Journal of Applied Pharmaceutical Science Vol. 4 (07), pp. 098-104, July, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.40717
ISSN 2231-3354

Formulation and evaluation of fluconazole pro-niosomal gel for topical administration

Sandeep G, Vasavi Reddy D, Srinivas Reddy Devireddy*

Department of Pharmaceutics, Vaageswari College of Pharmacy, Karimnagar, India.

ARTICLE INFO

Article history:
Received on: 10/05/2014
Revised on: 30/05/2014
Accepted on: 20/06/2014
Available online: 28/07/2014

Key words:
Fluconazole; proniosomes; surfactants; topical delivery; skin

ABSTRACT

The present investigation was aimed to explore the potential of proniosomal gel for the topical delivery of fluconazole. Fluconazole-loaded proniosomes were prepared by the coacervation method using different non-ionic surfactants (spans and tweens) and evaluated for various parameters like size, shape, stability, entrapment efficiency, in-vitro release, ex-vivo skin permeation and retention study. Results showed that proniosomes composed of span 20 (F1), span 60 (F4), span 80 (F7) were more stable compared with tween 20 (F10) and tween 80 (F13) with smaller size, "i.e." 4.08±0.18 µm, 2.61±0.15 µm, 2.01±0.12 µm, 8.56±0.20 µm, and 7.10±0.31 µm, respectively, along with higher entrapment efficiency (approx. >46%). Ex-vivo skin penetration and retention studies revealed that cutaneous deposition was affected by the nature of surfactant and vesicle size. Therefore the proniosomes containing span 60 having high amount of drug retained in skin, "i.e." 25.97±1.28 which can help in localized delivery of drug especially in fungal mediated skin diseases, thereby increased efficacy for prolonged period can be achieved.

INTRODUCTION

Though the oral route is the most favorable route for delivery of drugs it has limited importance especially in the treatment of skin diseases. Among the topical drug delivery systems (Vora *et al.,* 1998), the proniosomal gels are becoming more popular due to ease of application and better percutaneous absorption, than other semi solid preparations (Shamsheer Ahmad *et al.,* 2011). Transdermal delivery systems are becoming better alternatives ton oral delivery because it exhibits better control of plasma drug levels, no hepatic first-pass metabolism, a decreased systemic toxicity and a higher degree of patient compliance (Parikh *et al.,* 2005). Skin provides a physical protective barrier to the body against the external environment (Prausnitz *et al.,* 2004), it can also become major barrier for drug absorption as it is composed of stratum corneum (corneocytes sourrended by lipid region). Number of permeation enhancers has been introduced to establish a therapeutically effective plasma drug levels in case of poorly permeable drugs (Vora *et al.,* 1998).

* *Corresponding Author*
D.Srinivas Reddy, Vaageswari College of Pharmacy, Karimnagar, India.
Email: Srinivasreddydevireddy@gmail.com

Colloidal carriers such as niosomes (Shahiwala *et al.,* 2002; Mishra *et al.,* 2007; Vavrova *et al.,* 2005) are been extraneously used in drug delivery systems. These systems are prepared using non ionic surfactants (usually Spans) which are generally regarded as safe (Yoshioka *et al.,* 1994; Solanki *et al.,* 2007). Niosomes are capable of entrapping hydrophilic and hydrophobic solutes. Lower stability, expensive and the inconsistent purity problems of phospholipids have prompted the exploitation of niosomes as alternative promising drug carriers to liposomal vesicles for industrial production (Uchegbu *et al.,* 1998). Proniosome is dry formulation prepared using suitable carrier coated with non ionic surfactants and can be converted into niosome immediately upon hydration. Proniosomes are hydrated by agitation in hot water for a short period of time and the drug entrapped in the niosomal vesicles penetrates the skin at a faster rate than the free drug (Yoshioka *et al.,* 1994; Hu *et al.,* 1999). Fluconazole, an antifungal drug used in fungal infections caused by the pathogenic fungi, including *C. albicans*, which is a major contributory factor for cutaneous candidiasis (Grant *et al.,* 1990; Abdel-Mottaleb *et al.,* 2009). It is commercially available as parental and oral dosage forms, which are largely confronted with well-known adverse effects including taste disturbances and GI irritation.

The use of topical fluconazole in the treatment of skin diseases with various formulations including lecithin-based organogel, (Jadhav *et al.,* 2009) gel formulation (Bidkar *et al.,* 2007) and hydrogel is recommended. But these hydrogerl based systems can be vanished or washed off shortly after application over skin, a lipid based system can enhance it's permeability and cutaneous accumulation for localized effect in different strata of skin can be achieved.

