Original Article

Design, Development, and Characterization of Film Forming Spray as Novel Antifungal Topical Formulation for Superficial Fungal Infections

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ABSTRACT

Introduction: Miconazole Nitrate is prescribed as an antifungal agent in conventional dosage forms. To mask the disadvantages of sticky creams and their tendency to rub off, an intelligent dosage regimen needs to be designed. **Objectives:** The present study aimed to design, develop, and characterize Miconazole Nitrate (0.5% w/v) film-forming spray for the treatment of superficial fungal infections in nails, such as Tenia and Onychomycosis. **Materials and Methods:** Eutectic mixture of Menthol and Camphor in the ratio of 1:1 was used to enhance permeation and solubilize film-forming polymers, i.e., Eudragit L-100 and Ethyl Cellulose, and provide a cooling effect. **Results:** The prepared formulations were evaluated for various critical parameters, and based on the results obtained, Formulation F1 exhibited a drug content of 91.82% and 83.75% of % Cumulative drug release through Eggshell membrane and was found to be the best-suited formulation. Formulation F1 was further chosen for carrying out *in-vitro* permeation studies through shed snakeskin of *Ophiophagus Hannah* (Cobra), which gave % a cumulative drug release of 72.453 %, exhibited pH of 5.8 and evaporation time of four minutes yielding a non-sticky film. The prepared formulations were clear in appearance and formed Uniform, non-sticky, flexible films. The average time required for the release of 50% drug was found to be 120-180 min, and the drug transport kinetic was best fitted into the Korsmeyer's-Peppas model. **Conclusion:** The study concluded that the prepared transdermal film-forming spray formulations would be efficient for treating fungal infections of superficial nature and will prove to be a practical approach in the delivery of topical antifungal agents.

Keywords: Fungal Infections, Film-forming Spray, Miconazole Nitrate, Antifungal, Eutectic Mixture.

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INTRODUCTION

Fungal infections are commonly diagnosed infections that affect humans' cuticles, epidermis, hairs, and other body parts. Amongst three categories, i.e., superficial, subcutaneous, and deep or systemic, Onychomycosis and Tenia account for more than a third of all fungal infections. Wherein *Trichophyton rubrum (T. tonsurans)* and family of Candida species (*C. albicans, C tropicalis, C. krusei, C. parapsilosis*) have been identified as prevalent causal organisms for fungal infections.[1-2] Although various antifungal dosage forms and treatments are approved and available for the management of superficial infections, the ability of antifungal drugs is dependent on several factors, including the ability of the drug to transmit through the stratum corneum, the skin's outermost layer, its molecular mass and concentration, and the ability to achieve therapeutic drug concentration levels in the skin.[3-5] Miconazole nitrate chemically denoted as (RS)-1-[2-(2,4-Ichlorophenylmethoxy)2-(2,4-dichlorophenyl) ethyl]-1H-imidazole nitrate, is a drug with poor oral absorption and is very slightly soluble in water – which limits its efficacy and bioavailability

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in various dosage forms. It acts by inhibiting sterol 14-α-demethylase, which is a cytochrome P450-dependent enzyme system in the microsomal body, and thus impairs ergosterol synthesis in the fungal cell.[6-9]

There are now various innovative dosage forms available for the treatment of these infections, such as hydrogels and microemulsion systems that help the loaded drug penetrate the epidermal layer. Although available as commercial products, these dosage forms have several drawbacks and limitations, including poor patient compliance, cross-contamination, non-uniform distribution, and rubbing off from the application site.[10-19] Hence, to mask these disadvantages of conventional applications, a film-forming transdermal spray would be better in action, exhibit higher efficacy, have fewer side effects, have a lower dose frequency, and higher retention time.[20-28]

The developed formulation will facilitate rapid evaporation of solvents providing a cooling effect and reducing the tendency of rubbing off by forming a uniform thin layer onto the skin and infection site. The formulation will give rapid action as it will adhere to the skin for a longer period and penetrate through the skin faster.[29-32] Since it is self-applicable and easy to use, patient compliance/patient acceptability will improve, and a minimum quantity of dose will be able to maximize the compliance, ensuring a high margin of safety.

This study will result in the development of an efficient, easy-to-apply, film-forming spray formulation containing a Miconazole nitrate for treating superficial fungal infections in nails and peripheries of the skin.

