1. INTRODUCTION

In the last two decades, the diminishing research and development (R&D) efficiency of the pharmaceutical industry has become the global bottleneck for innovations and future expansion, for the R&D based pharmaceutical companies as well as for the generic drug manufacturers (Alexander et al., 2012). Billions of dollars and several years of development time are the reasons for selectiveness and hesitation of pharmaceutical industries for producing new drugs (Farokhzad and Langer, 2009). Therefore, preparation of novel formulations/modifications of the existing drugs seems to be a rational approach for overcoming the problems associated with the existing drug products and to partially fulfill the never ending requirement of newer drugs.

Value added generics (VAGs), also known as supergenerics refer to an approach of designing novel dosage forms of existing drugs, thereby giving a rapid, effective and problem solving alternatives of conventional drug products having certain setbacks (Stegemann et al., 2011). These types of generic products focus on areas of unmet medical needs, which are currently the setbacks of the available drug products. VAGs are generally intended to be used through different routes of administration than the existing drug products, or are to be administered in different dosage regimens (Bonifácio et al., 2014).

The recent introduction of novel colloidal (nanosized) carriers based VAGs of new and off-patent drugs for administration via every possible medication routes implies that the trend will sustain and these carriers have stretched out role as alternatives of conventional dosage forms of existing drugs (Prados et al., 2014). This innovative approach has led to an explosion of nanopharmaceutical research in last decade, which resulted in launch of several colloidal carriers based VAGs, which is the biggest triumph of pharmaceutical-nanosciences amalgamation. The success stories of Abraxane® (Abraxis Bioscience), an albumin bound paclitaxel for metastatic breast cancer; liposomal therapies such as Ambiosome® (Gilead Sciences), Doxil® (Alza Corp.) and Pevaryl® (Cilag Corp.) clearly show the vast potential of colloidal carriers based VAGs in the global healthcare sector (Kumar, 2010). The current enthusiasm and expectation for colloidal carriers based VAGs at industrial level is also reflected by recent filing of thousands of patents by the industries and research institutions across the world (Bamrungsap et al., 2012). The global market of colloidal carriers based VAGs is expected to grow by 3.5 trillion dollars in less than next thirty years (Bonifácio et al., 2014). Colloidal carriers possess salient “nanoproperties” due to their extremely small
size (in comparison to their bulk-phase counterparts) and their excessive surface-to-volume ratio (DeLouise, 2012). Therefore, the approach of using colloidal carriers based VAGs provides reformulation opportunities for existing pharmaceutical moieties, which originally had the problems of solubility, stability or inefficient targeting to specific site of body where pharmacological action was required. In other words, the drugs, which were previously unsuitable for conventional oral or parenteral formulations could be nanoformulated for delivery to specific targets due to superior pharmacokinetic and pharmacodynamic parameters, consequently leading to enhanced bioavailability, reduced therapy time and fewer side effects (Honeywell-Nguyen and Bouwstra, 2005; Ueda et al., 2010). The colloidal carrier based products in addition to altering the physicochemical microenvironment of the drug, also influence the performance of drug in terms of their tissue affinity, therapeutic efficacy, stability, biodegradability, safety and patient compliance (Biju et al., 2006; Kreilgaard, 2002).

These colloidal carrier based systems are essentially composed of one or more oils, fatty acids, lipids, phospholipids and amphiphilic materials (surfactants), which are capable of entrapping hydrophilic as well as lipophilic drug moieties. These systems have been very well established to play an important role in cellular communication and particle transportation (Grazu and Moros, 2012). The composition of these colloidal carriers imparts them a high structural similarity with skin lipids and therefore a capability to integrate and inter-digitate with the skin components, which have promoted their increasingly wider applications in dermal and transdermal delivery systems (Alexander et al., 2012; Liu and Hu, 2007). Therefore, they can effectively transport drugs to the target cells for release, allowing the drug to take effect as intended.

Conventionally like other dosage forms, these formulations have been developed using One-Factor-At-a-Time (OFAT) approach, which implies a method of designing experiments involving the testing of several factors, or causes, one at a time instead of all simultaneously. However, this approach is tedious and time consuming as it requires excessive experimental trials to attain considerable precision in estimation of effects. Also, the experimenter cannot estimate effect of factor interactions, which may lead to suboptimal setting of factors (Singh et al., 2005; Singh et al., 2011a).

Experimental design techniques enable formulation scientists to investigate simultaneously the individual as well as interactive effects of several factors that could affect the output results (response) in any design matrix. This approach also provides complete and rigorous information regarding interactions between different design
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elements; therefore, it helps to transform any standard experimental protocol into a robust one. In other words, experimental designs serve to pinpoint the critical parts and sensitive areas in designs that cause major alterations in the responses. Formulators are then able to rectify the problems and produce robust and higher yield designs prior going into production.

Itraconazole (ITR) is a triazole antifungal agent being used for more than a decade against a most of the known fungal pathogens including *Candida* spp., *Aspergillus* spp., *Trichophyton* spp., *Microsporum canis*, *Pseudallescheria boydii*, *Sporothrix schenckii*, *Histoplasma capsulatum*, and numerous other pathogenic dermatophytes like *Epidermophyton* spp., *Microsporum* spp. and *Trichophyton* spp. (Boogaerts et al., 2001; Gupta and Kohli, 2003; Kurnatowska et al., 2012; Olson et al., 2008). It is BCS class II drug having very poor solubility, causing its poor and variable absorption from oral solution and more commonly, oral capsules. The treatment spans from one day (e.g., for Vulvovaginal candidiasis) to several weeks (e.g., for Tinea pedis and Tinea corporis), depending on the type and site of infection. Also, the commonest minor side effects of oral ITR therapy are constipation, nausea, flatulence, abdominal pain, headache and diarrhoea (in case of cyclodextrin solutions) are frequently observed (Tucker et al., 1990). Also severe adverse effects like serious hepatotoxicity, including liver failure and also effects on the nervous system, gastrointestinal tract, hematologic, and renal insufficiency have been reported (Groll et al., 2002).

Therefore, the current study was aimed at utilizing statistical design based techniques for designing novel vesicular and nonvesicular colloidal carriers of ITR in order to circumvent the numerous shortcomings of conventional ITR therapy. After ascertaining the compatibility of drug and formulation additives, different colloidal carrier based hydrogels were formulated using established experimental designs. The response surface methodologies were employed for numerically achieving optimized formulations possessing desired characteristics including drug skin retention, skin permeation and other physical attributes. The *ex vivo* permeation studies in conjunction with dermatokinetic evaluation established that the statistically developed colloidal carriers suitably penetrate the skin, and provide sufficient drug deposition skin. Also, the results of pharmacodynamic studies carried out in Wistar rats supported the above findings, thereby revealing the excellent antifungal efficacy of the optimized colloidal formulations. In conclusion, the statistically optimized topical colloidal carriers of ITR appear to be a promising alternative to the conventional therapies of ITR.