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# Development of solid lipid nanoparticles based controlled release system for topical delivery of terbinafine hydrochloride

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ABSTRACT

The study describes the development and evaluation of solid lipid nanoparticles (SLNs) of terbinafine hydrochloride (TH) for sustained release and skin targeting. TH-loaded SLNs were prepared by solvent-injection technique and optimized using $3^3$ full-factorial design. Effect of drug:lipid ratio, surfactant concentration and volume of organic solvent were studied on % entrapment efficiency (%EE) and particle size (PS). The optimum formulation based on desirability (0.945) exhibited %EE of 73.74% and PS of 300 nm. Optimized SLNs were incorporated into Carbopol gel and evaluated for drug content, pH, *in vitro* release, *ex vivo* retention, *in vivo* pharmacodynamic and stability studies. Drug release from SLNs dispersion followed Korsmeyer–Peppas model, indicating Fickian drug release, while that from the gel followed Higuchi model. The *ex vivo* studies through rat abdominal skin indicated skin retention ability of SLNs as compared to commercial product. *In vivo* pharmacodynamic studies showed that the SLNs based gel reduced fungal burden of *Candida albicans* in rats as compared to commercial product in shorter duration of time. The SLNs dispersion and gel exhibited physicochemical stability under refrigeration upto 3 months. It was concluded that SLNs incorporated Carbopol gel had skin targeting ability and may serve as a promising carrier in treatment of fungal skin infections.

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## 1. Introduction

Solid lipid nanoparticles (SLNs) are novel drug carrier system which consists of a solid matrix composed of a lipid being solid at both room and body temperatures with a mean particle size (PS) between 50 and 1000 nm. SLNs are low cost products as the excipients and production lines are relatively cheap and the production costs are not much higher than those established for the production of parenteral emulsions (Muller et al., 2005). The use of SLNs as colloidal transporters (Attama, 2011; Kumar and Randhawa, 2013; Mehnert and Mader, 2001) have gained significant importance as an alternate colloidal drug delivery system to liposomes, lipid emulsions, polymeric nanoparticles and micelles. Compared to liposomes and emulsions, SLNs possess some advantages, like protection of incorporated drugs against chemical degradation and more flexibility in modulating the release of the drug. A clear advantage of the use of SLNs as drug carrier systems is the fact that its matrix is composed of physiological components or physiologically related components, i.e. excipients which come under generally recognized as safe (GRAS) status for oral and topical administration, which decreases the danger of acute and chronic toxicity.

SLNs possess a number of advantages for the topical route of administration. Due to small PS, SLNs ensure close contact to stratum corneum and thereby increase penetration of encapsulated drug into the skin (Lv et al., 2009). Sustained release of the drug from SLNs supplies the drug to the skin over a prolonged period and thereby reduces systemic absorption (Liu et al., 2007). For topical SLNs, all excipients used in current topical cosmetic and dermal pharmaceutical products can be used. To get a topical dosage form having the desired semisolid consistency, the SLN dispersion can be incorporated into commonly used dermal carriers like hydrogels or creams (Bhalekar et al., 2009; Montenegro et al., 2012). SLNs are reported to form an invisible, occlusive film with affinity for the stratum corneum, which ensures drug release for a prolonged period of time (Muller et al., 2000; Wissing and Müller, 2001). SLNs show occlusive properties as a result of film formation on the skin, which reduces transdermal water loss (Souto et al., 2004; Wissing and Müller, 2001). Increase of water content in the skin reduces the symptoms of atopic eczema and also improves the appearance of healthy human skin. Occlusion also favors the drug penetration into the skin (de Vringer and de Ronde,

*Abbreviations:* TH, terbinafine hydrochloride; SLNs, solid lipid nanoparticles; %EE, % entrapment efficiency; PS, particle size; FM, full model; RM, reduced model; DSC, differential scanning calorimetry; TEM, transmission electron microscopy.

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1995; Mei et al., 2003). SLNs also have high affinity to the stratum corneum, and therefore an enhanced bioavailability of the encapsulated material to the skin is achieved. SLNs enhance the penetration and transport of active substances, particularly lipophilic agents and thus intensify the concentration of these agents in the skin (Muller et al., 2002; Padois et al., 2011; Wissing and Muller, 2003). This makes the sustained release possible from these carriers, which is an important tool when it is necessary to supply the drug over a prolonged period of time.

