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Rutin nanostructured lipid cosmeceutical preparation with sun protective potential

Rabab Kamel *, Dina M. Mostafa

Department of Pharmaceutical Technology, National Research Center, Dokki, Al-Bohooth St., Cairo, Egypt

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ABSTRACT

Skin cancer is related to unprotected exposure to sunlight. Despite the broad expansion of sunscreen market, various researches are focused on the inefficiency and danger of sun products. This study was focused on the development of photoprotective nanoparticulate dermal preparations of the antioxidant flavonoid Rutin (RT). Nanostructured lipid carriers (NLCs) were prepared using different types of lipids. Based on particle size (PS), size distribution (PDI) and Zeta potential (Z) as well as rheological properties, NLC containing Plurol® stearique (NLC-P) and Apifil® (NLC-A) were selected and loaded with different concentrations of RT to form the medicated nanocreams. F4 (NLC-A with 2% RT) attained highest occlusive effect, drug encapsulation and release efficiencies as well as sun protective factor (SPF). Different concentrations of TiO_2 were added to F4 aiming to ameliorate the sun protective effect. F7 (containing 5% TiO_2) attained the highest SPF and area under the UV absorbance curve and had a critical wavelength above 370 nm, which proved its high efficiency as sunscreen. The in-vitro antioxidant effect of F7 was more than two fold that of the standard antioxidant. This study provides a suitable cosmeceutical lipidic colloidal system of Rutin to be employed as a successful photoprotective preparation.

1. Introduction

Drug delivery to or via the skin presents both unique opportunities and obstacles due to skin structure, physiology, and barrier properties. The skin, the largest organ of the body, can be considered as a natural protective barrier against penetration of toxic exogenous compounds, excessive loss of water and other essential compounds. The dermal route is also a promising portal of entry of drugs for local and/or systemic action. Semisolid systems are used widely in the formulation of topical pharmaceutical and cosmetic preparations [1]. Rheology of semisolids is an important physical issue related to technical (manufacturing, filling, storage) and esthetic term as well [2].

The large expansion of sunscreen market indicates that people are nevertheless conscious of accompanying dangers like actinic changes (wrinkling, premature aging of the skin, irregular thinning of the epidermis, hyperpigmented macules), development of premalignancies and skin cancer occurring as a result of excessive exposure to ultraviolet (UV) radiation. There are many examples of formulations that do not exhibit an increase in sun protection factor (SPF) by increasing the levels of sunscreen actives. Thus, it is clear that several other factors must be considered when formulating sunscreen products. Topical administration of antioxidants provides an efficient way to enrich the endogenous cutaneous protection system and thus may be a successful strategy for diminishing ultraviolet radiation-mediated oxidative damage in the skin. Recently, the cosmetic industry is directed towards the use of antioxidants as additions to UV filters, because almost all the post radiation reactions involve directly or indirectly reactive oxygen species (ROS) [3]. Flavonoids are a group of plant polyphenolic compounds possessing broad biological properties and low side effects. The capability to interact with protein phosphorylation and the antioxidant, iron-chelating and free radical scavenging activity may account for the wide pharmacological profile of flavonoids [4].

Rutin is a flavonoid glycoside composed of the flavonol, quercetin, and the disaccharide, rutinose [5]. It is a polyphenolic compound, having significant scavenging properties on oxidizing species and is effective against ultra-violet radiation induced damage. In addition, Rutin has several pharmacological activities, including antiallergic, anti-inflammatory, vasoactive, antitumor, antibacterial, antiviral, and antiprotozoal properties [6]. However its low aqueous solubility can lead to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Therefore, producing suitable formulations is essential to improve the solubility and bioavailability of such drugs [7].

Solid lipid nanoparticles are two-phase drug delivery systems consisting of a nanoscale drug-carrying solid phase composed of crystallized lipids at room temperature dispersed within an aqueous phase by means of different techniques. In the last years, some modifications have been done to these solid nanoparticles to form a delivery system known as nanostructured lipid carriers (NLCs), in which the solid lipid phase has been loaded with liquid lipids, i.e. oils. This type of carriers has attracted the attention as novel delivery systems [8].

* Corresponding author.
E-mail address: drrababk@hotmail.com (R. Kamel).

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NLCs can provide an effective delivery system for both organic and inorganic sunscreens; the reason resides not only in the intrinsic UV blocking properties attributed to their size (particularly in the size range between 200 and 400 nm) [9], but also in the possibility to incorporate organic and inorganic filters inside. This unique structure can combine the UV absorption properties of both. In this context, the use of SLNs or NLCs can accomplish this task because the entrapment of the organic sunscreen inside the lipid matrices may reduce their potential skin irritation and simultaneously can decrease the needed amount needed from each UV filter, thus, avoiding the use of unnecessary quantities of chemicals. Recently, it has been reported that those particles exhibited other interesting properties such as a homogeneous distribution of the active components within the formula and a very good long-term physical stability [10]. Furthermore, some types of NLCs have proved to improve the sun protection factor of some sunscreens when compared to the effect of these compounds in simple formula without the use of such complex formulations [11].