We have screened many surfactants to prepare drug-loaded proniosomes as transdermal delivery systems which are capable of increasing the cutaneous delivery of fluconazole. In this study, we report the ability of span series and tween series mixed with cholesterol and lecithin to form bilayered vesicles. Furthermore, the proniosomes were evaluated for various parameters including shape, size, entrapment efficiency, *in vitro* release study, ex-vivo skin permeation, and accumulation in skin.

MATERIALS AND METHODS

Materials

Fluconazole was provided as a gift sample from Gland pharmaceuticals Ltd. (Hyderabad, India). Spans (20, 40, and 80) were purchased from SD Fine Chemicals (Mumbai, India). Tween (20, 80) were purchased from CDH Laboratories (New Delhi, India). Soya Lecithin (30 %) and Cholesterol Extra pure were purchased from Hi-Media laboratories (Mumbai, India).

Preparation of Proniosomes

Proniosomes were prepared using a modified method reported by Alsarra *et al.*, 2005 the composition of different proniosomal formulations are listed in Table 1. Using a wide-mouth glass tube, 100 mg of Fluconazole with surfactant, lecithin, and cholesterol was mixed with 500 µl of absolute ethanol. Then the opening of the glass tube was covered with a lid and the tube was warmed in a water bath at 65 ℃ for 5 min. Then 1.5 ml of pH 7.4 phosphate buffer was added and the mixture was further warmed in the water bath for about 2 min so that a clear solution was obtained. The mixture was allowed to cool at room temperature until the dispersion was converted to gel. The obtained gel was stored in the same closed glass vial.

Characterization of Proniosomal Gels

Formation and Morphological Evaluation

The proniosomal gel was placed on a cavity glass slide and few µL of phosphate buffer saline was added drop wise along the side of the cover slip. The formation of vesicles was monitored at a magnification of 100X through an inverted microscope (Boeco NIB-100, Germany) and sequential photographs were taken and scanning electron microscopic (SEM) examination was also done for best formulae.

Determination of Entrapment Efficiency

In a glass tube 0.2 gm of proniosomal gel was taken and 10 ml of phosphate buffer was added. This aqueous suspension was sonicated in a sonicator bath, followed by centrifugation at 9,000 rpm at 20 ℃ for 30 min. The supernatant was collected and assayed by UV method for un-entrapped fluconazole content at 260 nm. The percentage of drug encapsulation (EE (%)) was calculated by the following equation:

$$Entrapment\ Efficiency = \frac{Total\ amount\ of\ drug - Un\ Entrapped\ drug}{Total\ amount\ of\ drug} * 100$$

Physical Stability of Vesicles at Storage Condition

The change in size and percentage entrapment of drug in the vesicle during and after storage was studied at refrigerated conditions (4 ±1 ℃) for two months. Samples from each batch were withdrawn at definite time intervals and vesicle size and residual amounts of drug were determined.

Table 1: Composition and appearance of Fluconazole loaded proniosomal gel.

CODE	RATIO (C:L:S)	Fluconazole (mg)	C (mg)	L (mg)	S1 (mg)	S2 (mg)	S3 (mg)	T1 (mg)	T2 (mg)
F1	1:9:9	100	200	1800	1800				
F2	1:4.5:4.5	100	200	900	900				
F3	1:4.5:9	100	200	900	1800				
F4	1:9:9	100	200	1800		1800			
F5	1:4.5:4.5	100	200	900		900			
F6	1:4.5:9	100	200	900		1800			
F7	1:9:9	100	200	1800			1800		
F8	1:4.5:4.5	100	200	900			900		
F9	1:4.5:9	100	200	900			1800		
F10	1:9:9	100	200	1800				1800	
F11	1:4.5:4.5	100	200	900				900	
F12	1:4.5:9	100	200	900				1800	
F13	1:9:9	100	200	1800					1800
F14	1:4.5:4.5	100	200	900					900
F15	1:4.5:9	100	200	900					1800

C:L:S – cholesterol : lecithin : surfactant ; C – cholesterol; L – lecithin; S1-span20; S2-span60;S3-span80; T1-Tween20; T2-Tween80

