Formulation and Evaluation of Proniosomal gel containing Luliconazole

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ABSTRACT

Background: Luliconazole is a topical broad-spectrum antifungal drug. It has lower aqueous solubility that limits dermal bioavailability and acts as a barrier to topical delivery. **Objectives:** Aim of the current study was to formulate proniosomal gel of Luliconazole in order to incorporate lipophilic or poorly water soluble drug in formulations and deliver topically using different surfactants (Span and Tween), cholesterol, solvent (ethanol) and aqueous phase (Distilled water). **Materials and Methods:** Coacervation phase separation method was used for preparation of proniosomal gel of Luliconazole. The proniosomes were prepared using Span 20, Span 60 and Tween 80 in varied concentration. The proniosomes were allowed to cool at room temperature until the dispersion was converted to gel. The prepared proniosomal gel was evaluated for organoleptic properties, pH, spreadability, viscosity, optical microscopy, drug entrapment efficiency, and *in vitro* release studies. **Results:** The organoleptic study for proniosomal gel showed creamy, white to pale yellow viscous gel. The vesicles under optical microscopy showed slightly rough and irregularly shaped particles. The pH of the proniosomal gels were found to be within acceptable range on pH scale ranging from 5.3 to 6.8. The viscosity of gel formulations F1 to F9 was found to be in the range of 505cps to 923cps. The spreadability of the formulations was found to be in the range of 10.5 to 15.8. The drug entrapment efficiency was observed in the range of 85.62 to 95.48%. The rank order of drug entrapment efficiency of formulations was found to be F1 < F4 < F6 < F2 < F9 < F7 < F3 < F8 < F5. The drug release profile showed that formulation F5 showed most desired release profile. The rate of drug release is found to be in the order Tween 80 < Span 20 < Span 60. **Conclusion:** The formulation F5 was found to be significant from all the characterization parameters. In a nutshell to conclude, proniosomal gel plays a vital tool in sustaining the drug release and improving the skin permeation.

Keywords: Proniosomal gel, Spans and Tweens, Luliconazole, Anti-fungal, Coacervation phase separation technique.

INTRODUCTION

At the present time the most familiar form of drugs delivery is the oral administration. Although oral route of drug administration has remarkable benefits but there are few disadvantages also and hence a novel route of drug delivery is necessary to overcome the difficulties associated with CDDS and to get better therapeutic effectiveness and supply of drugs at more specific site.

The proniosomes are one form of vesicular drug delivery system that has benefit of stability as they are hydrated just before the use and thus proniosomes would stay away from various tribulations related to hydrated niosomes. [1-4] The troubles of aggregation, fusion, and leak out of active moiety (physical stability) may possibly reduce when proniosomes are used. [5] *Proniosomal gel* is semisolid liquid crystal gel that are prepared by dissolving surfactant in minimal quantity of solvent and hydrating with small amount of water to form gel. These gels are semisolid transparent, translucent or white physically stable formulations that can be used topically/ transdermally. These proniosomes act as reservoir in transdermal drug delivery system. The Proniosomal gel is placed onto the backing membrane of the transdermal patch and release the drug accordingly. [6,7] The liquid crystalline proniosomes have exceptional benefits that make it the suitable choice for the pharmaceutical researchers in the field of provesicular drug delivery system. These include: Higher stability, Higher entrapment efficiency, Good penetration enhancer and easy to manufacture and economical. [8]

Luliconazole is a topical broad-spectrum antifungal drug. It has lower aqueous solubility that limits dermal bioavailability and acts as a barrier to topical delivery. The solubility of the drug in the lipid phase of stratum corneum also acts as a rate-limiting step for permeation. Fungal infection involves epidermis, dermis as well as deeper layers of skin that require customizing the drug delivery in such a way which localize high drug concentrations at epidermis and dermis layers. Luliconazole is used for its anti-fungal activity and it normally exist as antifungal drug but various dosage forms created show different disadvantages when used alone or as a combination of drug. [9, 10]

