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Formulation and Evaluation of Fluconazole Niosomal Gel

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ABSTRACT

Fluconazole is a triazole antifungal agent, is utilized for the treatment of specific susceptible bacteria. Niosomes play a vital role in drug delivery by modifying pharmacokinetics and enhancing bioavailability, while also reducing toxicity. The importance of Niosomes in drug administration is growing, particularly in topical applications. When applied topically, Niosomes can extend the retention time of medications in the stratum corneum and epidermis, thereby reducing systemic absorption of the drug. Fluconazole Niosomes was prepared by sonication method using span 80, span 20, and tween 80 as non-ionic surfactants, cholesterol, and glyceryl monostearate. The Niosomes were optimized and incorporated into a Carbopol gel. The optimized Niosomes showed entrapment efficiency of 90.6% and size 217.4nm of and zeta potential of -52.2 mV. The optimized Niosomes showed *in vitro* drug release of 94.91%. The Niosomal gel showed *in vitro* drug release of 95.27%.

Key words: Niosomes, non-ionic surfactants, Fluconazole, Niosomal gel, *in vitro* diffusion.

1. INTRODUCTION

Niosomes are generated through the self-assembly of non-ionic surfactants in an aqueous medium, forming vesicles with an aqueous core. These vesicles are advantageous for drug delivery due to their capability to encapsulate and release drugs in a controlled and targeted manner [3].

Composition

The primary components of Niosomes include non-ionic surfactants, cholesterol, and charged molecules.

Non-ionic Surfactants

Non-ionic surfactants play a crucial role in Niosomes formulation. These molecules, featuring a polar head and a non-polar tail, form bilayer structures with hydrophilic heads and hydrophobic tails [4]. The resulting vesicles fold inwards for thermal stability, and their lack of charge contributes to stability. Non-ionic surfactants exhibit lower levels of haemolysis and cause less irritation compared to other dosage forms. They enhance permeability and solubility, act as emulsifiers, and improve absorption and targeting by inhibiting p-glycoprotein [8]. Non-ionic surfactants with a high Hydrophilic-Lipophilic Balance (HLB) value are not suitable for Niosome preparation, with the maximum HLB value for effective entrapment being [8]. Examples of non-ionic surfactants include Spans and Tweens.

Cholesterol

Cholesterol plays a significant role in Niosome formulation, contributing to various properties of the formulation [4]. While not mandatory, it enhances stability when combined with surfactants with lower HLB values. Cholesterol is particularly beneficial for forming bilayers in vesicles, especially when the HLB value exceeds 6[8].

Charged Molecules

Charged molecules are included to prevent Niosome fusion and enhance stability. It's essential to maintain a concentration range of 2.5-5 mol% for effective results, as higher concentrations of charged molecules can inhibit Niosome production in formulations [4].

2. MATERIALS AND METHODS

2.1 METHODS

2.1.1 chemicals

Fluconazole was provided by Synergene active ingredients. Other materials used in the preparation were Span 80, Span 20, Tween 80 (Fluka company), Cholesterol (Riedel-de haen), Glyceryl monostearate (Accord labs), Carbopol 940 (Lubrizol), Ethanol (Changshu yang yuan chemicals), chloroform (SDFCL Company), distilled water, and phosphate buffer of pH 7.4.

2.1.2 Preparation of 7.4 pH Phosphate Buffer

2.38 gm of disodium hydrogen phosphate, 0.19gm of potassium dihydrogen phosphate and 8 gm of sodium chloride was added in sufficient distilled water to produce 1000 ml.

2.2. METHODOLOGY

2.2.1 PREFORMULATION STUDIES

Identification of Drug Physical appearance, colour and nature of drug were evaluated.

