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FORMULATION AND EVALUATION OF NIOSOMES OF KETOCONAZOLE

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Abstract:

Formulation of niosome of ketoconazole was prepare by hand shaking method (thin film hydration technique). Four formulations were prepared and characterized by different parameters like entrapment efficiency, drug content, morphology, pH, percentage yield, in- vitro release and stability studies. All formulations show good results but on the basis of drug content, percentage yield, in vitro release and stability studies F1 formulation found the best. It was concluded that Niosomes can be used for further formulation development like ointment creams or gel for topical use to treat fungal infections.

Keywords- *Niosomes, Carbopol 934, In-vitro release, Percentage yield*

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INTRODUCTION:

The market offers a variety of topical medicines containing antifungal drugs, such as creams, ointments, and powders for local dermatological therapy. Ketoconazole, a replacement for imidazole, is one of the antifungal medicines that has broad-spectrum efficacy against both systemic and superficial mycoses. After oral administration, it is quickly but insufficiently absorbed, and it varies across people.[1] Mild burning at the application site, severe allergic reactions, blisters, irritability, soreness, or redness are typical adverse effects of ketoconazole medication.

Localized medication distribution through the skin, vagina, rectal, and ocular cavities is known as topical drug administration. The stratum corneum, the epidermis' top layer, serves as the skin's primary barrier. The optimum properties of the medications for transdermal distribution include low molecular weight (500 Da), lipophilicity, and efficacy at a low dose.[2] As a result, by formulating the current medications in a beneficial method, their therapeutic effectiveness is increased. Recently, transdermal drug delivery systems were created with the goal of achieving systemic therapeutic goals by topical administration to the intact skin surface. Transdermal medication delivery utilizes the skin as a primary target and barrier.

The creation of a novel medicine delivery system has received a lot of attention during the last few decades. Chemical and physical methods have been investigated to reduce stratum corneum barrier characteristics in order to enhance permeability. These techniques include iontophoresis, electroporation, tape stripping, and vascular systems like liposomes and niosomes. In the cosmetic and dermatologic disciplines, liposomes and niosomes are frequently employed to improve medication permeability over the skin.[3] Vesicles have a significant role to play in the transportation and targeting of active substances, as well as in the modeling of biological membranes. There are several types of pharmaceutical carriers, such as cellular, macromolecular, polymeric, and particulate carriers. Lipid particles, microspheres, nanoparticles, polymeric micelles, and vesicular systems are examples of particulate type carriers, commonly referred to as the colloidal carrier system.[4] Niosomes have also been extensively researched as drug delivery systems for targeted and controlled medication delivery. Niosomes work in vivo like liposomes, extending the medication's circulation to change its metabolic stability and organ distribution or extending the time the drug is in touch with the tissues.

When non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol (CHO) are combined, tiny lamellar structures known as niosomes (non-ionic surfactant vesicles) are produced. These structures are then hydrated in aqueous environments.[5] Niosomes are gaining popularity because to their benefits in a variety of areas, including chemical stability, high purity, content homogeneity, cheap cost, easy storage of non-ionic surfactants, and a vast selection of surfactants accessible for niosome design.[6] Niosomes are a potential medication delivery system. Niosome-encapsulated medicines have the potential to boost drug bioavailability and target the disease region while reducing drug degradation and inactivation after delivery.[7] Because they may dissolve the mucous layer and disassemble functional compounds, surfactants also serve as penetration enhancers. Based on their amphiphilic nature, non-ionic surfactants produce a closed bilayer vesicle in aqueous fluids by utilizing some energy, such as heat and physical agitation. Their physiological characteristics, including composition, size, charge, lamellarity, and application circumstances, have a significant impact on their efficacy.[4] Research into niosomes as delivery systems for oral vaccines, anti-tubercular, anti-leishmanial, anti-inflammatory, and other medications has also been done.[8]

The purpose of present research is formulation and evaluation of ketoconazole niosomes by determine the viability of niosomes as a ketoconazole delivery system.

MATERIALS AND METHODS:

Ketoconazole is a synthetic drug with broad-spectrum antifungal properties. It belongs to the azole derivative and imidazole class of drugs. This compound has demonstrated high tolerance in patients.

Ketoconazole was a gift from Mankind Pharma Limited Paonta Sahib, H.P., while the companies that provided the coconut oil, Tween 80, and ethanol were National Chemicals in Baroda and Suvidhi nath Laboratories in Baroda. All additional compounds were of the analytical variety.

Preformulation tests like Physical Appearance, UV Spectroscopy, Partition Coefficient & Melting Point has carried out to establish the best possible conditions for a optimal delivery system.

Formulation of Ketoconazole Niosomes

Thin film hydration was used to create niosomes that were loaded with ketoconazole. Accurately weighed volumes of cholesterol and surfactant were dissolved in a chloroform-methanol mixture at a 2:1v/v ratio in a 100 ml volumetric flask. The solvent combination received the dose of medication and dicetyl phosphate that had been weighed. A thin layer will obtained on the surface of flask by removing the solvent combination from the liquid phase using a rotary evaporator at 60°C and 150 rpm. Applying vacuum can verify that all solvent has been removed completely. Up until the production of niosomes, the dry lipid film is hydrated with 5ml of pH 7.4 phosphate buffer saline at a temperature of 60°C. Using a probe sonicator, all of the batches were treated to a 2-minute sonication process. [9-10]

Table no. 1 Composition of ketoconazole niosomes

S.No.	INGREDIENTS	F1	F2	F3	F4
1.	Ketoconazole (mg)	100	100	100	100
3.	Cholestrol (mg)	20	30	40	50
4.	Chloroform (ml)	20	20	20	20
5.	Methanol(ml)	10	10	10	10
6.	Distilled water(ml)	10	10	10	10
7.	Tween 80(ml)	0.25	0.25	0.25	0.25

Solvent: chloroform methanol mixture (2:1v/v)

Hydration time: 2 hours

Hydration media: Phosphate buffer saline pH7.4 (5 ml)

Dicetyl phosphate: 15µM

Evaluation of Ketoconazole Niosomes

Removal of unentrapped drug from niosomes

The unentrapped drug from niosomal formulation was separated by centrifugation method at 15,000 rpm for 30 min using cooling centrifuge and temperature was maintained at 5°c. The supernatant was separated. Supernatant contained unentrapped drug and pellet contained drug encapsulated vesicles. To create a niosomal suspension free of unentrapped medication, the pellet was resuspended in phosphate buffered saline pH 7.4.[11-12]

Zeta potential

The zeta potential of optimized niosomal formulation was measured using Malvern zeta potential analyzer.

