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FORMULATION AND EVALUATION OF LIPOSOMAL GEL OF KETOCONAZOLE

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ABSTRACT

Ketoconazole is an imidazole derivative used for the treatment of local and systemic fungal infection. The oral use of Ketoconazole is not recommended as it has many side effects. The present study was designed to formulate and evaluate different ratio of topical gel containing Ketoconazole for treatment of fungal infection of skin. Antifungal drug, Ketoconazole was encapsulated in liposomes for topical application. Ketoconazole liposomes were prepared by thin film hydration technique using soya lecithin, cholesterol and drug in different weight ratios. The prepared liposomes were characterized for entrapment efficiency, in-vitro drug release (by franz diffusion cell) and viscosity, Release kinetic. The studies demonstrated successful preparation of Ketoconazole liposomes and effect of soya lecithin cholesterol weight ratio on entrapment efficiency and on drug release.

KEYWORD: Ketoconazole, soya lecithin, cholesterol, methyl paraben, Triethanolamine.

INTRODUCTION

Ketoconazole have broad spectrum activity against systemic and superficial mycoses. It is readily but incompletely absorbed after oral dosing and it varies among individuals. Common side effects associated with Ketoconazole therapy include mild burning at the application its,

severe allergic reactions, blisters, irritation, pain or redness.[1] Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Fungal infections of skin are one of the common dermatological problems. Among the topical formulations a wide choice for the treatment from solid dosage to semisolid doses forms and to liquid dosage formulation the transparent gels have widely accepted in both cosmetics and pharmaceuticals.[2] A wide variety of vehicles ranging from solid to semisolids and liquid preparations are available for topical treatment of dermatological disease as well as skin care. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical route. It is freely soluble in dichloromethane; soluble in chloroform and in methanol; sparingly soluble in ethanol (95%) practically insoluble in water and ether,[3] There are various medicated products that are applied to the skin. Such products are referred as topical or dermatological products. There are various Hydrophilic polymers such as carbopol 940, hydroxy propyl methyl cellulose (HPMC), Sodium alginate that are used in topical gel delivery system. Based on molecular fraction these polymers are used concentration between 1-5 % in topical formulation.[4]

Topical delivery

It is necessary to understand the anatomy, physiology and physiological properties of the skin. Microscopically skin is composed of three histological layers: epidermis, Dermis and Hypodermis (subcutaneous layer). The epidermis is 0.1 -1.5 mm thick. It is further divided into five parts: stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum, the epidermis forms the pigment melanin. The squamous cell layer is the thickest layer of epidermis and helps to move certain substances in and out of the body. Nerve endings are responsible for the sense of touch. The hypodermis also known as subcutaneous tissue is the deepest layer of skin which acts as an insulator conserving body heat and as a shock absorber protecting internal organ from injury. It also stores fat.[5] The blood vessels, nerves, lymph vessels and hair follicles also cross linking through these layers. The barrier properties of intact skin limit the permeability of wide variety of substance including pharmaceutical active agent. The drug release from all gelling agents through standard cellophane membrane was evaluated using Franz diffusion cell.[6]

Topical route of administration

Drug molecules contact at skin surface with cellular debris, microorganisms and other materials which effect permeation. The applied medicinal substances follow three pathways:

- Through hair follicles
- Across continuous stratum corneum
- Via sweat duct

This route of drug delivery has gained popularity because it avoids first pass metabolism, gastrointestinal irritation and metabolic degradation associated with oral administration. The pathway of drug movement through this layer is believed to be mainly transcellular. Although the paracellular pathways becomes important for small molecular weight compound.[4] Being a diffusion barrier the stratum corneum also serves as a reservoir for compound such as corticosteroids, grisofulvin and many other drugs. Upon reaching the subcutaneous tissue there is evidence that some drugs e.g. Like thyroxin estradiol and corticosteroids remain in this layer for an extended period of time or for prolonged release of drugs..Fungal infections are very common and can be topical as well as systemic. Treatment of fungal infection includes medicines like fluconazole, miconazole, ketoconazole, clotrimazole and grisofulvin.[7]

LIPOSOMAL GEL

Liposomes are microscopic vesicles composed of a bilayer of phospholipids or any similar amphipathic lipids. They are defined as "Liposome is simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule." Various amphipathic molecules have been used to form liposome. The drug molecules can either be encapsulated in aqueous space or intercalated into the lipid bilayer.[8] Liposome as a microstructure consists of one or more concentric spheres of lipid bilayer separated by water or aqueous buffer compartments. Liposomes are microscopic vesicular structures consisting of one or more concentric spheres of lipid bilayers, enclosing aqueous compartments.[9] Liposomes have many of the requirements for good drug delivery systems as they are relatively nontoxic and biodegradable. The formulation of an appropriate liposomal system as a carrier for a given drug is dependent on the type of the lipid used and the method of preparation. According to their size they are known as small unilamellar vesicles (SUV) or large unilamellar vesicles (LUV). If more bilayers are present they are referred to as multilamellar vesicles (MLV).[10] Drug candidates for liposomal encapsulation are those that have potent pharmacological activity and are either highly lipid or water soluble. If a drug is water soluble, it will be encapsulated within the aqueous compartment and its concentration in the liposomal product will depend on the volume of the entrapped water and the solubility

of that drug in the encapsulated water. They are usually applied to the skin as liquids or gels.[11] Skin has been considered as an alternative route for local and systemic treatment. Topical dosage forms provide relatively consistent drug levels for prolonged periods and avoid gastric irritation, as well as the other typical side effects of oral NSAID administration.[12] Considering the all above mentioned, liposome vesicles embedded into a suitable gel matrix, could be attractive candidates for the use as drug delivery vehicles for transdermal application of ketoconazole. Liposomes also facilitate intracellular delivery via fusion with the plasma membrane, receptor-mediated endocytosis and phagocytosis.[13]

