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FORMULATION AND EVALUATIONOF ITRACONAZOLE ETHOSOMAL GEL

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ABSTRACT

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery. The aim of present study is to Formulate and undergo Evaluation study of Itraconazole ethosomal gel. Preparation of Itraconazole ethosomes was followed by cold method, ten different formulations of Ethosomes were prepared by using different concentrations of polymer i.e., Soya Lecithin (2-5%) and Ethanol (20-50%). The best achieved ethosomal vesicles suspension, was incorporated into carbopol gel(1%, 1.5%, 2% w/w). Gel was evaluated with different parameters like its organoleptic character, pH measurement, Entrapment efficiency, drug content, Content uniformity, SEM and Drug release. Ethosomes containing 30% w/w ethanol and prepared by sonication showed highest value respect to all other formulation; so it is concluded that ethosomal prepared by sonication and containing 30%w/w ethanol as the best formulation considering all other aspects. The optimized formulation wasIF8 (30% alcohol) showed the drug release of 89.3%,The order of drug release for optimized gel formulation was found to be First order. Percentage drug accumulation into skin was also found to be maximum by the ethosomes containing 30% w/w ethanol. This showed effective subdermal deposition and indicates better subdermal action for fungal infections. With these findings it can be summarized that Itraconazole ethosomes are promising system in topical drug delivery for treatment of fungal disorders.

Key words: Ethosomes, Sonication, Entrapment, Iontophoresis.

INTRODUCTION

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery [1].

Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for systemic action. Improved methods of drug delivery for biopharmaceuticals are important for two reasons; these drugs represent rapidly growing portion of new therapeutics, and are most often given by injection. Discovery of new medicinal agents and related innovation in drug delivery system have not been only enabled the successful implementation of novel pharmaceutical, but also permitted the development of new medical treatment with existing drugs. Throughout the past two decades, the transdermal patches have become a proven technology holding the promise that new compound could be delivered in a safe and convenient way through the skin. Since the first transdermal patch was approved in 1981 to prevent nausea and vomiting associated with motion sickness, the FDA has approved through the past 22 years more than 35 transdermal patch products spanning 13 molecules [2].

Routes of Penetration

At the skin, molecules contact cellular debris, microorganisms, sebum and other materials, which negligibly affect permeation. The penetration has three potential pathways to the viable tissue - through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages.

Fractional appendageal area available for transport is only about 0.1%; this route usually contributes negligibly to steady state drug flux. The pathway is important for ions and large polar molecules that struggle to cross intact stratum corneum. Appendages may be providing shunts, important at short times prior to steady

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state diffusion. Additionally, polymers and colloidal particles can target the follicle.

The intact stratum corneum thus provides the main barrier; its 'brick and mortar' structure is analogous to a wall. The corneocytes of hydrated keratin comprise of 'bricks', embedded in 'mortar', composed of multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semicrystalline, gel and liquid crystals domains. Most molecules penetrate through skin via this intercellular microroute and therefore many enhancing techniques aim to disrupt or bypass elegant molecular architecture.

Viable layers may metabolise a drug, or activate a prodrug. The dermal papillary layer is so rich in capillaries that most penetrants clear within minutes. Usually, deeper dermal regions do not significantly influence absorption, although they may bind e.g. testosterone, inhibiting its systemic removal [1].

STRATUM CORNEUM AND TWO MICROROUTES OF DRUG PENETRATION

Optimizing Transdermal Drug Delivery

Transdermal route offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, and most importantly, it provides patient convince. But one of the major problems in transdermal drug delivery is the low penetration rate through the outer most layer of skin [3].

The non-invasive approaches for providing transdermal drug delivery of various therapeutics substances are

Drug and vehicle interactions

- Selection of correct drug or prodrug
- Chemical potential adjustment
- Ion pairs and complex coacervates
- Eutectic systems

➢ Stratum corneum modification

- Hydration
- Chemical penetration enhancers

➢ Stratum corneum bypassed or removed

- Micro needle array
- Stratum corneum ablated
- Follicular delivery

➢ Electrically assisted methods

- Ultrasound (Phonophoresis, Sonophoresis)
- Iontophoresis
- Electroporation
- Magnetophoresis
- Photomechanical waves

➢ Vesicles and particles

- Liposomes and other vesicles
- High velocity particles

Vesicular systems are drug delivery system to deliver the drug dermally and transdermally. Liposomes have the potential of overcoming the skin barrier, as these are bilayered lipid vesicles, consisting primarily of phospholipids and cholesterols [4].

