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NOVEL MEDISTICK FORMULATION OF ITRACONAZOLE FOR TREATMENT OF SUPERFICIAL MYCOSIS

Sarika R. Kale, Monita P. Gide, Apurva S. Belsarkar, Ankita Jorvekar
Assistant Professor, Principal and Students
Department of Pharmaceutics
Saraswathi Vidya Bhavan's College of Pharmacy, Dombivli, Thane, Maharashtra, India

ABSTRACT:

Most topical formulations are intended for skin application. For convenience of storage and requiring an applicator or the use of a fingertip to apply, the topical medication delivery methods have several drawbacks that could cause contamination. Therefore, it was imperative to find a solution to effectively combat all the drawbacks, The objective of this study is to develop innovative drug delivery system to cure topical fungal infection such as superficial mycosis. The incidence of superficial fungal infections of skin, hairs, and nails has been increased worldwide. Itraconazole has anti-fungal activity. For the formulation of 1% Itraconazole medistick, self-emulsifying drug delivery system (SEDDS) was prepared using appropriate oil, surfactants, and co-surfactants to improve solubility, penetration, and bioavailability. The microemulsion was then incorporated into the lipstick base containing appropriate amount of wax, lanoline, castor oil, cetyl alcohol, preservative, antioxidant, and perfume to prepare medicated lipstick. Results of evaluation tests like pH, breaking load, softening point, melting point, rancidity, etc. confirmed required physicochemical properties of formulated medistick. Overall, the findings of this research work imply that itraconazole medistick is a good patient friendly alternative to existing treatment of superficial mycosis.

Keywords: Itraconazole; Medicated stick; SEDDS; Superficial Mycosis

INTRODUCTION

A fungal infection known as superficial mycosis often affects the top layers of the skin, nails, and hair but can also spread to deeper tissues. Additionally, mycosis has been linked to lower life quality and a deleterious influence on host psychological and psychosocial characteristics. Mycosis, sometimes referred to as a fungal infection, is a condition brought on by fungi. According to the area of the body affected, various types are typically categorized into superficial, subcutaneous, and systemic. Yeast infections and frequent tinea capitis are examples of superficial fungal diseases infections. The subcutaneous forms of chromoblastomycosis and eumycetoma primarily impact the tissues in and below the skin. The severity of systemic fungal infections is higher. They comprise aspergillosis, pneumocystis pneumonia, histoplasmosis, cryptococcosis, mucormycotic.

For the treatment of mycosis, a variety of wide-spectrum antifungal azoles are available, including efinaconazole, fluconazole, ketoconazole, voriconazole, and itraconazole (ITZ). Importantly, azole groups prevent the cytochrome P-450 enzyme 14-demethylase from working, preventing the formation of ergosterol, a crucial component of fungal membranes. Additionally, compared to other antifungal medications, azole groups' selectivity toward the cytochrome P-450 enzymes of fungi rather than mammals allows for extremely selective antifungal action with comparably few adverse effects. Itraconazole (ITZ), one of numerous azole-based antifungal medications, has potent keratinophilic and lipophilic characteristics and has consequently become a successful broad-spectrum antifungal treatment for superficial mycosis. Additionally, ITZ has a

higher therapeutic index than amphotericin B and has lesser side effects when used to treat and prevent Aspergillus infections.

ITZ is typically used orally in clinical settings to treat cutaneous mycosis. Despite having a high absolute oral bioavailability (about 70%), the availability of ITZ at the desired site of action may be constrained by the absence of blood vessels in the stratum corneum and epidermis. Additionally, ITZ may not adequately diffuse from the dermis sublayer to other layers of the epidermis and stratum corneum due to its large molecular size (705.64 Da) and higher plasma-binding affinity. Since it has strong keratinophilic and lipophilic properties, itraconazole (ITZ), has become a popular broad-spectrum antifungal treatment for superficial mycosis.

MATERIAL AND METHOD

Materials: Itraconazole obtained as gift sample from Cipla Ltd. Mumbai. Cetyl alcohol pure, Lanolin (Loba Chemie Pvt. Ltd., Mumbai), Oleic acid, Iso-propyl myristate (S.D. fine chemicals ltd. Mumbai), Carnauba wax and Bees Wax (Sakshi Dyes and Chemicals) were used.

Preparation of Itraconazole stick:

Medicated dermasticks of itraconazole were prepared by heating and congealing method according to the formulae (Table 1).