Scanning electron microscopy (SEM)

Scanning electron microscopy was used to morphologically analyze the optimized formulation. The sample was mounted in the specimen stub for SEM examination using double-sided Scotch tape and an adhesive tiny sample. The sample was examined in a 15 kv Hitachi scanning electron microscope while a picture was taken.[13]

Morphology analysis

Prepared liposomes for all the formulations were viewed under for observing the vesicle formation and discreteness of dispersed vesicles. A slide was prepared by placing over it and this slide was viewed under optical microscope at 40x magnification. Photographs were taken to prepared slides using digital camera.

***In-vitro* drug release study**

All of the synthesized ketoconazole niosomes were released *in vitro* for 8 hours using phosphate buffer pH 6.8. The experiments were conducted in a USP dissolution apparatus running at 50 rpm and 370C +/- 0.50C. As a dissolving media, 900 cc of phosphate buffer with a pH of 6.8 were used, With pH 6.8 serving as a blank, 1 ml of samples were taken out every 30 minutes for 480 minutes, made up to 10 ml, and then tested for ketoconazole concentration at 294 nm.[14-15]

Percentage Yield of Niosomes

Niosomes that had been prepared were gathered and weighed. The amount of medication and excipients utilized to create the niosomes was multiplied by the measured weight.

$$\text{Percentage (\%) Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and exipients}} \times 100$$

pH measurement

The obvious pH of niosomal formulation was measured by digital pH meter intriplicate manner.

Determination of drug content

Drug content was determined by suspending 100 mg of multilamellar niosomes with drug entrapment in a chloroform:methanol (2:1) solution in 100 ml of water. The finished dispersion was filtered through a 0.45 m membrane filter after being mixed thoroughly for 20 min. with continuous agitation. Spectrophotometric analysis at 294 nm was used to calculate the drug content using a regression equation

generated from the reference graph. Triplicate analysis was used to determine the results.[16]

$$\text{Drug Content} = \frac{\text{Sample of absorbance}}{\text{Standard absorbance}} \times 100$$

Stability studies

By keeping the niosomes at two distinct temperatures for a month—40C (refrigerator RF), 250C, and 20C—it was possible to study the behavior of the niosomes to retain the medicine. The prepared niosomes were stored in sealed vials. [17]

RESULT AND DISCUSSION:

Preformulation Studies

Physical Appearance

Ketoconazole was physically identified by examining its color, odor, and look, or outward appearance. Result was given in table no.2.

Table no. 2: Physical appearance of Ketoconazole

S. No	Test	Specification	Observation
1.	Color	White\off white	white
2.	Odour	Odourless	odorless
3.	Appearance	Crystalline powder	powder

UV Spectroscopy of Ketoconazole

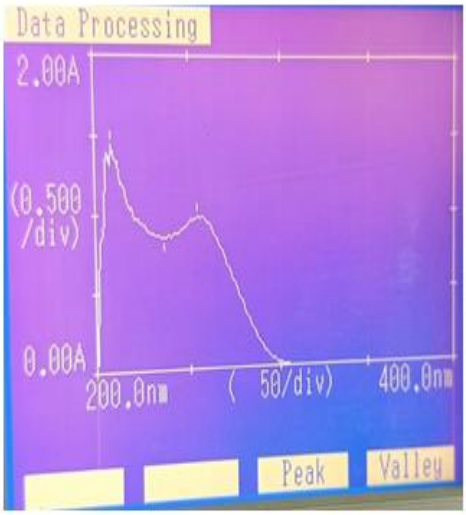

Figure 1: Medication scanning in a 7.4 pH buffer with phosphate.

Calibration data of Ketoconazole using Phosphate buffer pH 6.8

Different concentrations of ketoconazole in phosphate buffer pH 6.8 was analyzed at 264nm. Theabsorbance was tabulated in table no.3 and standard plot is shown in figure no.2

Table no. 3 Calibration data of Ketoconazole using Phosphate buffer pH 7.4

S. No.	Concentration(µg\ml)	Absorbance(nm)
1.	0	0
2.	2	0.102
3.	4	0.194
4.	6	0.276
5.	8	0.376
6	10	0.475

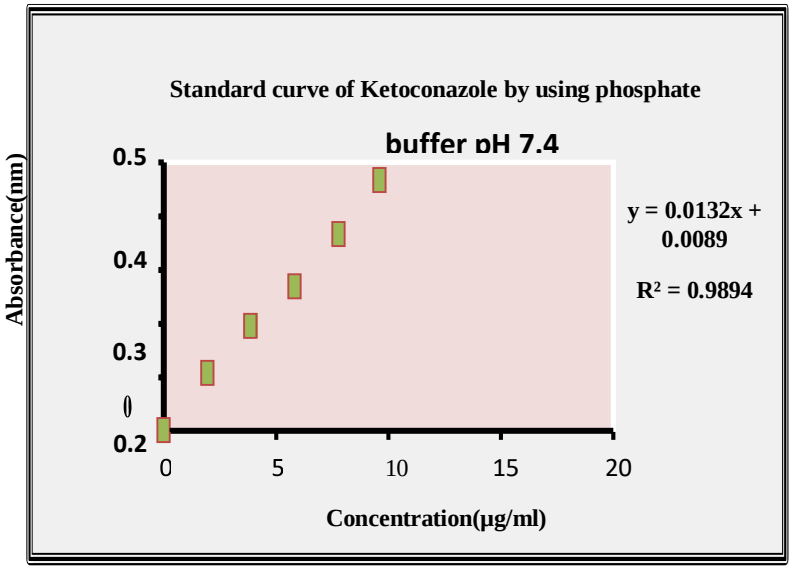

Figure 2 : Calibration curve of ketoconazole by using Phosphate buffer pH 7.4.

