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Effect of Essential oil as skin permeation enhancer to develop Itraconazole antifungal cream

Kuntal Das, Anuranjita Kundu*

Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Rd, Sahid Colony, Panihati, Khardaha, West Bengal 700114

Corresponding Author- Anuranjita Kundu, Email- anuranjita.kundu@gnipst.ac.in

Abstract: Fungal infections are caused by fungi that invade and grow on or inside the body. These infections can range from mild to life-threatening, depending on the type of fungus and the host's immune status. An antifungal medication called itraconazole (ITZ) is typically used to treat cutaneous mycoses and other fungal skin diseases. In this article developed formulation is Itraconazole cream with some essential oil and its evaluation. The developed Itraconazole cream formulation was necessary to ensure effective transport of ITZ to the skin tissues. The prospective of this work is to enhancement of skin permeation of Itraconazole by using essential oil like eucalyptus oil, peppermint oil, rosemary oil etc. Following the formulation's preparation, an evaluation is conducted based on a number of parameters, including pH, appearance, washability, spread-ability, homogeneity, and viscosity. In Vitro skin permeation study of Itraconazole cream was done by using Franz diffusion cell. Egg shell membrane is used as barrier membrane. Phosphate buffer pH 7.4 served as the dissolving media, and 37 ± 1°C was maintained as the temperature. In vitro permeation study of the formulated ITZ cream analysis showed a time-dependent rise in drug release during the course of the investigation. After using essential oil in the formulation, it is observed Eucalyptus oil shows better skin permeation as compared to other essential oils.

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Keywords: itraconazole; cream formulations; skin permeation enhancer; Essential oil.

1. Introduction:

Human skin conditions are quite common throughout the world and can be confusing if not appropriately treated. Since cutaneous fungal infections can result in potentially fatal systemic infections, widespread and resistant fungal infections are particularly important healthcare concerns [1]. The incidence of cutaneous fungal infections rises significantly with the number of immunocompromised people. Numerous fungal illnesses, including tinea and candidiasis, impact various populations.

Fungal species like Aspergillosis, Blastomycosis, Ringworm, Candida species, particularly Candida albicans (CA), are the cause of candidiasis. CA can penetrate the stratum corneum and reach the deeper dermal strata, resulting in cutaneous candidiasis

[2]. Newborns who wear diapers frequently suffer from diaper dermatitis (DD), which is caused by candidiasis [3].

There are several kinds of wide-spectrum antifungal azoles that can be used to treat mycosis, including Efinaconazole [EFN], fluconazole, ketoconazole, voriconazole, and itraconazole [ITZ]. Crucially, azole groups inhibit the cytochrome P-450 enzyme 14-α demethylase, which prevents the formation of ergosterol, a crucial component of fungal membranes. The azole groups' preference for the cytochrome P-450 enzymes of fungi rather than mammals allows for highly selective antifungal action with relatively little adverse effects.

As a result, higher ITZ concentrations have been attained using standard oral dosages of 200–400 mg daily [4]. However, a number of reproductive tissues, liver damage, and nephrotoxicity have all been linked to the high systemic concentration of ITZ that results

[5]. Because topical administration of ITZ has fewer side effects than oral administration, it may be beneficial for site-specific delivery. This could be ascribed to its high molecular weight (705.64 g/mol), low aqueous solubility and high lipophilicity (Log*P* = 5.66).

To enhance topical administration of ITZ, methods such creams, ointments, pastes, and liposomal formulations have been employed [6]. ITZ's solubility can be somewhat increased by colloidal carrier systems. Colloidal carriers, on the other hand, decrease medication release and formulation spreading on the skin's surface due to their semi-solid nature. Additionally, it results in restricted permeability through the skin's membrane [7]. Above the formulation, ITZ Cream is best suitable for topical administration.