On a magnetic stirrer, ITZ was dissolved in a beaker containing 1:1 v/v solution of oleic acid and isopropyl myristate until a clear solution was obtained. Sepeparately wax and oil mixture was prepared by melting wax at 70^0C in a China dish and mixed it with oil. The preservative, opacifier, and antioxidants were dissolved in leftover oil. The oil mixture and drug solution are then added to the wax/oil mixture with continuous stirring to prepare a homogeneous preparation. The perfume was added at a slightly lower temperature and the mass is stirred thoroughly but gently to avoid air entrapment. Gentle stirring is continued until homogeneous mass is obtained and then hot molten mass was poured into metallic mould. The mould is greased with isopropyl myristate before pouring the molten mass. Moulds were pre-warmed before pouring molten medicated mass to prevent ridge formation. After pouring the mass, the moulds are chilled to cause solidification of mass, making it easier to remove the sticks. The sticks were removed from the mould after 24 hours with the help of plunger and put into derma stick container.

Evaluation of medicated sticks:

Three sticks were selected randomly and evaluated for colour, odour, and appearance. The pH of medicated stick was recorded by checking pH of molten mass of medicated stick using calibrated pH meter. Melting point of a medicated stick was recorded by taking a 50mg sample of a medicated stick into a test tube to which a thermometer was inserted. Test tube was dipped into a beaker full of water and was heated with continuous stirring. Th temperature at which the mass starts melting was considered a melting point of medicated stick. To evaluate spreadability; medicated stick was spread over transparent glass at an angle of 45^0. The surface was observed, and the picture was taken against dark background. Breaking load test was performed wherein medistick was held horizontally in a socket at the midpoint of the medistick. The weight/load was gradually increased by a specific value at every 30 seconds and weight/load at which medistick breaks was considered as the breaking point. Rancidity of medicated stick was measured by iodimetry titration method using starch as indicator to find out Peroxide number. Test for heavy metals was performed using limit test for lead and results are reported. Drug content estimation (Assay) of medicated stick was performed using UV-Visible spectrophotometric analysis where absorbance of standard and test solution was measured at 267 nm and drug content was estimated in the sample solution accordingly.

IR spectra of ITR was obtained using KBR pellet method using Perkin-Elmer (Model: 161) spectrophotometer as identification test for drug sample. UV spectra of ITR was run and λ_{max} recorded. Melting point of ITR was also determined and verified with reported value. Identification test of ITR using thin layer chromatography (TLC) was also carried out using ethanol as solvent and dichloromethane as spaying agent and detection under UV light in UV chamber. TLC chromatographic identification test for medicated stick was also performed to check and confirm presence of ITR in the medicated stick.

***In vitro* antifungal studies of prepared medicated stick formulation:**

The anti-fungal studies were carried out for the prepared formulations by cup-plate method using *Candida Albicans* as test organism. The cultures of *Candida Albicans* were cultivated on nutrient agar media maintained on slants in the refrigerator (4±2ºC).

Cup-plate method: The composition of Nutrient agar media was taken in a 250 ml of conical flask and was dissolved in 100 ml of distilled water. The pH was adjusted to 5.6. The medium was sterilized in an autoclave at 121°C, 15 lbs for 15 minutes. After the completion of sterilization, the medium was kept aside at room temperature. 0.5 ml diluted suspension culture in NaCl (0.9%) were added to 100 ml of medium at 37±2ºC

and used as inoculated layer. The medium (20 ml) was poured into a sterilized petridish to give a depth of 3-4 mm and was assured that the layer of medium is uniform in thickness by placing petridish on a levelled surface. After solidifying the medium at room temperature, with the help of a sterile cork borer, cups of each 6 mm diameter were punched and scooped out from the petridish. Using sterile pipettes sample solutions (0.1 ml) of known concentration were fed into the cup. The petridish was then incubated for 24 hours at 37ºC. After incubation the zone of inhibition was measured (Table 3).