2.2.2 DRUG EXCIPIENT COMPATABILITY STUDIES

FTIR spectra were employed to assess the compatibility between the active pharmaceutical ingredient (API) and excipients. The solid powder sample was prepared by pressing it in a mortar with 100 times the quantity of potassium bromide, resulting in potassium bromide pellets via a KBr press. Utilizing a stainless-steel die, the finely ground powder was compressed between polished steel anvils. Spectra were recorded in the wavelength range of 4000 to 400 cm^{-1} using a Bruker alpha spectrometer. [18].

2.2.3 UV ANALYSIS

DETERMINATION OF λmax

The drug solution was scanned in the range of 200 nm to 400 nm to determine the absorption maximum (λmax).

- **Standard graph of Fluconazole drug in methanol**

100mg of Fluconazole was accurately weighed, transferred and final volume made with 100ml methanol to prepare stock solution. From this stock solution 50ppm, 100ppm, 150ppm, 200ppm, and 250 ppm were made and analyzed in UV spectrophotometer.

- **Standard graph of Fluconazole drug in Phosphate Buffer pH**

100mg of Fluconazole was accurately weighed, transferred into 100ml volumetric flask and final volume made with 100ml phosphate buffer to prepare the stock solution. From this stock solution, 5ppm, 10ppm, 20ppm, and 25 ppm were made and analyzed in UV spectrophotometer.

2.2.4 SOLUBILITY STUDIES OF IN VARIOUS SURFACTANTS

solubility studies of Fluconazole in various surfactants like span 80, tween 80, span 20 was performed. An excess amount of Fluconazole is taken and added to each vial containing 300 mg of surfactant. The vials are kept in shaking incubator for 35-40 hrs for mixing until equilibrium is achieved. Then the sample was centrifuged, diluted by methanol, and analyzed using UV spectrophotometer.

2.2.5 PREPARATION OF NIOSOMES BY SONICATION METHOD

A quantity of 200 mg of the drug is dissolved in a buffer solution and combined with a mixture of non-ionic surfactant, cholesterol, and solvent. The resulting mixture is placed in a beaker and homogenized at 1100 rpm. Subsequently, the beaker containing the drug and non-ionic surfactant mixture undergoes sonication for 15 minutes at 60ºC to form multilamellar Niosomes. Later the solution is sonicated for 15 min to produce unilamellar Niosomes [19].

Three different non-ionic surfactants (span 80, span 20, tween 80) were used in three different concentrations (200, 250, 300 mg) (table 1).

Table 1: Formulation table for the preparation of Niosomes

Ingredients	1	2	3	4	5	6	7	8	9
Fluconazole (mg)	200	200	200	200	200	200	200	200	200
Cholesterol (mg)	50	50	50	50	50	50	50	50	50
Glyceryl mono stearate (mg)	25	25	25	25	25	25	25	25	25
Span 80 (mg)	200	250	300	-	-	-	-	-	-
Tween 80 (mg)	-	-	-	200	250	300	-	-	-
Span 20 (mg)	-	-	-	-	-	-	200	250	300
Solvent (ml) chloroform: Ethanol (2:1)	10	10	10	10	10	10	10	10	10

2.2.6 PREPARATION OF NIOSOMAL GEL

Gel was prepared by dissolving 1gm of Carbopol 940 in distilled water. To this, Niosomal solution equivalent to 50 mg of Fluconazole was added while making gel. The gel was prepared using mechanical stirrer at 1200rpm [19].

3. EVALUATION

3.1 CHARACTERISATION OF NIOSOMES

The prepared Niosomes were assessed for their zeta potential, and entrapment efficiency and *in vitro* drug release of prepared Niosomes.

3.1.1 Particle Size, PDI and Zeta potential

Niosomes repel each other due to the charge present on them. Charge and zeta potential are determined using zetasizer. It is important to know the charge on the Niosomes as it is responsible for stability of the formulation [4, 8]. The niosomal solution was diluted with distilled water and particle size, PDI, ad Zeta potential was analysed using Malvern zetasizer.