The frequently shown disadvantages are slow/ poor skin permeation leading to repetitive application of drug on skin that may further cause skin irritation and reduce

patient compliance. To overcome these inherent drawbacks associated with conventional drug delivery of luliconazole, designing a substitute drug release arrangement is necessary which is by means of proniosomes form following compensation over the other topical preparation. The proniosomal gels minimize physical stability problems related to niosomes e.g. aggregation, blending, and leak out drug tendency provide additional convenience in transportation, distribution, storage and drying. The use of non ionic surfactant along with phospholipids in proniosomes, ability to penetrate across cell membrane enhances. Also, the troubles associated with liposomal vesicular system such as degradation or oxidation by hydrolyzing of API in addition to other tribulations of active ingredients. [11]

So in the present study, an alternative dosage form topical proniosomal gel of luliconazole would be developed that can overcome the above mentioned problems. Hence in present work, a challenge to prepare Proniosomal gel of Luliconazole in order to incorporate lipophilic or poorly water soluble drug in formulations and deliver topically.

MATERIAL AND METHODS

Materials

Luliconazole was received as gift sample. Other excipients like Span 20, Span 60, Tween 80, cholesterol, methanol, ethanol etc. were obtained from college laboratory.

Experimental Methods

Formulation of Proniosomal Gel

Proniosomes were prepared using coacervation phase separation method. Table 1 shows composition of each formulation. The proniosomes were prepared using Span 20, Span 60 and Tween 80 in varied concentration. In a beaker, the surfactant and cholesterol were mixed with 0.5ml of absolute ethanol, and then 50 mg of drug was added. Then, the beaker was covered with a lid to prevent the loss of solvent and the beaker was warmed in a water bath (55°C–60°C) for 5 minutes while shaking until the complete dissolution of cholesterol. Then, about 0.16 ml of hot distilled water (55°C–60°C) was added while warming in the water bath for 3–5 min till a clear or translucent solution was produced. The mixture was allowed to cool at room temperature until the dispersion was converted to gel. [1, 12, 13] The obtained gels were stored in the closed beaker.

Table 1: Composition of Proniosomal Gel

S. No.	Formulation	Drug (mg)	Ethanol (ml)	Surfactants (mg)			Water (ml)
				Span 20	Span 60	Tween 80	
1	F1	50	0.5	450	-	-	qs
2	F2	50	0.5	-	450	-	qs
3	F3	50	0.5	-	-	450	qs
4	F4	50	0.5	225	-	225	qs
5	F5	50	0.5	-	225	225	qs
6	F6	50	0.5	150	-	300	qs
7	F7	50	0.5	-	150	300	qs
8	F8	50	0.5	300	150	-	qs
9	F9	50	0.5	300	-	150	qs

Characterization of Proniosomal Gel [14-16]

Organoleptic properties

The prepared proniosomal gels were characterized for its appearance, color, and homogeneity by visual inspection.

pH

The pH of the proniosomal gels were measured using digital pH meter. Since the formulation is topical formulation to be applied to the skin, therefore, pH measurement is essential to ensure non-irritating nature of the formulation.

Rheological study

The viscosity of Proniosomal gels were measured by Brookfield type rotary viscometer.

Spreadability study

Spreading coefficient was measured on the basis of ‘Slip’ and ‘Drag’ characteristics of gels. It was calculated by using the formula:

$$S = M.L / T,$$

Where, M= weight placed on upper slide, L= Length of upper slide, T= time taken to separate the slide (in sec)

Drug entrapment efficiency

The drug entrapment efficiency of the proniosomal gel was determined by adding 0.2g of gel in 10ml of phosphate buffer (pH 7.4) taken in glass tube. This solution was

sonicated in sonicator and centrifuged at 20^{o}C for 30 minutes. The supernatant was collected and assayed in UV spectrophotometry for calculating the unentrapped drug content. The % entrapment efficiency was calculated using formulae:

$$\% \text{ Entrapped Efficiency} = \frac{\text{(Total amount of drug - Unentrapped drug)}}{\text{Total amount of drug}} \times 100$$

Optical Microscopy

The optimized proniosomal gel was determined for vesicle structure using ordinary light microscope. The photomicrographs were taken for the same.

***In vitro* drug release**

The *in vitro* drug release study will be performed using Franz Diffusion cell. The amount of drug is assayed by UV analysis.

RESULTS AND DISCUSSION

Preparation of Proniosomal gel

Proniosomes were prepared using coacervation phase separation method.