MATERIALS AND METHODS

Chemicals and reagents: Miconazole nitrate was received as a gift sample from Encube Ethicals Pvt. Ltd. Eudragit® L-100, and Ethyl Cellulose was purchased from Evonik Industries and Molychem Pvt Ltd., respectively. PEG 400, Glycerine, Methanol, Ethanol, Acetone, and Chloroform were purchased from SD Fine Chemicals Ltd. Camphor and Menthol were obtained from Dolphin Pharmacy Mumbai. All the chemicals and reagents used in the experiments were of analytical grade.

Pre-formulation Studies

Physical Properties of Drug, Solubility Studies, and Determination of Absorption maxima by UV spectroscopy: The received sample of Miconazole Nitrate was evaluated for physical properties, which included appearance, color, odor, and melting point. The solubility of Miconazole Nitrate in water, ethanol, methanol, chloroform, and phosphate buffer pH 7.4 was determined. Based on the preliminary solubility analysis results, a solution containing 10µg/ml of Miconazole Nitrate in phosphate buffer pH 7.4 was analyzed in the UV region to determine the maximum absorbance (λ_{max}).[33-35]

Solubility of Polymers in Eutectic Mixture: By observing physical appearance at room temperature, the ratio of the eutectic mixture of camphor and menthol for the formation of clear liquid formation was determined by taking their various ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) in a beaker. In the prepared eutectic mixture, the saturation solubility of Ethyl Cellulose and Eudragit (different grades) was determined. The mixtures were scrutinized for clarity and the polymers were chosen for the formulation based on the results of the same.[36-39]

Compatibility of drug and polymers: Compatibility studies of drug Miconazole Nitrate with polymers and other excipients used to formulate film-forming spray were carried out by FTIR studies. The FT-IR Spectrum of Miconazole Nitrate with other excipients was recorded by using Shimadzu FTIR spectrophotometer 8400. All the samples were analyzed between the range of 4000 cm^{-1} to 400$cm.^{-1}$

Preparation of formulation: Miconazole Nitrate was separately dissolved in a vehicle mix of 5:4:1 Ethanol, Acetone, and Chloroform. In the eutectic mixture, a solution of accurately weighed Ethyl cellulose and Eudragit® L-100 was prepared, and Miconazole Nitrate in the solvent system was gradually added to it. The solution was stirred for 15 min at 80–100 rpm before being sonicated for 10 min. Glycerin and PEG-400 were then added to the solution, and stirred for another 15 min. The solution was then placed in a refillable container with a 2 mm internal diameter plastic dip tube. The formulation batches' composition is displayed in Table 1.[40-42]

Evaluation Parameters

Appearance and Film Formation: The appearance of the formulated spray solutions was examined for clarity by visual examination against the black and white background. The films were cast on petri-dish and rated for film formation, uniformity, non – uniformity, with precipitation, without precipitation, and Opaque or Transparent.[43-45]

Viscosity, pH, Evaporation time, Spray angle, Volume actuated upon each spray, and Drug content: The viscosity of prepared spray formulations was measured by using brook-field DV-II pro- plus viscometer (Brookfield Engineering Labs. Inc.) at room

Table 1: Composition of ingredients.

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8
Miconazole Nitrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Eudragit L-100	10	9	10	9	10	9	10	9
Ethyl cellulose	4	4	5	5	4	4	5	5
PEG 400	0.25	0.25	0.25	0.25	0.3	0.3	0.3	0.3
Glycerine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Eutectic mixture	10	10	10	10	10	10	10	10
Solvent Mixture	100	100	100	100	100	100	100	100

temperature. The pH value of resulting spray solution was recorded with a digital pH meter (Elio (LI 120) India Sistroids, Ahmadabad). To test the time of evaporation, formulations were sprayed on ethyl alcohol sensitive paper/ filter paper and the drying time or evaporation time was noted. The spray angle was determined using the pigmentation technique of a spray-on slip of paper. Sudan red (10 mg) was solubilized in the formulation to aid visual representation, and the sprays were actuated horizontally on white paper mounted 15 cm from the nozzle. The spray angle was calculated using the formula below.

$$Spray\ angle\ (\theta) = tan\text{-}1\ (l/r)$$

Where l is the spacing between the nozzle and the sheet, and r is the mean radius of the circle.

The volume delivered after every actuation was estimated using the formula as follows by recording the difference in weight after each actuation.

$$A_L = (W_T - W_O)/ D_n$$

In Which A_L is the quantity of solution delivered with every actuation, W_T is the load of the formulation after actuation, W_O is the initial weight of formulation prior to actuation, and D n is the density.

