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Development and Evaluation of Ethosomal Cream of Luliconazole

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Abstract

Luliconazole is used for the treatment of local and systemic fungal infection. But one of the major problems for efficient drug delivery is low penetration rate of luliconazole due to its high solubility and low permeability. Further, the physicochemical modification in the drug by means of phospholipid membrane also promises to prolong the drug action. A number of problems associated with drug molecule such as bioavailability, degradation, stability and side effects can be overcome by incorporating it into ethosomes. In the present work, ethosomal formulation to enhance transdermal permeation of luliconazole was prepared and evaluated using different concentration and optimized formulation was evaluated. Colloidal suspensions of ethosomes were prepared by cold method. Ethosomal system was found to be easy to prepare and composed mainly of phospholipids and ethanol, compounds commonly found in pharmaceutical preparations. The present investigation was to design the ethosomal cream containing luliconazole using different concentration of ethanol and phospholipid. The smooth surface of vesicles and surface was confirmed by the images of ethosomes. The SEM and TEM mage was given in respectively. The entrapment efficiency of ethosome was determined.

Keywords: Luliconazole, Ethosome, Evaluation

Introduction

In the early 1980s, Mezei and his group described liposomes as the first topical lipid vesicular system for enhanced drug delivery to the skin. Since then, many works have shown that lipid vesicular systems are able to increase the accumulation of various molecules in the SC or other upper skin layers[1-5]. Drug delivery from such vesicles results in the formation of a drug reservoir in the horny layer of the skin and is generally characterized by a lack of penetration into the deeper layers of the skin. This behavior is useful both for local treatment of skin disorders[6]. Specific drug accumulation at the site of action and decreased systemic drug absorption can impart increased efficiency as well as decreased side effects for a compound applied topically.

It is an antifungal drug having imidazole. The drug has an azole antifungal indicated for the topical treatment of inter digital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older. Luliconazole is (2E)-2-[(4R)-4-(2,4-dichlorophenyl)- 1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetonitrile. The molecular formula is C14H9Cl2N3S2 with a molecular weight of 354.28. Luliconazole is the R enantiomer and contains one chiral center. The double bond adjacent to the dithiolane group is in the E configuration.[7-8]

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Ethosomes are capable of encapsulate high concentration of drug and delivers sufficient quantity of drug in small amount of dosage form. Ethosomal delivery of Luliconazole may show greater penetration rate due to smaller average particle size than other vesicular systems. The main objective of the present study is to formulate and evaluate ethosome containing Luliconazole for sustain drug delivery and to enhance the quick permeation of drug across skin.

Materials and Methods

Material

Luliconazole (LZ) was obtained as a gift sample from Alkem Pvt. Ltd., India. Soya lecithin was obtained as a gift sample from Hi Media laboratories Pvt. Ltd. Mumbai, India. Ethanol was purchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Preformulation studies of drug sample

Preformulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms. Following preformulation studies were performed.[8]

Organoleptic properties

The organoleptic studies like general appearance like nature, color, odor, etc. were performed by visual observations and compared with standard of drug given in pharmacopoeia for identification of drug.

Color: Small quantity of drug was taken on butter paper and viewed in well illuminated place.

Odor: Very less quantity of drug was smelled to get the odor.

Solubility studies

Semi quantitative determination of the solubility was made by adding solvent to glass tube containing accurately weighed amount of solute. The system is vigorously shaken and examined visually for any undissolved solute particles. The solubility is expressed in terms of ratio of solute and solvent. The solubility study of Luliconazole was performed in methanol, ethanol, acetone, hexane, ether, chloroform, propylene glycol, distilled water, 0.1 N HCL, phosphate buffer solution pH 5.5, 6.8, 7.4, separately by keeping the drug containing test tube on vortex mixture.

Determination of melting point

For determination of melting point USP method was followed. Small quantity of drug was placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature in the apparatus was gradually increased and the observation of temperature was noted at which drug started to melt and the temperature when the entire drug gets melted was noted.

Determination of partition co-efficient[9]

The known quantity of Luliconazole was added into 20 ml of octanol and it was mixed with 20 ml of phosphate buffer pH 7.4 in a separating funnel. Then two phases were allowed to equilibrate at 37 0 C for 2 hours with intermittent shaking. The concentration of drug in the aqueous phase and organic phase was determined by UV spectroscopic method at λmax 260 nm after necessary dilution. The apparent partition coefficient was calculated as the ratio of drug concentration in each phase by the following equation -

$$K\ p = C\ organic$$

C aqueous

C organic is concentration of drug in organic phase

C aqueous is concentration of drug in aqueous phase

Determination of drug pH

The pH of Luliconazole was determined using digital pH meter for freshly prepared 1% solution of Luliconazole in methanol.

