Enhancement of skin permeability of BCS classIV Bifonazole by Liposomal formulation approach: An in-vitro study

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Abstract:

Fungal infection of skin is now-a-days one of the common dermatological problem. The present work aimed to prepare and evaluate the liposomal formulation of an anti-fungal drug Bifonazole. Total nine batches of Bifonazoleloaded liposome was prepared by thin film method using varying ratio of cholesterol, soya lecithin and stearyl amine. The amount of soya lecithin was kept constant in all batches. Stearyl amine was used as charge imparting agent. The effect of formulation variable on entrapment efficiency, particle size, surface charge and drug release behaviour was studied. The optical microscopy and SEM study demonstrated that the particles had almostspherical and uniform shapes and did not aggregate to each other. Encapsulation efficiency of Bifonazole-loaded liposomes was determined by centrifugation method. The inclusion of positively charged surfactant such as stearyl amine significantly increases the entrapment efficiency of Bifonazole into the liposomes. The LF8 formulation showed the highest drug-loading capacity of 94.34%±3.03 when compared with the other formulations. The cumulative amount of drug release from Bifonazole liposome was 57.25%-93.21%, after 24 hours. The release of Bifonazole from liposomes changed with phospholipid and cholesterol ratio (LF1-LF6). Drug release delayed as molar ratio of soya lecithin increased in the formulation ($p < 0.05$). This might be due to the interaction of Bifonazole with the large surface of lipid bilayer membrane of liposome and soya lecithin layer thickness and fluidity of membrane. In conclusion, stable Bifonazole loaded liposomal formulation was successfully formulated for the topical administration.

Key words: Bifonazole, Liposome, soya lecithin and fungal infection

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INTRODUCTION

Transdermal administration of drug is gaining an important place in modern drug therapy. This therapy is used for non-ionized drug whose dose is usually low. Many drugs are poorly absorbed through the skin by passive diffusion alone because skin acts as a semi-permeable membrane, allows only a small amount of any drug molecule to passively penetrate through it. Ionic drugs do not easily penetrate skin barrier and are not suitable for transdermal delivery unless an external source of energy is provided to drive the drug across the skin. This external energy is provided in the form ultrasound (phonophoresis) or electrical (iontophoresis) energy. The use of topical agents often requires vehicles for modulations or chemical penetration enhancers that are potential irritants or sensitizers[1].

Liposomal system will be adopted because its organized structure could accommodate hydrophilic as well as lipophilic drugs separately, depending upon their solubility characteristics, in both the aqueous and lipid phases and prevent them from degradation, reduced side effects and incompatibility that may arise from undesirably high systemic absorption of drugs and enhanced accumulation of drugs at the site of administration as a result of the high affinity of liposomes with stratum corneum. Liposomes in the nano-meter size range can penetrate small capillaries and be taken up by the cells, thereby allowing an efficient drug accumulation in the target tissues and sustained drug release over a period of days or even weeks after administration[2,3].

Fungal skin infections are infections on the skin caused by a fungus. Fungal skin infection usually affects skin as they live off keratin, a protein that makes up skin, hair and nails.[4] The symptoms of fungal infection include rashes which a variety of different appearances like red, scaly, and dry skin. For the treatment of fungal infections various anti-fungal drugs were used[5].

Bifonazole is a broad-spectrum azole antifungal agent, used to treat skin infections such as tinea, Athlete's foot (tinea pedis), and ringworm of the body. Bifonazole is topically administered once a day (100 mg/day) for 2-3 weeks to treat Athlete's foot, but it shows very low absorption following topical administration through Bifonazole gel[6,7]. Hence, to increase the topical skin permeability, Bifonazole loaded liposome formulations was prepared by thin film hydration method using varying ratio of cholesterol, soya lecithin and stearyl amine.

MATERIALS AND METHODS

Materials:

Bifonazole and cholesterol were obtained from Yarrow Chem products, Mumbai, India. Triethanolamine and soya lecithin (HI media, Mumbai, India), and stearyl amine (Sigma-Aldrich, USA) were the other materials used in the study. All other chemicals and reagents used were of analytical grade.