3.1.2 Entrapment efficiency

1 ml of the Niosomal solution was taken into a centrifugation tube and centrifuged at 15000 rpm for 20min.The supernatant is analysed at 260nm by diluting with distilled water using UV spectrophotometer [18, 19].

$$\%\text{Entrapment Efficiency} = \frac{\text{amount of drug in the Niosome}}{\text{Total amount of drug taken}} \times 100$$

3.1.3 *In vitro* Release of Drug from Fluconazole Niosomes

pH evaluation is an important criterion for topical formulation. Ideal pH value for topical formulations is 5-7. If the pH is either acidic or basic, it causes skin irritation 25ml distilled water dispersed with 2.5g of gel was taken and then utilizing digital pH meter the pH was measured [18].

3.2 EVALUATION OF NIOSOMAL GEL

3.2.1 Physical Appearance

Niosomal gels were visually evaluated for odour, colour, homogeneity, phase separation, and grittiness [19].

3.2.2 pH Determination

pH evaluation is an important criterion for topical formulation. Ideal pH value for topical formulations is 5-7. If the pH is either acidic or basic, it causes skin irritation 25ml distilled water dispersed with 2.5g of gel was taken and then utilizing digital pH meter the pH was measured [18].

3.2.3 Spreadability

It shows the degree of uniformity with which the gel can spread when applied to skin. A formulation's therapeutic effectiveness is also influenced by how easily it spreads. Spreadability is quantified by the duration it takes for two slides to separate from the gel positioned between them under the application of a specific force [19]. Calculated as:

$$S = M \times L / T$$

M= wt. tied to upper slide

T = length of time required to separate the slides

L = length of glass slides

3.2.4 Drug Content

Gel equivalent to 100 mg of Fluconazole is dissolved in pH 7.4 phosphate buffer. The solution is diluted to 10ml with phosphate buffer. The absorbance was measured at 260nm using UV spectrophotometer.

3.2.5 *In Vitro* Release Study

The *in vitro* diffusion of a prepared gel was conducted using a Franz diffusion cell with an egg membrane. A receptor compartment containing 20ml of phosphate buffer was utilized.
Subsequently, 1 gm of fluconazole niosomal gel was uniformly applied to the membrane. The donor compartment was placed in contact with the receptor compartment, and the temperature was maintained at 37±0.50C. A Teflon bead was place in the donor compartment for stirring. At specified time intervals within a 24-hour period, 5 ml of the solution from the receptor compartment were pipetted out, and immediately replaced with fresh 5 ml phosphate buffer. The cumulative percentage release of the drug was then calculated over time.[18].

3.2.6 Calculation of Release Kinetics for Fluconazole niosomal gel

Mathematical equations for calculation of release kinetics and interpretation of diffusion mechanisms were calculated for optimised formulations. Release component "n" was calculated from Korsmeyer Peppas equation [19].

3.3 STABILITY-STUDIES

Stability studies were conducted for optimized Niosomal gel at two temperatures i.e., 4±0.2°C and at 25-28±2°C for 3 months [18].

4. RESULTS AND DISCUSSION

4.1 PREFORMULATION STUDIES

Description	Powder
Colour	white

4.2 DRUG-EXCIPIENT COMPATIBILITY STUDIES

Drug-excipient compatibility studies FTIR study was conducted to confirm that there are no interactions between drug and excipients. The below graph shows that there are no interactions between drug and excipients.