Ketoconazole is a selective, irreversible inhibitor of Type B monoamine oxidase is a drug used for the treatment of early-stage Parkinson's disease, depression and senile dementia. Following oral administration bioavailability of this drug is very low due to different path of metabolism. Because of prominent first pass effect and their tendency to inhibit monoamine oxidase in gut, alternative route of administration is developed. Minor side effects such as dizziness, dry mouth, and difficulty falling or staying asleep, muscle pain, rash, nausea and constipation have been seen. Thus bioavailability problems associated with oral administration generate interest of designing novel drug delivery system of Ketoconazole with an alternative route of administration. Transdermal delivery of drugs provides advantages over conventional oral administration.[11] The benefit of transdermal systems includes improved patient compliance, convenience and elimination of hepatic first pass effect. Nevertheless, most drugs are not applicable to this mode of administration due to the excellent barrier properties of the skin.[14] Molecules must first penetrate the stratum corneum, the outer horny layer of the skin. The molecule then penetrates the viable epidermis before passing into the papillary dermis and through the capillary walls into systemic circulation. It is the stratum corneum, a complex structure of compact keratinized cell layers that presents the rate limiting step and the greatest barrier to absorption of transdermally administered drugs.[15]

MATERIAL AND METHOD

MATERIAL

Ketoconazole and soya lecithin was obtained as a gift sample from Ananta Medicare Ltd., Sri Ganganagar (Raj).Cholesterol, Carbopol941, teriethanolamine etc. All excipients were of laboratory reagent grade.

METHOD

PREPARATION OF LIPOSOME

Liposome was prepared by thin film method. Briefly soya lecithin, cholesterol, and 10 mg ketoconazole were dissolved in 5ml chloroform. The quantities of lecithin and cholesterol were changed to enhance loading drug in liposome. Then the mixture was evaporated in a rotary evaporator at 150 rpm and with temperature below the boiling point of chloroform (62^0C) until the thin film formed in the round-bottomed flask (approximately 30-40min). Than it was hydrated with phosphate buffer saline for 30 min. Different ratio of all ingredient are given below:

Table 1: Compositions Ratio

Formulation no.	Compositions ratio (mg)		
	Lecithin	Drug	Cholesterol
F1	100	10	5
F2	100	10	10
F3	100	10	20
F4	100	10	40
F5	100	10	60
F6	100	10	80
F7	125	10	10
F8	125	10	20
F9	150	10	10
F10	150	10	20

PREPARATION OF LIPOSOMAL GEL

Carbopol 941 (1%) was added slowly to a PBS buffer solution (pH 7.4), under constant stirring by a paddle stirrer. For gel preservation, methyl paraben (0.2%) was added. Then triethanolamine was added for achieving neutral pH and clearing of the gels. After addition of the full amount of solid material, the gels were allowed to swell under moderate stirring.

Preparation of SUV liposome

SUV liposomes were obtained by sonication of MLV liposome in an ultrasonic bath 30 min at room temperature.

Determination of ketoconazole entrapment in liposomes

The liposomal suspension was centrifuged at 3000 rpm for 4-5hr. The supernatant was removed and the liposomes were disrupted with ethanol 70% and the quantity of drug was measured using a spectrophotometer at 291 nm.

Entrapment efficiency = $\frac{\text{drug Entrapped}}{\text{total drug}} \times 100$

Microscopy

liposomes were examined by optical microscope to determine the shape and lamellarity of vesicles.

Preformulation studies

Preformulation studies are 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.

1. Organoleptic properties / Description of drug

The organoleptic studies like general appearance like nature, color, odor, etc. were performed by visual observation. The sample of drug was observed for colour, state and solubility.

2. 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 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.

3. Solubility studies

Quantitative determination of solubility was made by adding solvent in small incremental amount to test tube or beaker containing accurately weighed amount of solute. After each addition, system is vigorously shaken and put the sample on water bath shaker for 24hrs at 37^0C. After 24 hrs centrifuge the sample at 3000 rpm for 3-4hrs, followed filter the sample with methanol and take absorbance using UV spectrometer.

4. Determination of absorption maxima (λ_{max}) of drug by UV spectrometer

UV scan was done to know the λmax for preparation of standard curve. For this purpose drug sample having concentration of 100µg/ml was prepared using phosphate buffer saline pH 7.4.

5. In-vitro drug release study from liposomes

Studies of the drug release/diffusion from liposomal system are directed toward the approaches that are relevant to the in vivo condition. In vitro diffusion studies were carried

out using Franz diffusion cell. Egg membrane was sandwiched between the lower cell reservoir and the glass cell top containing the sample and secured in place with a pinch clamp. The receive compartment (volume 21 ml) phosphate saline buffer solution pH 7.4 (to maintain sink condition). A sample was placed evenly on the surface of the membrane in the donor compartment. 2 ml of receptor fluid were withdrawn from the receiving compartment at5, 10, 15, 30, 45, 60 min and replaced with 2 ml of fresh solution. Samples were assayed spectrophotometrically for drug content at 242 nm.