Organoleptic properties

The prepared proniosomal gel were found to be white and creamy for formulation F1, F2, F5 and F8 whereas pale yellow with high viscosity for F3, F5, F6 and F7. The results are depicted in table 2.

Table 2: Characterization of Proniosomal gel (F1-F9)

S. No.	Formulation	Organoleptic Properties		
		Color	Odor	Appearance
1	F1	White	Odorless	Creamy
2	F2	White	Odorless	Creamy
3	F3	Pale yellow	Odorless	Clear Viscous
4	F4	Pale yellow	Odorless	Clear Viscous
5	F5	White	Odorless	Creamy
6	F6	Pale yellow	Odorless	Clear Viscous
7	F7	Pale yellow	Odorless	Clear Viscous
8	F8	White	Odorless	Creamy
9	F9	Pale yellow	Odorless	Clear Viscous

pH

The prepared formulations of proniosomal gel were found to be within acceptable range on pH scale. All the formulations have pH ranging from 5.3 to 6.8 as depicted in table 3.

Rheological studies

The viscosity of gel formulations F1 to F9 was found to be in the range of 505cps to 923cps and the results are depicted in table 3. The viscosity was found to increase with increase in HLB of surfactant.

Spreadability studies

The spreadability of the formulations was found to be in the range of 10.5 to 15.8. Lesser the time taken for separation of two slides, better the spreadability. The spreadability coefficient of gel is tabulated in table 3.

Drug entrapment efficiency

The drug entrapment efficiency was observed in the range of 85.62 to 95.48%. The formulation containing Span 60 and Tween 80 and Span 60 alone showed maximum entrapment efficiency. The formulation containing Tween 80 showed least entrapment efficiency. The entrapment efficiency depends indirectly on the HLB of the surfactant. The drug entrapment efficiency is tabulated in table 3.

Table 3: Characterization of Proniosomal gel (F1-F9)

Formulation	pH	Viscosity (cps)	Spreadability	Entrapment efficiency (%)
F1	5.3	545	13.7	85.62 ± 0.25
F2	5.6	505	15.8	89.64 ± 0.51
F3	5.5	662	12.7	91.35 ± 0.45
F4	6.2	681	11.9	88.12 ± 0.31
F5	5.9	795	13.9	95.48 ± 0.64
F6	6.8	803	12.3	89.17 ± 0.38
F7	5.9	815	14.1	90.14 ± 0.44
F8	6.2	745	13.6	92.18 ± 0.49
F9	6.3	923	10.5	89.9 ± 0.78

Optical microscopy

The photomicrograph of formulation F5 is depicted in figure 1. All the vesicles were observed to be irregular in shape and rough vesicles with sharp boundaries.

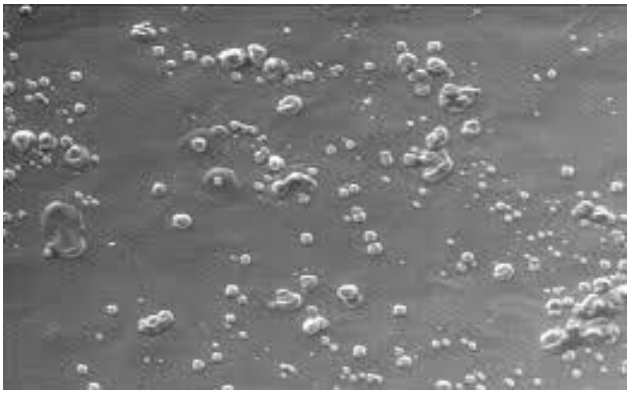

Figure 1: Photomicrograph for F5

***In vitro* drug release**

The *in vitro* drug release tests were performed using Franz diffusion cell. *In vitro* release data of Proniosomal gel for batch F1 to F9 is tabulated in table 4 and represented in figure 2.

The cumulative percentage drug release from gel prepared with Span 20 showed slower drug release when compared to Span 60 proniosomal gel. Similarly, the gel prepared using Span 60 and Tween 80 showed much lesser rate of drug release. The rate of drug release is found to be in the order Tween 80 < Span 20 < Span 60. The release pattern depends on the hydrophilic nature of surfactant. The formulation containing span 60 and tween 80 showed significantly prolonged drug release when compared to all other formulations.