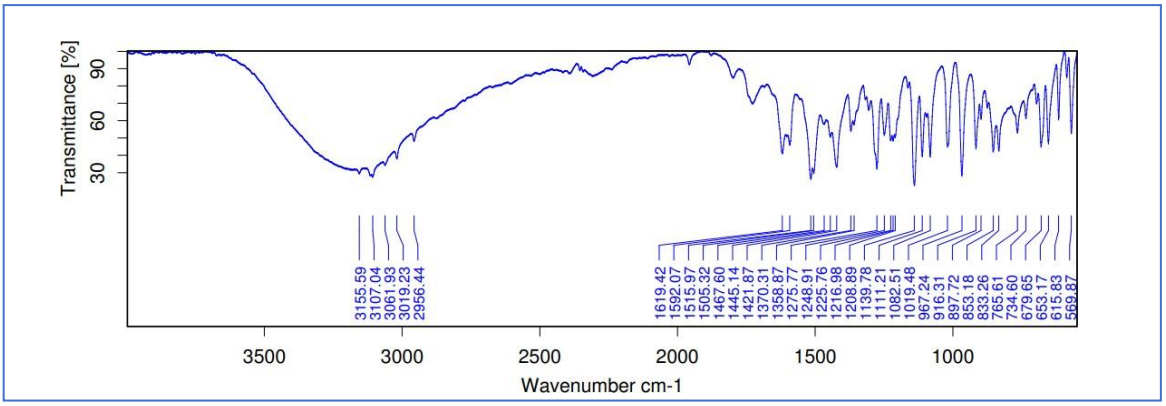


Fig 1: IR graph of Fluconazole pure drug

Table 2: Interpretation of IR graph of Fluconazole pure drug

Functional Group	**Wavenumber (cm^{-1})**
N-H stretch (amine)	3200-3000
C-H stretch (alkane)	2900-2800
C=C stretch (aromatic)	1575-1530
C-N stretch (amide)	1365-1350
C-F stretch (fluorine)	1250-1200
C-F stretch (fluorine)	1100-1000

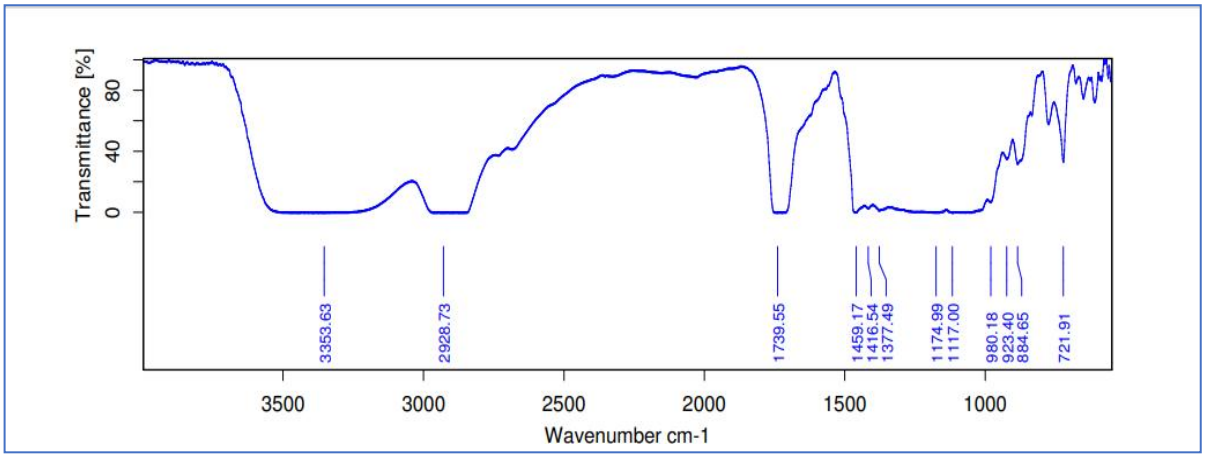


Fig 2: IR graph of Fluconazole + span 20

Table 3: Interpretation of IR graph of Fluconazole with span 20

FUNCTIONAL GROUP	FLUCONAZOLE	FLUCONAZOLE + SPAN 20
C-H stretching	2956.44	2928.73
C-H bending	1467.60	1459.17
O-H bending	1421.87	1416.54
O-H bending	1370.31	1377.49
C-N stretching	1111.21	1117.00
C=C bending	916.31	923.40
C=C bending	897.72	884.65
C=C bending	734.60	734.60

