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ORIGINAL ARTICLE

Preparation and characterization of minoxidil loaded nanostructured lipid carrier gel for effective treatment of alopecia

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Abstract In the present work attempts have been made to prepare the nanostructured lipid carrier (NLC) gel, by using minoxidil, which is preferably used in case of Alopecia, i.e. baldness pattern as a effective drug. The nine different formulations of Minoxidil-NLC (NLC1–NLC9) were prepared using solid and liquid lipids with Cholesterol and Soya lecithin in different concentrations by the melt dispersion ultrasonication method. Properties of NLC1–NLC9 such as the particle size and its distribution, the scanning electron microscopy (SEM), the drug entrapment efficiency (EE), and the drug release behavior were investigated. The nanoparticulate dispersion was suitably gelled and characterized with respect to drug content, pH, spreadability, rheology, and *in vitro* release. Safety of the NLC-based gel was assessed using primary skin irritation studies. The formulated NLC3 was spherical in shape, with average particle size of 280 nm, zeta potential of −42.40 mV and entrapment efficiency of 86.09%. Differential Scanning Calorimeter (DSC) measurements revealed that imperfect crystallization occurred in the inner core of the NLC particles. The drug release behavior from the NLC displayed a biphasic drug release pattern with burst release at the initial stage followed by sustained release. These results indicated that the NLC3 is a suitable carrier of minoxidil with improved drug loading capacity and controlled drug release properties. It has been observed that NLC gel produces the gel with good consistency, homogeneity, spreadability and rheological behavior. The developed NLC-based gel showed faster onset and elicited prolonged activity up to 16 h. The present study concluded that the NLC-based gel containing minoxidil dissolved in a mixture of solid lipid and liquid lipid in the nanoparticulate form helped us to attain the objective of faster onset yet prolonged action as evident from *in vitro* release.

1. Introduction

Pharmaceutical technology has taken the advantage of the advent of Nanotechnology; new pharmaceutical dosage forms are under development to deliver many physicochemically different drug molecules (Hommoss, 2008; Muller and Almeida, 2005). Poor water solubility and insufficient bioavailability of

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the new drug molecules are main and common problems. Therefore, there is an increasing need to develop a drug carrier system that overcomes this drawback (Hommoss, 2008). As a vehicle for controlled release of active substances and targeting to skin layers, nanodisperse systems such as Liposomes, nano emulsions, and lipid nanoparticles are gaining more and more importance (Utreja and Jain, 2001).

In the beginning of the 1990s, solid lipid nanoparticles (SLN) were developed as an alternative carrier system to the existing traditional carriers, such as emulsions, liposomes, and polymeric nanoparticles (Pardeike et al., 2009; Rajashree et al., 2011). Compared with the traditional carriers, SLN are well-tolerated, have high bioavailability, a nice targeting effect, and can be produced on a large industrial scale. The SLN features have been considered advantageous for topical administration of active substances (Uner and Yener, 2007). Potential problems associated with SLN namely, limited drug loading, risk of gelation and drug leakage during storage caused by lipid polymorphism have been further minimized by a new generation of lipid systems, the nanostructured lipid carriers (NLC) developed at the turn of the millennium (Muller et al., 2002a). NLC consists of a mixture of especially very different lipid molecules, i.e., solid lipid(s) is blended with liquid lipid(s) (oils). The resulting matrix of the lipid particles shows a melting point depression compared to the original solid lipid; however, the matrix remains solid at body temperature (Muller et al., 2000; Saupe et al., 2005). SLN and NLC are colloidal carrier systems providing controlled release profiles for many substances in tropical route. They are composed of physiological and biodegradable lipids as a carrier, exhibiting low systemic toxicity and low cytotoxicity (Muller et al., 1997).