Formulation of ethosomes of Luliconazole

Ethosomal formulations were prepared by using the cold method. The ethanolic vascular system was composed of phospholipid (2.0% to 4%W/V), ethanol (20% to 40% V/V), propylene glycol (20 % V/V), drug (Luliconazole, 0.5% W/V) and distilled water to 100% (V/V). Phospholipid was dissolved along with the drug in ethanol. This mixture was heated to 400 C ± 10 C and a fine stream of distilled water was added slowly, with constant mixing at 700 rpm with a mechanical stirrer in a closed container. Mixing was continued for an additional 5 minutes, while maintaining the system at 400 C ± 10 C. The preparation was left to cool at room temperature

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for 30 min and then it was sonicated at 40 C for five cycles of 3 minutes each with a minute rest between cycles using a probe sonicator. Nine formulations were prepared using different concentration of phospholipid and ethanol among them optimized formulation was selected for characterization and evaluation studies.[10-11]

Table 1: Compositions of different ethosomal formulation of Luliconazole

Formulation Code	Conc. Of Phospholipid (w/v)	Conc. of Ethanol (v/v)	Conc. Of Propylene Glycol (v/v)	Conc. Of drug (w/v)	Conc. Of distill water (v/v)
F1	2%	20%	20%	0.5%	Up to 100%
F2	3%	30%	20%	0.5%	Up to 100%
F3	4%	40%	20%	0.5%	Up to 100%
F4	2%	30%	20%	0.5%	Up to 100%
F5	3%	40%	20%	0.5%	Up to 100%
F6	4%	20%	20%	0.5%	Up to 100%
F7	2%	40%	20%	0.5%	Up to 100%
F8	3%	20%	20%	0.5%	Up to 100%
F9	4%	30%	20%	0.5%	Up to 100%

Preparation of the Cream

Carbopol934 forms very good consistency transparent cream at low concentration. 1% carbopol cream base was prepared by dispersing 1 g carbopol934 in 90 ml hot distilled water in which 10 ml glycerol was previously added. Accurately weighed quantity of methyl paraben and propyl paraben was also added into it. The mixture was stirred until thickening occurred and then neutralized by the drop wise addition of 50% (w/w) triethanolamine to achieve a transparent cream.[12-13]

Table 2: Composition of the cream base

Ingredients	Conc.
Carbopol 934	1%
Glycerol	5%
Methyl paraben	0.02%
Propyl paraben	0.01%
Distilled Water (qs)	100 %

Incorporation of ethosomes in the cream base

The ethosomal formulation was slowly added in carbopol 934 cream base with gentle stirring. Finally, the ethosomal cream was mixed using a mechanical stirrer for 5 min. [14-15]

Evaluation of ethosomes[16-20]

Drug entrapment efficiency

The total volume of the ethosomal suspension was measured. 5ml of this formulation was diluted with distilled water up to 8 ml and centrifuged at 15,000 rpm for 45 min at 40Cusing a cooling centrifuge. After centrifugation, the supernatant and sediment were recovered, their volume was measured.Then sediment was lysed using n-propanol and filtered through a 0.45 µm nylon disk filter.The concentration of Luliconazole in the supernatant and sediment was analyzed by UV- spectroscopic methodat 260 nm.The percent drug entrapment was calculated using the following equation:

$$\% \text{ Entrapment efficiency} = \frac{\text{Amount of entrapped drug recovered}}{\text{Total amount of drug}} \times 100$$

Vesicular shape and surface morphology

Ethosome vesicles were visualized using transmission electron microscopy (TEM Philips Technai electron microscope). A drop of ethosomal solution was dried on a microscopic carbon coated grid, to get adsorbed and the surplus was removed by filter paper. A drop of 1% aqueous solution of phosphotungstic acid (PTA) was then added and left in contact with the sample for 5 minutes. The excess solution was removed and the sample was dried at room

condition before the vesicles were viewed under TEM operating at an acceleration voltage of 200 KV.

Physical evaluation of ethosomal cream

The ethosomal cream formulation of Luliconazole was evaluated for organoleptic characteristics, occlusiveness and washability.

Measurement of pH of the ethosomal cream

1 g Luliconazole ethosomal cream was mixed in 100 ml distilled water with homogenizer. Then the electrode was immersed in the prepared cream solution and readingswere recorded from digital pH meter in triplicate and average value was calculated.