According to this method the value for correlation coefficient was found to be 0.999 forketoconazole by using phosphate buffer pH 7.4. The estimation procedure was found to be reproducible and acceptably sensitive in given concentration range.

Solubility determination in various solvent

Solubility of ketoconazole is shown in table no 4

Table No.4: Solubility Profile of Ketoconazole.

S. No.	Solvent	Standard Solubility	Solubility (ppm)	Observed
1.	Dichloromethane	Freely soluble	1-10	+++++
2.	Chloroform	Soluble	10-30	++++
3.	Methanol	Soluble	10-30	++++
4.	Ethanol	Sparingly soluble	30-100	+++
5.	Water	Insoluble	>1000	-
6.	Ether	Insoluble	>10000	-

The solubility of Ketoconazole was determined in various solvents. The drug was found soluble inchloroform and methanol, sparingly soluble in ethanol and almost insoluble in water.

Determination of Partition Coefficient:
The ratio of a solute's equilibrium concentration in one phase to that in another is known as the partition coefficient. Partition coefficient of ketoconazole was shown in table no. 5

Table 5: Partition coefficient of ketoconazole.

S. No	Solvent\drug	Reported value	Observed value
1.	n-octanol\Chloroform:water+ ketoconazole	4.35	4.01

According to be observed value of partition coefficient ketoconazole was found to be acidic and lipophilic in nature.

Determination of Melting point:
The melting point was taken as mean of the three values i.e., 150,147,150^{0}C. Therefore, the melting point of ketoconazole was calculated to be 149^{0}C.

Evaluation of Niosomes
Drug entrapment efficiency
The drug entrapment efficiency was carried out for all four formulations and the results are listedin table no 6 and graphically represented in figure no.3.

Table No.6 : The effectiveness of niosomal formulations for entrapment.

S. No.	Formulations	% Entrapment Efficiency
1.	F1	73.4
2.	F2	80.5
3.	F3	62.3
4.	F4	79.6
Mean ± S. D		**73.95 ± 8.38**

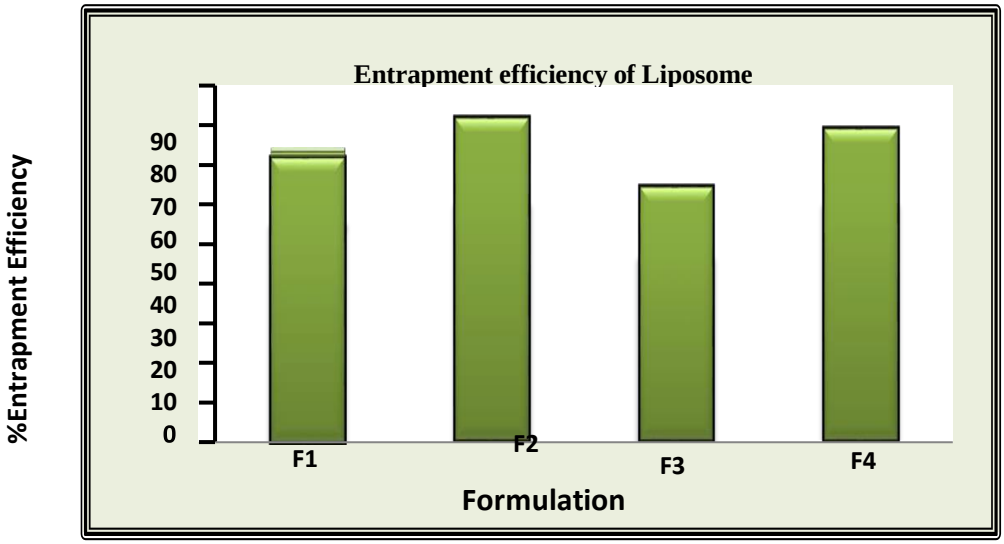

Figure No. 3 : Graphical representation between % Entrapment Efficiency vs. Formulations.

The drug entrapment efficiency of the formulation was in the range of 62.3 to 80.5%. The drug entrapment determination also showed that the drug was uniformly distributed throughout the preparation.