In Vitro Drug Release Study

In vitro release studies through artificial membrane was performed using fabricated vertical franz diffusion cell with an effective diffusion surface area of 4.153 cm^2. The dialysis membrane was soaked for 2 hrs prior diffusion study in the diffusion medium. The proniosomal gel/control gel equivalent to 25 mg of fluconazole was placed in the donor compartment. The receptor compartment was consisting of phosphate buffer pH 7.4 at a temperature of 37±2 °C under constant stirring up to 24 h. The donor chamber and the sampling port were covered by paraffin wax to prevent evaporation during the study. An aliquot of 3ml was withdrawn periodically from sampling port and replaced with equal volume to maintain constant receptor phase volume. At the end of the study the withdrawn samples were assayed for drug content by measuring the absorbance at 260 nm against a reagent blank, using the UV spectrophotometer (Shimadzu, 1800, Japan). Sink conditions were maintained throughout the experiment.

Ex-vivo Skin Permeation and Retention Studies

The animal experimentation was approved by the institutional animal ethical committee (IAEC Protocol NO. VCP/2013/01/6). After cervical dislocation, the abdominal and dorsal skin was removed surgically and the hair was removed with fine scissors. The full thickness skin was used after removing underlying fat and subcutaneous tissues. The *in vitro* skin permeation study was carried out using a Franz diffusion cell, as described earlier with slight modification (Gupta *et al.,* 2011). The skin was mounted between the donor and receptor compartments of the diffusion cell with the subcutaneous layer facing upward direction (towards donor compartment). The volume of receptor medium was 25 ml of PBS (pH 7.4) thermo stated at 37 ± 1 °C, which was continuously stirred at 100 rpm throughout the experiment. Proniosomal gel equivalent to 25 mg of Fluconazole was placed in the donor compartment.

At appropriate time intervals up to 24 hrs, samples of 3ml from the receptor compartment were withdrawn and replaced by an equal volume of fresh medium to keep a stable receiver volume. The experiment was conducted in triplicate. The samples from the receptor compartment were analyzed by UV spectrophotometer (Shimadzu, 1800, Japan) absorbance at 260 nm against reagent as blank.

Determination of the drug concentration in the subcutaneous layer was done by following the method with slight modification reported by, Gupta *et al.,* 2011. The gel present on compartment cell was removed and washed with PBS and methanol (1:1 v/v) and determined the UV absorbance at 260 nm. The remaining skin was cut into small pieces to determine the amount of drug in the viable skin (epidermis and dermis). They were pooled in a conical flask containing 50 ml of PBS (7.4 pH) and methanol (1:1 v/v), placed on to the rotary shaker for 48 hrs. After that the solution was filtered and the amount of drug extracted from skin sample was determined by using UV Visible Spectrophotometer at 260 nm.

RESULTS AND DISCUSSION

The Pro-niosomes of fluconazole were prepared by the coacervation method using different surfactants from Span and Tween series, for topical application and study for the viability of skin drug deposition and prolong drug delivery for local treatment. The ability of the studied surfactants to form vesicles is summarized in Table 2. In this study, Cholesterol is used at a fixed molar ratio (Gupta *et al.,* 2011). To investigate the effective concentrations of cholesterol, lecithin and surfactant ratios to get a précised vesicular shape, preliminary trials were done. The effect of cholesterol was investigated by varying the composition of phospholipid to cholesterol ratio. Based on the preliminary studies the cholesterol concentration fixed to one percent, upon increasing the cholesterol concentration reduction of vesicle size, thereby reduced entrapment efficiency was observed (Alam *et al.,* 2010). The surfactant and lecithin concentrations were altered, at lower concentration the vesicle size and shape were irregular. In this study 15 formulations (F1-F15) were taken which were divided into 3 groups depending on their cholesterol : lecithin : surfactant ratios (1:9:9,1:4.5:4.5,1:9:4.5) by altering the surfactants (span 20, span 60, span 80, tween 20, tween 80) respectively in each group cholesterol is the common additive used as a structural lipid to improve the stability and entrapment efficiency of vesicular formulations. (Rogerson *et al.,* 1987; Gregoriadis *et al.,* 1993) The shape and size were regular at 1:9:9 ratio of cholesterol: lecithin: surfactant respectively.

Vesicle Shape and Size

Vesicular structures were observed for diluted formulations with phosphate buffer 7.4 under inverted microscope (Boeco NIB-100, GERMANY) at 100x magnification, bi layered structure around and hollow space is seen in the centre, which resembles a typical vesicular structure (Figure 1). SEM photograph of the optimized formulation suggest that vesicles obtained were of almost spherical shape and uniform in size, as shown in (Figure 2). The average size of the prepared Pro-niosomes is recorded. Results indicate that size of vesicles is fully dependent on the composition of the bi-layer and drug load. The results obtained with Span 20 (HLB 8.6), Span 60 (HLB 4.7), Span 80 (HLB 4.3), tween 20 (HLB 16.7), and tween 80 (HLB 15.5) based proniosomes are shown in (Table 2). The results reveal that the size of Pro-niosomes tended to increase with a progressive increase in the HLB value of Span used in the formulation.

