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SOLID LIPID NANOPARTICLES BASED GEL FOR TOPICAL DELIVERY OF ANTIFUNGAL AGENT

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ABSTRACT: The aim of present work was to develop and evaluate solid lipid nanoparticles (SLNs) based gel for topical delivery of antifungal agent. Bifonazole (BFZ) is an imidazole antifungal agent having broad spectrum activity against dermatophytes, moulds, yeasts, fungi and some gram positive bacteria. BFZ SLNs systems were developed by melt emulsification followed by ultrasonication technique using Precirol ATO5 as a solid lipid and Tween 80 as a surfactant. Developed SLNs were evaluated for particle size, polydispersity index (PI), entrapment efficiency (EE) and drug release profiles. Process and formulation parameters were optimized. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies were carried out on SLNs to mark the changes in the drug and lipid modifications. The BFZ SLNs based gels were prepared using Carbopol 940 as a gelling agent. The SLNs based gels were evaluated for rheological parameters, *in vitro* drug release and permeation studies. *In vitro* antifungal study suggested that the SLNs based gel was more effective in inhibiting growth of *Candida albicans*. Thus the study concludes that SLNs based gel of BFZ gives a sustained release profile of BFZ and has the potential for treatment of topical fungal infections.

INTRODUCTION: Targeted drug delivery intends selective and effective transportation and accumulation of pharmacologically active drug in selected target organ thus increasing the effectiveness of the drug. To achieve this transportation and localization different carrier systems are used. Solid lipid nanoparticles (SLNs) are colloidal carrier systems developed in the beginning of 1990s as alternative to existing pool of carrier systems such as emulsions, liposomes and polymeric nanoparticles for the delivery of poorly water soluble drugs.

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SLNs combine their advantages such as controlled release, biodegradability, and protection of active compounds[1-3]. SLNs have been used in topical delivery as they can allow penetration of drug into the skin, offer sustained release of drug to avoid systemic absorption. The system also reduces irritation to the skin as they are made up of biocompatible excipients most of them have been in an approved status or are excipients used in commercially available cosmetic or pharmaceutical preparations [4-6].

Bifonazole (BFZ), 1-[phenyl(4-phenylphenyl) methyl]-1H-imidazole, is a substituted imidazole antifungal agent having a broad spectrum of activity against dermatophytes, moulds, yeasts, dimorphic fungi and some Gram-positive bacteria. BFZ is indicated in the treatment of superficial fungal infections of the skin such as dermatophytes,

cutaneous candidiasis and pityriasisversicolor. It is practically insoluble in water with a very short half-life of 1-2 h and is minimally absorbed (0.6% of applied dose) following dermal application [7, 8].

Since hyphae of fungi (mycelium) can penetrate deep into the epidermal layers by sliding past the corneocytes of the horny layer, improved penetration of the active ingredient is desired in antifungal therapy of the dermis [9]. Thus, topical application of SLNs based gel with increased penetration and retention through skin because of lipid nanoparticles will be much favorable for the treatment of infections and symptomatic relief. Hence, aim of present work was to formulate SLNs based gel of BFZ for topical application ultimately improving the efficacy of the drug.

MATERIALS AND METHODS:

Materials:

BFZ was procured as gift sample from Amoli Organics Pvt. Ltd., Mumbai, India. Solid lipids such as Compritol 888ATO (Glyceryl behenate), Precirol ATO5 (Glyceryl palmitostearate) were obtained as gift sample from Gattefosse India Pvt. Ltd. Imwitor 900 K (Glyceryl monostearate), Dynasan 114 were obtained as gift samples from Sasol GmbH, Germany. Poloxamer 188 was gifted by BASF, India. Glyceryl tripalmitate and Tween 80 were purchased from Sigma-Aldrich, Mumbai. Dialysis bag (Molecular weight cut off 12–14 kDa; pore size 2.4 nm) was supplied by Hi Media, Mumbai, India. All solvents and reagents used were of analytical grade.

Methods:

Screening of lipids:

The solubility of BFZ in different solid lipids was determined by a semi quantitative method which was slightly modified [10]. Fixed quantity of drug was accurately weighed in series of test tubes. Different lipids were added in increasing amount to respective test tubes and heated till drug is completely solubilised. The temperature of test tubes was maintained 10°C above the melting point of lipid used and shaken intermittently to dissolve the drug. Test tubes were observed visually for any drug residue. The amount of lipid required for solubilising fixed amount of drug was determined.

Preparation of SLNs:

The preparation of SLNs was based on Melt emulsification followed by Ultrasonication[11]. Initially BFZ was solubilised in molten lipid phase at temperature 5-10°C above the melting point of the lipid using temperature regulated water bath. The resulting drug-lipid mixture was then poured into aqueous surfactant solution maintained at same temperature as lipid melt.

The mixture was emulsified by high shear homogenization using Ultra Turrax T25 digital (IKA, Germany) at 10,000 rpm for 2 min. The pre-emulsion was then sonicated for 5 min at 20 Watt using Sonapros PR-250 M (Oscar Ultrasonics, Andheri). The resulting hot SLNs dispersion was cooled under magnetic stirring at 4-8°C. The composition of batches is as shown in **Table 1**.