Liposomes were discovered in the early 1960's by Bangham and colleagues and subsequently became the most extensively explored drug delivery system[5]. In early 1960's a great knowledge of vesicle derivatives have been tested for their abilities. Most experiments, however, have centered on liposomes, since derivations only add to their basic properties. Vesicles are closed, spherical membrane that separates a solvent from the surrounding solvent. Possible use of liposomes in topical drug delivery vehicles for both water and lipid soluble drug has been investigated. While it has been suggested that the external envelop of a liposomes would allow it to pass through lipophilic skin, most researches show that liposomal vesicles become trapped within the top layer of the stratum corneum cells [2]. Generally liposomes are not expected to penetrate into viable skin, although occasional transport processes were reported1. This behavior is useful both for local treatment of skin disorders and for cosmetic formulations. Specific drug accumulation at the site of action and decreased systemic drug absorption can impart increased efficiency as well as decreased side effect to a compound applied topically [6].

Ethosomes

The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have been understanding the properties of vesicle structures for use in better drug delivery within their cavities, that would allow to tag the vesicle for cell specificity. Vesicles would also allow to control the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and would be able to release just the right amount of drug and keep that concentration constant for longer periods of time. One of the major advances in vesicle research was the finding a vesicle derivative, known as an ethosomes [4,6].

Ethosomal carriers are systems containing soft vesicles and are composed mainly of phospholipid (Phosphotidyl choline; PC), ethanol at relatively high concentration and water. It was found that ethosomes penetrate the skin and allow enhanced delivery of various compound to the deep strata of the skin or to the systemic circulation.

Mechanism of penetration

Although the exact process of drug delivery by ethosomes remains a matter of speculation, most likely, a combination of processes contributes to the enhancing effect. The stratum corneum lipid multilayer at physiological temperature are densely packed and highly conformationally ordered. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization; therefore, when integrated into a vesicle membrane, it

gives that vesicles have the ability to penetrate the stratum corneum. Also because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure, giving it more freedom and ability to squeeze through small places such as the openings created in disturbing the stratum corneum lipid [7].

Ethanol interacts with lipid molecules in the polar hard group region, resulting in a reducing the rigidity of the stratum corneum lipids, increasing their fluidity. The intercalation of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effect of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier [4].

The interdigitated, malleable ethosome vesicle can forge paths in the disordered stratum corneum. In the case of ethosomes encapsulating drugs, the higher positive zeta potential imparted by the drug can improve skin attachment of the vesicles. While encapsulated drug in classic liposomes remained primarily at the surface of the skin the ethosomal system was showed to be highly efficient carrier for enhanced drug delivery through the skin. The efficient drug delivery shown together with the long-term stability of ethosomes make this system a promising candidate for transdermal delivery of drug.

Preparation

Formulation and preparation of ethosomes is reported by Touitou4 et al., according to which ethosomal system can be prepared from soyabean phosphatidyl choline 2 – 5 % (Phospholipon 90), 20 – 50 % w/w ethanol, drug and water to 100% w/w. For preparation of ethosomes phospholipon 90 and drug were dissolved in ethanol. Double distilled water was added slowly as a fine stream with constant mixing at 700 rpm in a well sealed container. Mixing was continued for additional 5 minutes. The system was kept at 30 °C throughout the preparation and then stored in cool place.

FACTOR AFFECTING CHARACTERS OF ETHOSOMES

Ethosomes consist of ethanol (10 – 50 %), phosphotidyl choline (0.5 – 4 %) and drug. Concentration of ethanol and phospholipid are the factors which affect the characters of ethosome e.g. vesicular size, entrapment efficiency and dermal delivery. Their effects are as follows

Ethanol

The effect of ethanol concentration on size distribution of ethosomal vesicles can be investigated using dynamic light scattering (DLS). In the ethanol concentration range of 10 - 50%, the size of the vesicles decreases with increasing the ethanol concentration. The largest vesicles are found in the preparations containing 10% ethanol and the smallest in the preparation containing 50% ethanol8. The data indicates entrapment efficiency also depends on the ethanol concentration. Increasing the ethanol from 10% to 30% w/w, increases the entrapment efficiency and with further increase in the ethanol concentration (>30% w/w) the vesicle membrane become more permeable that leads to decrease in the entrapment efficiency of ethosomal formulation [7]. The value of transdermal flux also depends upon ethanol concentration. As the concentration of ethanol increases, transdermal flux of entrapped drug increases upto 30% w/w and further increase in the ethanol concentration significantly decreases the transdermal flux. The reason for this is the deteriorating effect of ethanol on lipid bilayers at higher concentration of ethanol [7].

Ethosomes effect

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. So the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.