6. Percent yield

Thoroughly liposome were collected and weighed accurately. The percentage yield was then calculated using formulae given below,

$$\text{Percentage Yield} = \frac{\text{Mass of obtained by practicaly}}{\text{Total weight of drug, polymer \& } lecithin} \times 100$$

7. Drug content and content uniformity

The gel sample (100 mg) was withdrawn and drug content was determined using UV spectrophotometer. Similarly, the content uniformity was determined by analyzing drug Concentration in gel taken from 3 to 4 different points from the container. In case of liposomal gel, it was shaken with sufficient quantity of methanol to extract the drug and then analyses by using UV spectrophotometer.

8. Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

9. Spreadability

A sample of 0.5 g of each formula 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 results obtained are average of three determinations.

10. Viscosity Estimation

The viscosity of gel was determined by using a Brookfield DV-E viscometer model with a T-Bar spindle in combination with a helipath stand.

a) Selection of spindle

Spindle 64 was used for the measurement of viscosity of all the gels.

b) Sample container size

The viscosity was measured using 20 gm of gel filled in a 100ml beaker.

c) Spindle immersion

The spindle (64) was lowered perpendicular in the centre taking care that spindle does not touch bottom of the jar.

d) Measurement of viscosity

The spindle (64) was used for determining the viscosity of the gels the factors like temperature, pressure and sample size etc. Which affect the viscosity was maintained during the process. The helipath T- bar spindle was moved up and down giving viscosities at number of points along the path. The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.

11. Homogeneity

After the gels have been set in the container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.

Visual inspection

All developed gel formulae were inspected for their homogeneity, color and presence of lumps by visual inspection after the gels have been set in the container.

12. Extrudability study

After the gels were set in the container, the formulations were filled in the collapsible tubes. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

13. Release kinetics

Release kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of in vitro drug dissolution data to predict in vivo bio-performance can be considered as the rational development of

controlled release formulations. Data obtained from the in vitro release studies were fitted to various model dependent kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Peppas model.

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES

1. Description of drug

Table 2: Description of drug

S.no	Properties	Inference
1.	Colour	White Coloured
2.	Solubility	Practically insoluble in water, soluble in chloroform, methanol, ethanol
3.	Odour	Odourless

2. Drug Identification (λ_{max})

By absorption spectrum method

The accurately weighed quantity of drug was dissolved in sufficient volume of 1.2 pH of HCL 0.2 N and scan was obtained on UV-VIS spectrophotometer. The wavelength at which maximum absorbance obtained was considered as maximum wavelength (λ_{max}) i.e 269.6 nm for the drug.

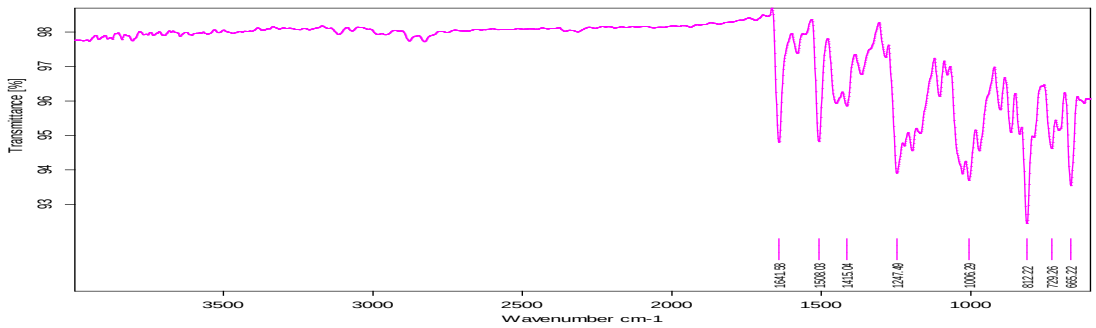

Figure 1: FTIR spectrum of ketoconazole (Fresh sample)

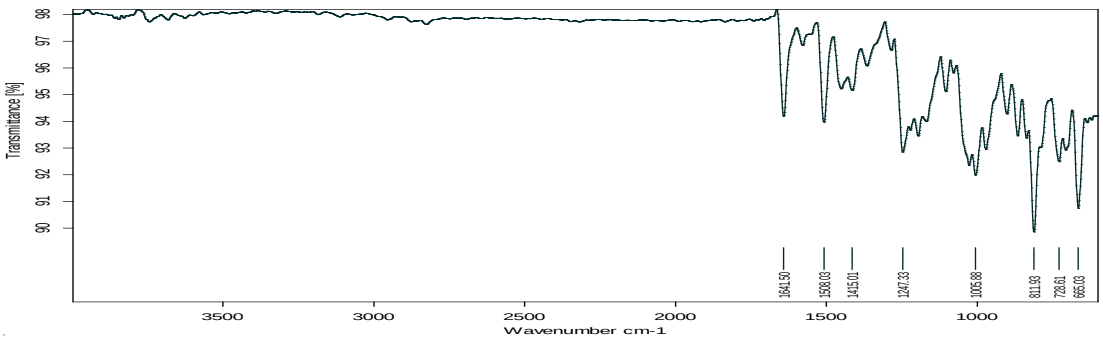

Figure 2: FTIR spectrum of ketoconazole (After 15 days)

The Infrared spectra of Ketoconazole were recorded between 600 to 3500cm^{-1} on FTIR from the FTIR studies at 666.22 and 1641.58 are the characteristics peaks of Ketoconazole. Peaks obtained in spectrum of pure drug (fresh & after 15 days) were similar to that given in standard.

Drug- excipients compatibility study by FTIR

Drug and excipients were accurately weighed and mixed and the resulting mixtures were scaled in screw glass vials and kept at a 50°C for 15 days The possible interaction between the drug and excipients were studied by Infra-red spectroscopy. Below spectrum shows the peaks of pure drug sample and polymers as compare to standard drug sample that is i.e. no chemical reaction occurs between polymers and drug samples.