For drug content assessment, 1 ml of the prepared formulation was derived in phosphate buffer pH 7.4 for 4 hr at 100 rpm. The samples were then filtered and appropriately diluted. The resulting mixture was further sonicated, and absorbance was recorded spectrophotometrically at λ_{max}.[46]

Film Flexibility, Stickiness of the film, and Washability and leak test: The flexibility of the prepared film was determined by a simple technique, i.e., the film was stretched in two to three directions after the film-forming Spray was sprayed on a petri-dish. If the film ruptures, it is rated as a non-flexible film, and if it doesn't, then it is rated as flexible. After the film was formed, a small ball of cotton wool was taken and pressed against the dried film with slight pressure, and the film was visually inspected for fibers attached. The more the number of fibers that get adhered to the film, the more "sticky" the film is. The stickiness was considered "medium" when a thin layer of cotton fibers adhered to the film. And the film is said to be "non-sticky" if no fibers have adhered to the film.

After drying, the washability of the film was checked with water, and it was rated as Good (+++), Moderate (++), and Poor (+). Further, the containers filled with solutions under test were arranged in an upright position at 30°C for 6 hr as a part of the leak test. The bottles were balanced, and weight was recorded before and after the test stage. The variation in the weight of the bottle was written down to anticipate leakage percentage.[47-48]

***In-vitro* diffusion study using eggshell membrane:** A 2 ml sample volume was positioned on an eggshell membrane that was tied to one end of an open-ended glass cylinder. The eggshell membrane was securely fastened with adhesive and thread, which served as a donor compartment. The experiment was carried out in a 100 ml beaker that served as a receptor compartment. The receptor section was filled with 50 ml of phosphate buffer pH 7.4, and the temperature was maintained at 37°C ±0.5. The donor section was dipped into the beaker filled with 25 ml phosphate buffer pH 7.4 in such a way that the membrane of the donor compartment just touched the upper level of phosphate buffer pH 7.4 present in the beaker. The whole assembly was kept on a magnetic stirrer with an optimal speed of 100 rpm. 5 ml sample was withdrawn from the receptor compartment periodically using a graduated pipette, and the same amount was replaced during every withdrawal with fresh phosphate buffer pH 7.4 to maintain the sink condition. The aliquots were analyzed at a wavelength of 272 nm spectrophotometrically.[43,47]

***In-vitro* drug permeation experiment:** The *in-vitro* drug permeation experiment was conducted for the best formulation using shed snakeskin of Cobra (*Ophiophagus Hannah* belonging to family Elapidae) as a membrane

in franz diffusion cell with a surface area of 2.2 cm^2. The diffusion medium was phosphate buffer pH 7.4 at 37°C and stirred with a magnetic stirrer at the speed of 100 rpm.

Samples were withdrawn at predefined time intervals, and the same volume of fresh medium was replaced. The supernatant of the withdrawn solution was analyzed spectrophotometrically, and cumulative release was plotted as a function of time.[43,47]

***In-vitro* Drug release kinetics:** To analyze the mechanism for drug release of the dosage form, the data obtained from *in-vitro* drug release studies was fitted into four models, i.e., Zero order, First order, Higuchi model, and Korsmeyer -Peppas model.

RESULTS AND DISCUSSION

Pre-formulation Studies

Physical Properties of Drug, Solubility Studies, and Determination of Absorption maxima by UV spectroscopy: The obtained sample of the drug was a white crystalline powder with a non-characteristic odor and melting point of 178°C. It was very slightly soluble in water, freely soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in phosphate buffer pH 7.4. The absorption maxima were observed at three wavelengths, i.e., 264nm, 272 nm, and 280 nm, from which 272 was chosen for analysis. The standard calibration curve was obtained with a correlation coefficient (R^2) value of 0.9995 in phosphate buffer pH 7. 4.

Solubility of Polymers in Eutectic Mixture Compatibility of drug and polymers: A eutectic mixture of menthol and camphor was obtained by using the ratio of 5:5 and 8:2. However, the results obtained for other ratios were not satisfactory. The ratio of 5:5 was chosen for the preparation of eutectic liquid. The solubility of eudragit S-100, eudragit L-100, eudragit E-100, and ethyl Cellulose was determined in a eutectic mixture wherein eudragit L-100 and ethyl cellulose were found to be the most soluble. In compatibility analysis of drug-excipient interaction, FTIR spectra were seen unaffected by the presence of polymers in combination with the drug.[44]

Preparation of formulation: The formulations F1 – F8 were prepared as per the formulation table with various ratios of ethyl cellulose, eudragit L-100, and PEG 400 and further evaluated for various parameters.