Compatibility Studies

➢ **FT-IR Spectral Analysis:**

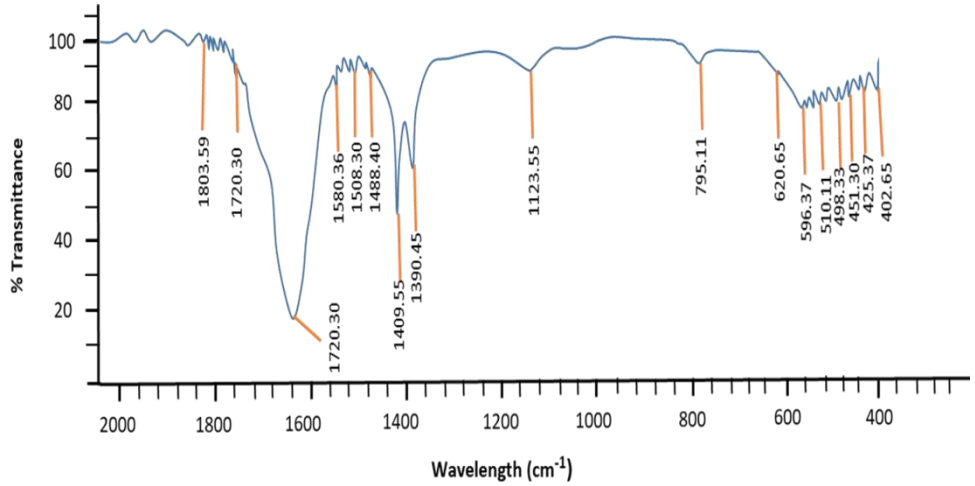

Figure No. 4: FTIR of Ketoconazole

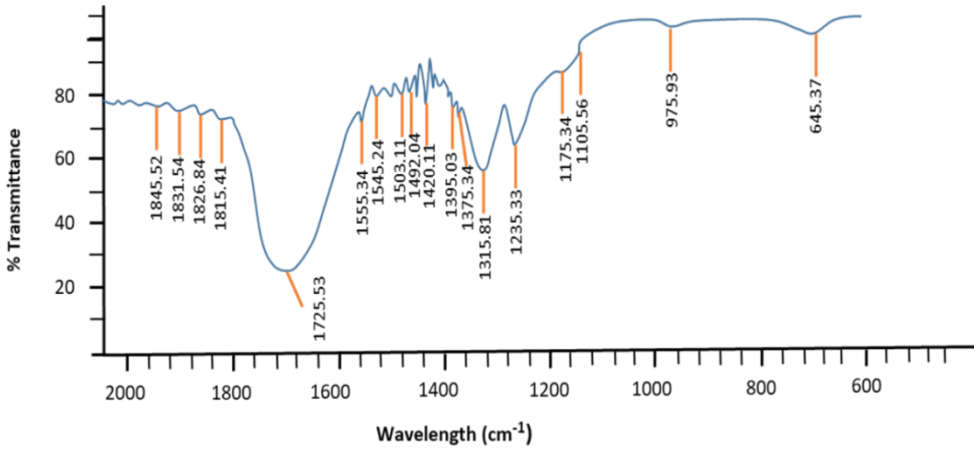

Figure No. 5: FTIR of Cholestrol

Table No.7: Interpretation of Fourier Transform Infrared Spectrum of Cholestrol

S. No.	Reference Peaks	Observed Peaks	Functional Group
1.	2000-1650	1845.03	C-H (Aromatic Compound)
2.	1760-1690	1751.85	C=O (Carboxylic acids)
3.	1650-1580	1597.16	N-H (Primary amines)
4.	1550-1475	1498.39	N-O (Nitro Compounds)
5.	1370-1350	1351.18	C-H (Alkanes)
6.	850-550	765.97	C-Cl (Alkyl halides)
7.	690-515	555.37	C-Br (Alkyl halides)

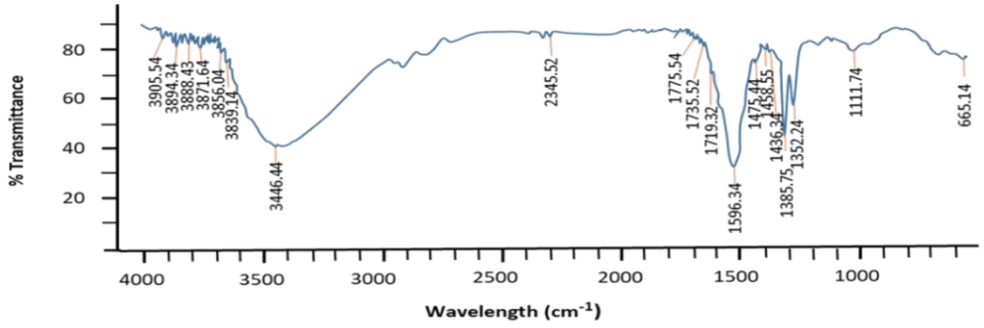

Figure No 6.: FTIR of Ketoconazole+ Cholestrol (Drug Excipient studies).
Table No. 8: Interpretation of FTIR of Ketoconazole+ Cholestrol + Soya

S. No.	Reference Peaks	Observed Peaks	Functional Group
1.	3700-3584	3630.43	O-H(Alcohol)
2.	3700-3584	3567.06	O-H(Alcohol)
3.	2400-2000	2344.50	O=C=O(Carbon dioxide)
4.	1800-1770	1772.35	C=O(Conjugated acid halide)
5.	1710-1665	1699.67	C=O(α,β-unsaturated esters)
6.	1650-1580	1595.30	N-H(Primary amines)
7.	1550-1475	1474.16	N-O(Nitro compounds)
8.	1385-1380	1384.71	C-H(Alkane)
9.	1250-1020	1110.75	C-N(Aliphatic amines)
10.	690-515	667.19	C-Br(Alkyl halides)

The typical C-Br peaks at 615.01, 555.37, 765.97, and 667.19 that are present in the FTIR spectrum of cholesterol are seen in the FT-IR spectrum of ketoconazole, indicating the presence of alkyl halides when ketoconazole is combined with cholesterol. The typical peaks at 1507.71, 1498.39, 1498.39, and 1474.16 corresponding to N-O, which are present in the FTIR spectrum of cholesterol, soyalecithin, and ketoconazole+cholestrol defining the presence of Nitro compounds, can be seen in the FT-IR spectrum of ketoconazole. When combined with cholesterol, ketoconazole exhibits the characteristic FT-IR peaks at 1457.39, 1351.18, 1351.16, and 1384.71, which correspond to C-H and indicate the existence of alkane molecules. It means that the peak of ketoconazole and excipients, and drug expients combination are maintained in the formulation of liposome, which means that the drug was intact in the formulation and did not react with either of the polymer.