Methods:

Preparation of Bifonazole Liposome:

Liposomes were prepared by thin film hydration method. Briefly, different concentrations of soya lecithin and cholesterol were dissolved in the chloroform-methanol (1:1) and 1 % Bifonazole was added to the above solution. Drug solution was transferred to a 250 ml round bottom flask and attached to the rotary vacuum evaporator. The flask was kept immersed in a thermostat water bath, with the temperature set at 40°C and rotated at about 100 rpm. Process was allowed to continue till all the liquid had evaporated from the solution and a dry lipid film had deposited on the wall of the flask. When the thin film was formed in the round-bottoms flask, it was hydrated with phosphate buffer of pH 6.8. The suspension was agitated by vortex for 15 minutes and then sonicated for one hour.[8-9]Formulation chart of Bifonazole hydrogel is shown in table 1.

Table 1: Formulation design of Bifonazole loaded liposome

Formulation	Bifonazole (%w/w)	Soya lecithin (mg)	Cholesterol (mg)	Stearyl amine (mg)	Chloroform: Methanol(ml)
LF1	1.0	250	37.5	--	5:5
LF2	1.0	250	50	--	5:5
LF3	1.0	250	100	--	5:5
LF4	1.0	250	150	--	5:5
LF5	1.0	250	200	--	5:5
LF6	1.0	250	250	--	5:5
LF7	1.0	250	150	50	5:5
LF8	1.0	250	150	100	5:5
LF9	1.0	250	150	150	5:5

Evaluation of Bifonazole Liposome

Compatibility study using FT-IR

Infrared spectroscopy was conducted using a Thermos Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm ^{1}. The procedure consisted of dispersing a sample (drug and drug-excipient mixture, 1:1 ratio) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. All spectra were collected as an average of three scans at a resolution of 2 cm ^{1}. The interaction between drug-excipients was observed from IR-Spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug.[10]

Determination of surface morphology

Surface morphology of Bifonazole loaded liposome was determined by optical microscopy and scanning electron microscopy (SEM). The vesicles were examined under an optical microscope and photographed at a magnification of 10× by means of a fitted camera. The morphology of optimized formula was determined using a scanning electron microscope. This determination was performed by applying one drop of optimized liposome to a collodion-coated copper grid, which was then left for about 2 min to allow drying and adherence of the proniosome to the collodion. Subsequently, one drop of uranyl acetate solution was added for 1 min on a grid. The sample was dried, followed by examination with SEM.[8-9]

Encapsulation Efficiency (%EE):

Encapsulation efficiency of Bifonazole in Bifonazole encapsulated liposomes was determined and compared to the original amount added. Free Bifonazole was separated from liposome by centrifugation using ultracentrifuge (Remi, India) at 15,000 rpm, and 25ºC for 30 minutes. A clear solution of supernatant and pellets of liposomes were obtained. The pellet containing only liposomes were disrupted with 0.1% Triton X-100 and vortexed for 5 minutes to ease lysis of the liposomal encapsulated Bifonazole. The vesicles were broken to release the drug, which was then estimated for the drug content.[8-9]The absorbance of the drug was noted at 254 nm. The entrapment efficiency was then calculated using following equation:

EE% = [Amount of entrapped Bifonazole /Total amount of Bifonazole added] × 100

Determination of particle size and zeta potential:

Particle size, zeta potential and polydispersity index (PDI) were measured for all prepared Bifonazole loaded liposome using the dynamic light scattering (DLS) technique at 25 ^{o}C using the Malvern Zettaliter, (Malvern, UK). The Bifonazole-loaded liposomal colloidal dispersion was diluted with purified water before being subjected for measurements.[10]

Drug content estimation:

Drug content estimation was determined by UV method. Briefly, 1 gram of liposome was dissolved in 100 ml of pH 6.8 PBS with Tween 80 (1%) by sonication. Sonication was done for 30 minutes, and drug separation was done by centrifugation (1500 rpm for 15 minutes). Then 1 ml of this solution was transfer to the 10 ml volumetric flask and final volume was made by same solutions. Finally absorbance of prepared solution was measured at 254 nm using UV visible spectrophotometer. The percentage drug content was calculated.[10]

In-vitro drug release studies:

In-vitro Bifonazole release from the liposome was determined using Franz diffusion cell with dialysis membrane with molecular weight cut-off of 8000 Dalton. The water jacketed recipient compartment had total capacity of 25 ml and it had 2 arms, one for sampling and another for thermometer. The donor compartment had internal diameter of 2 cm. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The receptor compartment contained pH 6.8 phosphate buffer saline (PBS) with Tween 80 (1%) as receptor medium (buffer solution) and temperature of receptor medium was maintained at 37°C±1.Then, 1 gram of liposome containing 1% (w/w) Bifonazole was placed on the donor compartment. Aliquots (1 ml) of the medium were withdrawn at 1, 2, 4, 6, 8, 10, 12 and 24 hours, and replaced with the same amount of buffer to maintain sink condition. All samples were filtered through Whatman filter paper (No. 2) and analyzed by UV spectrophotometer (Shimadzu-1800) at 254 nm.[8-9]