Viscosity study

Viscosity measurements were done on Brookfield viscometer by selecting suitable spindle number and rpm. 50 g of preparation was kept in 50 ml beaker which was set till spindle groove was dipped and rpm was set and dial reading was measured after three minutes. From the reading obtained, viscosity was calculated by using factor. The procedure was repeated three times and observations are recorded as mean.

Spreadability

It is the term expressed to denote the extent of area to which cream readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from creamand placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability.

It is calculated by using the formula:

$$S = M. L / T$$

WhereM = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

0.1 g of ethosomal cream was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The standardized weight tied on the upper slide was 125gm. The results obtained are average of three determinations.

Extrudability study

The extrudability of ethosomal cream was determined by filling ethosomal cream in the collapsible tubes. The extrudability of the ethosomal cream was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of cream in 10 second.

Percentage yield

The empty container was weighed in which the ethosomal cream formulation was stored then again the container was weighed with ethosomal cream formulation. Then subtracted the empty container weighed with the container with cream formulation then it gives the practical yield. Then the percentage yield was calculated by the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Homogeneity and grittiness

A small quantity of ethosomal cream was pressed between the thumb and the index finger. The consistency of theethosomal cream was noticed (whether homogeneous or not), if there was any coarse particles appeared on fingers. Also, the homogeneity could be detected when a small quantity of theethosomal cream was rubbed on the skin of the back of the hand. The grittiness of prepared ethosomal cream was also observed in the same manner.

***In vitro* release studies**

The dissolution studies were performed by using dissolution rate test apparatus (USP-II) for the assessment of the release of the drug from the ethosomal cream. The apparatus was equilibrated to 32 ± 0.50C and the dissolution medium was 0.01 N HCl in PBS pH 7.4. The paddle speed was kept constant at 50 rpm. The samples were withdrawn at appropriate time intervals upto 24 h and analyzed by UV spectrophotometer at 282 nm. After each sampling, an equal volume of fresh dissolution fluid was added to the dissolution vessel to maintain a sink condition.

Stability study

The stability study was carried out for ethosomal cream formulation. The most satisfactory formulation was sealed in a glass vial to a temperature of 40° C for 1 month, then at 25°C for1 month, then at 40°C for 1 month. After this ethosomal cream was exposed to ambient room

temperature and liquid exudates separating was noted. At the end of 3 months, the samples were analyzed for physical characteristic study and the drug content.

Results and Discussion

Preformulation studies

The following properties of drug were evaluated and results are obtained as:

Table 3: Organoleptic properties of luliconazole

Drug	Test	Specification	Observation
Luliconazole	Colour	White crystalline powder	White powder
	Odour	Odourless	Odourless

The observations noted were compared to the specifications given in the pharmacopoeia to confirm the identity of the drug and it was found that observations noted complied with the specifications.

Solubility studies

Solubility studies are performed to determine the solubility of drug in different solvents. The solubility is expressed in terms of ratio of solute and solvent. Luliconazole was found to be soluble in methanol, acetone, 0.1 N HCL, ethanol, distilled water, hexane, PBS of pH 5.5, 6.8, 7.4, chloroform, ether and propylene glycol.

Melting point

Melting point of luliconazole was found to be 152-154^{0}C.

Partition co-efficient

Partition co-efficient was measured three times and mean was noted. Hence partition coefficient was found to be 1.23± 0.32.

Determination of pH

The pH was measured three times and mean was noted. Hence pH of luliconazole was found to be 6.9.

Table 4: Solubility Profile of luliconazole

S/No.	Quantity of drug	Solvent	Quantity of solvent	Inference
1.	50 mg	Methanol	5 ml	Soluble
2.	50 mg	Acetone	5 ml	Soluble
3.	50 mg	0.1 N HCl	5 ml	Freely soluble
4.	50 mg	Ethanol	5 ml	Sparingly soluble
5.	50 mg	Distilled water	5 ml	Slightly soluble
6.	50 mg	Hexane	5 ml	Slightly soluble
7.	50 mg	PBS pH 5.5	5 ml	Slightly soluble
8.	50 mg	PBS pH 6.8	5 ml	Slightly soluble
9.	50 mg	PBS pH 7.4	5 ml	Slightly soluble
10.	50 mg	Chloroform	5 ml	Sparingly soluble
11.	50 mg	Ether	5 ml	Sparingly soluble
12.	50 mg	Propylene glycol	5 ml	Sparingly soluble

Drug entrapment efficiency

Entrapment efficiency of all the formulation was determined. Drug entrapment efficiency of formulation F8 was found to be maximum (89.64%) and minimum of F3 minimum(42.29%) . The results were mentioned in table.

