for the topical delivery of alpha lipoic acid (ALA). The ALA-loaded NLC were prepared by the ultrasound homogenization method, using mixture of Apifil CG and Myritol 312 as the lipid phase. The systems were stabilized by Plantacare 2000 UP. The stability of obtained formulations was assessed using macroscopic and microscopic analysis. Physicochemical properties of the carriers, such as particle size, polydispersity index, zeta potential and their viscosity were studied. *In vitro* release studies of the active were performed at the 32 °C, using cellulose membrane and the phosphate buffer (PBS, pH = 7,4) as a receptor solution. The obtained results confirmed a high physical stability of the empty and ALA-loaded formulations and showed that the prepared systems are suitable carriers for controlled release of ALA and can be a promising solution for skin delivery of this antioxidant.

1. Introduction

Alpha lipoic acid (ALA), also known as thioctic acid is naturally occurring kind of organosulfur compounds, synthesized by some plants and animals, involving humans [1]. As a biological antioxidant, ALA had received significant attention for the last few years [2,3]. Along with its reduced form, dihydrolipoic acid (DHLA), they have been considered as possessing reactive oxygen species scavenging action [4] and are recognized to revitalize other antioxidants from their inactive forms [5]. ALA also works as a chelator of transition and heavy metals and more recently, has been introduced to have anti-inflammatory properties [6]. Its versatile benefits as an antioxidant allows to apply it in many fields such as curing drug, vitamins supply in health food and in cosmetic as an anti-aging active material because it may prevent photooxidative stress in the skin [7]. ALA shows favorable physicochemical properties for dermal delivery but high lipophilicity makes it difficult to formulate in traditional carriers like emulsion. Additional problem is that the acid is extremely vulnerable to degradation by the sunlight and is characterized by unpleasant sulfur smell [8,9].

To avoid the above-mentioned shortcomings and improve physicochemical stability of alpha lipoic acid, its encapsulation in nanostructured lipid carries (NLC) was implemented. NLC in comparison to the traditional carriers like emulsions, liposomes and polymeric nanoparticles show some advantages i.a. biocompatibility and physiological

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lipids-like composition, avoidance of organic solvents in the preparation process, high bioavailability, controlled release behavior of the active substance and suitability to scaling-up production [10–12].

So far, results of numerous investigations have demonstrated the ability of lipid nanoparticles to be great carriers for delivering lipophilic compound improving at the same time insolubility challenges [13–16]. Nanostructured lipid carriers offer effective, controlled delivery and bioavailability of the lipophilic drugs [5]. Therefore, these colloidal lipid systems are recommended for many administration routes of the numerous actives, including its topical application [17,18].

The principal aim of this study was to prepare ALA-loaded NLC formulations as long term stable carrier systems for the alpha lipoic acid topical delivery. The applicability of the ALA-NLC formulations was illustrated by comprehensive characterization of the carriers. The release profile of the active was investigated along with the physicochemical properties of ALA-loaded NLC.

2. Materials and methods

2.1. Materials

The active ingredient (±)-α-Lipoic acid (ALA) was purchased from SIGMA-Aldrich Chemie GmbH, Germany. Table 1 shows the main properties of the acid. Modified beeswax (Apifil®) used as solid lipid and medium chain triglyceryde (Myritol®312) chosen as liquid lipid were delivered from Gattefossé GmbH, Germany and BASF Chem Trade GmbH, Burgbenheim, Germany, respectively. All NLC formulations were stabilized by alkylpolyglucoside surfactant (PlantaCare®2000UP), which was supplied by BASF Chem Trade GmbH, Burgbenheim, Germany. All reagents and solvents were of analytical grade. The ultrapurified water was freshly prepared by a MiliQ® System (Millipore, Schwalbach, Germany).