Drug release kinetics studies:

Investigation for the drug release from the Bifonazole liposome was done by fitting the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Korsmeyer Peppas model.[11]

Short term stability studies:

The stability of the optimized liposomal formulations was conducted for 3 months. Liposome was stored at room temperature (25±5^{0}C/60%RH) and accelerated temperature (40±5^{0}C/75%RH). At end of three months, formulations were tested for appearance, drug content and *in-vitro* drug release profile.[12]

RESULTS AND DISCUSSION

Fungal infection of skin is now-a-days one of the common dermatological problem. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. Among the topical formulation liposomes have widely investigated in both cosmetics and pharmaceuticals. Liposomes and other types of lipid vesicles have been employed for many years in the cosmetic industry and have been widely investigated for their potential to enhance transdermal absorption and local drug delivery of a variety of agents. In many cases skin penetration is enhanced when liposomal formulations are used compared with formulations containing free drug. Despite years of research the mechanism(s) responsible for liposome-enhanced dermal absorption of drugs by intact skin has not been established. Liposomes of different sizes and different properties can be made by varying the lipid composition, the manufacturing process, and the inclusion of surfactants, and these different factors serve to modify the transdermal transport of the enclosed drugs. Bifonazole liposomes were prepared by thin-film hydration method. Prepared liposome were evaluated for surface morphology, particle size, surface charge, drug content, encapsulation efficiency, drug content, *in-vitro* drug release behaviour, *in-vitro* release kinetics study and short-term stability studies.

Compatibility studies using FTIR:

Infra-red spectrum of drug and polymers were recorded over KBr disc method and obtained spectra were shown in the figure 1-4.The study of the FTIR spectra of Bifonazole demonstrated that the characteristic absorption peaks for the Aliphatic C-H stretching at 2924.87cm^{-1}, aromatic C-C stretching at 1488.48 cm^{-1}, C=N stretch at 1603.13 cm^{-1}, Aromatic amine (C-N stretching) at 1286.42cm^{-1} and Aromatic substitution (C-H bending)at 699.47cm^{-1}. This further confirms the purity of Bifonazole. All the characteristic peaks of Bifonazole were present in the spectrum of drug: soya lecithin, drug: cholesterol, and drug physical mixture, indicating compatibility between drug and excipients used. The spectrum confirmed that there was no significant change in the chemical integrity of the drug. There was no change in functional group peaks of Bifonazole in all the IR-spectra and results were tabulated in table 2.

Table 2: Results of FTIR spectrum of Bifonazole (BFZ)

Functional group	Observed peaks cm^{-1}			
	BFZ (Pure)	BFZ + Soya lecithin	BFZ + Cholesterol	Drug physical mixture
Aliphatic C-H (s)	2924.87	2927.83	2933.72	2938.70
Aromatic C-C (s)	1488.48	1414.81	1411.85	1454.46
Aromatic amine C-N (s)	1286.42	1244.45	1221.59	1221.85
C=N stretch	1603.13	1641.73	1643.70	1643.99
Aromatic substitution (C-H bending)	699.47	708.28	660.10	694.97