Morphology analysis:
The morphology analysis was carried out for all four formulations and the results showed that liposomes are oval and spherical in shape which are listed in figure no.7

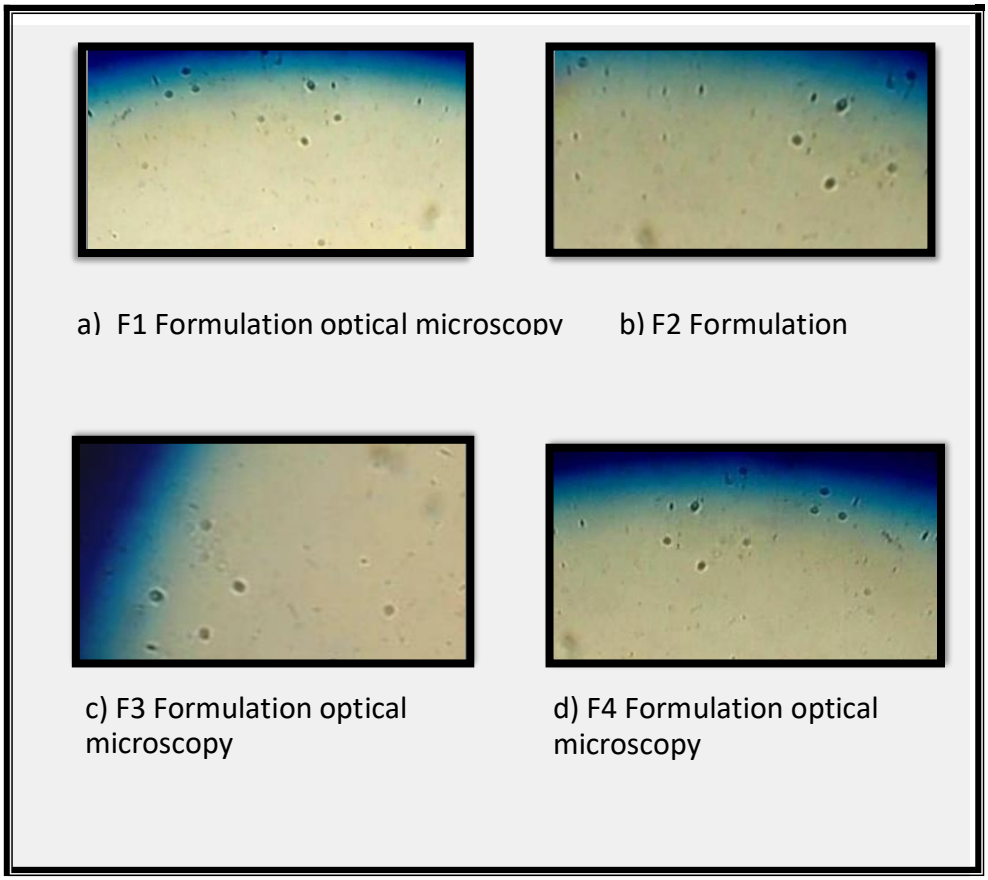

Figure No.7 Optical microscopy of niosomal formulation

***In-vitro* drug release studies:**

All niosome formulations were subjected to in-vitro drug release tests in phosphate buffered saline pH 7.4 solution. It was found that the medication release patterns described in table no. 9 are affected by the ratio of soyalecithin, drug, and cholesterol.

Table No.9 : *In-vitro* drug release study of niosomal formulations.

Time (in hours)	**Cumulative% drug release**			
	F-1	**F-2**	**F-3**	**F-4**
1	23.21	29.41	25.61	26.78
2	35.24	39.39	36.46	38.68
3	45.12	49.32	43.53	48.76
4	53.16	57.32	54.46	58.78
5	60.25	63.45	61.56	62.77
6	73.24	77.35	72.65	75.78
7	81.32	84.52	81.79	81.98
Mean± S. D	53.22± 20.7	57.25±19.7	53.86±20.16	56.21±19.68

When compared to formulations with a different ratio (F1 and F3), compositions with F2 and F4 demonstrated a higher drug release. Figure 8-9 shows the cumulative medication release plotted against time (hours) for all formulations.

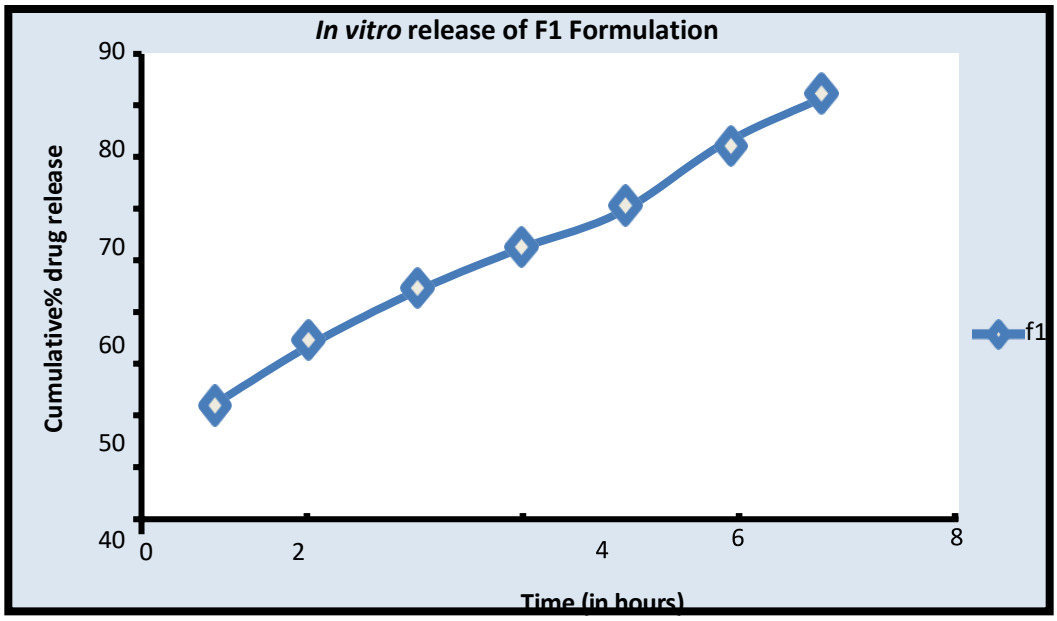

Figure No. 8: Graphical representation of *in-vitro* release of F1 formulation.