Evaluation Parameters

Appearance and film formation: All spray formulations had good clarity and were free from interfering particles. The dried film formed on the petri-dish after spraying was transparent and uniform. No precipitation was observed after film formation.[41-42] This makes it evident that use of the different grades of polymers does not affect the appearance or formation of the film. However, it would affect evaporation time and viscosity of the formulation which is further evaluated.

Viscosity, pH, Evaporation time, Spray angle, Volume actuated upon each spray, and Drug content: The viscosity of all the formulations from F1 to F8 was found to be in the range of 27-53 cps, whereas the pH of the solution was in the range of 5.5 to 6.5 which lies in the normal pH range of skin and would not cause any kind of skin irritation. The evaporation time was found to be between 3 min to 7 min, which was well in the desired range for an ideal film-forming spray formulation. The spray angle of prepared formulations was between 25° to 30° depicting its uniform delivery on the surface of the skin.[45-46] The solution was analyzed for drug concentration spectrophotometrically at λ_{max} of 272 nm, for which formulation F1 reported the highest drug content. The spray pattern and Volume of actuation after each Spray were in a compact range and varied slightly as the concentration of the polymers was modulated (Table 2). Time required for film formation/evaporation, viscosity and volume actuated upon each spray was found directly proportional to

Table 2: Results for pH, viscosity, evaporation time, spray angle, volume actuated upon each Spray, and drug content.

Formulation Code	Viscosity (cps)	pH	Evaporation time (mins)	Spray angle	Volume actuated upon each Spray (ml)	Drug Content (%)
F1	52.45	5.8	4	26.22 ± 0.05	0.413	91.82
F2	41.23	6	5	25.89 ± 0.11	0.1605	81.36
F3	48.91	6.3	3.5	33.87 ± 0.05	1.3191	88.24
F4	51.3	5.7	5	28.26 ± 0.05	0.7226	85.39
F5	39.97	6.4	7	28.26 ± 0.05	0.955	84.37
F6	27.86	6.2	6	28.26 ± 0.05	0.4615	89.08
F7	38.1	6.2	5	25.90 ± 0.11	1.6716	90.607
F8	35.68	6	4.5	30.03 ± 0.05	0.1631	90.413

the concentration of polymers incorporated in the formulation i.e., higher the amount of polymer more viscus the formulation and more time is required for the formation of film. However, drug content and pH were not found to significantly affected by the same.

Film Flexibility, Stickiness of the film, and Washability and leak test: The flexibility and rupturing of formed films were observed, followed by stickiness and washability of the same. There was no leakage observed from any of the containers of the spray formulations even after six hours of staging for the leak test (Table 3).

***In-vitro* diffusion study using eggshell membrane:** *In vitro* diffusion studies were conducted for all the prepared formulations of film-forming spray solutions for a period of 360 min. Figure 1 and Figure 2 are the graphical representations of % cumulative drug release for the same. It was observed that formulation F1 showed the highest *in vitro* drug release, whereas formulation F2 showed the lowest. Since % cumulative drug release was found to be maximum, it was found to be the best formulation of all.[46]

Table 3: Evaluation of film flexibility, stickiness, and washability.

Formulation Code	Film Flexibility	Stickiness	Washability
F1	+ + +	+ + +	+ + +
F2	+ +	+	+ + +
F3	+ +	+ +	+ +
F4	+ + +	+	+ +
F5	+ +	+ +	+ +
F6	+ + +	+ +	+ + +
F7	+ +	+ +	+ +
F8	+ +	+ +	+ + +

Good (+++), Moderate (++) and Poor (+).

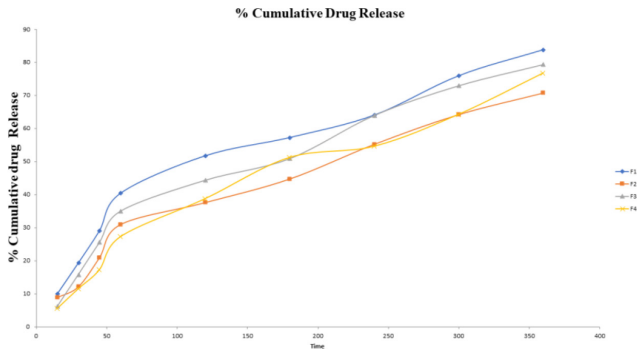

Figure 1: Cumulative drug release for formulation F1 to F4.