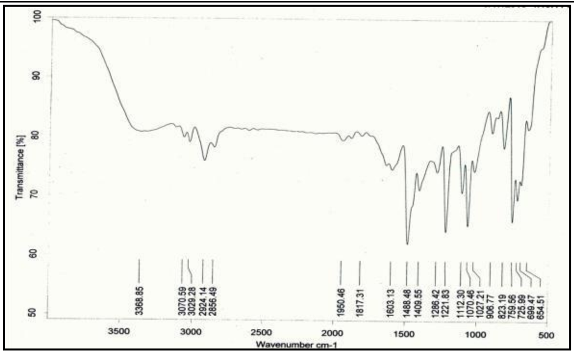

Figure 1: Infrared spectrum of Bifonazole

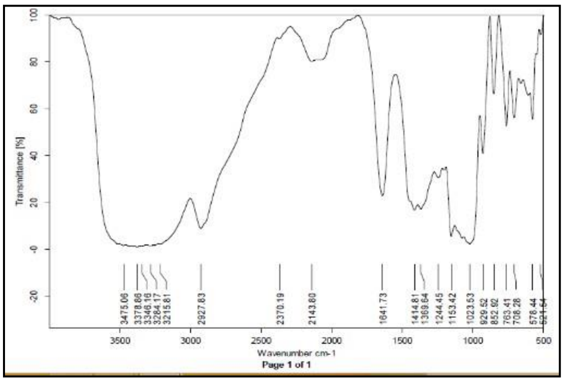

Figure 2: Infrared spectrum of Bifonazole and Soya lecithin mixture

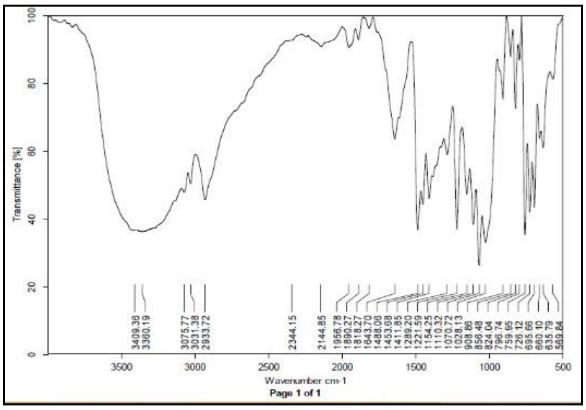

Figure 3: Infrared spectrum of Bifonazole and Cholesterol mixture

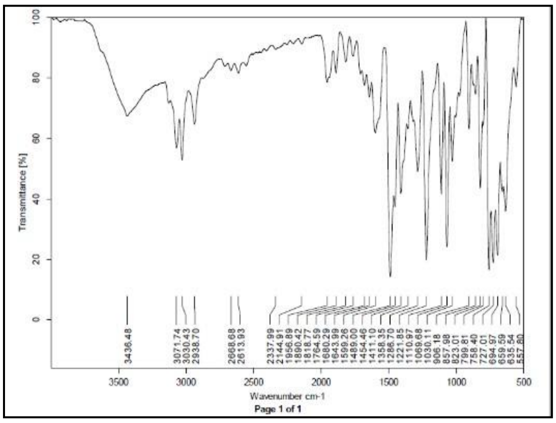

Figure 4: Infrared spectrum of drug physical mixture

Surface morphology of Liposomes:

The morphology of the liposome vesicles were assessed by optical microscopy and scanning electron microscopy for justifying the vesicular characteristics. Optical microscopy was found to be the fast and useful method for preliminary experiment. Scanning electron microscopy enabled the determination of particle size of liposomes formed. The optical microscopy and SEM study demonstrated that the particles had almost spherical and uniform shapes and did not aggregate to each other (figure 5 and 6).

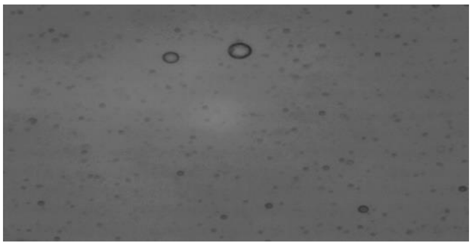

Figure 5: Optical microscopy image of Bifonazole loaded liposome

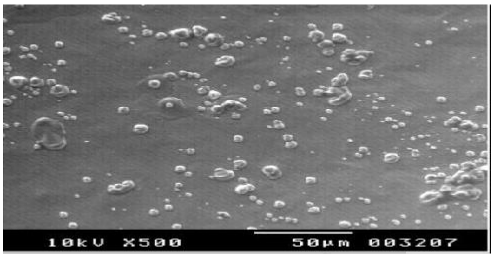

Figure 6: Scanning electron microscopy of Bifonazole loaded liposome

Encapsulation Efficiency (%EE):