Pharmaceutical excipients of natural origin that are biocompatible, biodegradable, and toxicologically innocuous can be used to improve ITZ skin penetration and help formulate topical solutions that meet key objectives: by enhancing the finished product's cutaneous effectiveness, safety, and tolerability profile. [8]

Essential oils are used natural skin penetration enhancers because their capability to increase the skin penetration of drugs from topical products is based on consistent scientific evidence. Furthermore, a number of published studies have shown that essential oils, which are complex combinations of several volatile and non-volatile chemicals, have a wide range of antibacterial activity against bacteria, viruses, fungus, and protozoa.[9]

Some essential oil such as Rosemary oil, Eucalyptus oil, Peppermint oil, Lavender oil are used for enhancing the skin permeability an also helps to open the compact structure of skin for better absorption of ITZ. [10]

Hence the main focus of the study is the skin permeation of ITZ Cream and enhancement of skin permeation of ITZ cream by using different natural essential oils as skin permeation enhancer and finding the best one.

2. Materials and Methods:

2.1. Materials

ITZ, Cetyl alcohol, Glyceryl mono-stearate, stearic acid and propylene glycol, water.

Table:1

Phase of Cream Formulation	Ingredients	Content (%)
Oil phase	ITZ	1.0
	Glyceryl mono-stearate	4.0
	Stearic acid	10.0
	Cetyl alcohol	6.0
Water phase	Propylene glycol	9.0
	Distilled water	40.0

Table 1: Composition of ITZ cream formulation (without essential oil).

2.2. Preparation of O/W Cream Formulation:

Table 2 shows the composition of the O/W cream formulation of ITZ established based on the result of the solubility test of ITZ in different excipients. The oil phase consisting of glyceryl monostearate, stearic acid, and cetyl alcohol was heated up to 80 ◦C, and then ITZ was added to the oil phase and mixed by stirring for 10 min. After completely dissolving the drug in the oil phase, the aqueous phase composed of propylene glycol and water was added to the oil phase and heated at 80 ◦C. The mixture was homogenized for 30 min and degassed under vacuum condition. The O/W cream formulation was then cooled to room temperature (~22°C). After that essential oil is added.

Table2:

Phase of Cream Formulation	Ingredients	Content (%)				
		F1	F2	F3	F4	F5
Oil phase	ITZ	1.0	1.0	1.0	1.0	1.0
	Glyceryl mon-stearate	4.0	4.0	4.0	4.0	4.0
	Stearic acid	10.0	10.0	10.0	10.0	10.0
	Cetyl alcohol	6.0	6.0	6.0	6.0	6.0
Water phase	Propylene glycol	9.0	9.0	9.0	9.0	9.0
	Distilled water	40.0	40.0	40.0	40.0	40.0
Essential Oil	Peppermint Oil	--	----	--	2	--
	Eucalyptus Oil	--	--	---	--	2
	Rosemary Oil	--	2	--	---	--
	Lavendar Oil	--	--	2	--	----

Table 2: Composition of ITZ cream formulation (with different essential oils).

Fig-1: ITZ CREAM FORMULATION

2.3. Characterization of Cream Formulation:

2.3.1. Organoleptic Properties

The cream formulation and the physical mixture were visually examined for colour, texture, and phase separation. The feel of the cream formulation and physical mixture such as stiffness, grittiness, greasiness, and irritation also examined. Written informed consent was obtained after thoroughly explaining the study including purpose and risks. The O/W cream formulation and the physical mixture on each back of their hands using a spatula and gently rubbed the cream formulation and physical mixture. The participants assessed the physical mixture and cream formulation's feel, including its stiffness, grittiness, greasiness, and irritation, after two minutes. To determine if solid drug powder was present or not, a tiny portion of each cream formulation and the physical mixture were additionally squeezed with the thumb and index finger.