Table 5: Entrapment efficiency of ethosomes

Formulation Code	Entrapment efficiency (%)
F1	67.29
F2	52.94
F3	42.49
F4	74.18
F5	79.17

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F6	82.64
F7	89.64
F8	78.29
F9	72.48

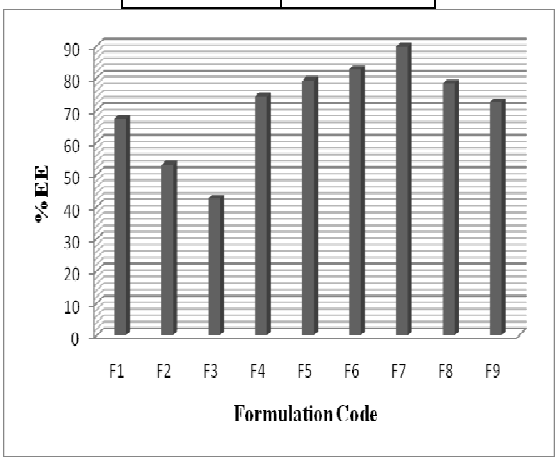

Fig. 1: Entrapment efficiency of ethosomes

Evaluation of ethosomal cream

The ethosomal cream formulation of luliconazole was evaluated for organoleptic characteristics. The pH of cream base and freshly prepared ethosomal cream noted down The pH of cream base was found to be 7.2 & pH of ethosomes cream of different formulation was presented in table. The viscosity of carbopol 934 cream base was found to be 740,00 cps whereas viscosity of ethosomal cream was given in table. The spreadability of ethosomal cream was also recored. The spreadability results showed that ethosomal cream was most effective i.e. it showed best result for spreadability. The extrudability of ethosomal cream was found to be positive except in F2 & F3. The % yield of ethosomal cream was found in between 94.71 to 98.43 %. Ethosomal cream was found to be homogeneous and no grittiness was noted. The results are given in table 6.

***In vitro* release study**

In vitro release study was performed to determine amount of drug released at different interval of time.

SEM and TEM of Ethosomes (F7)

The entrapment efficiency of Formulation F7 was found to be maximum, therefore, the same has been subjected for SEM and TEM.

Stability Study

Stability studies of ethosomal cream, formulation code F7 was performed at 40°C±1°C, 25ºC±1ºC for 3 months showed good storage stability. It was observed that optimized cream kept for 3 months under 40ºC ± 1ºC as well as 25ºC ± 1ºC temperature conditions showed no change in their physical appearance. No phase seperation was observed in the optimized ethosomal cream. Optimized ethosomal cream kept for 3 months under 40ºC±1ºC as well as 25ºC±1ºCtemperature conditions were studied for uniformity of content. The results showed no significant changes in content uniformity at 40ºC±1ºC after 2 months. At 40ºC±1ºC content uniformity was found to show approximately (98.43to 96.39%) decrease and at 25ºC±1ºC content uniformity decreased from (98.43% to 89.97%).

Table 6: Evaluation Parameters of Ethosomal cream of Luliconazole

Parameters	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Color	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Odor	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic
Appearance	Translucent	Translucent	Translucent	Translucent	Translucent	Translucent	Translucent	Translucent	Translucent
Phase separation	Yes	No	Yes	No	No	No	No	No	No

Occlusiveness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Washability	Washable	Washable	Washable	Washable	Washable	Washable	Washable	Washable	Washable
pH	7.2	7.4	6.9	7.0	7.2	7.7	7.9	8.2	7.8
Viscosity (cps)	71200	72300	69400	70500	71200	71300	73500	70800	71600
Spreadability ($g/cm^{2)}$	11.40	12.01	12.82	13.14	14.83	14.29	13.84	10.82	11.11
Extrudability	+	-	-	+	+	+	+	+	+
Percentage yield	96.29	95.62	96.71	95.86	96.60	97.27	98.43	94.71	97.18
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
Grittiness	No	No	No	No	No	No	No	No	No