Encapsulation efficiency of Bifonazole-loaded liposomes was determined by centrifugation method. Entrapment efficiency is expressed as the percentage of the total amount of drug used initially. Entrapment efficiency of all liposomes was in the range of 48.85% ± 3.74 to 94.34 % ± 3.09. Table 3 shows that Bifonazole entrapment efficiency varied with lipid composition and cholesterol content. The results show that the percentage entrapment efficiency of Bifonazole increased by increasing the cholesterol content. The percentage entrapment efficiency of Bifonazole loaded liposomes (LF1) containing soya lecithin: cholesterol in the ratio 1:0.15 was 48.85%, whereas the entrapment efficiency was higher (84.27%) in liposome LF4, prepared with soya lecithin: cholesterol in the ratio 1.0:0.6. Further increase in entrapment efficiency was not recorded for liposomes composed of soya lecithin: cholesterol in the ratio 1:0.8 and 1:1. Cholesterol molecules are placed between the adjacent phospholipid molecules in liposomal bilayer and hence occupy some space and compete with Bifonazole for incorporation into the bilayer. Additionally, cholesterol makes the bilayer more rigid, which makes the incorporation of the Bifonazole molecules harder. In this study, 1:0.8 and 1:1 molar ratio of cholesterol to the phospholipid caused a dramatic decrease in encapsulation efficiency, which is speculated to be due to defect in the regular linear structure of the liposomal bilayer. Disruption of the regular linear structure of liposomal bilayer causes a prominent decrease in encapsulation efficiency for both lipophilic and hydrophilic molecules. A potential benefit of cholesterol in liposomes is that although the encapsulation efficiency could be decreased, the escape or release of drug molecules from liposomal membrane could also be decreased due to an increase in membrane rigidity. The inclusion of positively charged surfactant such as stearyl amine tends to increase the inter lamellar repeat distances between successive bilayers in the liposome, swelling the structure with the greatest proportion of the aqueous phase. These effects lead to a greater overall entrapped volume. Among the liposome formulation containing Stearyl amine, formulation LF8 (containing 1.0:0.6:0.4 ratio of soya lecithin: cholesterol: Stearyl amine) showed highest percentage of entrapment (94.34%). Further increase in entrapment efficiency was not recorded for liposomes composed of soya lecithin: cholesterol: Stearyl amine in the ratio 1:0.6:0.6.

Table 3: Formulation design of Bifonazole loaded liposome

Formulation	% Entrapment efficiency (n=3, ±SD)
LF1	48.85±3.74
LF2	57.39±2.49
LF3	65.20±3.62
LF4	84.27±3.36
LF5	78.59±2.90
LF6	71.43±3.67
LF7	89.32±3.41
LF8	94.34±3.03
LF9	90.22±3.19

Determination of particle size and zeta potential:

Liposomes were developed through thin-film hydration method, which is the most common method for liposome preparation. Since lipidic composition and concentration could have a significant impact on developing a therapeutically efficient liposomal carrier system, we examined different parameters such as increase in cholesterol ratio, and the presence of more unsaturation's in phospholipid's acyl chain. Since cholesterol has a rigid ring and an ultra-smooth face in its structure, the squeezing process has most likely taken place by allowing the lipids to turn quickly at the extremities. This leads to lipids of high lateral mobility, as well as packed acyl chains. Consequently, this contributes to the variation of sizes since the packing factor affects the intensity and duration of van der Waals forces present in liposomes. In addition, by increasing the concentration of Cholesterol in the formulation, the structural interaction propitiates vesicular aggregations which may lead to slightly bigger liposomes. The results of a study demonstrated that the size of the drug loaded liposome increased significantly from 68.0 nm to 164.6 nm when the cholesterol concentration was increased. Formulation LF1 showed lowest particle (68.0 nm) and formulation LF6 showed highest particle size (164.6 nm).

The effect of stearyl amine concentration on particle size of liposome was also studied. With increase in the stearyl amine concentration the particle size increased. It may attribute the fact the presence of high stearyl amine to the inclusion of a charge inducer in liposomes, which modified the spacing between the adjacent bilayers. The results of a study demonstrated that the size of the drug loaded liposome increased significantly from 137.4 nm to 195.0 nm when the stearyl amine was added in the formulation. It has been previously shown that drug delivery to deeper layers of skin requires liposomal particle size smaller than 600 nm. Vesicles larger than 600 nm tend to stay on the stratum corneum and may dry to form a lipid layer on the skin. Vesicles smaller than 300 nm were able to deliver their payload to some extent into deeper layers of skin. All the formulations used in this study showed a polydispersity index below 0.3, indicating a good homogeneity for the prepared liposomes.

Zeta potential was measured by dynamic light scattering at room temperature. Liposome dispersions were diluted with phosphate buffer before the measurement to adjust the intensity.