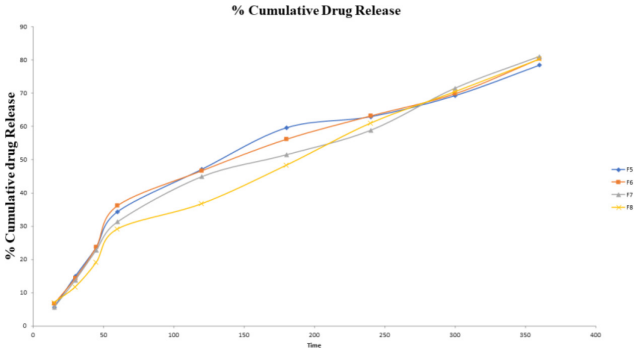

Figure 2: Cumulative drug release for formulation F5 to F6.

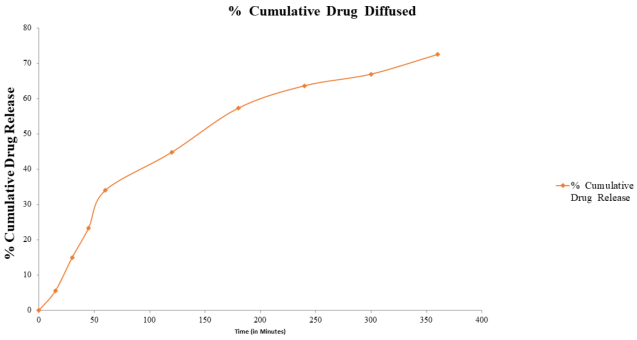

Figure 3: Cumulative drug diffused from formulation F1.

In vitro drug permeation experiment

In vitro skin permeation experiment was carried out using shed snakeskin of *Ophiophagus Hannah*. for formulation F1, as it gave the highest drug content % cumulative drug release, and % cumulative permeation was plotted as a function of time. (Figure 3)

In-vitro Drug release kinetics

The *in vitro* drug release data was analyzed for the drug release kinetics model fitting for Zero order, First order, Higuchi Model, and Korsmeyers - Peppas model of drug transport. Wherein Korsmeyer's - Peppas model was found to be the best fit model for drug release. However, the formulated film forming spray might not be stable or have long shelf life in extreme temperature and pressure conditions.

CONCLUSION

In the present study, an attempt was made to formulate and characterize a transdermal film-forming spray. Various polymers were used in different concentrations to form a uniform film after the solution was sprayed. Prepared formulations were analyzed for various evaluation parameters, including evaporation time, spray angle, spray pattern, volume actuated, drug content, and *in-vitro* drug release. Results concluded that formulation

F1 exhibited good physical properties, drug content, and an *in-vitro* drug transport of 83.075% and hence was also further evaluated for *in vitro* penetration studies through shed snakeskin of *Ophiophagus Hannah* (Cobra). Based on the results of all the evaluative responses, formulation F1 having 10% of Eudragit L-100 and 4 % Ethyl cellulose, was found to be the best formulation. Thus, on the accounts of results of evaluative studies, it can be concluded that the prepared transdermal film-forming spray formulation can be a promising approach for the treatment of superficial fungal infections.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

PEG 400: Polyethylene glycol 400, **UV:** Ultraviolet; **FTIR:** Fourier transform infrared spectroscopy.

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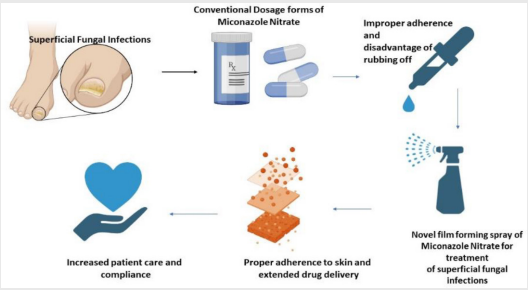
PICTORIAL ABSTRACT



SUMMARY

- Patient compliance is the prime factor in concern with topical formulations and especially antifungal ones. Antifungal preparations should be adhered to the skin for an extended period to facilitate the delivery of the drug and for its proper penetration. Miconazole nitrate has been used for the treatment of fungal infections for a long time. But consistent drug delivery and penetration in case of superficial infections has been a crucial factor that is not yet achieved.
- The film-forming spray is one such approach for the treatment of superficial fungal infections and retaining the drug delivery for a long-time frame. Not only for fungal infections, but this dosage delivery system will also prove to be a game-changer in the drug delivery system for skin infections and topical drug delivery. The developed film forming spray was found to be yielding best results as per the evaluation parameters. Hence it can be taken to further stage of development, which would be beneficial for the patients.

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