In the Formulations F1-F15, smallest average size (2..01±0.12 μ m) was measured in the case of Span 80 based vesicles while vesicles were of larger size, i.e. 8.56±0.2 μ m in the case of Tween 20 based proniosomes. This might be due to surface-free energy as it decreases with increasing hydrophobicity (Gupta *et al.,* 2011). Among all the formulations, F4 (cholesterol-lecithin ratio 1:9 and span 60) was chosen as the best formulation as it has smaller vesicular size which helps in easy drug loading and permeation through skin and reaching the target site and helps us to have a control over the release of drug.

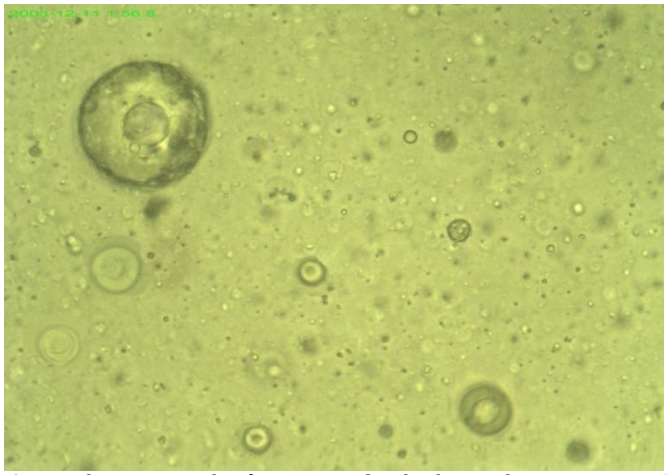

Fig. 1: photomicrograph of Proniosomal gel taken under Boeco NIB-100 (germany) at 100X magnification.

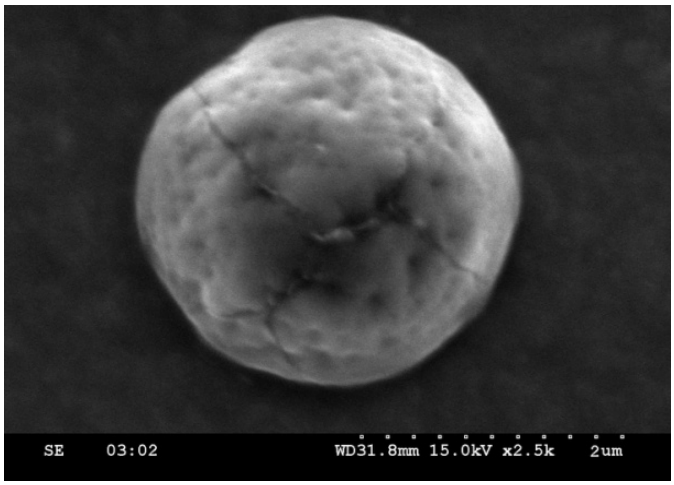

Fig. 2: SEM photograph of optimized Fluconazole loaded vesicular system prepared by Span60.

Entrapment Efficiency

Entrapment efficiency of different formulations are been calculated and values are given in the table 2. In all the formulations highest entrapment efficiency in each series of proniosomes were found in the following order i.e, Span 60 > Span 20 > Span 80 > Tween 80 > Tween 20 respectively. The data showed that Span 60 based proniosomes has significantly higher entrapment efficiency, compared to other formulations. This could be explained on the basis that the highly lipophilic portion of the drug is expected to be housed almost completely within the lipid bilayer of the proniosomes. Similar findings were reported by, (Vora *et al.,* 1998) in levonorgestrol proniosomal delivery of Span 40.

The alkyl chain length plays a major role in the permeability behavior (Hao *et al.,* 2002). Based up on the vesicular shape and size as well as entrapment efficiency from the each surfactant, F4 was selected as best formulation.

Physical Stability Studies

Stable proniosomal dispersion must maintain average vesicle size as well as drug content. In the present study, stability studies were conducted on selected formulations. They were stored at 4±1 ℃ for a period of 2 months and observed for the leakage of encapsulated fluconazole and the change in average particle size of the vesicles.