Advantages of ethosomes

- Enhanced permeation of drug molecules to and through the skin to the systemic circulation.
- Contrary to deformation liposomes, ethosomes improve skin delivery of drugs both under occlusive and non-occlusive conditions.
- Since composition and components of ethosomes are safe, they have various applications in pharmaceutical, veterinary and cosmetic field.
- Better patient compliance.
- Better stability and solubility of many drugs as compared to conventional vesicles.
- Relatively smaller size as compared to conventional vesicles.

Limitations of ethosomes

- Poor yield
- In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
- Loss of product during transfer from organic to water media.

MATERIALS AND METHODS

Standard calibration curve

Preparation of Itraconazole Ethosomes (By Cold Method)

Preparation of Itraconazole ethosomes was followed by method suggested by Touitou et al. with little modification [7].

The ethosomal system of Itraconazole comprised of 2-5 % phospholipids, 20-50 % ethanol, 10 % of propylene glycol, 0.005g of cholesterol and aqueous phase to 100 % w/w. Itraconazole 0.20 g was dissolved in ethanol in a covered vessel at room temperature by vigorous stirring. Propylene glycol was added during stirring. This mixture was heated to 30^0 in a separate vessel and was added to the mixture drop wise in the center of the vessel, which was stirred for 5min at 700rpm in a covered vessel the vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion

method. Finally, the formulation is stored under refrigeration. Ethosomes were formed spontaneously by the process.

Preparation of Itraconazole Ethosomal Gel

The best achieved ethosomal vesicles suspension, was incorporated into carbopol gel (1%, 1.5%, 2% w/w).the specified amount of carbopol 934 powder was slowly added to ultrapure water and kept at 100^0c for 20min. triethanolamine was added to it dropwise.Appropriate amount of formula EF-2 containing Itraconazole (1.5% w/w was then incorporated into gel-base. Water q.s was added with other formulation ingredients with continuous stirring until homogenous formulation were achieved (G-1,G-2 and G-3).Gel containing free Itraconazole was prepared by similar method using 1.5% carbopol.

CHARACTERIZATION OF ETHOSOMES

Entrapment Efficiency

The entrapment efficiency of Itraconazole by ethosomal vesicle was determined by ultracentrifugation 10 ml of (ethosomal suspension) each sample was vortexed for 2 cycles of 5 min with 2 minutes rest between the cycles. 1.5ml of each vortexed sample and fresh untreated ethosomal formulations were taken into different centrifugal tubes. These samples were centrifuged at 20,000 rpm for 3 hours. The supernatant layer was separated, diluted with water suitably and drug concentration was determined at 265 nm in both vortexed and unvortexed samples. The entrapment efficiency was calculated as follows

$$\text{Entrapment Efficiency} = \frac{T - C}{T} X\ 100$$

'T' is total amount of drug that detected from supernatant of vortexed

'C' is the amount of drug unentraped and detected from supernatant of unvortexed

RESULTS AND DISCUSSION

Preformulation Studies

Description

These tests were performed as per the procedure and the results were illustrated in the following table:

Result: The results were found as per specifications**.**

Solubility

These tests were performed as per procedure and the results are illustrated in the following table.

Melting Point

This test is performed as per procedure and the result was illustrated in the following table.

FTIR Studies

IR spectra was compared and checked for any shifting in functional peaks and non-involvement of functional group. From the spectra it is clear that there is no interaction between the selected carriers, drug and mixtures. Hence the selected carrier was found to be compatible in entrapping the selected Itraconazole with carriers without any mutual interactions.

Preparation of Itraconazole Ethosomes

Ethosomal formulations composed of phospholipid, drug and ethanol were prepared using the method detailed in last chapter materials and methods and also according to literature with little modification. Ethosomal suspension obtained with sonication were slight yellowish in colour and hazy in appearance. Different characteristics of ethosomes and the effect of sonication were further evaluated and results are reported under the characterization.

Characterization of Ethosomes

Since the physical characterization is meant for physical integrity of the dosage form, the result were pooled at one place. Discussion on the results, described for ethosomes formulation under the same heading.

Size and Shape Analysis

Microscopic analysis was performed under different magnification to visualize the vesicular structure, lamellarity and to determine the size of ethosomal preparations.

Entrapment Efficiency

Once the presence of bilayer vesicles was confirmed in the ethosomal system, the ability of vesicles for entrapment of drug was investigated by ultra-centrifugation. Ultra-centrifugation was the method used to separate the ethosomal vesicles containing drug and un-entrapped or free drug, to find out the entrapment efficiency.