RESULTS AND DISCUSSION

Medicated sticks of Itraconazole were prepared by heating and congealing method using Bees wax and Carnauba wax as stiffening agent while Cetyl alcohol used as emollient. Oleic acid and isopropyl myristate were used as solubilizer for drug. As the molten mass was uniformly filled in mould, the sticks obtained were smooth in texture with creamy white colour and pleasant odour. The pH of medicated stick was found to be 6.8 close to neutral pH of 7.0. The melting point of medicated stick was found to be 65^0C much above ambient room temperature. Spreadability of medicated stick was good along with acceptable tensile strength as determined from breaking point test where it required a significant load of 250g to break the stick. The medicated stick formulation passes the limit test for Lead. Rancidification is the decomposition of fats, oils and other lipids by hydrolysis or oxidation. It leads to obnoxious odour, bad taste & sticky product & sometimes changes of colour of the product. Testing of rancidity of medicated stick was done by determining its peroxide number. Peroxide values of fresh oils are less than 10 milliequivalents/kg; when the peroxide value is between 30 and 40 milliequivalents/kg, a rancid taste is noticeable. Peroxide number for Itraconazole medicated stick was found to be 9.2 milliequivalents/kg confirming that there is no rancidity in the prepared formulation. Average drug content was found to be 94.55%. Rf value of pure ITR and medistick formulation were found to be 0.90 and 0.89 respectively. The IR spectra and UV-Visible spectra showed all the characteristic peaks of pure drug and λ_{max} same as that of reported standard value, respectively (Table 2 & Figure 5). Antimicrobial studies revealed that the drug in formulation show equal zone of inhibition as that of pure drug (Table 3 & Figure 6).

SUMMARY AND CONCLUSION:

The objective of this study is to develop innovative drug delivery system to cure topical fungal infection such as superficial mycosis. The incidence of superficial fungal infections of skin, hairs, and nails has been increased worldwide. For the formulation of 1% Itraconazole medistick, self-emulsifying drug delivery system (SEDDS) was prepared using appropriate oil, surfactants, and co-surfactants to improve solubility, penetration, and bioavailability. The microemulsion was then incorporated into the lipstick base containing appropriate amount of wax, lanoline, castor oil, cetyl alcohol, preservative, antioxidant, and perfume to prepare medicated lipstick. Results of evaluation tests like pH, breaking load, softening point, melting point, rancidity, etc. confirmed required physicochemical properties of formulated medistick. Overall, the findings of this research work imply that itraconazole medistick is a good patient friendly alternative to existing treatment of superficial mycosis. This research work paves the way for development of several similar unique formulations in the pharmaceutical industry.

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19.

Table 1: Composition of Itraconazole medistick

Sr.No.	Ingredients	Quantity/stick
1.	Itraconazole	0.04g (1% w/w)
2.	Oleic acid : isopropyl myristate (1:1 v/v)	4.0 ml
3.	Beeswax	0.6g
4.	Carnauba wax	0.2g
5.	Anhydrous lanolin	0.6g
6.	Castor oil	2.0g
7.	Cetyl alcohol	0.1g
8.	Titanium dioxide	0.1g
9.	Propyl parahydroxybenzoate	0.006g
10.	BHA	0.0006g
11.	BHT	0.0006g
12.	Perfume (Orange flavor)	q.s. to 4.0g

Table 2: Reported and observed IR frequencies of Itraconazole.

Reported frequency (cm^{-1})	Observed frequency (cm^{-1})	Functional group
1640-1690	1695	C=O stretching
2823-2880	2879-2823	C-H stretching
1400-1600	1453-1551	C=C stretching in aromatic ring
1000-1300	1221	C-O stretching
2210-2260	2358	C-N stretching

Table 3: Antifungal study showing the comparative zone of inhibition of ITR as pure drug and in medistick formulation

Formulation Code	Zone of inhibition (mm) after 36 hr		
Pure Drug	16.9	17.2	16.6
Medistick formulation (Plate 1)	15.5	16.7	16.1
Medistick formulation (Plate 2)	16.6	16.3	15.9
Medistick formulation (Plate 3)	15.6	16.6	16.1

