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Pharmaceutical Composition of a Topical Dosage form of Itraconazole for the Treatment of Athlete's Foot

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Abstract---*Athlete's foot is a cutaneous fungal infection that usually begins between the toes. It usually happens in people whose feet are very sweaty while confined in fitting shoes. Signs and symptoms of the athlete's foot include a scaly rash which usually causes "itching, stinging and burning". It is caused by the fungus "Trychophytonrubrum". In severe cases, the skin may blister (A collection of fluid below the top layer of skin i.e. epidermis). Many oral and topical treatments are available to cure Athlete's foot. Oral itraconazole (Mw~705.64 g, Melting Point~166.3°C, Weak base pKa~3.7) is the most commonly used antifungal drug in the treatment of Athlete's foot at the dose of 100 mg once-a-day for 30 days. The anti-fungal drug itraconazole is used to treat fungal infections in adults. Infection of the lungs, mouth or throat, toenails or fingernails includes infections in any part of the body. Some of the brands of itraconazole cannot be used for the treatment of fungal infections of the fingernails or toenails. Mechanistically, itraconazole inhibits the fungal-mediated synthesis of ergosterol, via inhibition of lanosterol 14α-demethylase. However, poor physicochemical attributes, interference of food, side-effects (Nausea, diarrohea, and hepatotoxicity) and lesser bioavailability (55%) alters the therapeutic efficacy of itraconazole. in present investigation, a pharmaceutical dermal cream of itraconazole was formulated by oil in water (O/w) emulsion method to improve skin penetration in the treatment of tineapedis infection. Among several chemical permeation enhancers, dimethyl sulfoxide was used in the pharmaceutical dermal cream of itraconazole to augment the penetration of drug in skin.*

Keywords--- *Athlete's foot, fungal infection, scaly rash, itching, stinging, Trychophytonrubrum, itraconazole, ergosterol, lanosterol 14α-demethylase*

I. INTRODUCTION

Tineapedis (Athlete's foot) is caused due to the fungi and gets infected through bacteria [1] (figure 1). It is believed to be a disease of relatively recent onset and the first case of the athlete's foot was recorded in Italy in 1888. It is closely related to the occlusive footwear [2]. The people who do not wear shoes are almost free of fungal infection. Nonetheless, roughly 10 percent of the population in more developed countries has the foot of athletes at some point. The population between 30% and 70% affected people will have athlete's foot at some time in their lifetime and the infection spreads to other parts of the body also. Moreover, asymptomatic carriers are very numerous [3].

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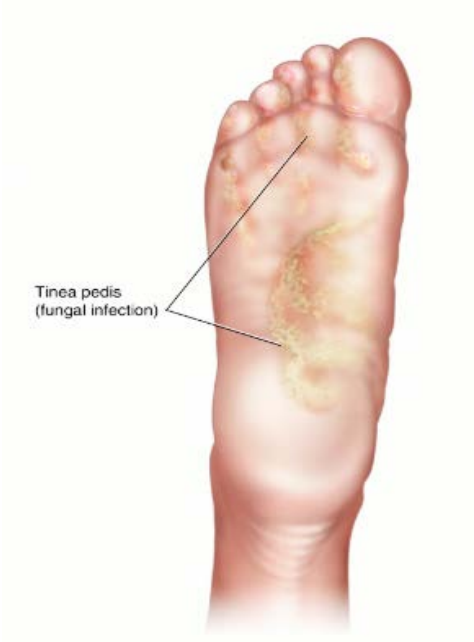

Fig.1. Athlete's Foot

Athlete's foot is distinguished into two clinical forms: acute (with self-limited, intermittent, and recurrent attacks) and chronic, which occurs recurrently if not treated properly or untreated [4].

Athlete's foot is one of the most common diseases which is found in many people [5][6]. However, this disease is considered to be found in the adults, but it is also common in children, especially boys. According to a study, it has been demonstrated that the athlete's foot is found equally in men and women but still most of the cases are found in the men after the age of puberty or at puberty. The main cause of this disease in normal people is hot climates and the use of public bathrooms or pools, whereas the cause of this disease in athletes is use of communal locker rooms and showers.