Table 7: *In vitro* drug release of ethosomal cream of luliconazole

Time (mts)	**% Drug release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
15	9.20	9.02	9.10	12.20	11.19	12.10	13.18	10.82	11.32
30	12.71	11.19	10.10	19.30	18.20	19.28	20.72	18.83	19.42
45	19.63	18.26	12.29	31.91	30.42	36.08	37.28	33.72	34.55
60	22.84	23.36	12.32	37.12	36.33	38.11	39.15	35.62	37.47
120	29.90	29.41	22.82	41.10	40.29	42.29	43.27	40.10	41.55
180	39.04	35.82	32.83	46.19	45.82	46.05	47.25	45.14	46.67
240	49.92	50.99	48.77	59.17	58.82	59.78	60.71	58.18	59.93
300	55.62	52.29	52.53	64.29	63.88	63.16	64.36	60.19	63.34
360	67.01	69.02	66.49	67.22	69.72	70.25	70.52	69.32	69.62
420	71.72	74.30	68.82	79.20	78.20	84.83	86.95	74.20	85.73
480	85.52	86.88	79.29	89.32	89.22	92.81	94.16	88.10	91.84

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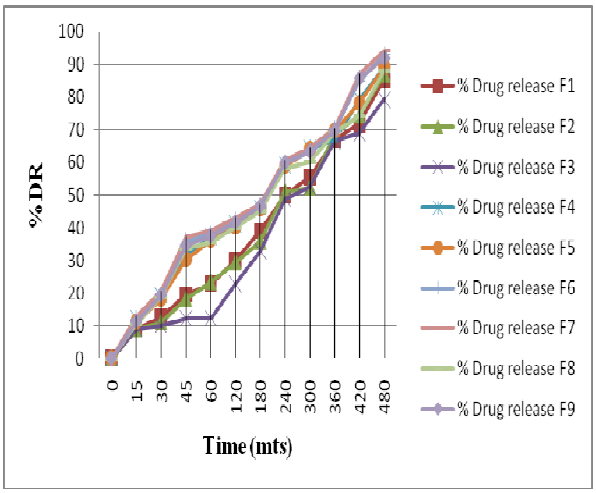

Fig. 2: *In vitro* drug release of ethosomes cream of luliconazole

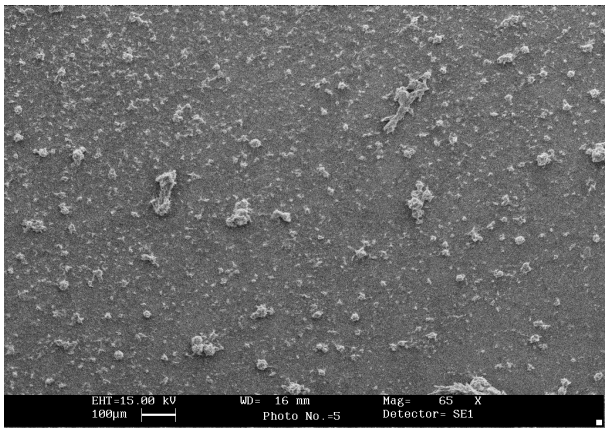

Fig. 3: SEM of Ethosomes

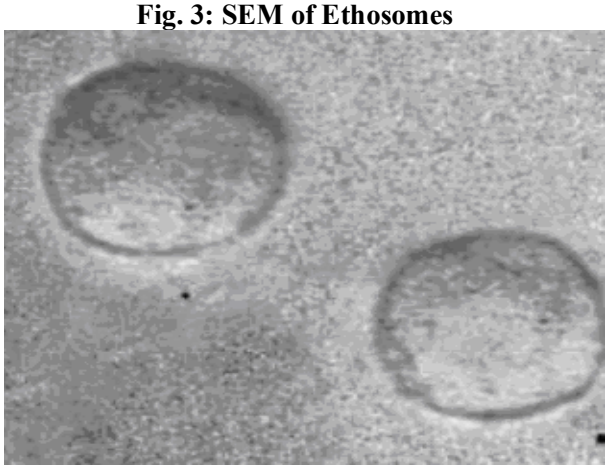

Fig. 4: TEM of Ethosomes

Conclusion

The ethosomes of luliconazole was prepared by cold method and was evaluated. *In vitro* release of F7 formulation was higher than other formulation prepared. The ethosomal cream formulation of luliconazole was evaluated for organoleptic characteristics. The pH of cream base and freshly prepared ethosomal cream noted down The pH of cream base was found to be 7.2 & pH of ethosomes cream of different formulation was presented in table. The viscosity of carbopol 934 cream base was found to be 740,00 cps whereas viscosity of ethosomal cream was given in table. The spreadability of ethosomal cream was also recored. The spreadability results showed that ethosomal cream was most effective i.e. it showed best result for spreadability. The extrudability of ethosomal cream was found to be positive except in F2 & F3. The % yield of ethosomal cream was found in between 94.71 to 98.43 %. Ethosomal cream was found to be homogeneous and no grittiness was noted. Hence, it was concluded that the formulation F7 has better results as compared to other formulations.

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