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Development and characterization of griseofulvin loaded nanostructured lipid carrier gel for treating dermatophytosis

Neelam Datt[a,*], Rajasekhar Reddy Poonuru[b], Pankaj K. Yadav[a]

[a] Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture Technology and Sciences, Prayagraj 211007, U.P., India
[b] Department of Pharmaceutical Sciences, St. Peter's Institute of Pharmaceutical Sciences, Vidyanagar, Hanamkonda 506001, Telangana, India

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ABSTRACT

The present investigations were aimed at formulating topical gel containing nanostructured lipid carriers (NLCs) of griseofulvin and assess its effectiveness on superficial infections. The drug solubility studies were executed using various lipids and surfactants like Glyceryl monostearate, Oleic acid, Pluronic F 68, and Tween 80, and the concentrations of lipids, surfactants, and emulsifier were optimized using Box-Behnken design (BBD). Microemulsions were made utilizing sonication. The prepared batches (F1 to F15) were analyzed and observed that the optimized batch (F12), containing 0.2% w/w drug, 2% GMS, 2% Pluronic F68 and Tween 80 (in the ratio of 1:1) showed a particle size of 209 nm, zeta potential of -44.12 mV, entrapment level of 85.24% along with a drug release of 92.12%. Carbopol 940, 1.5% was used to make the topical gel. The results of biochemical studies reflected that griseofulvin-loaded-nanogel produced a more significant decrease in lipid peroxidation as compared to the standard drug. The in-vitro cytotoxicity studies showed better safety of nanogel in human keratinocyte cells (HaCaT). The results of antifungal activity showed complete clinical and mycological cure in a duration of 21 days against superficial infections like Tenia pedis and also ringworm in Wistar rats while using T.rubrum and M.canis fungal strains. These preclinical investigations have proved that the nanogels have a better potential in treating the aforementioned superficial infections providing an effective alternative for currently existing products.

Introduction

Fungi are the most common microbial agents responsible for the prevalence of skin diseases globally. Pathogenic fungi dwell in hair, nails, epidermis, and mucosa causing superficial fungal infections. The three most common superficial infections are Dermatophytosis (tinea or ringworm), Pityriasis versicolor, and Candidiasis (Kelly, 2012).

Dermatophytosis has become more common in recent decades with an estimated incidence of 25% of the global population (Teklebirhan & Bitew, 2015) representing the third most common fungal illness globally (Rouzaud et al., 2017). Trichophyton *spp.*, particularly Trichophyton, Microsporum, and Epidermophyton are the major agents accountable for skin infections.

There are several antifungal medications that are previously generated and proven themselves to be effective in killing the superficial fungi, but they have failed in providing the required therapeutic effect due to their poor aqueous solubility and permeability. As a result, fresh and more advanced antifungal therapeutic alternatives are desperately needed (Arnold et al., 2010). Griseofulvin is a heterocyclic benzofuran found in the *Penicillium.* It belongs to BCS class II medication with a log P value of 2.17 and shows high permeability and low solubility (Arida et al., 2007). A study revealed that despite all the favorable molecular features such as lipophilicity, molecular mass (352.77 Da), and hydrogen bond accepting capacity (Veber et al., 2002) topical dosage for griseofulvin is not so promising due to limitations of solubility and penetrability to the deeper layers of the skin.

Topical management of fungal infections has various benefits like fewer side effects, site-specific administration, high patient compliance, and effective cure. Antifungal treatment tactics have become increasingly complex and expensive due to a lack of effective medications and a rising proportion of drug resistance. There have been a lot of recent findings on topical formulations of griseofulvin to increase penetration through skin by dissolving the agent in a variety of vehicles (Aggarwal & Goindi, 2012), use of new carrier systems (Pierri & Avgoustakis, 2005), and more recently, by using penetration enhancers (Fujii et al., 2000). The topical delivery of antifungal agents into the skin is improved by new drug delivery technologies such as vesicular carriers, colloidal systems, and nanoparticles (Lee & Maibach, 2006). There are some recent findings where researchers explored the potential of griseofulvin in colloidal carriers viz polylactide micelles

* Corresponding author.
E-mail address: neelima12pharm@gmail.com (N. Datt).

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