It was observed that there is a small increase in vesicular size after two months and slight decrease in entrapment efficiency. Span 60 proniosomal formulations were most stable compared to other surfactant-based formulations. Our findings were in accordance with the study done by Gupta *et al.,* 2011. This may be accepted due to the partial leakage of drug in the case of Span 60 surfactant-based formulation due to its high phase transition temperature and low permeability.

***In Vitro* Release Study**

The *in vitro* release behavior of Fluconazole from proniosomes was studied. The percentage drug release from different formulations was represented in figure 3. The release of fluconazole from control was nearly 79% within 12 h which clearly suggest the permeability of the membrane and prevalence of the sink condition for the drug. A typical biphasic release pattern observed with proniosomal formulations. Initially a rapid burst release followed by sustained release for a period of 24 h was observed.

The rapid initial phase may be accounted to the leached drug in the dispersion medium, whereas subsequent slower release may be due to slow and controlled diffusion of drug through the bilayer.

Formulation F4, containing span 60 as surfactant, is showing more *in vitro* drug release i.e., 84.3% among all the surfactants. The release rate is also dependent on membrane fluidity, as a function of either acyl chain length and saturation or cholesterol content (Gupta *et al.,* 2011). When we compare the release patterns of the control formulation with that of proniosomal formulation, a significant retardness in drug release was observed in proniosomes. In order to treat the fungal diseases, long term treatment is required with extended release pattern.

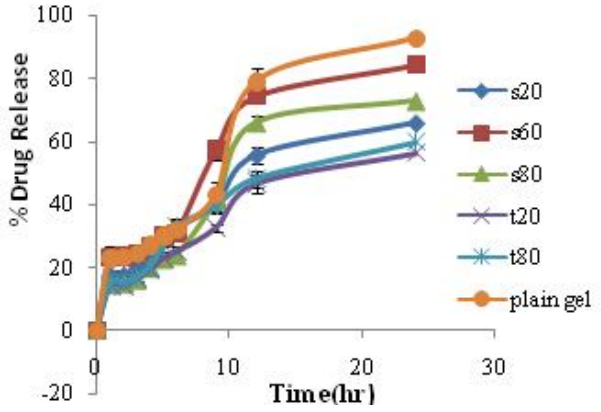

Fig. 3: *In vitro* % release of Fluconazole with cholesterol: lecithin (1:9) ratio. In order to treat the fungal diseases, long term treatment is required with extended release pattern.

Table 2: Vesicular characterization of proniosomal gel.

		Immediate release		After storage for two months	
S. No	**Formulation code**	**Vesicle size (µm)**	**Entrapment efficiency (%)**	**Vesicle size (µm)**	**Entrapment efficiency (%)**
1	**F1**	4.08±0.18	60.26±2.00	8.56±0.12	53.60±2.05
2	**F2**	5.35±0.20	52.92±2.41	10.7±0.18	42.00±2.13
3	**F3**	4.80±0.19	55.74±2.23	9.63±0.16	47.97±2.19
4	**F4**	2.61±0.15	67.6±1.98	4.28±0.14	52.40±2.00
5	**F5**	4.28±0.18	53.87±2.12	5.88±0.17	48.60±2.09
6	**F6**	3.21±0.17	58.39±2.01	5.35±0.15	53.01±2.03
7	**F7**	2.01±0.12	57.2±2.20	3.98±0.15	46.00±2.30
8	**F8**	3.98±0.15	48.8±2.45	5.46±0.17	39.40±2.41
9	**F9**	2.98±.013	53.27±2.24	4.96±0.14	42.67±2.37
10	**F10**	8.56±0.20	46.53±2.31	17.12±0.23	34.80±2.48
11	**F11**	9.63±0.24	39.35±2.50	16.59±0.27	26.70±2.58
12	**F12**	9.10±0.23	42.67±2.36	16.05±0.25	31.10±2.47
13	**F13**	7.10±0.31	48.53±3.01	14.98±0.33	39.07±3.33
14	**F14**	10.16±0.35	41.99±3.22	16.50±0.37	27.40±3.58
15	**F15**	8.56±0.33	45.14±3.18	16.00±0.38	36.40±3.47

Table 3: *In vitro*% release of Fluconazole with cholesterol: lecithin (1:9) ratio.

