Nanostructured lipid carriers (NLC) – based hydrogel formulation for topical delivery of Minoxidil

Silva, A.C.[1]*, Lopes, C.M.[2], Doktorovová, S.[2], Santos, D.[1], Ferreira, D.C.[1], Souto, E.B.[2]
[1] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Porto, Porto, Portugal
[2] Faculty of Health Sciences, University of Fernando Pessoa, Porto, Portugal
***Corresponding author: ana.silva@ff.up.pt**

Introduction

Minoxidil has been widely used for the topical treatment of alopecia [1]. The lipophilic characteristics of this drug implies that conventional topical formulations consist of propylene glycol-water-ethanol solution [2]. Applications of such formulations may cause severe adverse reactions [3-7]. To minimise these side effects and to improve therapeutic efficiency, the development of new systems for topical delivery of minoxidil is a demand.

Biodegradable nanoparticles, such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) [8, 9], are stable colloidal systems with notable advantages as drug delivery systems, i.e. physicochemical stability, versatility, biocompatibility, biodegradability and controlled drug release. 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 [10].

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 [11].

The purpose of this work was the development and characterization of a semi-solid formulation, composed of a water-soluble polymer, such as perfluorocarbon (PFC), which incorporate NLC for topical delivery of minoxidil. Rheological behaviour of NLC-based hydrogel has been evaluated by means of continuous shear investigations.

Materials and Methods

Materials

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

Methods

Preparation of NLC dispersions

Aqueous NLC dispersions were produced containing 20% (w/w) of lipid matrix (stearic acid and oleic acid) with 70% of solid and 30% of 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.

Particle size analysis

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).

Preparation of NLC-based hydrogel

For the production of NLC-based hydrogel, optimized formulations composed of PFC, propylenoglicol and water were admixed, stirred for 10 min at 1500 rpm, and immediately neutralized with triethanolamine until pH 6.5. Hydrogel were further allowed to equilibrate for 24 hours at room temperature and then used to disperse a freshly prepared NLC suspension. Aqueous NLC dispersion and hydrogel were mixed in a high speed stirrer (Cito Unguator Konietzko, Bamberg, Germany) at approximately 1000 rpm for 5 min.

Rheological analysis

Rheological tests were performed on a cone and plate rheometer (Haake RS-100) at 25 ± 1ºC. The data obtained were analysed and adjusted to Ostwald's model ($\tau = k\gamma n$) to assess the correlation coefficients. A rheometer RheoStress RS 100 (Haake, Karlruhe, Germany) was used for oscillatory shear flow measurements using the cone and plate geometry (a plate of radius 10 mm with a cone angle of 4º).

For the rheological characterization of the semi-solid formulations containing NLC an oscillation frequency sweep test was performed over a frequency range from 0 to 10 Hz at constant stress amplitude of 5 Pa. The rheological properties of the developed hydrogel containing NLC were studied by continuous shear investigations, which were performed in order to evaluate the shear rate [1/s] as a function of shear stress [Pa]. This study started with a shear rate of 0.1 1/s up to a maximum of 500 1/s and the resulting shear stress was measured.

Results and Discussion

The composition of the NLC formulations is shown in Table 1.

Table1: Composition of NLC formulations [%(w/w)] (MF, minoxidil-free NLC dispersions; ML, minoxidil-loaded NLC dispersions).

Composition	Formulations [%(w/w)]	
	MF-NLC	ML-NLC
Stearic acid	13.3	13.3
Oleic acid	5.7	5.4
Poloxamer 188	1.0	1.0
Minoxidil	-	0.3
Water	79.0	79.0

The mean particle size of NLC formulations were approximately 250 nm before the entrapment within the gel network and remained below 500 nm after admixing with hydrogel.

The freshly prepared NLC dispersions (30g) were first produced and further admixed to freshly prepared hydrogels (70g).

In order to clarify the effect of the addition of NLC dispersions on the physicochemical properties of the prepared semi-solid formulations, rheological analysis of hydrogels were performed. Figure 1 depict the plots of the shear stress [Pa] as a function of shear rate [s^{-1}] of the hydrogels, before and after the admixture with NLC dispersions.

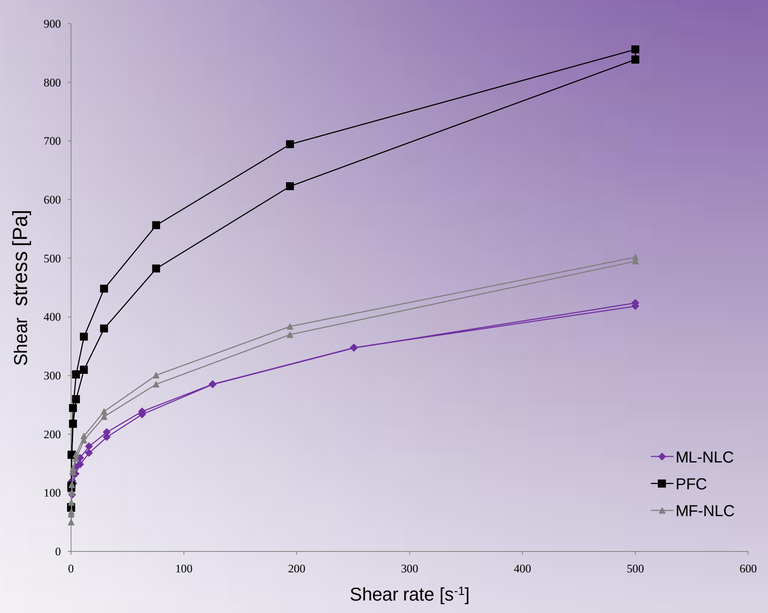

Figure 1: Shear stress as a function of the shear rate, measured on the day of production of the perfluorocarbon-based hydrogels without nanoparticles (PFC) and with nanoparticles (MF-NLC and ML-NLC).

The characteristic shape of the rheograms indicates that all formulations exhibited pseudoplastic flow, which are suitable for topical purposes. Thixotrophy was also observed after incorporate the nanoparticles in the hydrogel, because the up and down curves did not overlap.

Conclusions

The developed minoxidil-loaded NLC-based hydrogel formulation was shown to be a promising alternative to the conventional solution of minoxidil, avoiding the risk of undesirable side effects, typically known from the use of alcoholic solutions, such as skin dryness and irritation.

In addition, the physically entrapment of the drug in the lipid matrix increase its bioavailability for topical delivery.

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