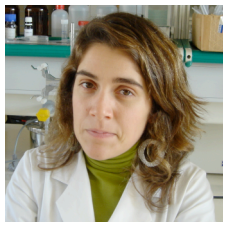
Nanostructured lipid carriers (NLC) as potential carriers for topical delivery of minoxidil



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Introduction

Minoxidil was initially developed as an oral antihypertensive agent (Dargie 1977; Swales 1982). However, its major clinical attraction is related to its common side effect on the promotion of hair growth, i.e. hypertrichosis (Zappacosta 1980). In the last 20 years, minoxidil has been widely used for the topical treatment of androgenic alopecia in men and subsequently in women (Messenger 2004).

Because of the lipophilic characteristics of minoxidil, conventional topical formulations consist of propylene glycol-water-ethanol solution (Tata 1995). Applications of such formulations may cause severe adverse reactions, such as scalp dryness, irritation, burning, redness and allergic contact dermatitis (Pavithran 1993). To minimise these side effects and to improve therapeutic efficiency of minoxidil, the development of new systems for topical delivery of such drug is a demand.

In the beginning of the nineties, the first nanoparticulate delivery system produced from solid lipids was developed, the so-called solid lipid nanoparticles (SLN) (Müller 1996). Potential problems associated with SLN have been further minimised by a new generation of lipid systems, the nanostructured lipid carriers (NLC) developed at the turn of the millennium (Müller 2002).

SLN and NLC are stable colloidal systems with notable advantages as drug delivery systems, i.e. physicochemical stability, versatility, biocompatibility, biodegradability and controlled drug release. They consist of physiological biocompatible lipids, which are suitable for the incorporation of both lipophilic and hydrophilic drugs. The advantage of NLC over SLN results from the liquid lipid which is present in the solid matrix, avoiding the drug expulsion during storage that can occur when the lipid matrix undergoes polymorphic transformations from unstable to more stable configurations (Müller 2002).

Aqueous dispersions of lipid nanoparticles are being investigated as drug delivery systems for different therapeutic purposes. One of their interesting features is the possibility of topical use, for which the systems have to be incorporated into commonly used dermal carriers, such as creams or hydrogels, in order to have a proper semisolid consistency (Souto 2004).

The purpose of this work was to develop a new NLC formulation containing minoxidil, using different concentrations of solid and liquid lipids, to study their physicochemical properties and to assess their storage stability.

Materials and methods

Stearic Acid, Oleic Acid and Minoxidil were purchased from Guinama (Spain). Poloxamer 188 (Lutrol®) was a gift from Gattefossé (France). The water used in all experiments was purified, obtained from a MilliQ Plus, Millipore.

Three aqueous NLC dispersions were produced containing 20% (w/w) of lipid matrix (stearic acid and oleic acid) with different proportions of solid and liquid lipid, and stabilized with 1% (w/w) of surfactant (poloxamer 188). For the production of NLC a modified oil-in-water emulsion procedure has been applied. The mixture of liquid and solid lipids and surfactant was heated 5-10ºC above the melting point of the solid lipid, followed by the addition of purified water heated at the same temperature, and put into an Ultra-Turrax T25 (Janke & Kunkel GmbH, Staufen, Germany), at 8000 rpm for 20 minutes. The obtained emulsion was further diluted with 10 mL of purified hot water and cooled down under magnetic stirring, until 30ºC has been reached. Finally, 4 mL of ethanol was added and stirred for more 25 minutes.

For minoxidil-loaded NLC, the drug was dissolved in the liquid lipid (oleic acid) prior to emulsification. Minoxidil was used in a concentration of 5% with regard to the liquid lipid.

The particle size analysis was performed by photon correlation spectroscopy (PCS). The PCS yielded the mean diameter of the main population and polydispersity index (PI) as a measure for the width of the particle size distribution. For PCS measurements, all the samples were diluted with purified water to suitable concentration and measured with a Malvern Zetasizer 5000 (Malvern Instruments, UK).

To investigate the long-term stability as a function of storage conditions, the selected placebo and drug-loaded NLC formulations were stored at different temperatures (4ºC, 25ºC and 40ºC) for 30 days and the mean diameter and PI of the nanoparticles were measured.

The NLC morphology of the selected placebo formulation was observed under cryo-scanning electron microscopy (cryoSEM). For cryoSEM the sample was mounted on metal stubs, frozen with liquid nitrogen, gold coated under vacuum and then examined.

Results and discussion

Six different formulations were developed, with different liquid lipid and solid lipid concentrations, according to Table I.

Composition	A1	A2	B1	B2	C1	C2
Stearic Acid	17.1	17.1	15.2	15.2	13.3	13.3
Oleic Acid	1.9	1.8	3.8	3.6	5.7	5.4
Poloxamer 188	1	1	1	1	1	1
Minoxidil	-	0.1	-	0.2	-	0.3
Water	79	79	79	79	79	79

Table I: Composition of NLC formulations (% w/w)

Figure 1 shows the mean diameter and the PI of all formulations measured on the production day.