Time(hr)	S20 (1:9:9)	S60 (1:9:9)	S80 (1:9:9)	T20 (1:9:9)	T80 (1:9:9)	plain gel
1	17.3±1.98	23.4±0.98	14.6±1.42	14.0±1.24	14.8±2.00	23.0±2.55
2	17.5±1.31	23.5±1.08	14.9±1.55	14.2±1.22	15.0±2.12	23.2±3.95
3	19.9±1.33	24.2±1.21	16.0±1.32	16.3±1.32	16.7±1.98	24.3±3.74
4	22.4±1.42	26.7±1.24	19.8±1.57	19.0±1.36	20±1.22	27.0±2.78
5	29.3±2.01	29.9±0.99	22.6±1.67	23.0±1.52	26.7±1.35	30.0±2.98
6	32.5±1.98	30.6±1.35	23.8±1.28	25.0±1.35	33.0±1.87	32.0±3.25
9	40.0±2.22	57.3±1.75	41.3±1.98	32.7±1.87	39.7±1.98	43.3±3.45
12	55.7±2.84	74.3±2.98	66.0±2.33	46.7±1.25	48.3±1.78	79.0±3.77
24	66.0±2.57	84.3±1.98	73.0±2.01	56.3±2.77	59.7±2.65	92.7±4.37

Table 4: *Ex vivo* % release of Fluconazole with cholesterol: lecithin (1:9) ratio.

Time(hr)	plain gel%	S20% (1:9:9)	S60% (1:9:9)	S80% (1:9:9)	T20% (1:9:9)	T80% (1:9:9)
1	4.0±2.11	19.6±1.02	14.5±1.82	17.3±2.01	19.6±1.82	19.9±2.46
2	7.3±2.41	19.8±1.32	14.7±1.38	17.4±2.22	19.6±1.67	20.0±2.37
3	10.5±2.66	22.0±1.54	16.6±1.37	19.9±2.70	22.7±1.37	23.2±2.11
4	12.4±2.19	25.6±1.65	18.8±1.65	21.2±1.00	27.4±1.46	26.4±2.37
5	16.3±2.32	26.6±1.11	20.3±1.29	24.3±1.28	30.7±1.66	27.7±2.39
6	19.9±2.01	27.3±1.58	23.8±1.28	26.6±1.65	33.2±1.22	29.1±3.87
9	30.0±1.98	31.0±1.62	28.0±1.65	28.2±1.73	36±1.98	32.7±1.37
12	37.7±2.32	33.0±1.39	30.9±1.75	32.3±1.37	40±1.78	34.3±1.55
24	56.7±2.59	45.7±1.98	36.7±1.02	44.0±1.55	52.3±2.01	49.3±2.55

Ex vivo Skin Permeation and Retention Studies

To evaluate the influence of the drug carriers on the permeation and deposition of drug into the skin, ex-vivo skin penetration (table 4) and retention (table 5) studies were performed using hairless rat abdominal skin by Franz diffusion cells. The significant permeation of Fluconazole results only when the drug is released from the niosomes formed after the hydration of proniosomal gel with the skin fluid. (Hwang *et al.,* 1997) The penetration data obtained from different surfactant-based Proniosomal formulations were compared with a control of equivalent drug concentration. The results revealed that the amount of drug permeated through the skin in the first period was higher. Afterwards with all vesicular formulations, penetration rate was slow (Figure 4). Results appear to indicate that proniosomal formulations clearly delayed the drug penetration through the skin. The penetration was high for the control formulation i.e., 56.7%. A significant improvement in retardation of drug in skin was observed with proniosomes as they consisted of cholesterol, lecithin and a surfactant. All the proniosomal formulations were having greater skin retardation capacity than control gel. Increase in cholesterol: lecithin concentration (1:9) led to increase in retention of drug in skin. Results (Table 3 and Figure 4), described that, cumulative amounts of drug permeated in the receiver compartment after 24 hrs, there have been considerable difference in the cumulative amount of fluconazole permeated which could be due to the bilayer structure. Proniosomes containing span 60 as surfactant were having greater skin retention when compared to proniosomes comprised of other surfactants. In formulation F4 (Proniosomes containing 1:9, cholesterol-lecithin ratio with span-60 as surfactant) only 36.7% of the drug is been permeated remaining amount was retained in the skin where actually the drug is required and was considered as better formulation among all the formulations. In fact, permeated amount increased in the order: Span 60 > Span 80 > Span 20 > Tween 80 > Tween 20. The vesicular formulations could improve drug retention in rat skin over control (13.33%) formulation. Moreover, the higher