2.3.2. pH

The pH of the O/W cream formulation and the physical mixture was evaluated using a pH paper. A small quantity of the cream formulation was applied on the one side of the pH paper. The pH of the cream formulation and the physical mixture was determined by comparing the change in colour of the pH paper on the other side with the colour chart. [13]

2.3.3 Determination of Viscosity –

The viscosity determinations were carried out using a Brookfield Viscometer (DV II + Pro model) using spindle number S-64 at a 20 rpm at a temperature of 25degree C. [11]

2.3.4 Stability Study:

For 20 days, the created cream was kept at room temperature in order to conduct stability tests. Homogeneity, viscosity, physical changes, pH, and smear type were among the parameters examined during the stability investigations.

2.3.5 Spread-ability test: The spread ability of the formulated cream was judged by spreading over skin.

2.3.6 Washability: -

The cream was removed from the skin by washing it under tap water with very little pressure. [12]

2.3.7 Irritancy test:

Marked an area (1sq. cm) on the left - hand dorsal surface. The cream was applied to the specified area and time was noted. Irritancy, erythema, edema, were checked if any for regular intervals up to 24 hrs and reported.

2.3.8 Homogeneity: Homogeneity was tested via visual appearance.

Creaming formation: After heating the sample vanishing cream in an appropriate test tube for ten minutes, the outcome was noted. The emulsion is of the o/w type if the creaming is upward. The emulsion is w/o type if the creaming is downward. [20]

2.3.9 In Vitro Skin Deposition and Penetration Analyses

The in vitro permeation study of the prepared ITZ cream was carried out through egg shell membrane because the egg shell membrane resembles human stratum corneum as it consists mainly of keratin [14]. The membrane was accordingly prepared before use. The water in the outer jacket of the cell was warmed and set at 37 ± 1∘ C throughout the experiments to provide a skin surface temperature. Phosphate buffer solution of pH 7.4 was used as dissolution medium in the receptor compartment. A 5 × 5 mm2 piece of patch was taken and applied over the mounted membrane in diffusion cell. After that, the samples were withdrawn from the receptor compartment at regulated intervals. The sampling schedule was at 10, 20, 30, 40, 50 and 60 minutes for the first hour of release and then it was at every hour interval till 6th hour of release [15]. After that the whole system was kept in its normal position overnight and then next day reading was taken at 24th hour. One mL of the receptor solution was collected as sample each time and simultaneously one mL of phosphate buffer solution was added back to the receptor cell for maintaining the same initial volume of the receptor cell solution. The collected samples were analysed using UV-vis spectrophotometer [16].

Fig- 2: Franz diffusion cell

3. Results:

3.1 Organoleptic Characteristics of Cream Formulation:

S. No.	Parameter	Observation				
		F1	F2	F3	F4	F5
1	Appearance	white and opaque	white and opaque	white and opaque	white and opaque	white and opaque
2	odour	Pleasant	Pleasant	Pleasant	Pleasant	Pleasant
3	pH	6.4- 6.5	6.5- 6.6	6.5-6.62	6.6- 6.7	6.6- 6.8
4	Viscosity	480 N s m-2	480 N s m-2	480 N s m-2	480 N s m-2	480 N s m-2
5	Stability Study	Stable	Stable	Stable	Stable	Stable
6	Washability	Washable	Washable	Washable	Washable	Washable
7	Irritancy test	No irritancy	No irritancy	No irritancy	No irritancy	No irritancy
8	Homogeneity	Homogenous Smooth and Consistent	Homogenous Smooth and Consistent	Homogenous Smooth and Consistent	Homogenous Smooth and Consistent	Homogenous Smooth and Consistent
9	Spread-ability	Uniform and easily spreadable	Uniform and easily spreadable	Uniform and easily spreadable	Uniform and easily spreadable	Uniform and easily spreadable
10	Type of Cream	O/W cream	O/W cream	O/W cream	O/W cream	O/W cream

3.6. In Vitro Skin Deposition and Penetration Analyses:

After performing In vitro skin permeation study, according to the data we can conclude that formulations with essential oils have superior permeability properties when compared to formulations without essential oil. As per data, the below graph is plotted.