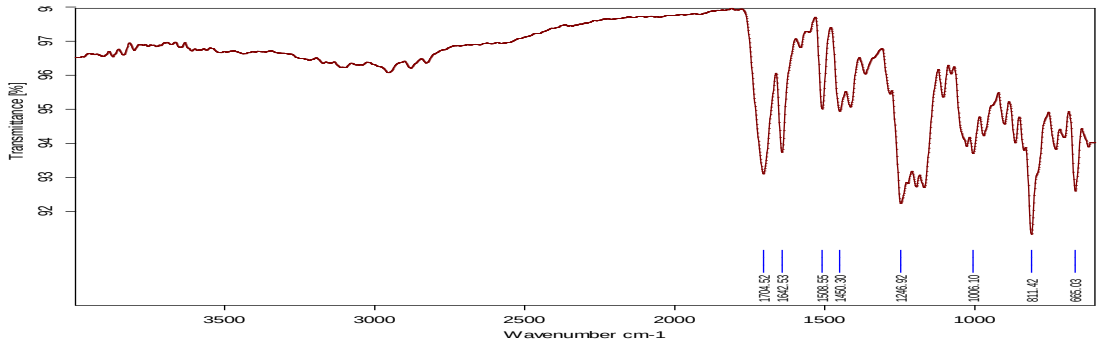

Figure 3: FTIR Spectrum of ketoconazole with carbopol 941

FT-IR study showed that there was no major change in the position of peak obtained in the carbopol 941 alone and in a mixture of drug with, which shows that there was no interaction between drug and carbopol 941.

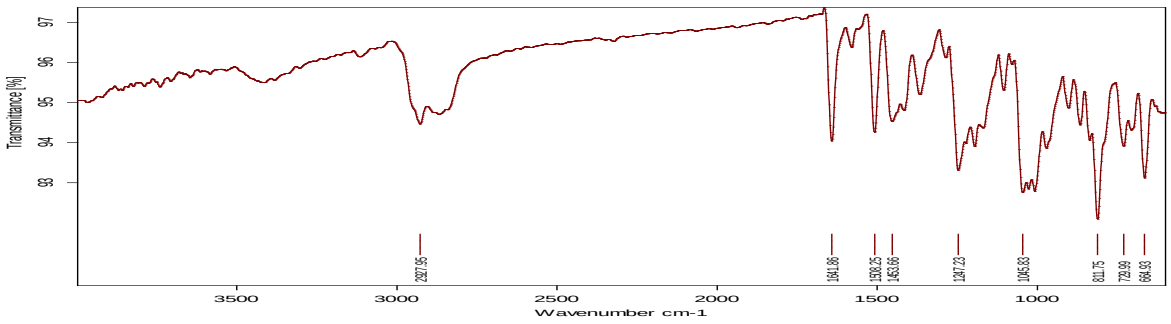

Figure 4: FTIR Spectrum of ketoconazole with cholesterol

FT-IR study showed that there was no major change in the position of peak obtained in the cholesterol alone and in a mixture of drug with , which shows that there was no interaction between drug and cholesterol.

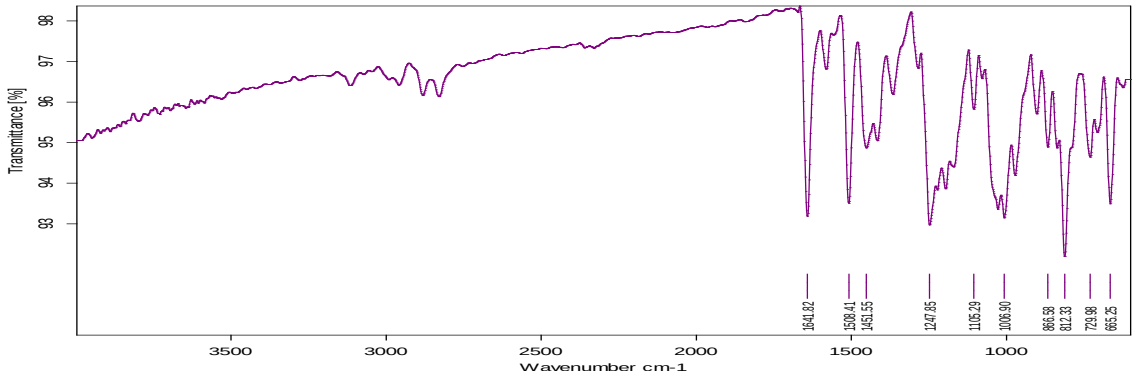

Figure 5: FTIR Spectrum of ketoconazole with soya lecithine (fresh)

Preparation of standard calibration curve

Obtained absorbance was shown in the tables and standard calibration curves of Ketoconazole in different solvents of varying pH were shown in figures 6.