Approximately 90% of fungal skin infections are caused by 'dermatophytes', which are parasitic fungi affecting the skin, hair, or nails. Terbinafine hydrochloride (TH) is a broad spectrum antifungal drug which is effective against *Dermatophytes*, *Aspergillus* species, *Candida species* and *Pityrosporum* yeasts. Currently, it is available in the form of topical and oral formulations. Systemic treatment is usually reserved for infections of the nails, extensive cutaneous infections or those which have not responded to topical therapy. Conventional topical formulations are unable to retain the drug over the skin for a prolonged period and hence necessitate longer treatment duration or have to be supplemented by oral therapy. When SLNs are incorporated in gel, the contact between nanoparticles decreases and aggregation can be avoided. The network of the gel hampers the polymorphic SLN transitions and thus enhanced the stability of SLNs (Jenning et al., 2000). We hypothesized that incorporation of the drug in SLNs incorporated in a bioadhesive gel would facilitate prolonged contact of the drug on the skin and the SLNs would improve its skin retention ability, thereby improving the topical treatment of fungal skin infections. TH loaded SLNs were prepared by solvent injection technique and were further incorporated in Carbopol gel for the purpose of treating fungal skin infections by targeting the skin. Carbopols (carbomers), a group of carboxyvinyl polymers cross-linked with allyl sucrose, form hydrophilic gels which thicken better than natural gums. Hydrogels based on Carbopol 934 have been tested as dispersion medium for colloidal carriers such as SLNs (Silva et al., 2007). By incorporation of TH loaded SLNs into Carbopol gel, it is hypothesized that SLNs do not only sustain the release of drug and enhance percutaneous absorption, but may even allow for drug targeting to the skin or even its substructure, thereby enhancing drug efficacy and improving patient compliance by reducing application frequency.

## 2. Materials and methods

### 2.1. Materials

TH was received as gift sample from FDC Ltd., Mumbai, India. Glyceryl behenate (Compritol 888 ATO) and Glyceryl palmitostearate (Precirol ATO 5) were obtained as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Pluronic F-127 was received as gift sample from BASF, Germany. All other chemicals were of analytical grade and obtained commercially.

### 2.2. Preparation of SLNs

SLNs loaded with TH were prepared by solvent injection method (Schubert and Muller-Goymann, 2003). Lipids and drug were dissolved in isopropyl alcohol (4, 5, 6 ml) at 5 °C above melting point of lipid. Simultaneously, Pluronic F-127 solution in 10 ml distilled water was prepared at the same temperature. The lipid solution was then added to aqueous phase with continuous stirring on magnetic stirrer (1 MLH, Remi equipments, Mumbai, India). Stirring was continued for 3–4 h at 40 °C to allow complete evaporation of the organic solvent. The SLNs dispersion was centrifuged at 50,000*g* for 30 min at 4 °C (3K30, Sigma Laboratory Centrifuge, USA) and pellet of settled SLNs was re-suspended in water.

### 2.3. Drug content and entrapment efficiency

To determine TH content in SLNs dispersion, SLNs were separated by gel filtration using Sephadex G-50 column (Beck et al., 1990; Liu et al., 2008). Column was washed initially with dispersion medium (distilled water) to saturate the column. SLNs dispersion (1 ml) was poured into the column and allowed to move down the column. Distilled water was added as continuous mobile phase and different fractions (each of 0.5 ml) were collected. SLNs were collected from column with dispersion medium in initial fractions while free drug retained in Sephadex column was collected in later fractions. Each fraction was dissolved in tetrahydrofuran and the solution was analyzed for TH content using UV–visible spectrophotometer (UV-1601, Shimadzu, Japan) at 283 nm (El-Saharty et al., 2002).

### 2.4. Particle size analysis

The size analysis and polydispersity index of the SLNs were determined using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK). Each sample was suitably diluted with filtered distilled water (up to 2 ml) to avoid multi-scattering phenomena and placed in a disposable sizing cuvette. The polydispersity index was studied to determine the narrowness of the particle size distribution. The size analysis of a sample consisted of three measurements, and the results were expressed as mean size ±SD.

### 2.5. Zeta potential

Zeta potential distribution was measured using a Zetasizer (Nano ZS, Malvern Instruments, UK). Each sample was suitably diluted five times with filtered distilled water and placed in a disposable zeta cell. Zeta limits ranged from −200 to +200 mV. The electrophoretic mobility was converted to zeta potential by inbuilt software using the Helmholtz–Smoluchowski equation. The average of three measurements of each sample was used to derive the average zeta potential.

### 2.6. Optimization of formulation parameters

Various formulation parameters were optimized based on their effect on response parameters. Some of the formulation parameters like organic solvent, type of lipid and type of stabilizer were optimized in preliminary stages, while drug:lipid ratio, surfactant concentration and volume of organic solvent were optimized by $3^3$ full factorial design. Here, percentage entrapment efficiency (%EE) and PS were considered as dependent variables (response parameters). All the experiments were performed in triplicate.

#### 2.6.1. Factorial design for optimization of independent parameters

Optimization of various formulation parameters were studied by $3^3$ full factorial design (Mehta et al., 2007; Subramanian et al., 2004). Based on the results obtained in preliminary experiments, drug:lipid ratio, surfactant concentration (% w/v) and volume of organic phase were found to be the major variables in determining the %EE and PS. Hence, these variables were selected to find the optimized formula for high %EE and low PS using $3^3$ factorial design and contour plots. The responses ($Y$) were measured for each experiment and then a simple linear (Eq. (1)), interactive (Eq. (2)) or quadratic model (Eq. (3)) was generated by carrying out multiple regression analysis and $F$-statistics to identify statistically significant terms (Bolton and Bon, 1997).

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