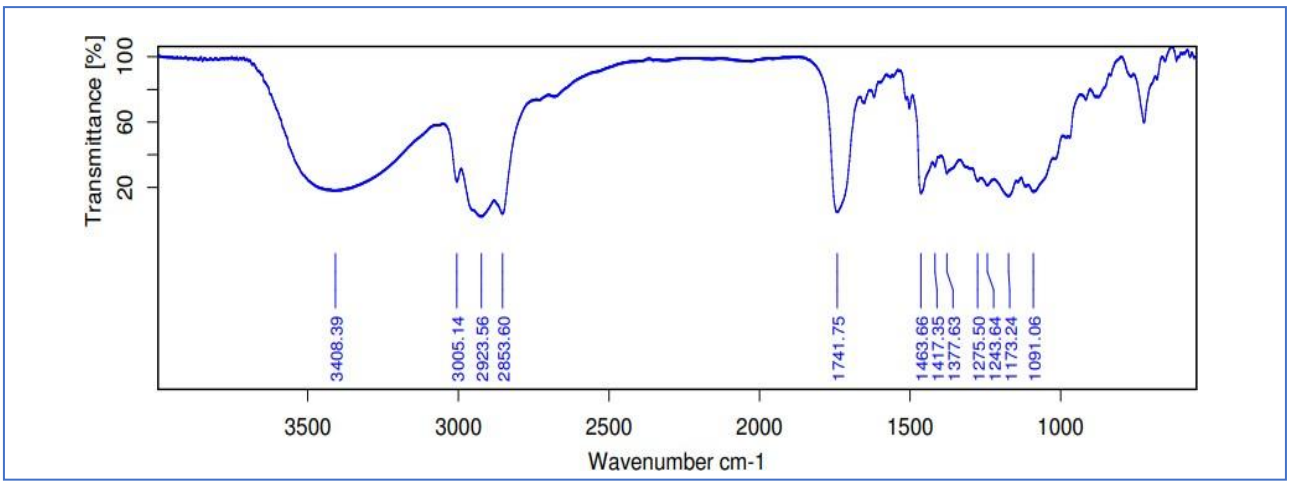


Fig 3: IR graph of Fluconazole + span 80

Table 4: Interpretation of IR graph of Fluconazole with span 80

FLUCONAZOLE + SPAN 80	FLUCONAZOLE	FUNCTIONAL GROUP
3005.14	3019.23	C-H Alkane
2923.56	2956.44	C-H Alkane
1463.66	1467.60	C=C Alkene
1417.35	1421.87	C=C Alkyne
1377.63	1370.31	C-H Alkane
1275.77	1275.77	C-O Alcohol
1243.64	1248.91	C-N Amine
1091.06	1082.51	C-F bond