TABLE 1: COMPOSITION OF BFZ SLNS

Batch No	Precirol ATO5 (%)	Tween 80 (%)	Poloxamer 188 (%)	Water (ml)
A	1.5	1.5	-	97
B	1.5	2.5	-	96
C	1.5	-	1.5	97
D	1.5	-	2.5	96
E	2	1.5	-	96.5

Evaluation and characterization of BFZ SLNs:

Particle size analysis:

The particle size analysis of formulations were performed using NANOPHOX® (NX0073) particle size analyzer (Sympatec GmbH, Germany) based on photon cross correlation spectroscopy. An aliquot of SLNs dispersion was diluted suitably prior to measurements. All the measurements were carried out at a temperature of 25±2°C and at a fixed angle of 90° to the incident laser beam. Data was analyzed by Windox software (Version 5.0) and values of mean particle size, polydispersity index (PI) and particle size distribution curve were recorded.

Entrapment efficiency (EE):

EE corresponds to the percentage of drug encapsulated within and adsorbed onto the nanoparticles. Nanoparticle dispersion was centrifuged at 14,000 rpm (Remi instruments, India) for 20 min to separate the nanoparticles. Separation of nanoparticles from the SLNs dispersion was carried out using electrolyte such as NaCl by aggregation of nanoparticles. Supernatant was analyzed for amount of free drug by using UV-

spectrophotometric method after suitable dilution with methanol at λ_{max} of 254 nm[12].

The EE was calculated by the following equation:

$$\% \text{ Entrapment efficiency} = \frac{W_{\text{Initial drug}} - W_{\text{Free drug}}}{W_{\text{Initial drug}}} \times 100$$

Where, '$W_{\text{Initial drug}}$' is the weight of total drug added in the dispersion and '$W_{\text{Free drug}}$' is the weight of free drug found in the supernatant after centrifugation.

***In vitro* drug release:**

Drug release was evaluated by using dialysis bag diffusion method[13]. The pre-soaked dialysis bag was filled with BFZ SLNs dispersion, tied at both ends and then immersed in the dissolution medium phosphate buffer pH 6.8: ethanol (60:40 v/v) to ensure perfect sink conditions and temperature was maintained at 37±0.5°C. Samples withdrawn at different time intervals were analyzed by UV spectrophotometer at 254 nm to determine the amount of BFZ released in to the receptor medium from the formulations.

X-ray diffraction study (XRD):

X-ray scattering measurements were carried out with Pan-analytical Xpert PRO MPD X-ray diffractometer. Anode material used was copper having $K\alpha_1$ and $K\alpha_2$ radiation wavelength of 1.5405 and 1.5444 respectively with generator voltage of 45 KV and tube current of 40 mA and detected using Xcelerator diffracted beam monochromator.

Differential scanning calorimetry (DSC) study:

Drug‑lipid interaction in nanoparticulate formulations and crystallinity of drug was analyzed by performing DSC analysis. Samples were analyzed using SII Nanotechnology EXSTAR DSC 6220 in scanning range of 30-300°C at a heating rate of 10°C/min. Plain drug, lipid, Drug-lipid physical mixture and SLNs formulation DSC scans were recorded and compared.

Preparation of SLNs based gel:

The SLNs dispersion was converted into gel carrier system using gelling agents such as Polycarbophil AA1, Xanthan gum and Carbopol (different grades 940, 934). Gelling agent at various concentrations were dispersed under stirring in to the SLNs dispersion till they were uniformly mixed to form gel with suitable consistency[14]. In some cases, pH of dispersion was adjusted in between 5.5-6.5 by triethanolamine to form gel with good consistency. The conventional gel was prepared by simply dispersing the drug into the gel matrix.

Evaluation of SLNs based gel:

Rheological behavior:

The viscosity of the gel was determined by using Brookfield Cone and Plate viscometer (Brookfield Engineering Laboratories, USA) using spindle # CPE 5 at 25±0.3ºC. The software used for the calculations was CapCalc V2.1. Spredability was evaluated as per method reported by Desai (2004)[15]. Weighed amount gel was placed within a circle of 1cm diameter pre-marked on a glass plate over which a second glass plate was placed. A fixed weight was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to spreading of the gel was noted.

***In vitro* drug release and *ex vivo* permeation studies:**

In vitro drug release studies for SLNs based gel was performed using Franz diffusion cell. The receptor compartment was filled with phosphate buffer pH 6.8: ethanol (60:40 v/v) to ensure perfect sink conditions. Cellulose acetate membrane was placed between the donor and the receptor compartment. The cells were thermostated at 37±0.5°C and stirred with a magnetic stirrer for uniform mixing of the contents. Donor compartment was filled with 1 g of SLNs based gel. Samples withdrawn at different time intervals were analyzed by UV at λ_{max} of 254 nm to determine the amount of BFZ released into the receptor medium from the formulations.