In present investigation, a pharmaceutical dermal cream of itraconazole[7][8] has been formulated that contains the active ingredient, itraconazole, and pharmaceutically acceptable permeation enhancer dimethylsulfoxide. In addition, other excipients namely stearic acid [9], cetostearyl alcohol, octadecanol, potassium hydroxide, sodium hydroxide, polysorbate 60, glycerine, benzyl alcohol, and water have been also incorporated. The dispersion of the oil phase ingredients in aqueous phase ingredients produces the white colored O/w dermal cream. Oral itraconazole (Mw~705.64 g, Melting Point~166.3°C, Weak base pKa~3.7) is the most commonly used antifungal drug in the treatment of Athlete's foot at the dose of 100 mg once-a-day for 30 days [10][11]. Mechanistically, itraconazole inhibits the fungal-mediated synthesis of ergosterol, via inhibition of lanosterol 14α-demethylase[12]. However, poor physicochemical attributes, interference of food, side-effects (Nausea, diarrohea, and hepatotoxicity) and lesser bioavailability (55%) alters the therapeutic efficacy of itraconazole. In addition, itraconazole can't be administered to patients having the issue of hepatic and renal impairment. Moreover, log partition coefficient (log P) value of itraconazole is equivalent to 5.66 at pH~8.1 that indicates hydrophobicity of the drug. Owing to these limitations, administration of itraconazole through topical route for the treatment of tineapedis infection would be more

advantageous as compared to oral route of administration [13][14]. Ideally, a drug having molecular weight (Mw) less than 600 Da, log P value in the range of 1-3, solubility in both oils and water and low melting point penetrates the skin effortlessly. Therefore, in present investigation, a pharmaceutical dermal cream of itraconazole was formulated by oil in water (O/w) emulsion method to improve skin penetration in the treatment of tineapedis infection [15].

II. PHYSIOLOGICAL CHARACTERIZATION AND RESULTS

Among several chemical permeation enhancers, dimethyl sulfoxide was used in the pharmaceutical dermal cream of itraconazole to augment the penetration of drug in skin. Moreover dimethyl sulfoxide also exhibits fungicidal activity against tineapedis infection. The pharmaceutical dermal cream of itraconazole was characterized under a set of stringent parameters to establish its stability and therapeutic efficacy against tineapedis infection. The color, state, texture and homogeneity was recognized by visual appearance and noticed to be white, semi-solid, smooth and uniform, respectively. The pH of the cream was estimated to be 6.6±1.52. The spreadability of dermal cream was measured to be 52.17±3.03 g.cm/sec. The drug content analysis was carried out by non-aqueous titration and estimated to be 8.64 mg/gm of cream. The rheological analysis of the cream followed the non-Newtonian fluid behavior. No phase separation on centrifugation was noticed in any batch of the itraconazole dermal cream. Next, stability studies were carried out as per ICH guidelines to optimize the storage conditions for itraconazole dermal cream. The itraconazole dermal cream was stable at room temperature (25°C/60% RH) for more than one year as well as at 40°C/75% RH for more than 6 months. The therapeutic efficacy of itraconazole dermal cream was measured by in vitro antifungal assay using cup-plate method. The minimum inhibitory concentration (MIC) of itraconazole was calculated to be 100-µg/ml significantly (Unpaired t test, $P<0.05$) higher than 30-µg/ml of dimethyl sulfoxide against Trichophytonrubrum. On the other hand, itraconazole dermal cream exhibited the MIC of 480-µg/ml significantly (One way ANOVA test, $P<0.05$) lower than ≤ 960 µg/ml of itraconazole dermal cream lacking permeation enhancer and ≤ 960 µg/ml of dermal cream lacking itraconazole. The drug content analysis was carried out by non-aqueous titration. Non-aqueous titration is a well-established method for analytical estimation of itraconazole. If the dosage form is aqueous, then analyte should be extracted to non-aqueous solvent. The non-aqueous titration analysis was carried out using 0.1M per chloric acid ($HClO_4$) as a titrant. 0.1 M $HClO_4$ was standardized with primary standard, potassium hydrogen phthalate using crystal violet as an indicator. The purity of itraconazole was estimated to be 100.8±0.00%. The acceptable limit of purity of itraconazole is specified in the range of 98.5% to 101.5% on the dried basis in United States Pharmacopoeia. In this way, the drug content of optimized dermal cream of itraconazole was estimated to be 8.64±0.21 mg/gm of cream (as shown in Table 1).

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Table 1. Comparative characterization of optimized intraconazole dermal cream and representative marketed cream

Sr. No.	Characterization Parameters	Observation	
		Optimized itraconazole dermal cream	Representative marketed cream
1	Color	White	White
2	State	Semi solid	Semi solid
3	Texture	Smooth	Smooth
4	Homogeneity	Uniform	Uniform
5	pH	6.6±0.15	6.7±0.13
6	Spreadability	52.17 ± 3.03 g cm/sec	33.43 ± 1.18 g cm/sec
7	Drug content	8.64±0.21mg/gm	-

Viscosity of cream was determined by Brookfield viscometer using CP-75 spindle. The dermal cream was poured into the adaptor of the viscometer and the angular velocity increased gradually from 100 rpm. The rheological analysis of the cream followed the non-Newtonian fluid behavior. This indicated that the cream is easily spreadable by small amounts of shear. However, no phase separation upon centrifugation at 10,000 rpm (20°C) for 15 min was noticed in any batch of the itraconazole dermal cream. Next, stability studies were carried out as per ICH guidelines to optimize the storage conditions for itraconazole dermal cream. The itraconazole dermal cream was stable at room temperature (25°C/60% RH) for more than one year as well as at 40°C/75% RH for more than 6 months (as shown in Table 2 A-B).