accumulation of fluconazole recorded in the case of Span 60 and 80 based vesicles. Fluconazole skin diffusion was obtained with smaller size Spans than Tweens. Span 60 and 80 showed higher skin accumulation (25.97% and 22.56%) as compared to Tween 80 and 20 (17.44% and 16.05%). It appeared that Proniosomal vesicles composition and smaller size of these niosomes may be well correlated with higher skin penetration (Gupta *et al.*, 2011). The smaller vesicles may rapidly collapse on the skin surface, resulting in close contact between skin lipids and vesicle constituents. Finally, material exchange between vesicles and intercellular lipids may occur that may allow the penetration of free drug as well as small into the skin (Manconi *et al.*, 2006). The percent of fluconazole permeated through the skin and accumulated into the stratum cranium, as well as in viable skin as measured for all formulations. The drug retention was high in stratum cranium consistently for all the formulations. Considerably higher stratum cranium retention of drug was observed in the case of Span 60 and Span 80 based niosomes as compared with the control.

Table 5: Percent of Fluconazole accumulated in the skin at the end of permeation experiments (24 hrs).

Surfactants	Fluconazole permeated though the skin at 24 hr (%)	Total Fluconazole accumulated to Skin (%)
Span20(F1)	45.7±1.98	21.23±1.92
Span60(F4)	36.7±1.02	25.97±1.28
Span 80(F7)	44±1.55	22.56±2.37
Tween20(F10)	52.3±2.01	16.05±1.53
Tween 80(F13)	49.3±2.55	17.44±1.60
Control	56.7±2.59	13.33±2.01

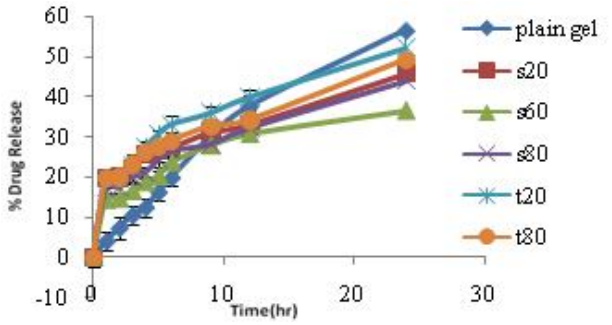

Fig. 4: *Ex vivo* permeation of Fluconazole with cholesterol: lecithin (1:9) ratio.

CONCLUSION

Rationale of the present study was to form the vesicles of fluconazole by using various non-ionic surfactants, consequently to increase permeation of the drug and accumulation at the target site i.e, skin in the form of transdermal gel. Fluconazole an antifungal drug, used for the fungal infections caused by the pathogenic fungi, including *C. albicans*, which is a major contributory factor for cutaneous candidiasis. It is commercially available in parental and oral dosage forms, which are largely confronted with well-known adverse effects including taste disturbances as well as causing irritation of GIT. For cutaneous accumulation for localized effect in different strata of skin, and low extent of permeation of drug to the systemic circulation could be of obvious advantages for transdermal delivery.

The proniosomal gel of fluconazole were prepared by modified test- tube method by using span- (20,40,60,80) and tween-(20,80) , evaluated for general physical parameters like size and of the vesicle and other evaluation tests like entrapment efficiency, physical stability studies, microscopic evaluation, in-vitro release and ex-vivo permeation and skin retention studies using rat skin. The gel was finalised by screening all the above parameters.

Formulation F4 (cholestrol:lecithin-1:9) ratio with span-60 as surfactant has shown minimum vesicular size(2.61µ), with highest entrapment efficiency (67.6%), this formulation has shown the optimum in-vitro drug release, ex vivo drug permeation for 24 hours and skin retention, hence formulation F4 was said to be optimized formulation. Good correlation between the *In vitro* drug release and *Ex-vivo* drug permeation was obtained.

REFERENCES

Abdel-Mottaleb, M.M.A., Mortada, N.D., El-Shamy, A.A., Awad, G.A.S. Physically cross-linked polyvinyl alcohol for the topical delivery of fl uconazole. Drug Dev Ind Pharm. 2009; 35 :311–320.

Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm Biopharm. 2005; 59:485-490.

Bidkar, S., Jain, D., Padsalg, A., Patel, K., Mokale, V. Formulation development and evaluation of fl uconazole gel in various polymer bases. Asian J Pharm. 2007; 1:63–68.

Bouwstra, J.A., Honeywell-Nguyen, P.L., Gooris, G.S., Ponec, M. Structure of the skin barrier and its modulation by vesicular formulations. Prog Lipid Res. 2003; 42:1–36.