Ex vivo permeation studies were carried out using the same protocol as mentioned above using excised rat skin[16]. Franz diffusion cells were mounted with excised rat skin with stratum conium facing the donor compartment. Amount of BFZ permeated into the receptor medium from the formulations was calculated using high performance liquid chromatography (HPLC). To calculate the amount of BFZ deposited within the skin, the skin was cut in small pieces, subjected to

vortexing for 15 min in methanol using a cyclomixer[17]. The resulting solution was filtered through a 0.45 µ membrane, injected into HPLC and concentration of drug in skin was measured.

The HPLC analysis was carried out using an Agilent Technologies 1200 series system fitted with quaternary pump, autosampler, and Ultra Violet detector (UV detector). The column used was a HiQSil® C18HS (250 X 4.6 mm, 5 µm) maintained at temperature of 25°C. Samples were analyzed using mobile phase acetonitrile: methanol: water (5:90:5 v/v) with the flow rate of 1ml/min and UV detection at λ_{max} of 254 nm. The operation of system and data acquisition was done using EZ-Chrome software.

***In vitro* antifungal activity:**

Cup plate method was used for testing *in vitro* antifungal activity of the formulation[18, 19]. Sabouraud dextrose agar media was prepared, sterilized by autoclaving and poured into sterile petri plates to solidify. Solidified media was inoculated with fungal suspension (equivalent to McFarland standard no. 0.5). Presterilized stainless steel borer was used to bore wells in the media. SLNs based gel; marketed formulation and BFZ STD solution were placed in respective bored well. Petri plates were allowed to incubate for growth of fungi and zone of inhibition was measured after incubation period.

RESULTS AND DISCUSSION:

Screening of lipids:

The screening of lipids was carried out to select a lipid with high affinity for drug which will affect the entrapment. Solubility of BFZ in different lipids was in order of Preciol ATO5 (27.91 ± 2.607 mg), Compritol 888ATO (21.19 ± 2.863 mg), Imwitor 900K (18.83 ± 2.726 mg) and Glyceryl tripalmitate (3.750 ± 2.106 mg). Dyanasan 114 was not able to dissolve the drug. Higher solubility in Precirol ATO5 and Compritol 888ATO could be because of mixture of mono, di and triglycerides.

Preparation of SLNs:

Melt emulsification followed by ultrasonication is a method of choice for SLNs preparation for drugs showing high solubility in molten lipids. It is a very simple and reproducible method. Tween 80 and Poloxamer 188 (in concentration of 1.5 and 2.5%) were used as surfactants for stabilization of the SLNs dispersions. Precirol ATO5 (1.5%) was selected as lipid matrix based on the results of screening studies. It was observed that Poloxamer 188 was not able to stabilize the SLNs dispersions. The batches prepared with Poloxamer 188 as surfactant (Batch C and D) showed signs of aggregation and gelling after cooling. At higher concentrations Poloxamer 188 has the ability to form gels. On the contrary, batches with Tween 80 didn't show any signs of aggregation and obtained batches showed narrow size distribution. Hence, Tween 80 was selected for development of BFZ SLNs.

Evaluation and characterization of BFZ SLNs:

Particle size analysis:

The particle size of batches A, B and E is as shown in **Table 2**. Batches C and D were not analyzed for particle size and EE as they showed immediate aggregation and gelling during preparation. From the results of batch A and B it was observed that the particle size decreased as the concentration of surfactant increased. As the surfactant concentration is increased the interfacial tension between the lipid and aqueous phase is decreased. This causes the particles to be broken down to much smaller size than expected offering narrow particle size distribution as evident from the polydispersity index values. It is also observed that the increased concentration of surfactant gives additional stearic effect helping in stabilizing the dispersion[20, 21]. In case of Poloxamer 188 the high surfactant concentration caused the gelling of the SLNs systems. Batch E showed particle size of 372.97 ± 3.41 nm which was prepared after optimization of lipid and surfactant concentrations.

TABLE 2: RESULTS FOR PARTICLE SIZE, EE AND POLYDISPERSITY INDEX OF BFZ SLN BATCHES

Sr. No.	Particle Size (nm)	EE (%)	Polydispersity index
A	430 ± 13.4	95.06 ± 3.52	0.16 ± 0.0198
B	255 ± 2.76	69.97 ± 2.78	0.35 ± 0.0287
E	372.97 ± 3.41	94.88 ± 2.01	0.50 ± 0.0152

Entrapment efficiency:

EE values are based on the ability of the lipid to incorporate the drug in the matrix and the concentration of surfactant. As seen from **Table 2**, increase in concentration of surfactant decreased

the EE to a significant level (Batch A and B). This may be because of the increased solubilization of BFZ at increased concentration of Tween 80 in the aqueous medium. Theoretically a partition phenomenon explains that high surfactant concentration in the external phase might increase the partition of drug from internal to external phase of the medium [22]. For Batch E, prepared after optimization of the lipid and surfactant concentrations, EE was found to be 94.88 ± 2.01%.