The zeta potential values of liposomal formulations (LF1-LF6) were found to be negative and in the range of -18.6 mV to -28.1 mV owing to the net charge of the lipid content in the nano-formulations. Surface charge of liposome LF6-LF9 were found to be positive and in the range of 21.9 mV to 26.2 mV. In general charged liposomes were more stable against aggregation and fusion than uncharged liposomes. The magnitude of zeta potential in all prepared formulations is sufficiently high to prevent coagulation and provide stability for the vesicles. Results of particle size, PDI and zeta potential are showed in table 4.

Table 4: Evaluation of Bifonazole loaded liposome

Formulation	Particle size (nm)	PDI	Zeta potential (mV)
LF1	68.0	0.190	-23.4
LF2	122.1	0.231	-20.5
LF3	129.0	0.229	-23.1
LF4	134.5	0.204	-24.0
LF5	147.2	0.166	-26.6
LF6	164.6	0.199	-18.6
LF7	137.4	0.237	26.9
LF8	182.6	0.219	29.5
LF9	195.0	0.213	34.22

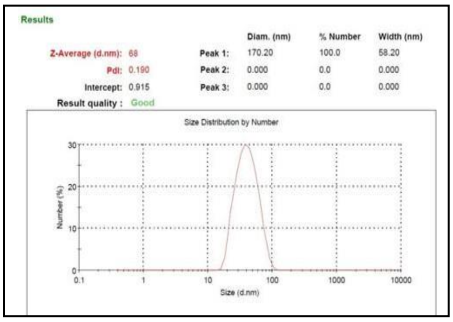

Figure 7: Particle size distribution of Bifonazole loaded liposome

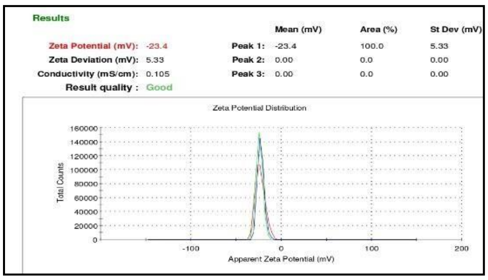

Figure 8: Zeta potential determination of Bifonazole loaded liposome

In-vitro drug release studies:

The drug release profiles of Bifonazole liposomes are displayed in figure 9. Optimal conditions for drug release were determined from the equilibrium solubility of Bifonazole. Bifonazole has good solubility in phosphate buffer solution (pH 6.8) containing 1.0% Tween 80. The cumulative drug release from Bifonazole liposome was 57.25%-93.21%, after 24 hours. As seen in figure 9, the release of Bifonazole from liposomes changed with phospholipid and cholesterol ratio (LF1-LF6). Drug release delayed as molar ratio of soya lecithin increased in the formulation ($p < 0.05$). This might be due to the interaction of Bifonazole with the large surface of lipid bilayer membrane of liposome and soya lecithin layer thickness and fluidity of membrane. The release of Bifonazole from liposomes was not completed during the test and the amount of released drug decreased with the increase of cholesterol content in the liposomes (LF1-LF6). Bifonazole release from LF6 formulation, which contained the highest molar ratio of cholesterol, was the lowest among all other formulations (68.42%). High membrane permeability and the stabilizing effect of cholesterol on membrane structure may be the possible reason. As seen in figure 9, when electropositive detergent like Stearylamine was added into the formulation, the electropositive charge of the liposomes increased and thus slows the release of Bifonazole from liposomes. The findings of present investigation showed that the drug release was slower with the addition of Stearyl amine into the liposomal formulations (LF7-LF9).

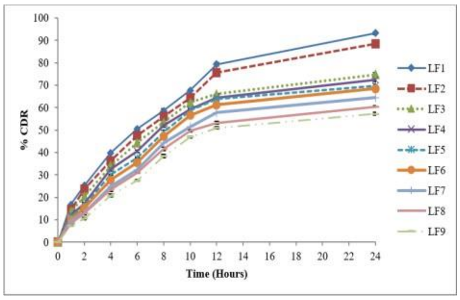

Figure 9: Comparative *in-vitro* drug release profile of Bifonazole liposomes (LF1-LF9)

Drug Release Kinetics:

The kinetics of drug release from a liposomal formulation is a critical part of the rational design of drug delivery systems, as it is a major determinant on the efficacy of delivery of the carrier *in-vivo* and the subsequent release of the free drug. An *in-vitro* release profile reveals important information on the structure and behaviour of the formulation, possible interactions between the drug and carrier composition, and their influence on the rate and mechanism of drug release. The pattern of the drug release from the Bifonazole liposome was investigation by different kinetic equations. The data of cumulative release were subjected to various kinetics models and results obtained from release kinetics studies were depicted in table 5. The *in-vitro* release profile of drug from all liposomal gel formulations could be expressed by Higuchi kinetics, as the plots shows high linearity (r^2 = 0.990-0.998) in comparison to zero order (r^2 = 0.801-0.896) and first order kinetics (r^2 = 0.921-0.976). Liposome gel had the highest r^2 for the Higuchi model indicating that the drug release process was controlled by diffusion. This is in agreement with previous reports. The correlation coefficients obtained for the Korsmeyer–Peppas equation were also quite high (0.870 to 0.932). All of the values of the release exponent (n) were higher than 0.85, which corresponds to supercase II release mechanism.

Table 5: Drug release kinetics of formulation LFG1 to LFG9

Formulation code	KINETIC MODELS					Model Followed
	Higuchi	Zero order	First order	Korsmeyer-Pappas		
	r^2	r^2	r^2	r^2	n	
LFG 1	0.995	0.872	0.956	0.927	0.901	supercase II
LFG 2	0.991	0.869	0.973	0.921	0.870	supercase II
LFG 3	0.997	0.801	0.934	0.932	0.896	supercase II
LFG 4	0.998	0.895	0.921	0.929	0.890	supercase II
LFG 5	0.995	0.878	0.976	0.978	0.932	supercase II
LFG 6	0.990	0.892	0.968	0.960	0.884	supercase II
LFG 7	0.996	0.890	0.970	0.989	0.919	supercase II
LFG 8	0.994	0.894	0.938	0.981	0.925	supercase II
LFG 9	0.994	0.896	0.938	0.981	0.922	supercase II

r^2=Regression coefficient, **n=** Exponential value

Physical Stability at Storage Condition:

Stability of liposomes is an essential requirement concerning its size and efficacy. Stability of Bifonazole loaded liposomes (LF8) was examined over a period of 30 days, 60 days and 90 days in triplicate. Drug content and release profile were monitored and did not display any significant change compared to initial sample (Day 1). Interestingly, significant changes in drug content were not observed up to 90 days of storage. Moreover, there was no significant change in the appearance of liposome. Thus, the developed liposome formulation was physiochemically stable throughout the stability period. Results of stability studies were shown in table 6.

Table 6: Stability studies for liposome formulation LF8

Days	25°C/60% RH		40°C/75% RH	
	% Drug content	**% CDR**	**% Drug content**	**% CDR**
Initial	101.16±0.60	56.91 ±0.42	101.16± 0.60	56.91 ±0.42
30	101.12±0.47	56.86 ±0.11	101.02± 0.36	56.54 ±0.57
60	101.05±0.93	56.42 ±0.40	100.56± 0.71	56.22 ±0.90
90	100.32±0.35	56.10 ±0.83	100.18± 0.94	56.08 ±0.48
P value	>0.05	>0.05	>0.05	>0.05

CONCLUSION

Liposomes are microscopic vesicles consisting of phospholipid bilayers that enclose aqueous compartments and are utilized as drug-delivery systems for both hydrophilic and lipophilic drugs. Liposomes are one of the most suitable drug-delivery systems to deliver a drug to the target organ and minimize the distribution of the drug to non-target tissues. The importance of liposomes as a drug-delivery vehicle is now becoming more established, and they deliver drugs in a controlled manner when compared with conventional dosage forms. In the present research work, Bifonazole loaded liposome was prepared by thin film method. Nine different formulations of liposome was prepared by varying ratio of cholesterol, soya lecithin and stearyl amine. The amount of soya lecithin was kept constant in all batches. Encapsulation efficiency of Bifonazole-loaded liposomes was determined by centrifugation method. The inclusion of positively charged surfactant such as stearyl amine significantly increases the entrapment efficiency of Bifonazole into the liposomes. The LF8 formulation showed the highest drug-loading capacity when compared with the other formulations. Bifonazole-loaded liposomal gel showed prolonged drug release profile. Taken together, these results revealed that the merits of the developed liposomal formulation as an effective and safe treatment of fungal infection among patients justify their potential in strengthening the efficacy and safety of the drug.

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