Table 3: Standard calibration curve in 0.2N HCl pH 1.2 at λ_{max} 269.6 nm

Concentration in µg	Absorbance
20	0.038
40	0.070
60	0.110
80	0.144
100	0.183

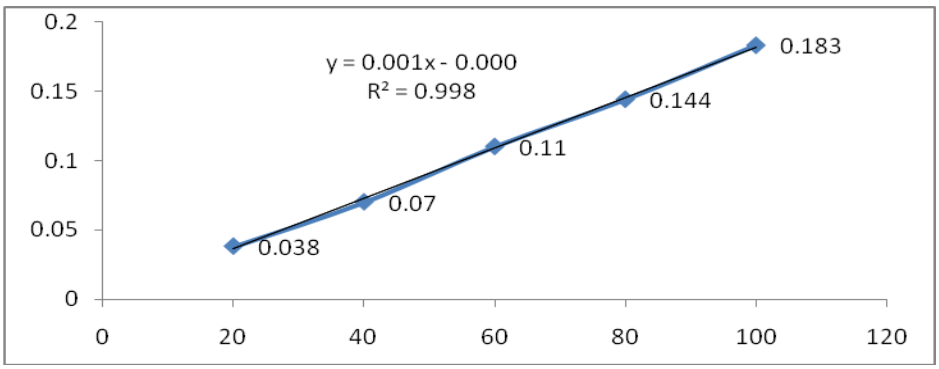

Figure 6: Standard calibration curve in 0.2N HCl pH 1.2 at λ_{max} 269.6 nm

Table 4: Standard calibration curve in phosphate buffer saline pH 7.4 λ_{max} 242.0 nm

Concentration in µg	Absorbance
20	0.178
40	0.224
60	0.295
80	0.348
100	0.432

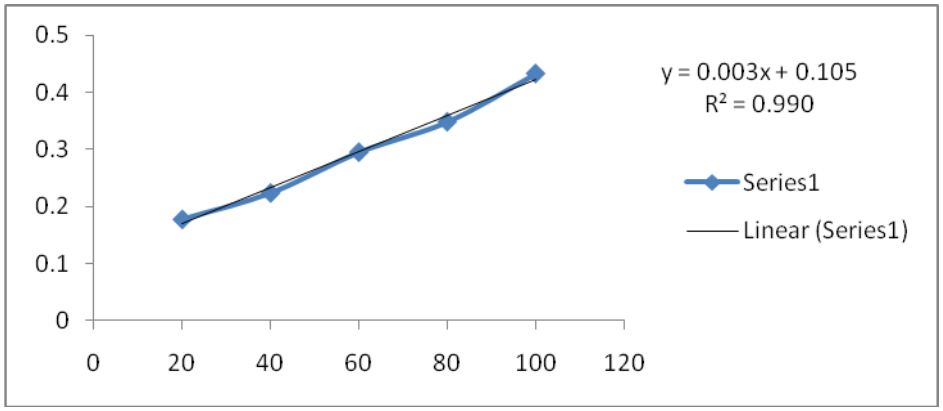

Figure 7: Standard calibration curve in PBS pH 7.4 λ_{max} 242.0 nm

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 melting point apparatus. The temperature in the apparatus was gradually increased and the observed of temperature was 150^0C.

Table 5: melting point

SNo	Melting point	Average± S.D.
1	150^0	150±0.577
2	150^0	
3	151^0	

pH determination

The pH of the F_2 with carbopol941 was found in between 6.6-6.9. This pH is found to be close with the pH of human skin and hence it can be assumed that no skin irritation will occur after application of gel containing liposomal drug.

Table 6: pH determination

S.NO.	pH determination	Average± S.D.
1	6.7	6.733 ± 0.152
2	6.9	
3	6.6	

Solubility studies

Solubility of ketoconazole in distilled water, phosphate buffered saline (PBS; pH 7.4), Phosphate buffer pH 7.4 at 32^0C was determined. The low solubility of ketoconazole in

distilled water was found, which proposed that ketoconazole is lipophilic in nature. The solubility of ketoconazole in PBS (pH 7.4) was found to be good solubility.

Determination of ketoconazole Entrapment in liposomes

The liposomal suspension was centrifuged at 3000 rpm for 4-5 hrs. The supernatant was removed and the liposomes were disrupted with ethanol 70% and the quantity of drug was measured using a spectrophotometer at 291.0nm.

Table 7: Determination of ketoconazole entrapment in liposomes

Formulation no.	Compositions ratio in mg			Drug entrapment
	lecithin	Drug	Cholesterol	
F1	100	10	5	79.5±0.002
F2	100	10	10	90.5±0.002
F3	100	10	20	80.5±0.003
F4	100	10	40	51.5±0.006
F5	100	10	60	68.0±0.001
F6	100	10	80	63.5±0.001
F7	125	10	10	60.0±0.002
F8	125	10	20	55.5±0.001
F9	150	10	10	53.5±0.001
F10	150	10	20	52.5±0.006

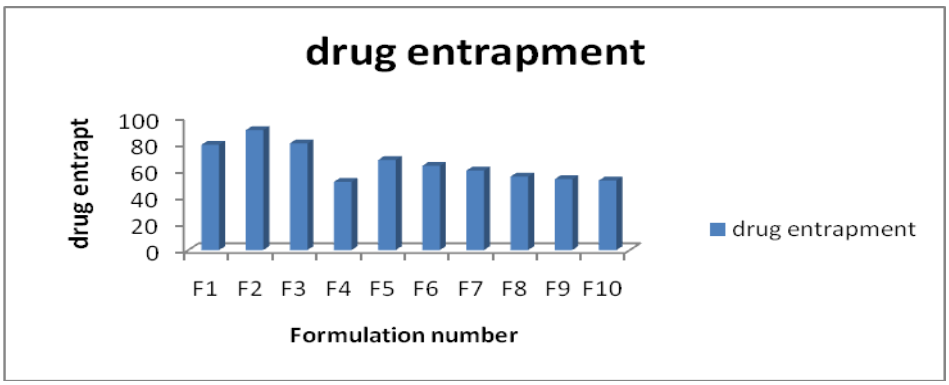

Figure 8: drug entrapment efficiency of ketoconazole gel

Results of drug entrpment are shown in table 7. After various formulation of ketoconazole gel the drug Entraptment efficiency of the formulated gel (F_2) was estimated and the results were in the range of 52.5 to 90.5 %. The drug entrapment determination also showed that the drug was uniformly distributed throughout the gel.