***In vitro* drug release:**

Drug release from the BFZ SLNs system (Batch E) was found to be in a sustained manner as compared to the drug suspension (**Fig. 1**). The BFZ SLNs showed a biphasic release pattern, initial burst release followed by slow release. Initial burst release was owing to the large specific surface area of the small lipid nanoparticles leading to increased drug dissolution. Later the formulation released drug slowly in a sustained manner leading to almost 50 % release at the end of 10 h.

This suggested entrapment of drug particles in the lipid matrix. Similar results have been reported by Ramasamy *et al.* (2012)[23] where they have studied the drug release properties for ketoconazole SLN systems. On the contrary BFZ suspension released 90% of drug at the end of 6 h. Drug release kinetics showed highest coefficient of regression for Hixon-Crowell model which describes that the release rate is dependent on the drug particles dissolution rate where there is a change in the surface area and the diameter of particles [24].

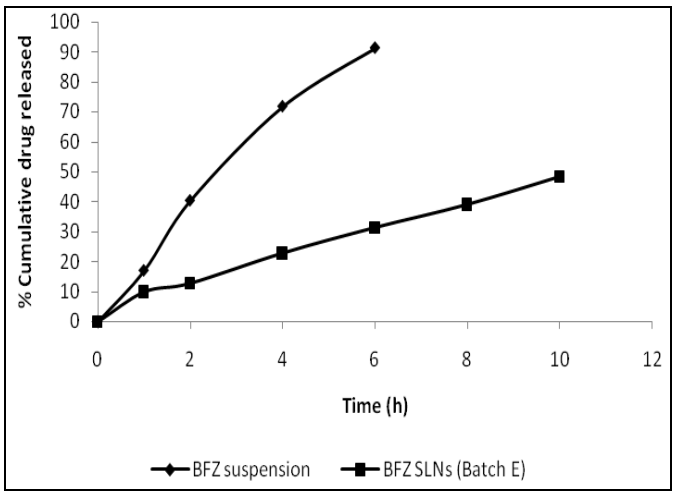

FIG. 1: DRUG RELEASE FROM BFZ SLNS (BATCH E) AND BFZ SUSPENSION

X-ray diffraction study:

Fig.2 represents the comparative XRD scans for pure BFZ, PREC, Trehalose and BFZ SLNs. XRD scan for pure drug shows the characteristic sharp peaks for drug at the diffraction (2θ) angle of 10.62°, 15.88°, 15.90°, 15.94°, 16.0°, 18.48°, 21.24°, 21.30°, 21.38°, 26.72° and 37.72° suggesting crystalline nature of the drug. BFZ SLN scan shows the disappearance/lesser intensity of the characteristic peaks due to incorporation of the drug into the matrix of the lipid and conversion to amorphous nature.

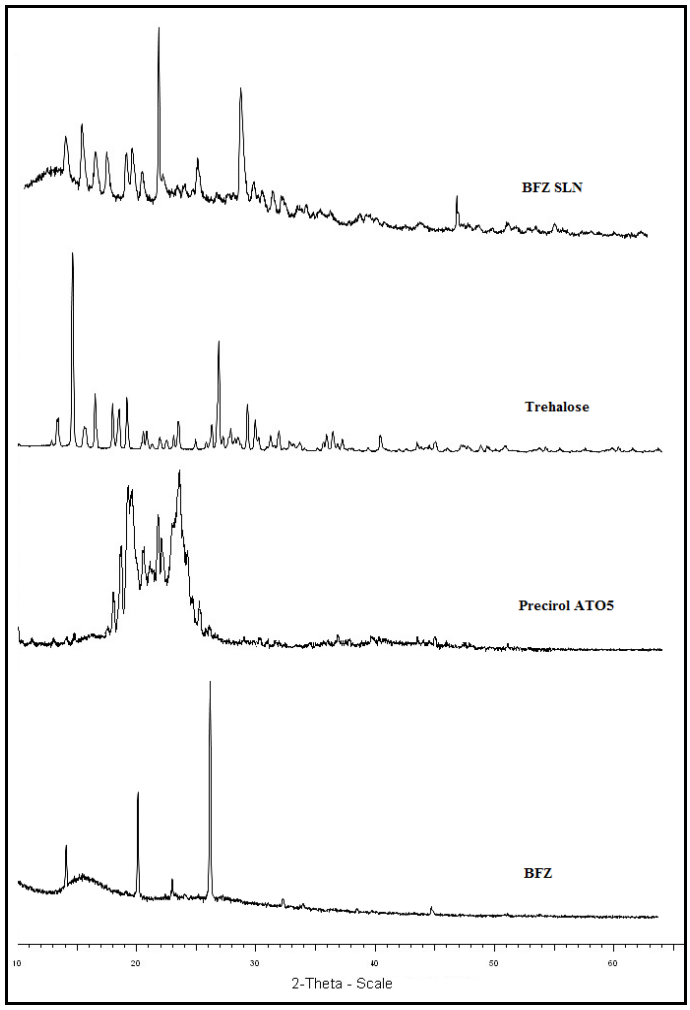

FIG. 2: XRD PATTERNS FOR BFZ, PRECIROL ATO5, TREHALOSE AND BFZ SLNs

DSC study:

DSC thermogram of BFZ and Precirol ATO5 exhibited a sharp endothermic peak at 150.02°C and 57°C respectively which indicated the absence of traces of impurities (**Fig. 3)**. From the DSC results of physical mixtures of BFZ with Precirol ATO5 (Melting at 58.9°C), it was confirmed that the drug was solubilised in the lipid because there was no peak observed at the melting point of BFZ.