The maximum entrapment efficiency of ethosomal vesicles as determined by ultracentrifugation was 87.8% for ethosomal formulation containing 30% ethanol (IF8).As the ethanol concentration increased from 20% to 50% w/w, there was increase in the entrapment efficiency and with further increase in the ethanol concentration (>40% w/w) the vesicle membrane becomes more permeable that lead to decrease in the entrapment efficiency. Results of entrapment efficiency also suggest that 3% phospholipid is optimal concentration for entrapment efficiency and hence increased or decreased in concentration of phospholipid reduces the entrapment efficiency of vesicles. These result further supported by observation made by Jain NK *et al*., [14]

Entrapment efficiency of ethosomal formulations are significantly different and are reported in Table. Increase in entrapment efficiency may be due to the possible reduction in vesicle size. The detrimental effect on the vesicle during ultra-centrifugation which are larger in size. Sonication gives the more uniform lamellae, smaller vesicle and uniform size and hence it may be the reason for higher vesicular stability and lesser vesicular disruption during ultra centrifugation.

EVALUATION OF ETHOSOMAL GEL

Stability studies

The stability studies were carried out according to the procedure described in the section of chapter . The results are shown in the table.

Figure 1. Calibration curve of Itraconazole graph

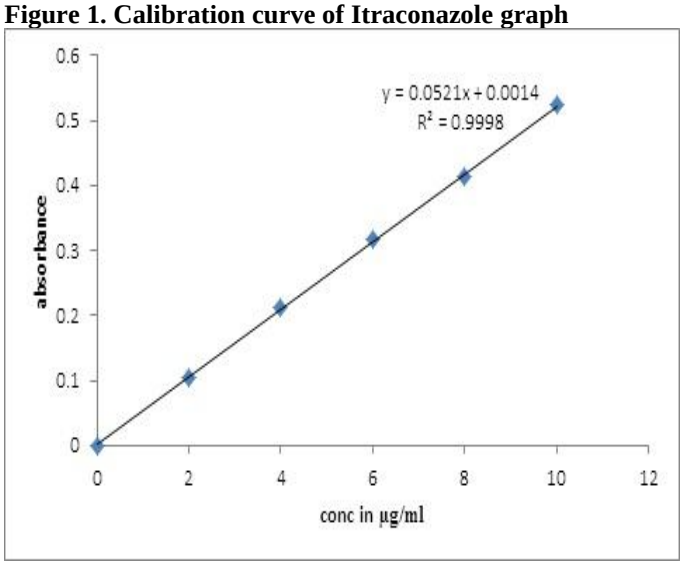

Figure 2. FTIR Spectra of Itraconazole pure drug

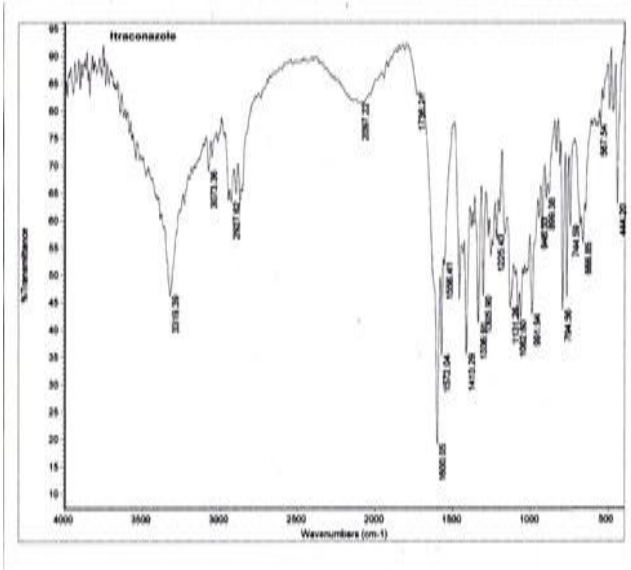

Figure 3. FTIR Spectra of Itraconazole Final formulation

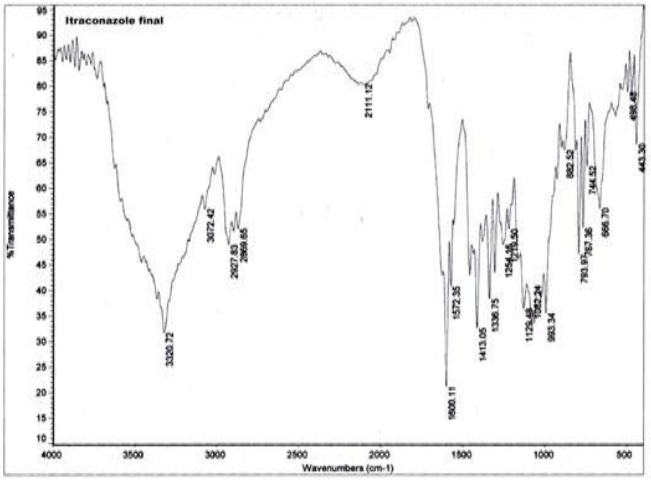

Figure 4. Scanning Electron Microscope (SEM)