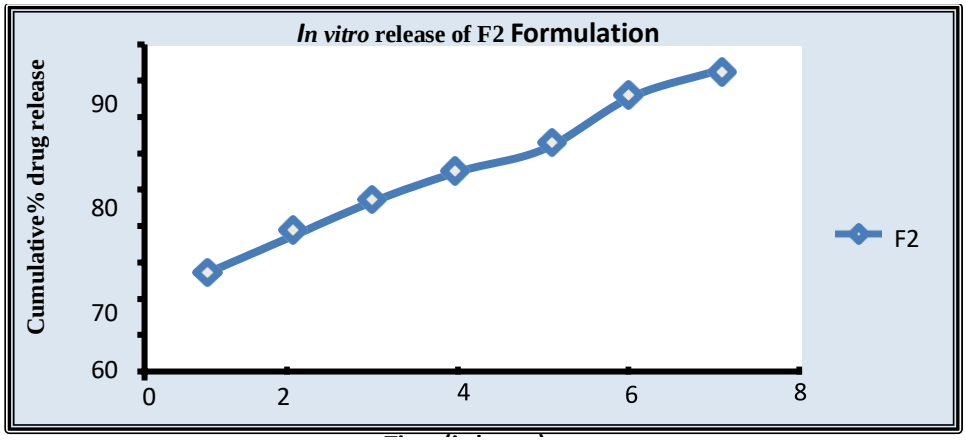

Figure No. 9: Graphical representation of *in-vitro* release of F2 formulation**.**

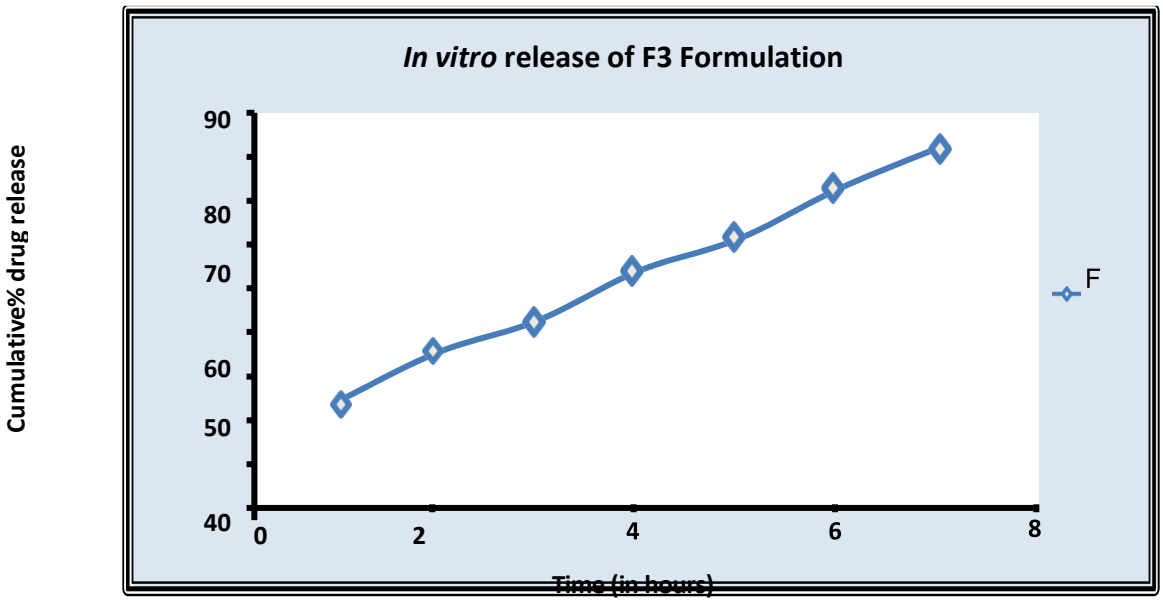

Figure No. 10: Graphical representation of *in-vitro* release of F3 formulation**.**

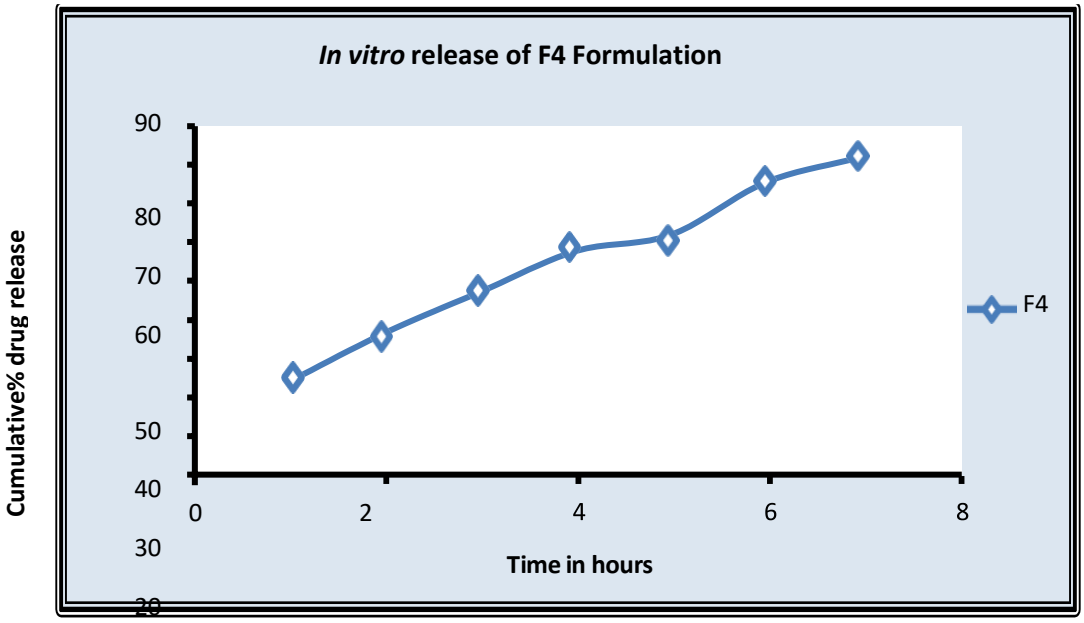

Figure No. 11: Graphical representation of *in-vitro* release of F4 formulation**.**