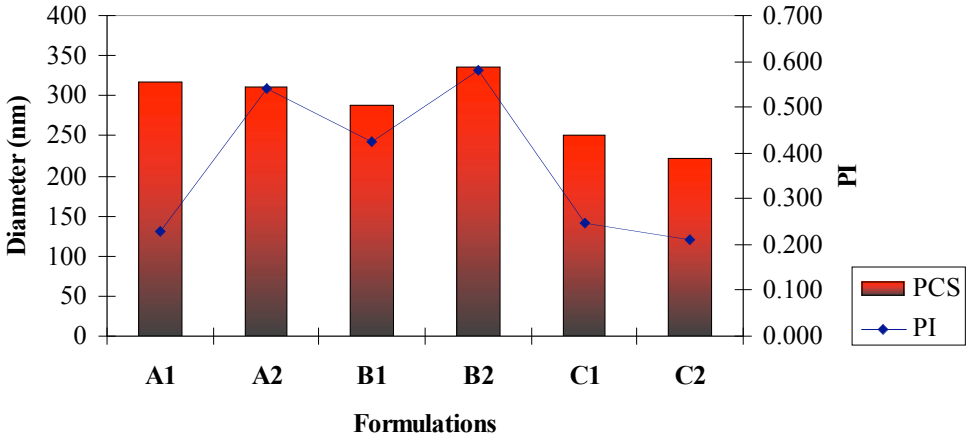

Figure 1: PCS diameter and PI of NLC formulations measured on the day of the production.

The formulations C1 and C2 were selected for further analyses, once they show lower particle size on the day of production, a higher loading of oleic acid and therefore a higher drug-loading capacity for minoxidil. The particle size of such formulations was monitored for 30 days under three different storage temperatures. Figure 2 shows the results of the long-term stability studies of formulations C1 and C2 as function of storage conditions (4ºC, 25ºC and 40ºC). It is clearly observed a lower size of formulation C2 although both revealed colloidal sizes (below 1 µm) after 30 days of storage.

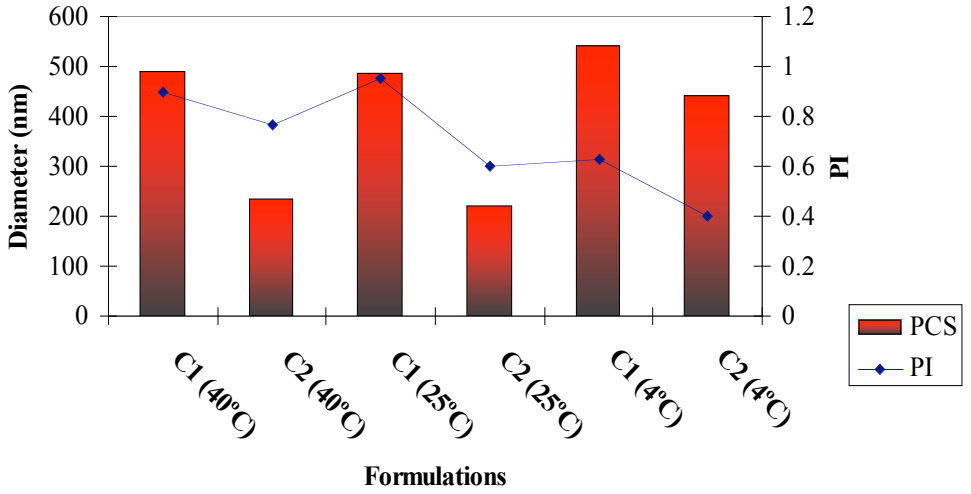

Figure 2: PCS diameter and PI of formulations C1 and C2 after 30 days of storage at different temperatures (4ºC, 25ºC and 40ºC).

To assess particle shape of C1 formulations (placebo NLC), cryoSEM has been performed. As observed in Figure 3, cryoSEM analysis of formulation C1 shows nanoparticles of spherical shape with smooth surface and regular morphology. These characteristics were expected because of the increased oleic acid content of the formulation (30% regarded to the lipid matrix) (Hu 2005).

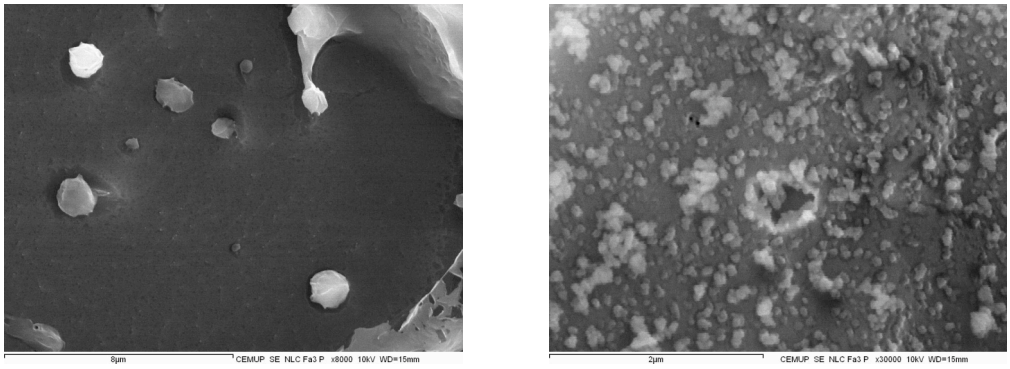

Figure 3: CryoSEM micrographs of formulation C1. Global image (right) and detail of the surface morphology (left) of the NLC.

Conclusions

The results show that minoxidil can be incorporated in NLC dispersions, prepared by a novel oil-in-water emulsion procedure, revealing that these nanoparticles are promising minoxidil delivery systems. Further studies of these systems are in progress in order to investigate drug entrapment efficiency, physicochemical stability for longer periods and their potential as carriers systems for topical delivery, when incorporated in semisolid dermal carriers, such as hydrogels.

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