Furthermore, a small increase on the onset and on the melting temperature of the lipid when it is mixed with drug was observed. These phenomena were previously described by Müller *et al.* (2008)[25]. Also, a decrease of enthalpy was recorded after mixing drug and lipid, indicating the presence of more unstable polymorphic forms and predicting high drug loading capacity[26]. Similar results were obtained from DSC of BFZ SLNs system (Batch E). Complete disappearance of drug peak was observed with slight shift in the melting temperature of lipid and an additional peak at 215.3°C for cryoprotectant trehalose was observed.

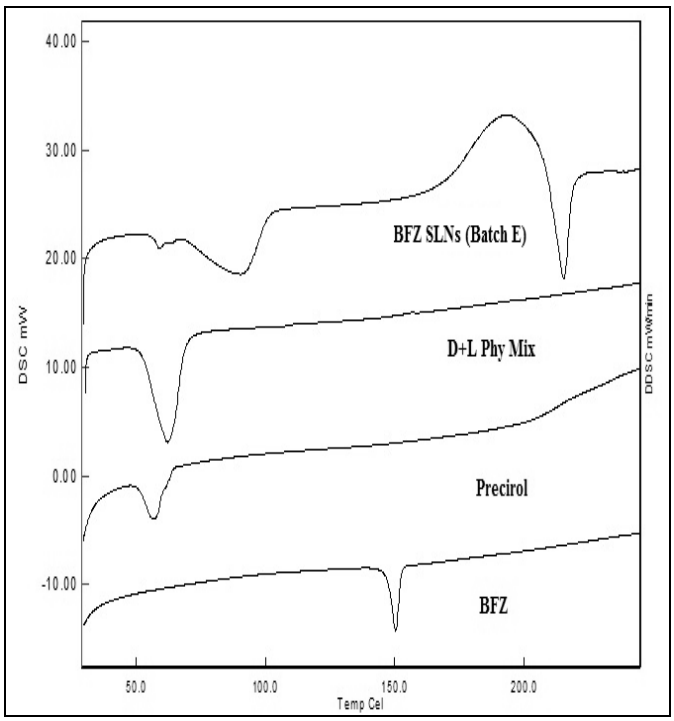

FIG. 3: DSC SCANS FOR BFZ, PRECIROL, D+L PHY MIX (DRUG + LIPID PHYSICAL MIXTURE) AND BFZ SLNS (BATCH E)

Preparation and Evaluation of SLNs based gel:

Batch E was selected for preparation of SLNs based gels. From the results of screening for gelling agents it was observed that the Polycarbophil AA1 and Xanthan gum were not able to form gels of desired consistency when dispersed in SLNs dispersion. Polycarbophil AA1 was not able to gel the suspension and it made the SLN formulation unstable as aggregates/lumps were formed and the aqueous phase was separated. Gels with xanthan gum and carbopol 934 were of loose consistency and did not offer the required viscosity. On the contrary it was found that Carbopol 940 gave gel of desirable consistency and appearance. Therefore, Carbopol 940 was selected as a gelling agent for the preparation of BFZ SLNs based gel.

Rheological behavior:

It was found that there is a decrease in viscosity with increasing shear rate (rpm) indicating non Newtonian flow. Viscosity of the BFZ SLNs based gel was found to be 6638 cPs as compared to viscosity of conventional gel was found to be 9375 cPs.

Spreadability is an important property of topical formulation from patient compliance point of view. If the formulation exhibits high spreadability then it would be easier for application on the desired part[23]. The diameter for SLNs based gel was found to be 44 mm and that of the conventional gel was found to be 32 mm. High spreadability value of SLNs based gel indicates better spreading ability at the site of application.

***In vitro* drug release and *ex vivo* permeation studies:**

Comparative release profile of SLNs based gel and conventional gel is shown in **Fig. 4.** It was observed that there was significant retardation of release from BFZ SLNs and conventional gel matrix. Release profile observed over period of 10 h showed that 37.18% of drug permeated from BFZ SLNs gel along with initial burst release. In dermal formulations both burst release, useful to improve the penetration of drug and for faster onset of action, as well as sustained release to supply the drug over a prolonged period of time are desired[27].