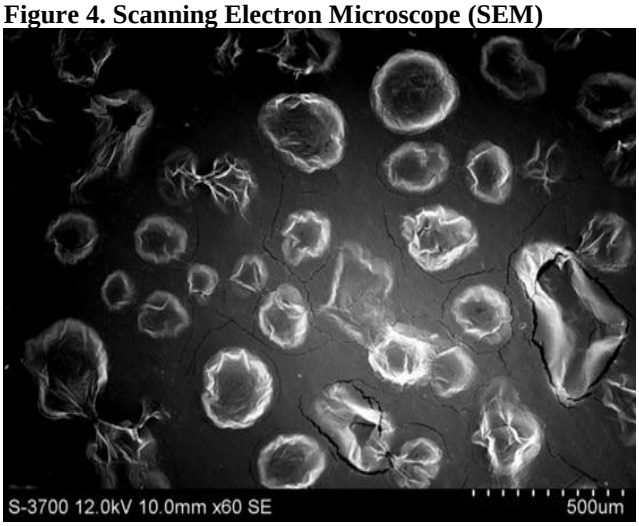

Figure 5. pH measurements

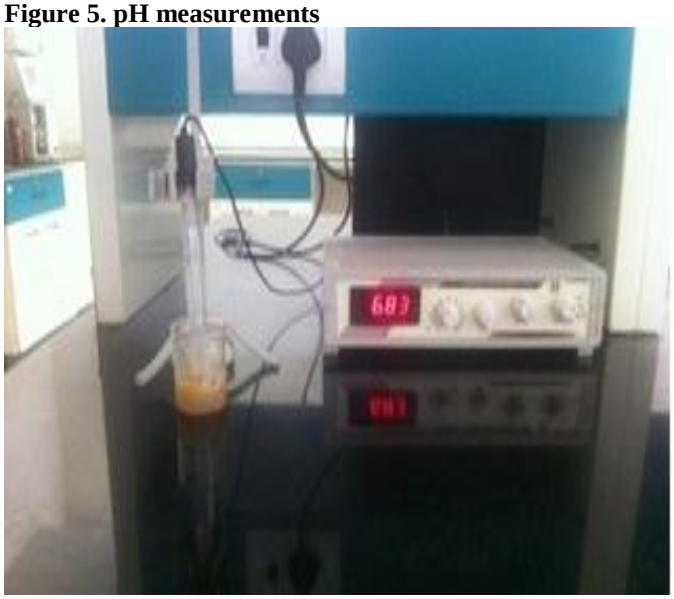

Figure 6. Graph showing dissolution profile for formulations IF1-IF Cumulative drug release of in-vitro studies