Percentage Yield of Liposomes:

Weighing was used to calculate the percentage of realistic yield for various formulations. The range of the percentage yield for various formulations was 77 to 94%. Table 10 and Figure 12 both show that Formulation F1 has a higher percentage yield than Formulation F2, and Formulation F4 has a higher percentage yield than Formulation F3.

Table No.10 : Percentage yield of niosomal formulations.

S. No.	Formulations	Percentage yield (%)
1.	F1	94
2.	F2	84
3.	F3	77
4.	F4	87
Mean ±S. D		85.5±7.04

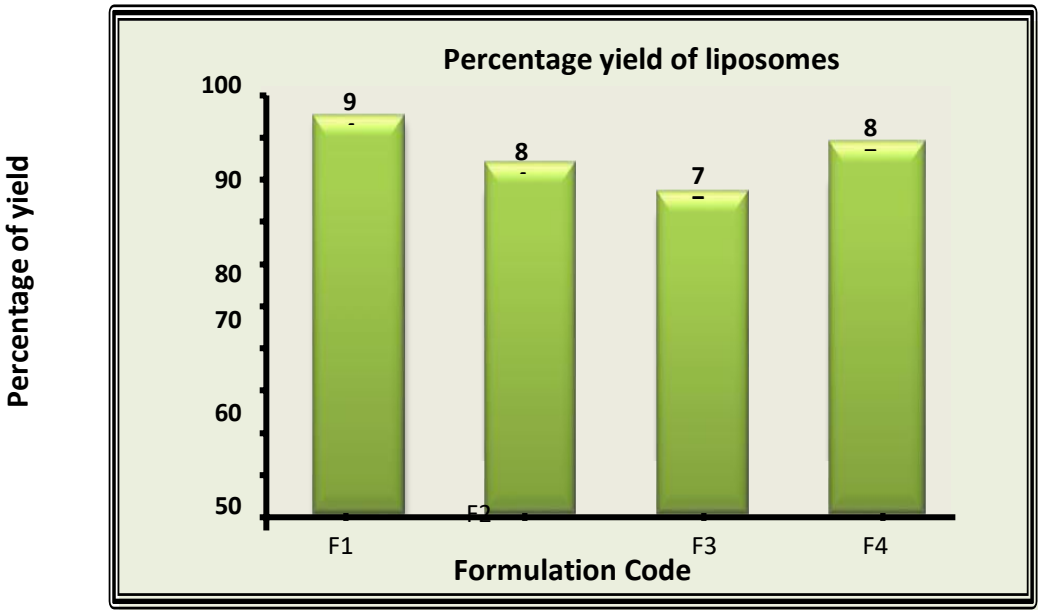

Figure No.12 : Graph plotted between percentage yield vs. Formulation code.

pH measurement:
A digital pH meter was used to measure the pH of all four formulations. All of the formulations' pH values, which are documented in table 11 and fell between 5.75 and 5.99.

Table no. 11: pH of niosomal formulations

S. No.	Formulations	pH
1.	F-1	5.87
2.	F-2	5.99
3.	F-3	5.85
4.	F-4	5.75
Mean ± S. D		5.86±0.098

Determination of drug content:
The medication content of the four formulations ranged from 85 to 92%, as shown graphically in table no. 12,

Table No. 12: Drug content of niosomes formulations

S. No.	Formulations	Drug Content (%)
1.	F-1	89
2.	F-2	92
3.	F-3	85
4.	F-4	90
Mean± S. D		89±2.94

Stability studies:
The stability studies of liposomal predations carried out after one month at two different temperature conditions., 4^0C (refrigerator RF),25^0C± 2^0C (room temperature) which were shown in below table no.13 and graphically represented in figure no.13 &14

Table No.13: Drug entrapment efficiency of all Ketoconazole niosomes formulations afterstability study, compared with before stability**.**

S. No.	Formulation code	Immediately after preparation	After stability study	
			At 4^0C	At 25^0C±2^0C
1.	F-1	73.4	72.5	70.6
2.	F-2	80.5	79.9	75.8
3.	F-3	62.3	61.8	64.6
4.	F-4	79.6	78.5	73.7

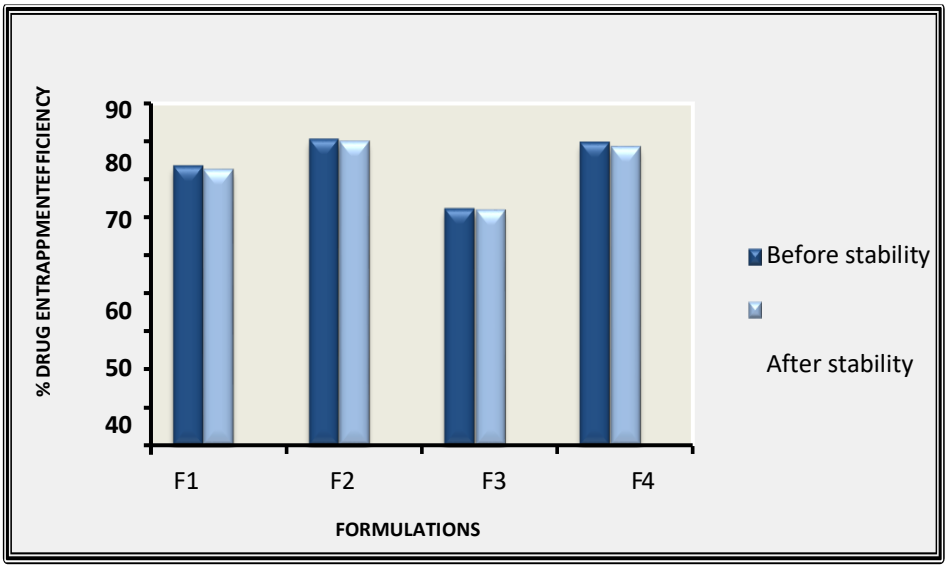

Figure No.13: Graph plotted drug entrapment efficiency before and after stability studies atroom temperature.