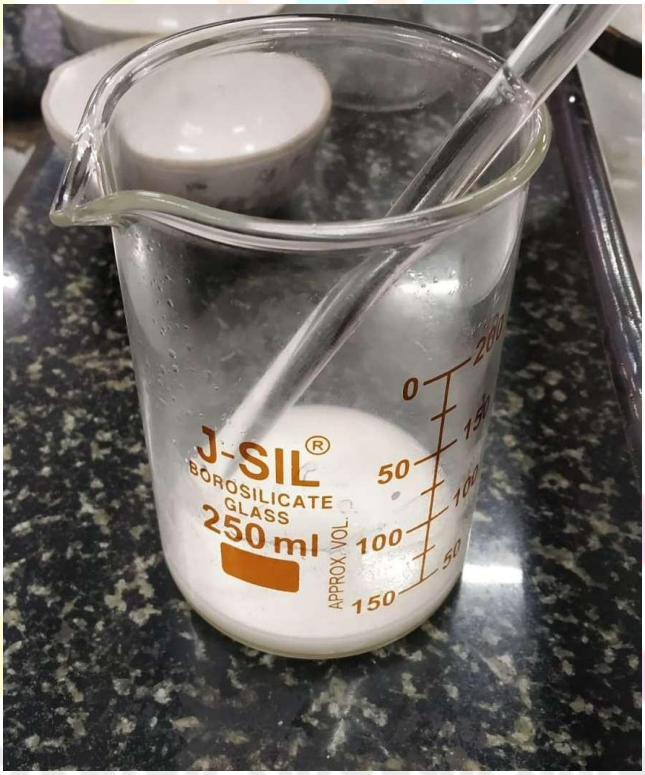

Figure 1. Preparation of drug solution in oleic acid: IPM (1:1) mixture

Figure 2. Preparation of final molten mass

Figure 3. Molding of sticks

Figure 4. Medistick in final pack/container

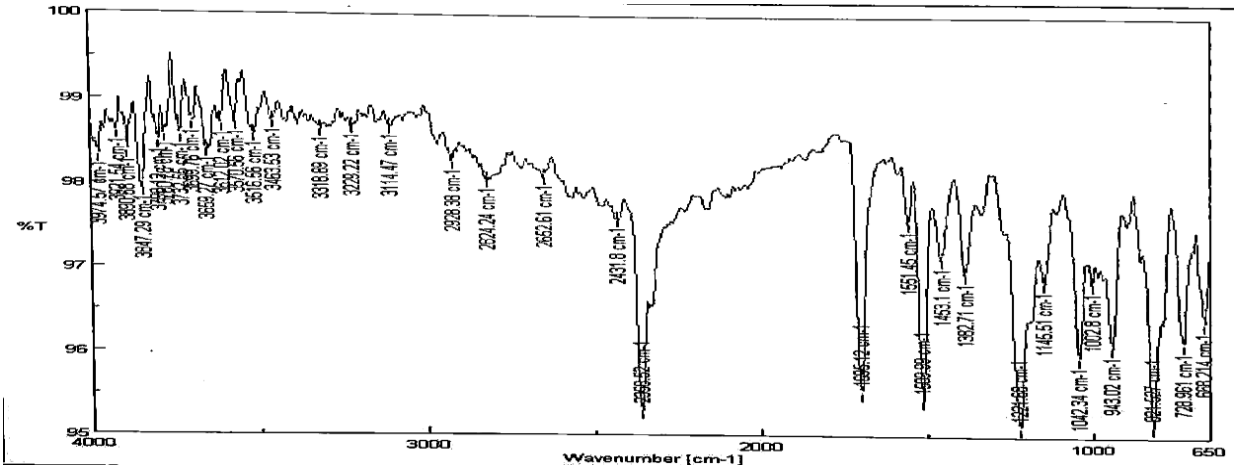

Figure 5. IR spectra of Itraconazole

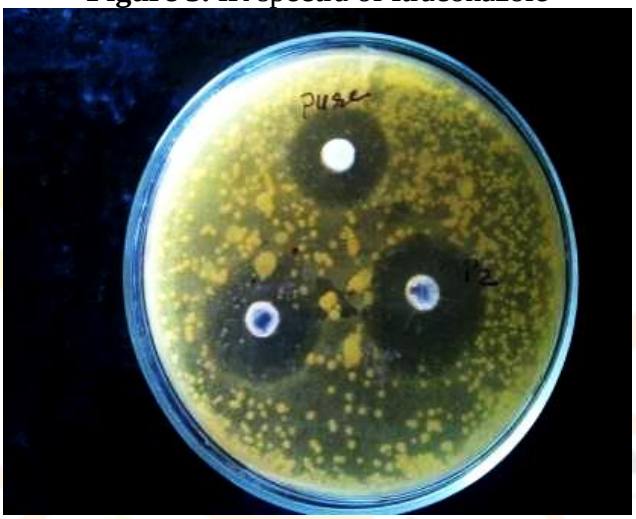

Figure 6A. Antifungal study-Zone of inhibition with pure ITR

Figure 6A. Antifungal study-Zone of inhibition with Medicated stick