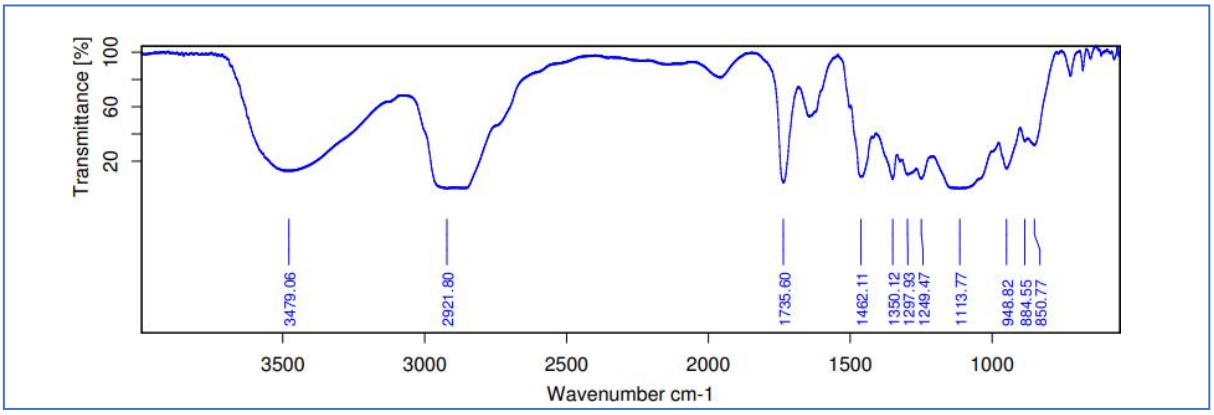


Fig 4: IR graph of Fluconazole+ tween 80

Table 5: Interpretation of IR graph of Fluconazole with tween 80

FUCTIONAL GROUP	FLUCONAZOLE	FLUCONAZOLE + TWEEN 80
C-H Alkane	2956.44	2921.80
C=C Alkene	1467.60	1462.11
C-N Amine	1358.87	1350.12
C-O Alcohol	1275.77	1297.93
C-N Amine	1248.91	1249.47
C-F	1111.21	1113.77
C-O Alcohol	897.72	884.55
C-N Amine	853.18	850.77

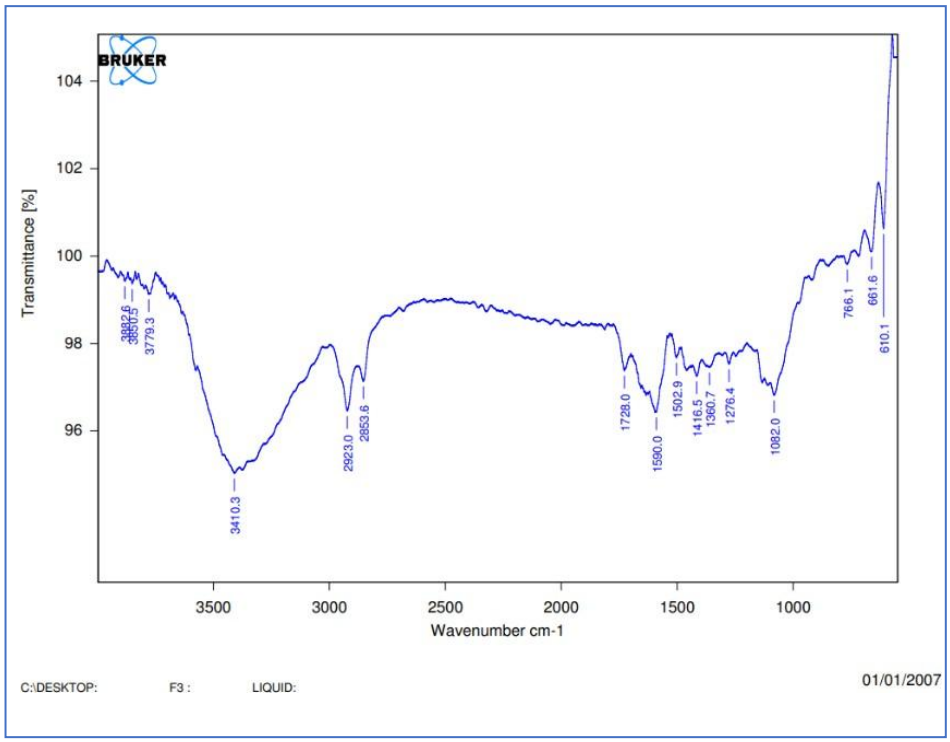


Fig 5: IR graph of F3 formulation

4.3 UV ANALYSIS

4.3.1 UV spectrum of Fluconazole in Methanol

UV spectrum of Fluconazole in methanol was scanned in the range of 200 nm to 400 nm. Fluconazole showed an absorption maximum (λmax) at 260 nm.