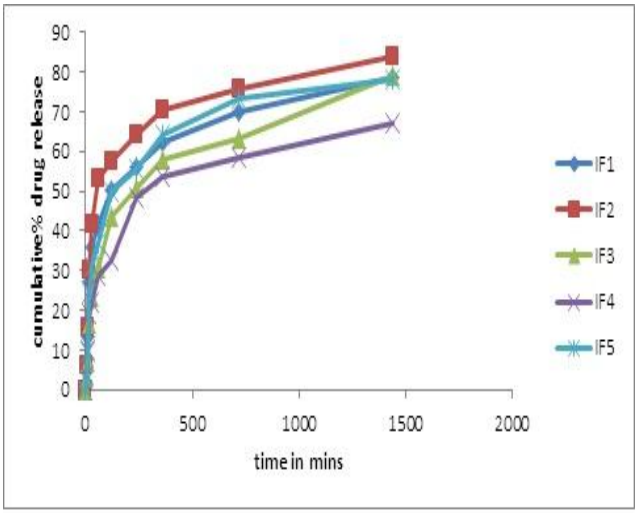

Figure 7. In-vitro release study for IF6-IF10

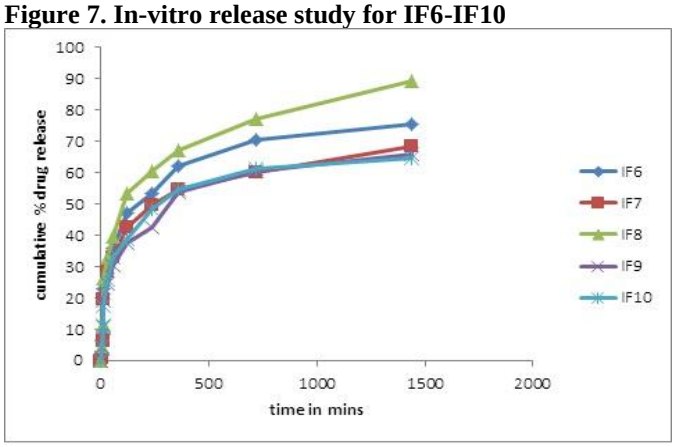

Figure 8. Zero Order Kinetics For IF8 Ethosomal gel

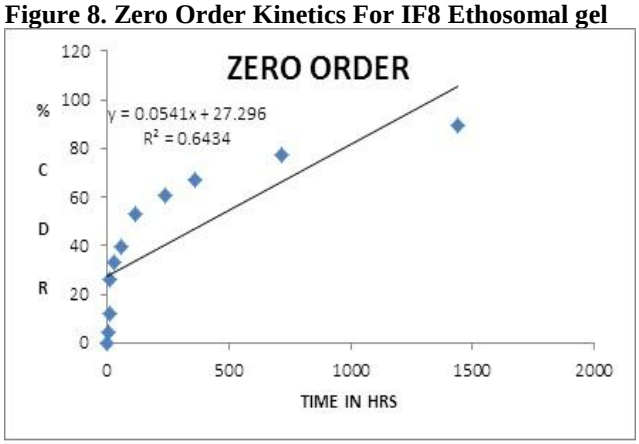

Figure 9. First Order Kinetics for IF8 Ethosomal gel

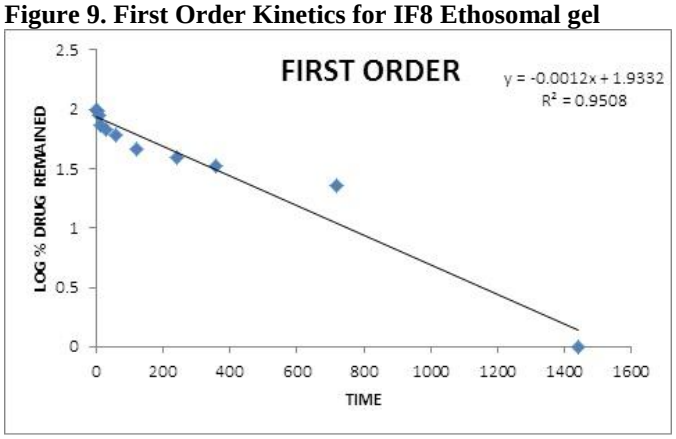

Figure 10. Higuchis model For IF8 Ethosomal gel

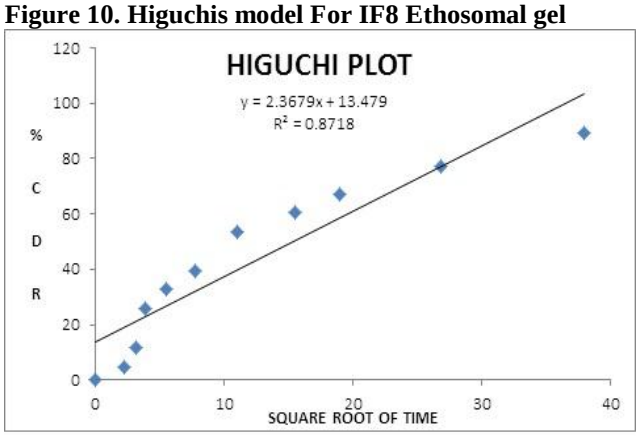

Figure 11. Peppas model For IF8 Ethosomal gel

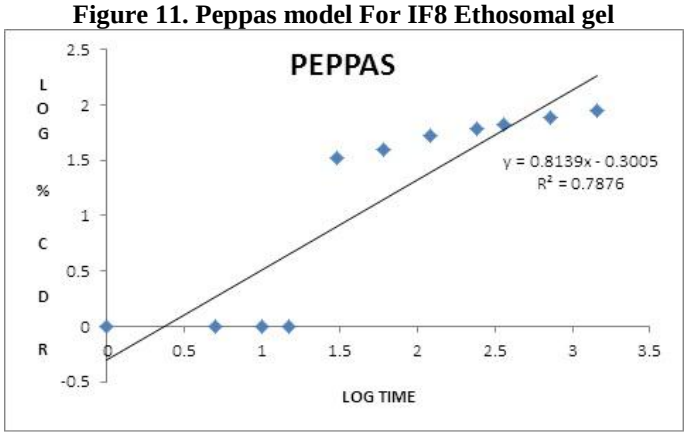

Table 1. Different Additives Employed in Formulation of Ethosomes

Class	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane As a penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorescene Isothiocynate (FITC) 6- Carboxy fluorescence	For characterization study