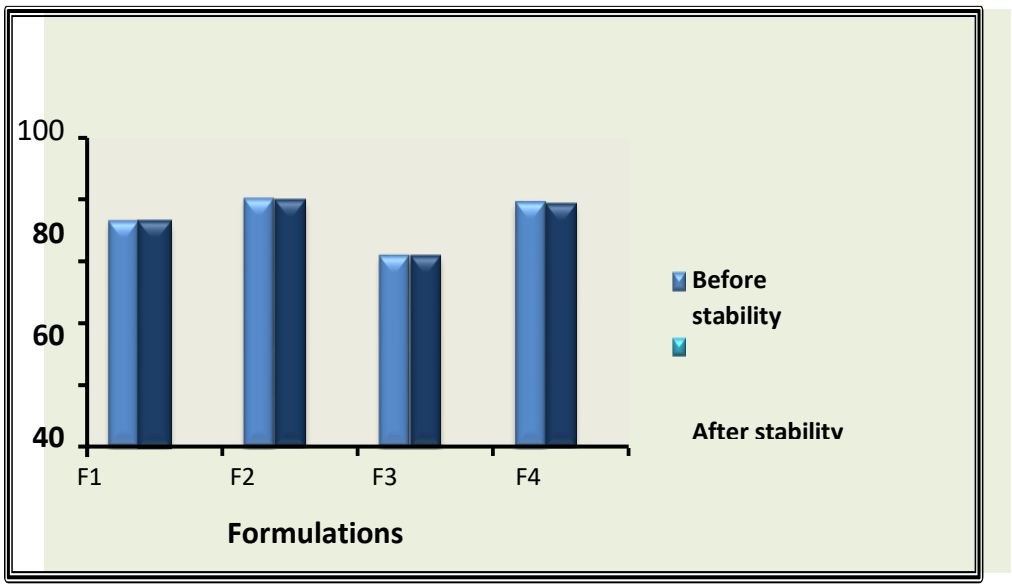

Figure No.14: Graph plotted between drug entrapment efficiency before and after stability studies at refrigerator condition.

Physical appearance: Physical appearance of all Ketoconazole niosome formulations after stability study, compared with before stability is shown in Table no. 14 & 15 and figure no. 15

Table No. 15 : Physical appearance of all Ketoconazole niosome formulations

S.no.	Formulation	Appearance	At 4^0C	At 25^0C±2^0C
1.	F-1	Milky White	Milky White	Milky white
2.	F-2	Whitish and yellow	Whitish and light yellow	Milky white and yellowish
3.	F-3	Transparent pale yellow	No change	Faded pale yellow
4.	F-4	Lightish transparent yellow	No change	Faded light yellowish

Drug Content: Drug content of all Ketoconazole niosome formulations after stability study, compared with before stability shown in table no.3.15 and graphically represented in figure no.3.21.

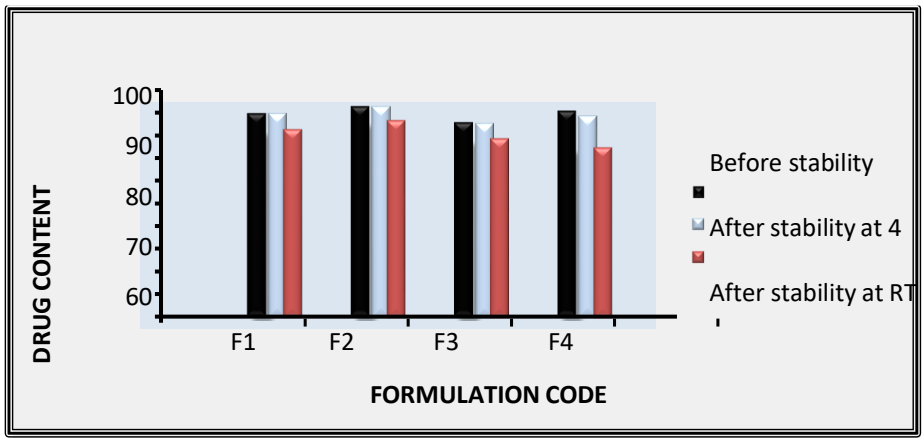

Figure No.15: Graph plotted of drug content before and after stability study at different temperatures

CONCLUSION:

In the present research investigation, niosomes containing ketoconazole were formulated using the hand-shaking method, precisely the thin film hydration technique. These niosomes were subsequently transformed into a gel form through the incorporation of the gelling agent Carbopol 934. Four distinct formulations were meticulously prepared and subjected to comprehensive characterization, encompassing parameters such as entrapment efficiency, drug content, morphology, pH, percentage yield, in-vitro release, and stability assessments.[18]

The study's findings showed that all of the formulations were likely to produce positive effects. But after careful analysis based on factors including drug concentration, yield %, in-vitro release, and stability tests, it was found that the F1 formulation performed the best. As a result, this work offers convincing data to support the possible use of these niosomes for later formulation development, such as the production of ointments, creams, or gels for topically applied treatments of fungal infections.[19]

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Author's contributions All the authors have contributed equally.

Conflicts of interests Declared none

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