Grant, S.M., Clissold, S.P. Fluconazole: A review of its pharmacodynamic and pharmacokinectic properties, and therapeutic potential in superfi cial and systemic mycoses. Drugs. 1990; 39:877–916.

Gregoriadis G. 1993. Liposome Technology, 2nd ed. CRC Press, Boca Raton, FL. Hao Y, Zhao F, Li N, Yang Y, Li K. Studies on a high encapsulation of colchicine by a niosome system. Int J Pharm. 2002; 244: 73–80.

Hu C, Rhodes D. Proniosomes: A novel drug carrier preparation. Int J Pharm. 1999; 185:23–35.

Hwang BY, Jung BH, Chung SJ, Lee M, Shim C. In vitro skin permeation of nicotine from proliposomes. J Control Release. 1997; 49: 177-184.

Jadhav, K.R., Kadam, V.J., Pisal, S.S. Formulation and evaluation of lecithin organogel for topical delivery of fl uconazole. Curr Drug Deliv. 2009; 6:174–183.

M. Intakhab Alam, Sanjula Baboota, Kanchan Kohli, Javed Ali, Alka Ahuja. Pharmacodynamic evaluation of proniosomal transdermal therapeutic gel containing celecoxib. ScienceAsia.2010; 36:305-311.

Madhu Gupta, Bhuvaneshwar Vaidya , Neeraj Mishra and Suresh P. Vyas. Effect of Surfactants on the Characteristics of Fluconazole Niosomes for Enhanced Cutaneous Delivery Drug Delivery Research Laboratory. 2011; 39: 376-384.

Manconi M., Sinico C., Valenti D., Lai F., Fadda A.M. Niosomes as carriers for tretinoin III. A study into the in vitro cutaneous delivery of vesicle-incorporated tretinoin. Int J Pharm. 2006; 311:11–19.

Mishra D, Garg M, Dubey V, Jain S, Jain NK. Elastic liposomes mediated transdermal delivery of an anti-hypertensive agent: propranolol hydrochloride. J. Pharm. Sci. 2007; 96: 145-155.

Niven RW, Carvajal MA, Schreier H. Nebulization of liposomes. III. The effects of operating conditions and local environment. Pharm Res. 1992; 9:515–20.

Parikh D.K, Ghosh T.K. Feasibility of transdermal delivery of fluoxetine. AAPS PharmSciTech. 2005; 6:144-9.

Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004; 3:115-124.

Rogerson A, Cummings J, Florence AT. Adriamycin loaded niosomes: drug entrapment, stability and release. J Microcapsul. 1987; 4:321–328.

Shahiwala A, Misra A. Studies in topical application of niosomally entrapped Nimesulide. J. Pharm. Pharm. Sci. 2002; 5: 220-225.

Shamsheer Ahmad S, Sabareesh M, Patan Rafi Khan, Sai krishna P, Sudheer B. Formulation and Evaluation of Lisinopril Dihydrate Transdermal Proniosomal Gels. J App Pharm Sci. 2001; 01 (08):181-185.

Solanki AB, Parikh JR, Parikh RH. Formulation and optimization of piroxicam proniosomes by 3-factor, 3-level Box-Behnken design. AAPS Pharm Sci Tech. 2007; 8(article 86):E1–7.

Uchegbu IF, Schatzlein AG, Tetley L, Gray AI, Sludden J, Siddique S, et al. Polymeric chitosan-based vesicles for drug delivery. J Pharm Pharmacol. 1998; 50:453–8.

Uchegbu IF, Vyas SP. Nonionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm. 1998; 172:33–70.

Vavrova K., Zbytovska, J., Hrabalek, A. Amphiphilic transdermal permeation enhancers: structure-activity relationships. Curr Med Chem. 2005; 12:2273–91.

Vora B, Khopade A.J, Jain N.K. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release. 1998; 54:149-165.

Wong M, Thompson T. Aggregation of dipalmitoylphosphotidylcholine vesicles. Biochemistry. 1982; 21:4133–9.

Yoshioka, T., Strenberg, B., Florence, A.T. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60, and 80) and a sorbitan trimester (Span 85). Int J Pharm. 1994; 105:1–6.

How to cite this article:

Sandeep G, Vasavi Reddy D, Srinivas Reddy Devireddy. Formulation and Evaluation of Fluconazole Pro-Niosomal gel for Topical Administration. J App Pharm Sci, 2014; 4 (07): 098-104.