Table 2. Concentration and absorbances

S.NO	Concentration	Absorbances
1	0	0
2	2	0.105
3	4	0.212
4	6	0.318
5	8	0.414
6	10	0.523

Table 3.Composition of different ethosomal formulations

Ethosomal formulation	Lecithin (Soya lecithin %)	Ethanol (%)	Propylene glycol (%)	Drug (g)	Cholesterol(g)	Water
IF_1	2	20	10	0.20	0.005	q.s
IF_2	3	20	10	0.20	0.005	q.s
IF_3	4	20	10	0.20	0.005	q.s
IF_4	5	20	10	0.20	0.005	q.s
IF_5	2	30	10	0.20	0.005	q.s
IF_6	2	40	10	0.20	0.005	q.s
IF_7	2	50	10	0.20	0.005	q.s
IF8	3	30	10	0.20	0.005	q.s
IF9	3	40	10	0.20	0.005	q.s
IF10	3	50	10	0.20	0.005	q.s

Table 4.Composition of different ethosomal gel formulation

Gel formulation	Itraconazole ethosomal suspension(ml)	Carbopol (%)	Triethanolamine (ml)	Phosphate buffer (pH 6.8)
G-1	20	1	0.5	q.s
G-2	20	1.5	0.5	q.s
G-3	20	2	0.5	q.s

Table 5. Table showing the description of Itraconazole (API)

Test	Description
Colour	A white to slight yellowish powder

Table 6. Solubility of Itraconazole (API) in various solvents.

Solvents	Solubility
Water	Insoluble
pH6.8Phosphate buffer	Soluble
DMSO	Freely soluble
Ethanol	Freely soluble

Table 7. Showing the melting point of API's

Material	Melting Point	Melting Point Range
Itraconazole	167^0c	166-170^0c

Result: The Result was found to be within limit.

Table 8. Characteristic peaks in FTIR Spectrum of Itraconazole

Wave numbers in cm^{-1}	Functional Groups	Pure Drug Itraconazole
1000-650	=C-H Bend	991.94
1500-1400	C-C Stretch	1413.29
1660-1500	NO_2 Asymmetrical Stretch	1600.05
3000-2850	C-H Stretch	2927.62
3400-3250	N-H Stretch	3319.39

Table 9. Drug entrapment efficiency of Itraconazole Ethosomal Gel

Formulation code	Entrapment efficiency (%)
IF1	81.2
IF2	85.6
IF3	77.5

IF4	75.2
IF5	85.1
IF6	72.5
IF7	70.6
IF8	87.8
IF9	71.5
IF10	70.3

Table 10. Organoleptic characteristics of ethosomal gel

Organoleptic Characteristics:	Color: golden yellow Greasiness: Non greasy Grittiness: Free from grittiness Ease of application: Easily/smoothly applied Skin irritation: No skin irritation
Washability:	Easily washable without leaving any residue on the surface of the skin.

Table 11. pH measurements of Ethosomal gel

Formulation code	pH
IF1	6.6
IF2	6.5
IF3	6.6
IF4	6.8
IF5	6.8
IF6	6.6
IF7	6.7
IF8	6.8
IF9	6.5
IF10	6.7

Table 12. Drug content

Formulation code	Drug content (%)
IF1	98.6
IF2	99.3
IF3	98.6
IF4	98.3
IF5	95.3
IF6	95.6
IF7	99.7
IF8	99.3
IF9	98.9
IF10	95.4

Table 13. *In-vitro* cumulative % drug release profile for Itraconazole Ethosomes

Time (min)	IF1	IF2	IF3	IF4	IF5
5	5.42	6.26	3.25	3.6	2.31
10	13.5	15.95	7.2	10.08	9.42
15	27.15	30	16.94	19.2	24.4
30	35.68	41.68	23.42	22.04	31.24
60	41.68	53.3	30.6	28.7	37.02
120	50.5	57.7	43.5	32.4	49.7
240	56.22	64.4	50.68	48.6	55.5
360	62.5	70.6	57.9	53.7	64.4
720	70.2	75.6	63.4	58.5	73.3
1440	78.4	83.7	79.2	67.11	78.2

Table 14. *In-vitro* release study for IF6-IF10

Time (min)	IF6	IF7	IF8	IF9	IF10
5	1.46	0.75	4.57	4.20	4.59
10	8.4	6.26	11.8	10.6	11.3
15	22.97	19.68	26.04	19.3	17.3
30	30.01	28.48	33.02	24.7	25.7
60	35.68	33.02	39.6	30.5	32.9
120	47.1	42.6	53.3	37.49	38.6
240	53.5	49.7	60.44	42.36	48.2
360	62.22	54.77	67.1	53.83	54.8
720	70.6	60.1	77.3	60.39	61.36
1440	75.5	68.44	89.3	65.75	64.7