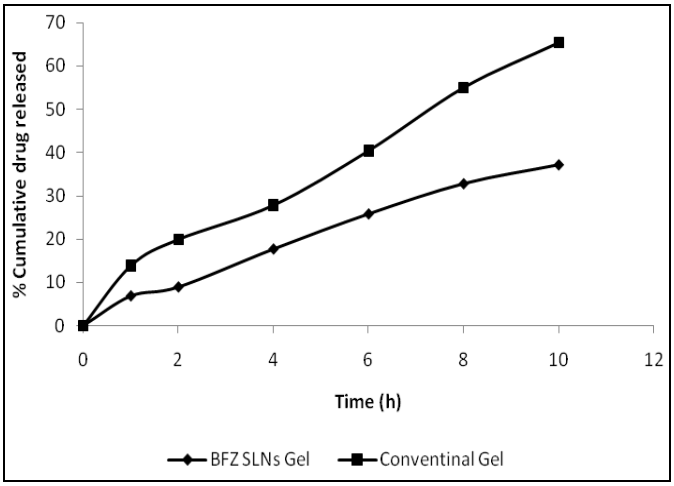

FIG. 4: *IN VITRO* DRUG RELEASE FROM BFZ SLNS GEL AND CONVENTIONAL GEL

The retardation of drug release from the SLN gel formulation could be due to the fact that the drug molecules were entrapped in to the lipid matrix which in turn is incorporated in to the gel system. Drug release kinetics from SLNs based gel was checked by goodness of fit for different models. It was observed that drug release from the SLNs gel followed first order model indicating that the drug release from gel is concentration dependent. Release exponent 'n' was found to be 0.812, indicating (0.5< n < 1.0) non Fickian diffusion (anomalous transport) [24].

The *ex vivo* skin permeation of BFZ through rat skin from SLNs based gel and conventional gel was calculated in terms of mean cumulative amount diffused at each sampling time point during time period of 10 h (**Fig. 5**). It was observed that the drug shows higher flux value of 9.87 µg/cm^{2}h from SLNs gel in comparison to the conventional gel 1.02 µg/cm^{2}h. Though the flux value for SLNs gel is high, the total amount of drug permeated was found to be around 100 µg/cm^2 which is very low if compared with the total amount of drug added in the donor compartment. A linear relationship was found for the plot of the amount of BFZ permeated as a function of time, showed a linear relationship (For SLNs gel, r^2 = 0.991 and for conventional gel r^2=0.948), indicating that BFZ permeation followed pseudo-first-order kinetics.

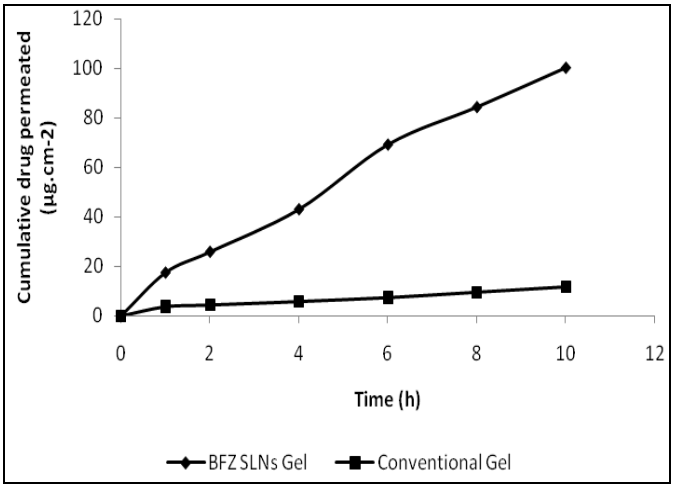

FIG.5: *EX VIVO* SKIN PERMEATION PROFILE OF BFZ SLNS GEL AND CONVENTIONAL GEL

Results of the skin retention study showed that SLNs based gel showed higher skin retention than the conventional gel formulation (**Table 3**). These results were in contrast to the higher flux values exhibited by the SLNs based gel. In the literature it is proposed that nanoparticles get deposited in the skin, thus acting as a depot to give sustained release. There are mainly two reasons for more skin retention with SLNs and nanostructured lipid carriers (NLCs); (1) The lipid nature of the formulation and (2) The occlusive effect by forming a film on the skin surface. The lipid nature of the formulation helps in fluidization of the skin lipids present in stratum corneum providing increased nanoparticle and drug penetration. Smaller size of the particles increases the adhesive effect of the formulation and provides occlusive films on skin surface which increases the skin retention[28].

TABLE 3: AMOUNT OF BFZ RETAINED AND DEPOSITED IN SKIN

Formulation	Amount of BFZ permeated (µg/cm^2)	Amount of BFZ deposited in the skin (µg/cm^2)	% Skin deposition
SLNs based gel	100	158	16.08
Conventional gel	12	14	1.31

Similar to most of the topical formulations, BFZ entrapped in the lipid matrix gets transported across the skin. During the transport, entrapped BFZ is expelled out of SLNs lipid matrix as a result of polymorphic transitions occurring in the solid lipid. This phenomenon has been hypothesized in the literature. Use of SLNs/NLCs for improvement in the dermal localization of several topical therapeutic as well as cosmetic agents has been reported[29-31].

***In vitro* antifungal activity:**

Results of anti fungal activity are shown in **Table 4.** The value of mean zone of inhibition of the SLNs based gel was larger than that of the marketed formulation but lesser than the BFZ STD solution.

The enhanced *in vitro* anti fungal activity of SLNs based gel as compared to the marketed formulation can be because of the increased solubility leading to higher permeability of BFZ through the fungal cell walls to inhibit the ergosterol synthesis[32, 33]. **Fig. 6** shows the photographs for *in vitro* antifungal activity.