Table 2(A) Stability studies of optimized itraconazole dermal cream carried out at room temperature as per ICH guidelines

Sr. No.	Characterization parameters	Room Temperature (25°C/60% RH)		
		After 4 months	After 8 months	After 12 months
1	Color	White	White	White
2	State	Semisolid	Semisolid	Semisolid
3	Texture	Smooth	Smooth	Smooth
4	Homogeneity	Uniform	Uniform	Uniform
5	pH	6.6 ± 0.15	6.5 ± 0.13	6.6 ± 0.03
6	Spreadability	52.17 ± 3.03 g.cm/sec	51.12 ± 2.33 g.cm/sec	52.13 ± 3.73 g.cm/sec
7	Drug content	8.64 ± 0.21 mg/gm	8.60 ± 0.34 mg/gm	8.60 ± 0.42 mg/gm

Table 2(B) Stability studies of optimized intraconazole dermal cream carried out in stability chamber as per ICH guidelines

Sr. No.	Characterization parameters	Stability Chamber (40°C/75% RH)		
		After 4 months	After 8 months	After 12 months
1	Color	White	White	White
2	State	Semisolid	Semisolid	Semisolid
3	Texture	Smooth	Smooth	Smooth
4	Homogeneity	Uniform	Uniform	Uniform
5	pH	6.6±0.15	6.6±0.43	6.6±0.87
6	Spreadability	52.17±3.03 g.cm/sec	53.22±1.14 g.cm/sec	52.25±2.11 g.cm/sec
7	Drug content	8.64±0.21 mg/gm	8.63±0.23 mg/gm	8.62±0.29 mg/gm

The therapeutic efficacy of itraconazole dermal cream was measured by in vitro antifungal assay using cup-plate methodofitraconazole was calculated to be 100-µg/ml significantly (Unpaired t test, P<0.05) higher than 30-µg/ml of dimethyl sulfoxide against Trichophytonrubrum. On the other hand, itraconazole dermal cream exhibited the MIC of 480-µg/ml significantly (One way ANOVA test, P<0.05) lower than ≤ 960 µg/ml of itraconazole dermal cream lacking permeation enhancer and ≤ 960 µg/ml of dermal cream lacking itraconazole (as shown in Table 3).

Table 3. Measurement of zone of inhibition induced by optimized intraconazole dermal cream, intraconazole, dimethyl sulfoxide (DMSO), optimized intraconazole cream without DMSO, optimized cream without intraconazole, optimized cream without intraconazole and DMSO.

Sr.No	Concentration of itraconazole (µg/ml)	Zone of inhibition (mm)					
		Optimized itraconazole dermal cream	Itraconazole	Dimethyl sulfoxide	Optimized itraconazole dernal cream without dimethyl sulfoxide	Optimized dermal cream without itraconazole	Optimized dermal cream without itraconazole and dimethyl sulfoxide
1	5	0	6.98±0.26	9.33±3.11	8.45±0.47	6.98±0.26	5.56±0.43
2	15	0	8.76±0.40	10.10±0.54	8.76±0.40	7.76±0.27	5.77±0.20
3	30	0	11.33±0.57	13±2.64	9.43±0.05	7.66±0.37	5.54±0.46
4	100	13±2.11	14.33±2.08	12.66±0.57	10.37±0.54	8.45±0.47	5.96±0.29
5	160	10±2.17	13±1.73	13±1.73	10.10±0.88	7.78±0.46	5.66±0.48
6	240	9.33±3.11	15.33±2.99	11.66±1.15	9.19±0.89	7.14±0.09	5.85±0.17
7	480	15.66±2.33	15.66±2.51	13±1.00	11.76±1.13	7.35±0.53	5.85±0.26
8	960	15.33±2.3	15.33±3.05	13.66±1.52	9.83±0.33	7.58±0.47	5.69±0.13

III. CONCLUSION

In conclusion, itraconazole dermal cream exhibited promising antifungal activity against Trichophytonrubrum strain. Calculation ad compilation of the data indicated that percutaneous cream of itraconazole showed efficient and promising results alternative to oral medicated antifungal therapy of itraconazole.

The dermal cream of itraconazole overwhelms the poor physicochemical and toxicity issues of itraconazole. Dermal cream of itraconazole retains therapeutic concentration of drug within skin. Dermal cream of itraconazole offers enhanced safety and efficacy for locally manifested diseases as compared to existing oral dosage forms..

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