Table 15. Release kinetics for optimized formulation

Release kinetics	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	0.054071196	-0.00124158	2.367889828	0.813927961
Intercept	27.29603757	1.933243954	13.47850215	-0.30054412
Correlation	0.802092707	-0.97509645	0.94532271	0.887456923
R 2	0.643352711	0.950813088	0.893635026	0.787579791

Table 16. Table % Entrapment efficiency and % Drug content after stability studies

Number of Days	% Entrapment Efficiency at temperatures			% Drug Content at temperatures		
	4±2°C	25±2°C	37±2°C	4±2°C	25±2°C	37±2°C
15	87.7	87.63	87.59	99.3	99.19	99.81
30	87.6	86.82	86.76	98.16	98.94	98.77
45	87.27	86.67	86.56	97.23	98.48	98.58
90	86.93	86.40	85.84	97.45	98.39	98.06

DISCUSSION

Transdermal route offers several potential advantages over conventional routes. These advantages includes avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in the blood levels, and most important. It provides patient convenience. But one of the major problems for efficient drug delivery is low penetration rate.

While optimizing the topical drug delivery, vesicular system (liposomes and niosomes) appears as upcoming development. Recently advancement in liposomes was done and result obtained "Ehosomal system" which showed topical delivery with higher transdermal flux and higher skin deposition as it is attractive and has desirable advantages. Itraconazole ethosomes were prepared using the method reported by Touitouetal, (2000) with little modification. Studies were performed on ethosomes containing 20%, 30%, 40% and 50%w/w ethanol with sonication.

After confirm existence of vesicles and their size, drug entrapped by vesicular system was evaluated by ultra-centrifugation. sonicated ethosomes containing 30% w/w ethanol showed higher value i.e. 87.3%. In-vitro release was carried out using dialysis membrane. The values of drug release IF1 (20% alcohol) 78.4%, IF2 (20%) 83.7%, IF3 (20% alcohol) 79.2, IF4 (20% alcohol) 67.11%, IF5 (30%) 78.2%, IF6 (40% alcohol) 75.5%, IF7(50% alcohol) 68.44%,IF8(30% alcohol) 89.3%,IF9 (40% alcohol) 65.75 and IF10 (50% alcohol) 64.7%.The order of drug release for optimized gel formulation was found to be First order. Percentage drug accumulation into skin was also found to be maximum by the ethosomes containing 30 % w/w ethanol. This showed effective subdermal deposition and indicates better subdermal action for fungal infections. With these findings it can be summarized that Itraconazole ethosomes are promising system in topical drug delivery for treatment of fungal disorders.

CONCLUSION

It is well known that if drug molecules presenting any difficulties in its solubility and bioavailability along the GI tract are candidates for other routes of administration and if the site of action for drug candidate is subdermal, effective penetration enhancers are required to provide the drug molecule deeper into skin tissue for optimized therapeutic delivery of drug. It is generally agreed that classic liposomes are of little or no value as carriers for transdermal drug delivery because they do not penetrate the skin.

Recently derived ethosomal system can deliver drug molecules into and through the skin. An attempt was made to formulate the highly efficient ethosomal drug delivery system using Itraconazole as model drug.

.The method described by Touitou et al., (2000) was employed with little modification for the preparation of various ethosomal formulations containing different concentration of ethanol (20 % to 50 %) with sonication. The techniques used were simple and reproducible. The prepared ethosomes were spherical and discrete in shape.

However ethosomes prepared by sonication method were more uniform and small in size which is essential for skin penetration. While comparing the entrapment efficiency, ethosomes containing 30% w/w ethanol and prepared by sonication showed highest value respect to all other formulation; so it is concluded ethosomal prepared by sonication and containing 30 % w/w ethanol as the best formulation considering all other aspects. The highest value of transdermal flux for sonicated ethosomes containing 30% w/w ethanol is the indication of complete and rapid penetration through the skin may be because of tiny vesicular size. This is an encouraging observation for drugs which are poorly absorbed from skin

When effect of sonication was compared on ethosomal formulation, sonicated formulation possessed better or suitable characteristics (smaller size, uniform size, distribution, highest entrapment efficiency).

From the above observations it can be concluded sonication is an essential tool for the preparation of ethosomes.

Thus, the specific objectives listed in the introduction chapter of this thesis were achieved namely design, characterization and release studies of Itraconazole ethosomes. Certainly these finding can be applied for transdermal drug delivery of Itraconazole for treatment of fungal disorders. Further these findings may help the industry for development and scaling up a new formulation.

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