In view of topical administration, these systems possess occlusive properties because of film formation on the skin surface (Wissing and Muller, 2002b). It reduces the transepidermal water loss and therefore enhances the penetration of drugs through the stratum corneum by increased hydration. It has also been reported that the occlusion factor of SLN and NLC is related to their particle size, that is, it increases with the decrease of the mean particle diameter (Wissing and Muller, 2002a, 2003). The small size of the lipid particles ensures close contact with the stratum corneum and can increase the amount of drug penetrating into the mucosa or skin. Due to their solid lipid matrix, a controlled release from these carriers is possible (Muller et al., 2002a). In addition, by controlling the amount of liquid lipids added to the formulation, the NLC remains in its solid state at body temperature and the modulation of drug release profile can be achieved. This becomes an important tool when it is necessary to supply the drug over a prolonged period of time, to reduce systemic absorption, and when drug produces irritation in high concentrations (Muller et al., 2000; Chaudhari, 2012).

Minoxidil, a pyridine-derivative, was initially developed as an oral antihypertensive agent. However, its major clinical attraction is related to its common side effect on the promotion of hair growth (Atrux-Tallau et al., 2009). Alopecia is a common form of hair loss in both men and women. Minoxidil is widely used for the treatment of alopecia (Messenger and Rundegren, 2004). Commercial products containing minoxidil are usually solutions with high percentage of ethyl alcohol and/or propylene glycol. Twice-daily applications are recommended as proper use (Wagner and Kenreigh, 2007; Aronson, 2006). However, repeated applications of high ethyl alcohol and/or propylene glycol content products lead to severe adverse effects such as scalp dryness, irritation, burning, redness and allergic contact dermatitis. Since most of the products containing minoxidil available on the market consist of ethyl alcohol–propylene glycol–water solutions, new dermatological formulations free of organic solvents are needed to minimize adverse effects and optimize androgenic alopecia treatment (Padoisa et al., 2011). Hence to minimize the side effects and to improve the therapeutic efficiency of minoxidil, the development of new systems for topical delivery of such drug is in demand.

Therefore, the aim of the present work was to develop the NLC gel formulation containing minoxidil, using different concentrations of solid and liquid lipids, to evaluate its physicochemical properties and stability.

2. Materials and methods

Minoxidil, was obtained as gift from Dr. Reddy's Laboratory, Hyderabad, India. Tristearin was provided by Glenmark Generics, Mumbai, India. Oleic acid, Cholesterol and Tween-80 were purchased from Merck Pvt. Ltd., Mumbai, India. Soya lecithin (Phosphatidylcholine), Pluronic F-68, Triton X-100, Carbopol 934 and Triethanolamine were purchased from Hi-Media Laboratories, Mumbai, India. Chemicals and reagents were of the highest purity grade commercially available from Merck Pvt. Ltd., Mumbai, India.

2.1. Preparation of minoxidil loaded NLC

The NLCs were prepared by the melt dispersion ultrasonication method. The lipid (oleic acid and tristearin), cholesterol and phosphatidylcholine (soya lecithin) were blended and melted at 75 °C, along with the minoxidil, to form a uniform and clear oil phase. Meanwhile, the aqueous phase consisting of dispersing surfactant Tween-80 in double distilled water was maintained at 75 °C. The oil phase was added to the aqueous phase, and both phases were mixed by the aid of agitation at 600 rpm for 10 min at this temperature to form a microemulsion. This warm microemulsion was diluted in cold water (2–3 °C) under mechanical stirring to form NLC dispersion such that the concentration of minoxidil in the final dispersion remains 2% w/w (Jain et al., 2009; Wang et al., 2010).

2.2. Preparation of gel formulations

The nanoparticulate dispersion obtained after diluting the warm microemulsion templates was gelled using gelling agents. Based on the compatibility with nanoparticulate dispersion, the esthetic appeal and the ease of spreadability carbopol (2%) was selected as the gelling agent. Carbopol was added to the nanoparticle dispersion under overhead stirring at 800 rpm (Remi, Mumbai, India). Stirring was continued until carbopol was dispersed. The carbopol dispersion was neutralized using 0.05% (w/w) Triethanolamine and pH of gel was adjusted to 7.4 (Joshi and Patravale, 2006).