2.2. NLC preparation

All NLC dispersions in accordance with the composition presented in Table 2 were prepared by ultrasound homogenization method. The oil and aqueous phases were prepared independently. The proper quantity of solid lipid, liquid lipid and the active compound in the case of the ALA-loaded formulations, were melted at 80° C. The concentration of α-lipoic acid (ALA) was 0,5% wt. for all loaded NLC. The aqueous phase with an adequate concentration of the surfactant were heated to the same temperature and added to the melted oil phase, under magnetic stirring, with 600 rpm, for 5 min. So, obtained dispersion of the hot pre-emulsion, was further processed for another 5 min, by ultra sound homogenization, using probe-type sonicator (Sonics Vibra-Cell, Sonics & Materials, INC.) Subsequently, the obtained homogenous NLC systems were cooled down to room temperature resulting in lipid phase recrystallization to form empty or ALA-loaded nanoparticles. ALA oil solution for comparative study were prepared by dispersing the active in Myritol®312, using IKA® Vortex shaker.

Table 1
Characteristics of lipoic acid.

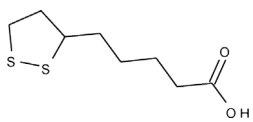
Structure	Molecular weight	logP	Polar surface area (Å^2)
	206.318	2.11	37.3

Table 2
The composition of loaded and unloaded NLC formulations.

Formulation Name	Ingredients (% wt.)				
	Oil	Solid Lipid	Surfactant	Water	ALA
NLC I	13	2	7	q.s.	–
NLC-ALA I	13	2	7	q.s.	0.5
NLC II	3	7	4	q.s	–
NLC-ALA II	3	7	4	q.s.	0.5
NLC III	2	8	5	q.s.	–
NLC-ALA III	2	8	5	q.s.	0.5
Oil-ALA	99.5	–	–	–	0.5

2.3. NLC characterization

2.3.1. Particle size, polydispersity index and zeta potential analysis

The particles size (Z-ave), polydispersity index (PDI) and zeta potential of the systems studied were determined using dynamic light scattering technique (Zetasizer Nano ZS, Malvern Instruments Ltd., UK), at a fixed angle of 173°, and a temperature of 25° C. The Zeta potential (ZP) as a quantification of a particle surface charge was performed by measuring the electrophoretic mobility of particles dispersed in a liquid. The formulations samples were analyzed after appropriate dilution, with double-distilled water prior, to generate a suitable scattering intensity. For each samples the measurements were carried out in triplicate and average values of the parameters and standard deviation were calculated.

2.3.2. Stability study

The stability of NLC formulations was firstly evaluated by macroscopic observation and estimating the cream increasement in time. The samples were checked during storage at room temperature, for three weeks, in case of any destabilization processes (creaming or coalescence) would occur. Light microscopy is an important procedure to know if the relatively larger particles detected by dynamic light scattering technique (DLS) are really particles or agglomerates of nanosized particles as well as solid lipid crystals formation. Motic B1 Series optical microscope, equipped with a camera was used to observe changes of the formulations structure during storage time.

2.3.3. Rheological measurement

Viscosity measurements of NLC formulations were performed using Brookfield Rheometr Model − R/S plus, equipped with a cone and plate type measuring system (cone C75-1), at 25 °C, in the range of shear rate values from 1 to 1000 s^{-1}. The measurements were carried out for the fresh formulations (t = 0) and after 24 h storage.

2.4. In vitro release investigation

In vitro release behavior of lipoic acid from various NLC systems were performed by dialysis bag method [19], using the dialysis cellulose membrane (Spectra/Por® Dialysis Membrane) of molecular weight cut-off between 6 and 8 kDa. An appropriate amount of ALA-loaded NLC was filled into the dialysis bag which next was placed into thermostatic dialysis chamber, containing 200 cm^3 of a receptor solution (PBS, pH = 7,4), maintained at 32 °C ± 0,5 °C and stirred at 200 rpm. Sink conditions were accomplished for all of the terpenes during the performance of the dialysis. At the predetermined intervals of time, 1 cm^3 of the receptor solution with the released active was withdrawn and the same volume of fresh receptor solution was added to maintain the constant volume. The concentration of the released ALA, in the receptor medium, was analyzed spectrophotometrically using Nanocolor UV–vis Spectrophotometer (Machery-Nagel), at room temperature. The amount of active released from the formulations was expressed as the ratio of the quantities of substances released to the total