TABLE 4: COMPARISON OF SLNS BASED GEL AND MARKETED FORMULATION FOR ANTIFUNGAL ACTIVITY

Sr. No.	Formulation	Mean zone of inhibition in cm (n=3) (Mean ± SD)
1	BFZ STD	1.75 ± 0.11
2	Marketed formulation (Reference)	1.23 ± 0.089
3	SLNs based gel (Test)	1.32 ± 0.096

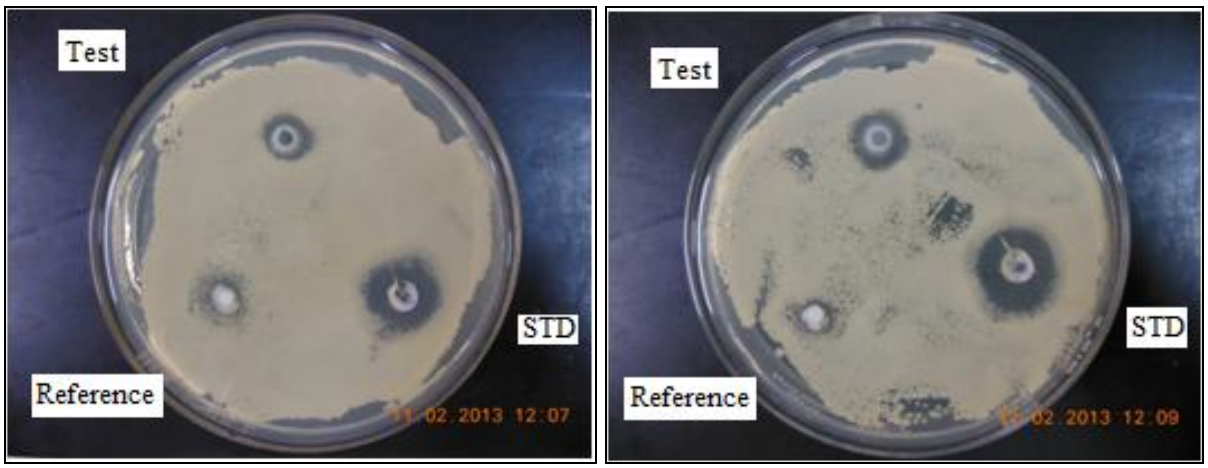

FIG.6: PHOTOGRAPHS SHOWING COMPARATIVE ANTIFUNGAL ACTIVITY OF SLNS BASED GEL, MARKETED FORMULATION AND STD SOLUTION

CONCLUSION: Melt emulsification followed by ultrasonication was successfully employed to produce BFZ SLNs. It is a very simple, economic and reproducible method. It was found that stable BFZ SLNs could be prepared using Precirol ATO5 and Tween 80 as formulation components with particle size of 372.97 nm and EE of 94.88%. *In vitro* release from the SLNs dispersions showed sustained release profile suggesting entrapment of drug in the inner cores of lipid. DSC and XRD studies revealed that BFZ converted in amorphous form when incorporated SLNs.

Carbopol 940 could be successfully employed in formulation of gels for better patient compliance. *Ex vivo* drug permeation studies for gel showed increased deposition of BFZ SLNs in to the skin layers. *In vitro* anti fungal activity for BFZ SLNs was found to be higher. This suggests use of lipid nanoparticulate systems for transdermal delivery of drugs against the conventional cream/gel. Further *in vivo* studies could be performed to prove the *in vitro-in vivo* correlation.

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REFERENCES:

1. Müller RH, Mäder K and Gohla S: Solid lipid nanoparticles (SLN) for controlled drug delivery - review of the state of the art. European Journal of Pharmaceutics and Biopharmaceutics 2000; 50:161-177.
2. Sylvia A, Müller RH, Wissing SA: Cosmetic applications for solid lipid nanoparticles (SLN). International Journal of Pharmaceutics 2003; 254:65-68.
3. Utreja S, Jain NK: Solid lipid nanoparticles, Advances in Controlled and Novel Drug Delivery, CBS Publishers & Distributors, First Edition 2001.
4. Wissing SA, Müller RH: The influence of solid lipid nanoparticles on skin hydration and viscoelasticity - *in vivo* study. European Journal of Pharmaceutics and Biopharmaceutics 2003; 56: 67-72.
5. ZurMühlen A, Schwarz C, Mehnert W: Solid lipid nanoparticles (SLN) for controlled drug delivery - drug release and release mechanism. European Journal of Pharmaceutics and Biopharmaceutics 1998; 45:149-155.
6. Maia CS, Mehnert W, Schäfer-Korting M: Solid lipid nanoparticles as drug carriers for topical glucocorticoids. International Journal of Pharmaceutics 2000; 196:165-167.
7. Lackner TE, Clissold SP: Bifonazole: A review of its antimicrobial activity and therapeutic use in superficial mycoses. Drugs 1989; 38: 204-225.
8. Drug Bank–Open data drug and drug target database version 3. http://www.drugbank.ca/drugs/DB04794 (Accessed on November 2012).