Percentage yield of the prepared liposome

Percentage yield of different formulation was determined by weighing the lipsome and take absorbance by UV Spectroscopy. The percentage yield of different formulation was in range

of 51.25-92.66 % as shown in Table 8. The maximum percentage practical yield was found in F_2.

Table 8: Percentage yield of the prepared liposome

Formulation Batch	Initial Weight of Ingredients (mg)	Theoretical Yield (mg)	Yield of Formulation (mg)	% Yield
F_1	575	575	423	73.56
F_2	600	600	556	92.66
F_3	650	650	503.2	77.41
F_4	750	750	442.0	58.93
F_5	850	850	590.3	69.44
F_6	950	950	635.4	66.88
F_7	725	725	463.7	63.95
F_8	775	775	452.9	58.43
F_9	850	850	463.5	54.52
F_{10}	900	900	461.3	51.25

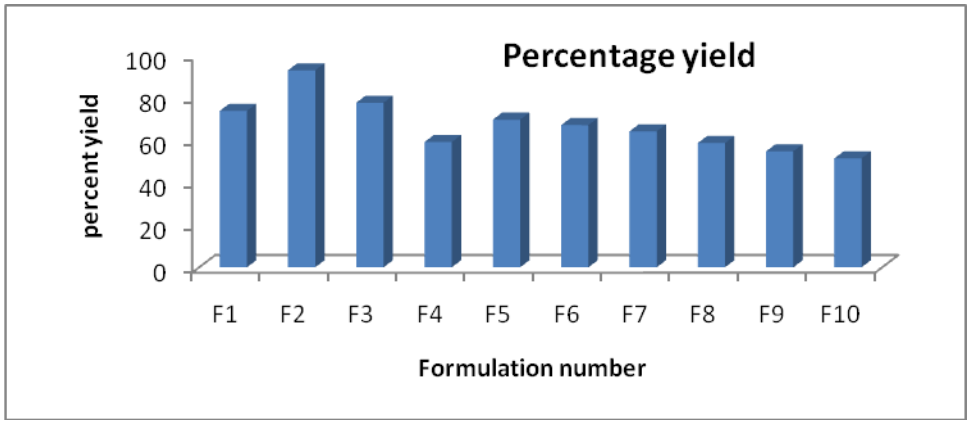

Figure 9: Percentage yield of liposome

Determination of Drug Content

Table 9: Drug content of formulation batches

Formulation Batch	Drug content in %
F_1	73.56%
F_2	92.66%
F_3	77.40%
F_4	58.92%
F_5	68.64%
F_6	66.88%
F_7	63.94%
F_8	58.42%
F_9	54.52%
F_{10}	51.24%

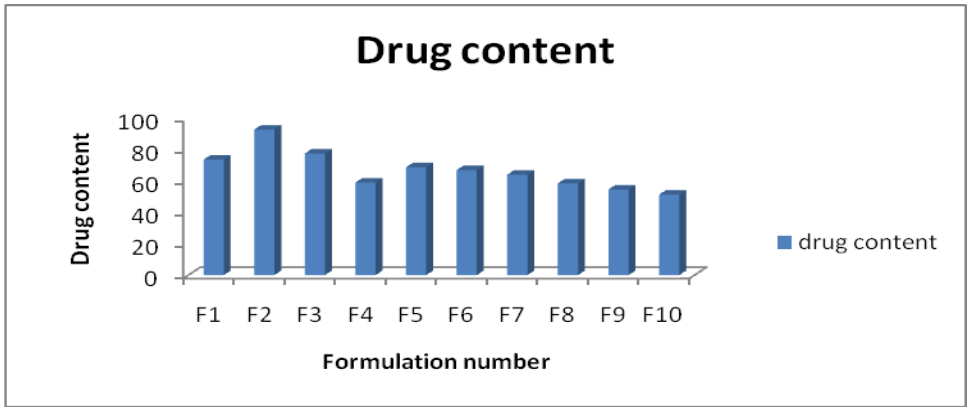

Figure 10: Drug contant of ketoconazole gel

Results of drug content are shown in graph 10. After various formulation of ketoconazole gel the drug content of the formulated gel (F_2) was estimated and the results were range of 51.24 to 92.66 %. The drug content determination also showed that the drug was uniformly distributed throughout the gel. The drug content of formulation F_2 showed highest drug content percentage.

In-vitro drug release study from liposomes gel in 7.4 PBS buffer

Table 10: Cumulative % Release at Different Time intervals

Cumulative % Release at Different Time Intervals										
Time	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
0 min	0	0	0	0	0	0	0	0	0	0
5 min	18.88	19.55	14.44	14.22	14.00	16.00	14.22	16.66	10.22	14.00
10min	22.88	31.33	26.22	18.44	16.66	17.77	15.77	18.66	12.22	15.77
15min	27.77	42.88	40.88	23.55	20.66	21.33	20.00	20.88	16.44	17.11
30min	38.88	53.33	46.66	33.77	26.00	24.00	23.55	23.77	17.11	25.77
45min	46.44	61.55	57.77	39.55	28.88	27.55	26.66	25.77	20.66	30.66
60min	56.66	65.77	63.77	43.11	36.88	34.66	33.33	28.22	25.77	35.55

In vitro drug release studies of all the formulations of liposomal were carried out in phosphate buffer saline pH 7.4 solution. It was observed that the drug release pattern of different ratio of liposomal gel containing ketoconazole. These gels showed the drug effects in vitro release.