Thakur *et al.* observed in a study that the delay in release of proniosomal gel formulations is due to the slower drug release from proniosomes and this may be attributed to the larger time taken by the proniosomes to be hydrated to form niosomal vesicles before drug release. [17]

Table 4: % cumulative drug release (mean ± S.D., n=3)

Time (hrs)	% cumulative drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	10.2±0.6	5.1±0.1	5.2±0.7	5.6±0.1	4.8±0.1	4.1±0.9	2.5±0.8	6.6±0.9	3.6±0.9
2	21.2±0.4	16.7±0.5	11.6±0.1	13.5±0.5	10.9±0.3	11.5±0.1	8.6±0.5	15.5±0.4	9.5±0.1
3	36.1±0.5	29.6±0.2	18.4±0.1	22.1±0.5	18.4±0.5	20.4±0.5	15.4±0.5	26.1±0.6	17.4±0.5
4	50.3±0.04	36.5±0.7	28.9±0.5	37.7±0.3	26.1±0.7	37.9±0.4	28.9±0.4	39.7±0.02	32.9±0.4
5	62.3±0	51.2±	39.4±0	49.6±	37.4±	46.3±	35.4±	52.6±0	41.3±0

	.5	0.1	.8	0.5	0.9	0.9	0.7	.3	.9
6	74.1±0.3	64.3±0.3	51.5±0.08	63.2±0.4	52.1±0.5	58.2±0.8	49.5±0.8	66.2±0.95	53.2±0.81
7	85.6±0.2	75.6±0.5	70.2±0.1	72.2±0.9	68.2±0.1	73.1±0.4	64.2±0.4	76.2±0.2	69.1±0.4

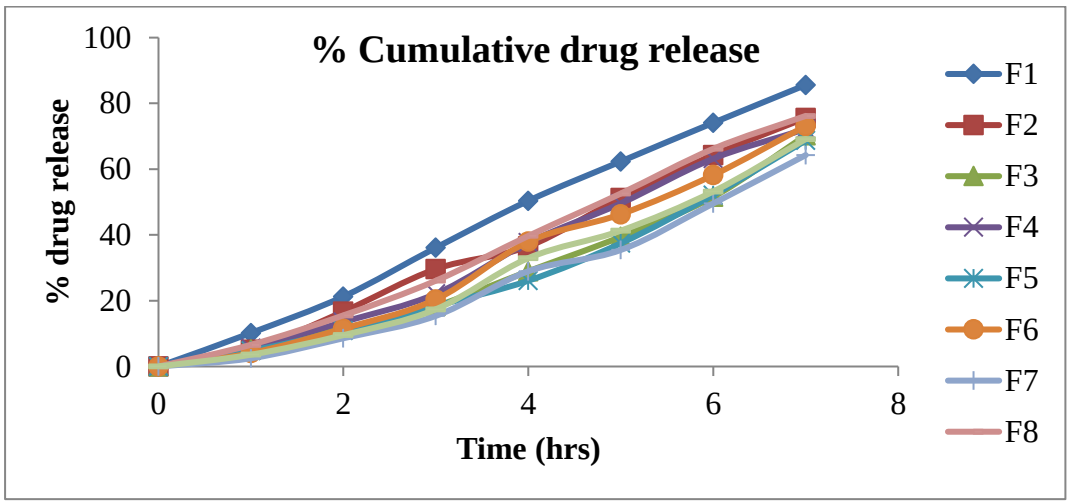

Figure 2: % cumulative drug release for Proniosomal gel (F1-F9)

CONCLUSION

In conclusion, Luliconazole loaded proniosomal gel formulation prepared by coacervation phase separation method. The formulation F5 emerged as the overall ideal formulation based on characterization parameters. Hence it can be concluded that the proniosomal gel formulation of Luliconazole is an ideal option for topical drug delivery with improved stability, sustaining the drug release, improving the skin permeation, high bioavailability, patient compliance and therapeutic efficacy when compared to other tablet formulation.

ACKNOWLEDGEMENT

I would like to express my special thanks of gratitude to my guide Ms. Kaushalya Bains for their able guidance and support in completing my research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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