9. Müller-Goymann CC: Physiochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. European Journal of Pharmaceutics and Biopharmaceutics 2004; 58: 343-356.
10. Pople PV, Singh KK: Development and evaluation of colloidal modified nanolipid carrier: Application to topical delivery of tacrolimus. European Journal of Pharmaceutics and Biopharmaceutics 2011; 79: 82:94.
11. Fang JY, Fang CL, Liu CH, Su YH: Lipid nanoparticles as vehicles for topical psoralen delivery: Solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC). European Journal of Pharmaceutics and Biopharmaceutics 2008; 70: 633-640.
12. Patravale V, Patel P: AmbiOnp: solid lipid nanoparticles of amphotericin B for oral administration. Journal of Biomedical Nanotechnology 2011; 7: 632-639.
13. Jain S, Jain S, Khare P, Gulbake A, Bansal D, Jain SK: Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. Drug Delivery 2010; 17: 443-451.
14. Esposito E, Ravani L, Contado C, Costenaro A, Drechsler M, Rossi D, Menegatti E, Sacchetti G, Cortesi R: Clotrimazole nanoparticle gel for mucosal administration. Materials Science and Engineering: C 2013; 33: 411-418.
15. Desai K.GH: Enhanced skin permeation of rofecoxib using topical microemulsion gel. Drug Development Research 2004; 63: 33-40.
16. Chen YC, Liu DZ, Liu JJ, Chang TW, Ho HO, Sheu MT: Development of terbinafine solid lipid nanoparticles as a topical delivery system. International Journal of Nanomedicine 2012; 7: 4409-4418.
17. Bhalekar MR, Pokharkar V, Madgulkar A, Patil N, Patil N: Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS PharmSciTech 2009; 10(1): 289-96.
18. Ananthanarayan R, Panicker CKJ: Laboratory Control of Antimicrobial Therapy. Textbook of Microbiology, India, Universities Press. 2009.
19. Sabale V, Vora S: Formulation and evaluation of microemulsion-based hydrogel for topical delivery. International Journal of Pharmaceutical Investigation 2012; 2: 140-149.
20. Mehnert W, Mader K: Solid lipid nanoparticles: production, characterization and applications. Advanced Drug Delivery Reviews 2001; 472:165-196.
21. Lim S, Kim C: Formulation parameters determining the physicochemical characteristics of solid lipid nanoparticles loaded with all-trans retinoic acid. International Journal of Pharmaceutics 2002; 243:135-146.
22. Agrawal Y, Petkar KC, Sawant KK: Development, evaluation and clinical studies of Acitretin loaded nanostructured lipid carriers for topical treatment of psoriasis. International Journal of Pharmaceutics 2010; 401: 93-102.
23. Ramasamy T, Khandasami US, Ruttala H, Shanmugam S: Development of solid lipid nanoparticles enriched hydrogels for topical delivery of anti-fungal agent. Macromolecular Research 2012; 20: 682-692.
24. Costa P, Lobo JMS: Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Science 2001; 13:123-133.
25. Müller RH, Runge SA, Ravelli V, Thunemann AF, Mehnert W, Souto EB: Cyclosporine - loaded solid lipid nanoparticles (SLN): drug - lipid physicochemical interactions and characterization of drug incorporation. European Journal of Pharmaceutics & Biopharmaceutics 2008; 68: 535-544.
26. Souto EB, Anselmi C, Centini M, Müller RH: Preparation and characterization of n-dodecyl-ferulate-loaded solid lipid nanoparticles (SLN). International Journal of Pharmaceutics 2005; 295: 261-268.
27. Joshi M, Patravale V: Nanostructured lipid carrier (NLC) based gel of celecoxib. International Journal of Pharmaceutics 2008; 346: 124-132.
28. Muller RH, Radtke M, Wissing SA: Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Advance Drug Delivery Reviews 2002; 54: S131-S155.
29. Lombardi Borgia S, Regehly M, Sivaramakrishnan R, Mehnert W, Korting HC, Danker K, R¨oder B, Kramer KD, Sch¨afer-Korting M: Lipid nanoparticles for skin penetration enhancement - correlation to drug localization within the particle matrix as determined by fluorescence and parelectric spectroscopy. Journal of Controlled Release 2005; 110:151-163.
30. Mei Z, Chen H, Weng T, Yang Y, Yang X: Solid lipid nanoparticles and microemulsion for topical delivery of triptolide. European Journal of Pharmaceutics & Biopharmaceutics 2003; 56:189-196.
31. Pardeike J, Hommoss A, Müller RH: Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. International Journal of Pharmaceutics 2009; 366: 170-184.
32. Bachhav YG, Patravale VB: Microemulsion-based vaginal gel of clotrimazole: formulation, *in vitro* evaluation and stability studies. AAPS PharmSciTech 2009; 10(2):476-481.
33. Patel MR, Patel RB, Parikh JR, Bhatt KK, Solanki AB: Investigating the effect of vehicle on *in vitro* skin permeation of ketoconazole applied in O/W microemulsions. Acta Pharmaceutica Sciencia 2010; 52: 65-77.

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