Formulations with different ratio of ketoconazole (F_1, F_2, and F_3) showed high release of drug when compared to formulations with combination of different ratio of ketoconazole (F_4-F_{10}). The formulation F_2 was more solubilized and drug release was also high. The formulation of F_9 was less solubilized which retards the drug release to a greater extent. The plot of

cumulative percentage drug release V/s time (hr.) for all formulations was plotted and depicted in Figure 12 respectively.

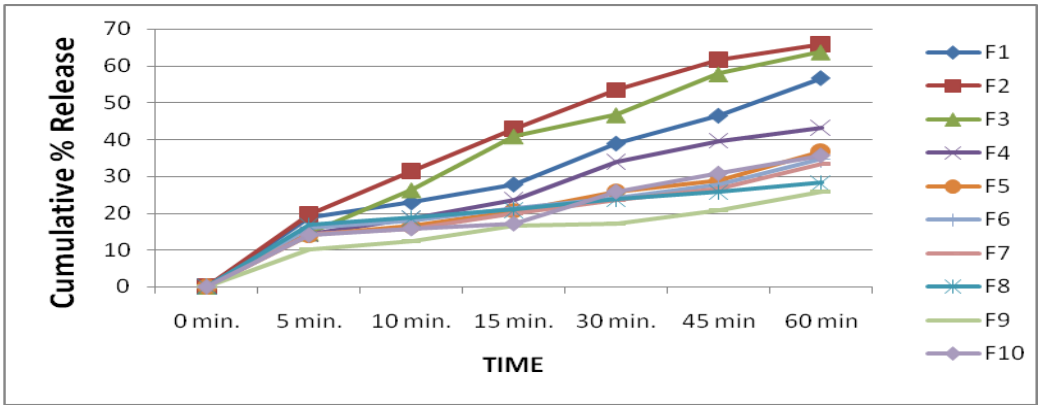

Figure 11: Comparative Dissolution Profile Data of all Formulations

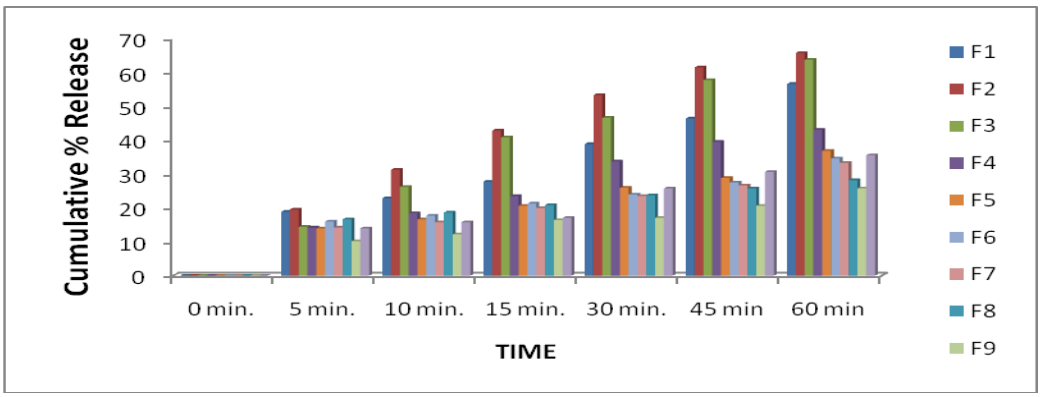

Figure 12: Comparative Dissolution Profile Data of all Formulations

As per as the percentage yield, drug content and dissolution studies are concerned, it indicated that F_2 formulation gives best percentage practical yield, and drug content shows best dissolution release. By the result observation, it can conclude that F_2 formulation should be a better candidate for liposomal gel.

Homogeneity

Visual examination

The prepared gel of F_2 formulae was inspected visually for their color and syneresis. The developed preparation of F_2 is much clear and transparent. The developed gel F_2 showed good homogeneity with absence of lumps and syneresis.

Viscosity

Brookfield digital viscometer was used to measure the viscosity (in cps) of the prepared gel formulation. The spindle no. 64 was rotated at 50 rpm. The viscosity of formulations was

more correct which was near to 100% torque. Reading was detected 30 sec after measurement was made, when the level was stabilized.

Table 11: Determination of viscosity

S. No.	Viscosity(cps)	Average±S.D.
1.	1125	1128±3.51
2.	1128	
3.	1132	

Spreadability

The spreadability is very much important as show the behavior of gel comes out from the tube. The values of spreadability shown in table 12 indicate that polymers used gave gels spread by small amount of shear. The diameters of the spreaded circles ranged from 2.6 cm to 3.3 cm.

Table 12: Determination of spreadability

S.NO.	Spreadability ($gm.cm^2$)	Average± S.D.
1	2.6	2.96 ± 0.351
2	3.0	
3	3.3	

RELEASE KINETICS

The in vitro release data obtained from Formulation F_9 was fitted to kinetic models shown in Table 13 . In case of zero order $(Q_t = Q_0 + K_0 t)$the graph was plotted in cumulative percent of drug released versus time and in first order release kinetics (Log C= log C_0- Kt/2.303) the graph was plotted in log cumulative percent of drug remaining versus time. For Higuchi model kinetics ($Q= K_H \times t^{1/2}$) the graph was plotted in cumulative percent of drug released versus square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = Kt^n$) the graph was plotted in log cumulative percent of drug released versus log time. The release of ketoconazole from the liposomal gel was Korsmeyer-peppas model diffusion controlled as indicated by highest R^2values in first order. The n values obtained from the Korsmeyer-Peppas model showed that the release mechanism was non- Fickian.