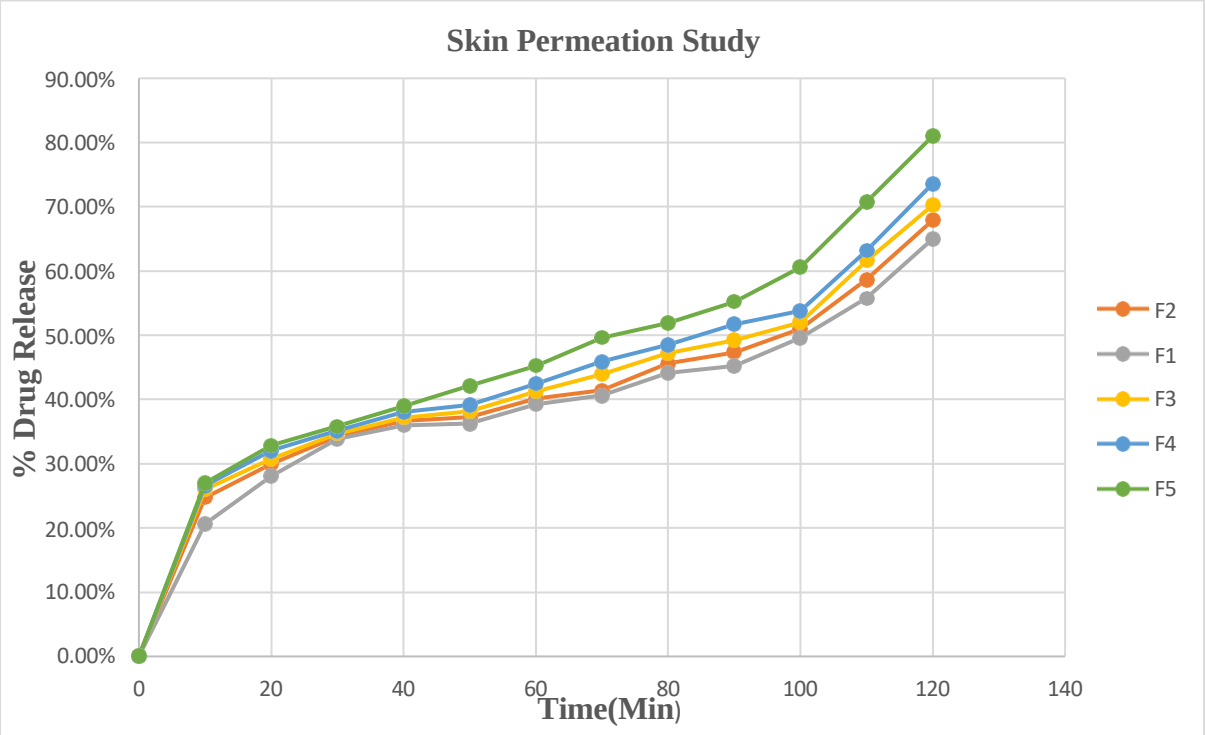

Fig-3

F1-Base formulation without essential oil, F2-Formulation with Rosemary Oil, F3- formulation with Lavendar oil, F4- Formulation with peppermint oil, F4- Formulation with Eucalyptus oil.

4. Discussion:

After performing the experiment the organoleptic properties are evaluated. It is observed that the cream appearance looks white. The ITZ cream formulation has pH between 6.4-6.7 that optimum for use in the skin. The formulated cream demonstrated excellent consistency, spread-ability, homogeneity, non-greasiness, and no phase separation during the testing. The cream applied on skin was easily removed by washing with tap water. In-vitro skin permeability study of ITZ cream is done by using Franz diffusion cell. Essential oils are also used in the formulation as skin permeation enhancer for better penetration of cream into the skin. Eucalyptus oil, Peppermint oil, lavender oil, Rosemary oil are used as essential oil. From the above study it is observed that ITZ cream formulated with essential oil shows better result as compared to cream without essential oil. Among the above essential oil eucalyptus oil shows better result as skin permeation enhancer as compared to other essential oil.

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