The mechanism of action of organic sunscreens (chemical sunscreens), is generally based on the UV absorption properties attributed to the conjugated double bonds of their chemical structures [12]. While for the titanium dioxide (inorganic physical sunscreen), the UV absorption is explained by the semiconductor properties of its crystal lattice, on which, a fully occupied valence band separated from empty conduction band by an energy gap is formed so that when it is irradiated by light, of energy equal to or higher than that of the band gap, an absorption of this energy takes place favoring the promotion of electrons into the conduction bands. Thus, considering the intrinsic properties of both materials; organic and inorganic sunscreens, it could be expected that an increased UV protection would take place if both substances were combined to provide a physical and chemical sun screen effect [11].

The simplicity of the preparation method as well as the availability and low cost as well as safety of the used chemicals are additional advantages for the proposed formulae.

This manuscript is focused on the innovation and development of Rutin (RT) lipid nanosystems for topical delivery and study of the feasibility of their use as dermal care products with photoprotective effect.

2. Materials and methods

2.1. Materials

Apifil® GC (A), Gelucire®50/13 (G), Plurol® stearique WL 1009 (P) and Tefose ® 2000 CG (T) were a gift from Gattefosse (St Priest, France). DPPH (1,1-diphenylpicryl-hydrazyl) was procured from Sigma Chem. Co., St. Louis, MO, USA. Rutin (RT) was provided by the Kahira Pharmaceuticals and Chemical Industries Company (Cairo, Egypt). White soft paraffin, liquid paraffin and propylene glycol (PG) were purchased from the El-Nasr Company for Pharmaceutical Chemicals (Cairo, Egypt). All other chemicals used in the study were of analytical grade and were obtained from the El-Nasr Company for Pharmaceutical Chemicals (Cairo, Egypt).

2.2. Methods

2.2.1. Preparation of NLCs

The nanostructured lipid carriers (NLCs) investigated were prepared by the probe sonication method where the oil and solid lipid components were mixed to form the lipid phase which was melted at temperatures between 60 and 70 °C. The aqueous phase, containing water, methanol and PG, was heated to the same temperature and then added to the oily phase to form a coarse emulsion. Subsequently, the coarse emulsion was sonicated using Sonifier® Model 250 (Branson Ultrasonics, USA) probe sonicator at 20 W for 90 s (as indicated in Table 1) [1]. Subsequently, suitable formulae based on physical as well as physicochemical properties were loaded with the drug (1 or 2% w/w) which was added to the lipid phase during preparation.

Table 1
Composition of prepared formulae.

Component		Weight (mg)
Lipid[a]		90
White soft paraffin		150
Liquid paraffin		100
Methanol		60
Propylene glycol		100
Distilled Water		500
Formula (medicated nanocream)	**Lipid type**	**Drug % (w/w)**
F1	P	1
F2		2
F3	A	1
F4		2

[a] Lipid added was: Apifil® GC (A) or Gelucire®50/13 (G) or Plurol® stearique WL 1009 (P) or Tefose® 2000 CG (T).

2.2.2. Measurement of particle size (PS), size distribution (PDI) and Zeta potential (Z) of NLCs

Mean vesicle size and size distribution of prepared formulae were performed by photon correlation spectroscopy (PCS) using the Malvern Zetasizer Nano ZS (Malvern Instruments Ltd., Malvern, UK). Before measurement, samples were appropriately diluted with distilled water (1:10).

2.2.3. Rheological properties of NLCs

Viscosity measurements were done using cone and plate method (Rheometer Anton Paar GmbH, MCR301 Rheometer Series, applying software RHEOPLUS/32 V3.40 21003304-33025. St. Albans, Hertfordshire AL4 0LA, United Kingdom). Measurements were carried out at 25 ± 0.1 °C, 45 measurement points were investigated starting with shear rate 1–300 1/s with measurement point duration 10 s.

After performing the above-listed investigations, selected NLCs were loaded with the drug; RT (1 or 2% w/w) according to Table 1 to form medicated nanocreams. Prepared drug-loaded nanocreams were then subjected to the following investigations.

2.2.4. Determination of drug entrapment in RT-loaded nanocreams

A known amount of the nanocreams (100 mg) was dissolved in 10 ml methyl alcohol by sonication to ensure complete extraction of the drug. After filtration using 0.45 μ Millipore filter, the samples were assayed for drug content by UV-spectrophotometry (Shimadzu UV Spectrophotometer) at 357 nm after suitable dilution. Blank experiment was done simultaneously [1]. The % encapsulation efficiency (EE) was calculated as follows:

$$EE = (\text{Calculated drug amount}/\text{Theoretical drug amount}) \times 100.$$

2.2.5. Determination of occlusive properties of RT-loaded nano-creams

Twenty five milliliter beakers were filled with 15 ml distilled water and covered with Whatman® filter paper No 41 with pore size of 8 μm (England) and sealed with silicon. The nanocreams were applied on the filter papers, in 10 mg/cm^2, and evenly spread with a spatula. The beakers were weighed and stored in an incubator (Shellab model 1545, USA) at 32 °C and 50% RH for 48 h. The beakers were weighed at zero, 6, 24 and 48 h and occlusion factor (F) calculated according to the equation [13]:

$$F = 100 * (A - B)/A$$

where A = weight difference (water loss) in case of control (without any application) and B = weight difference in case of tested formulae.

2.2.6. In-vitro drug release

Release experiments were carried out according to the paddle method [14] using phosphate buffer at pH 5.5 containing 15% methyl alcohol