Table 13: Release kinetics of liposomal gel of ketoconazole from formulation F_2

Time in min	Square root of time	log time	%CDR	log % CDR	log % CDR remaining
0	0	0	0	0	0
5	0.288	-1.0801	19.55	1.291270257	1.905496033
10	0.407	-0.778	31.33	1.496006553	1.836745987
15	0.50	-0.602	42.88	1.632344806	1.756720601
30	0.707	-0.301	53.33	1.726998701	1.669006812
45	0.866	-0.1249	61.55	1.789267287	1.584833539
60	1	0	65.77	1.818079212	1.534308179

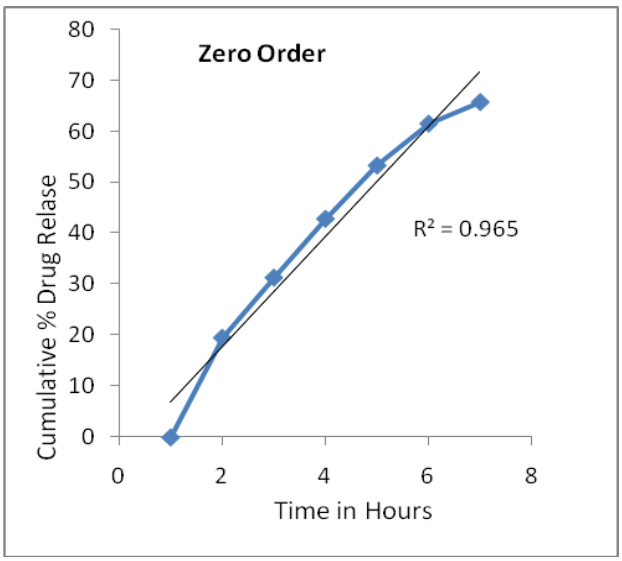

Figure 13: Zero order kinetic

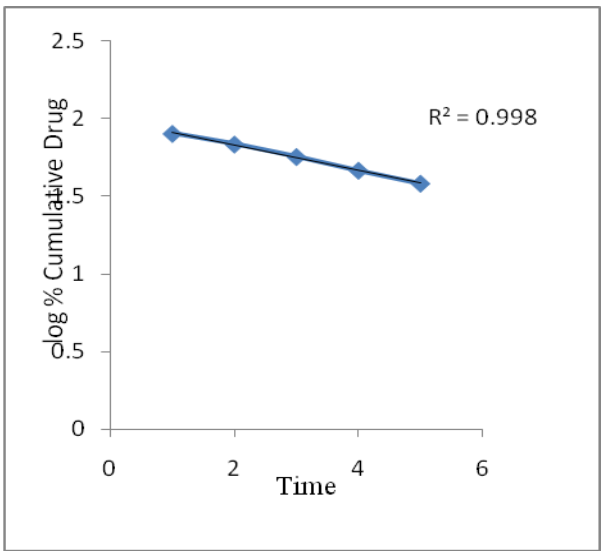

Figure 14:First order kinetic

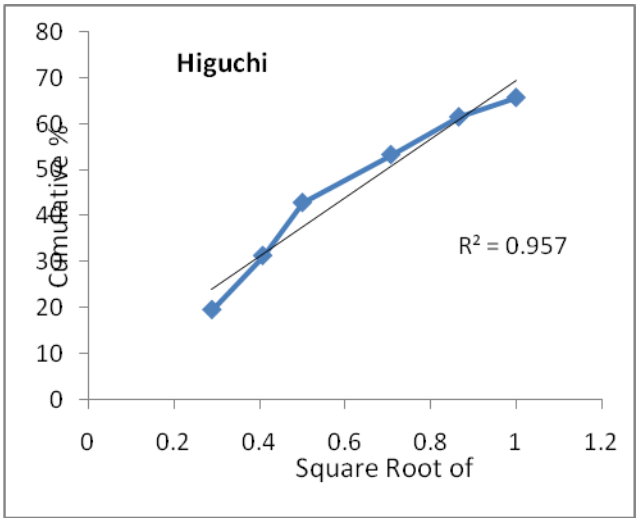

Figure 15: Higuchi release kinetic

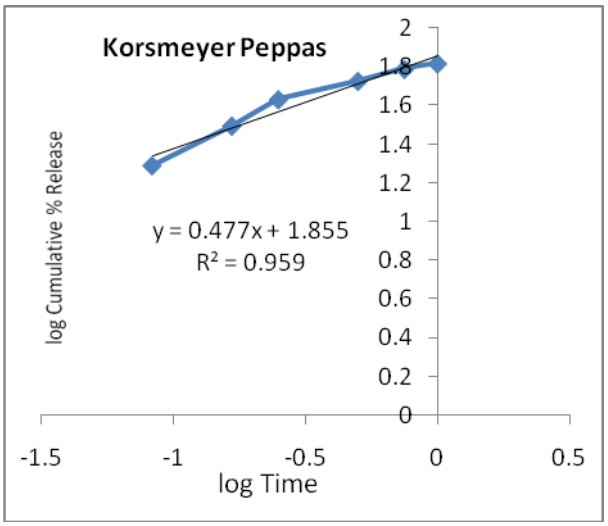

Figure 16: Korsmeyer peppas release kinetic

CONCLUSION

The present study showed that F_2 formulation (soya lecithin, cholesterol, ketoconazole, triethanolamine) gives best percentage yield, drug content, entrapment efficiency and shows best dissolution release. So it was conclude that F_2 formulation should be a better candidate for liposome gel with best. Therefore, it was concluded that our formulae could be very promising topical alternative for the treatment of skin fungal infections.

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