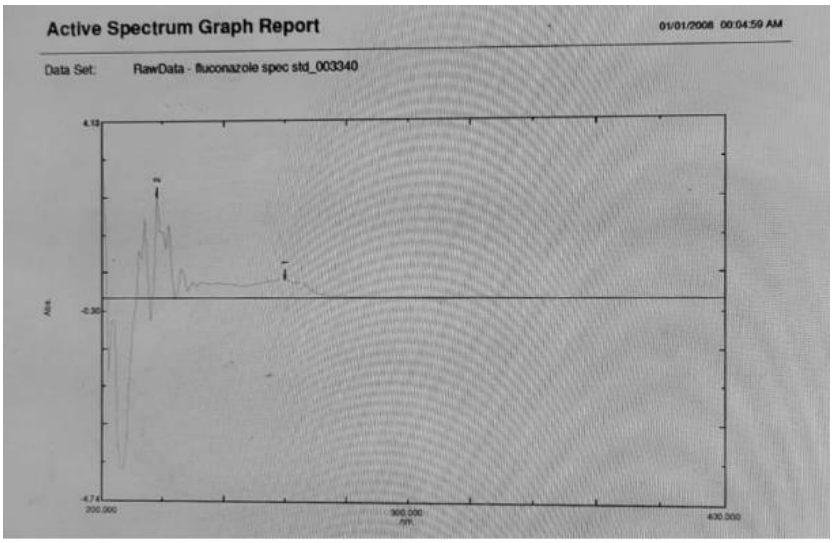


Fig 6 UV spectrum of Fluconazole

4.3.2 Standard graph of Fluconazole in methanol

Standard graph was determined for Fluconazole in methanol as solvent using UV Visible spectrophotometer and the correlation coefficient was found to be R2=0.9917

Table 6: Linearity table of Fluconazole

Concentration in µg/ml	Absorbance
50	0.271
100	0.436
150	0.653
200	0.800
250	0.929

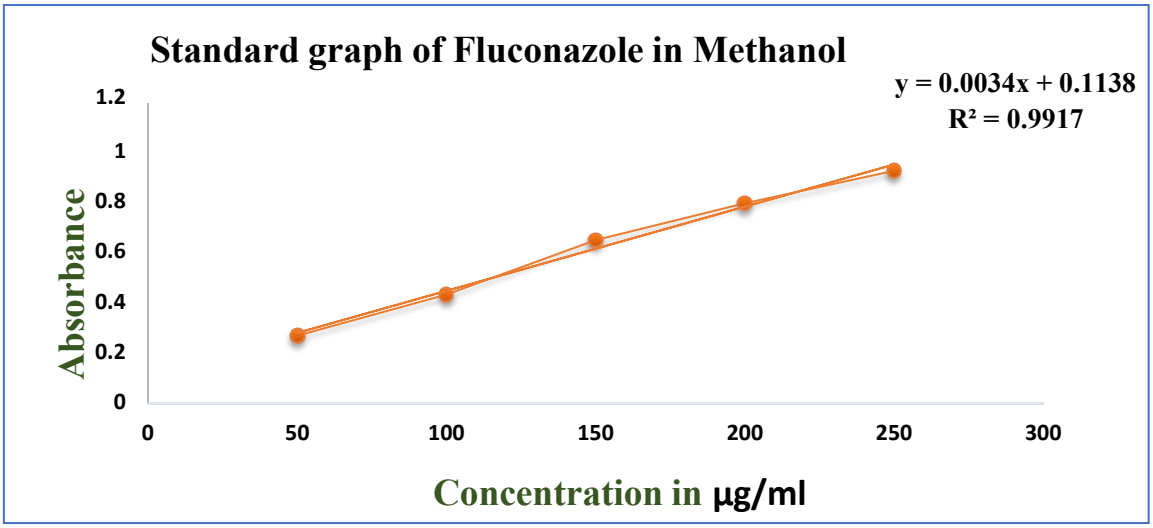


Fig 7: Standard graph of Fluconazole in methanol

4.3.3 Standard graph of Fluconazole drug in Phosphate Buffer pH

Standard graph was determined for Fluconazole in pH buffer 7.4 as solvent using UV Visible spectrophotometer and the correlation coefficient was found to be $R^2 = 0.9941$.

Table 7: Linearity table of Fluconazole in phosphate buffer

Concentration in µg/ml	Absorbance
5	0.025
10	0.039
15	0.059
20	0.07
25	0.086

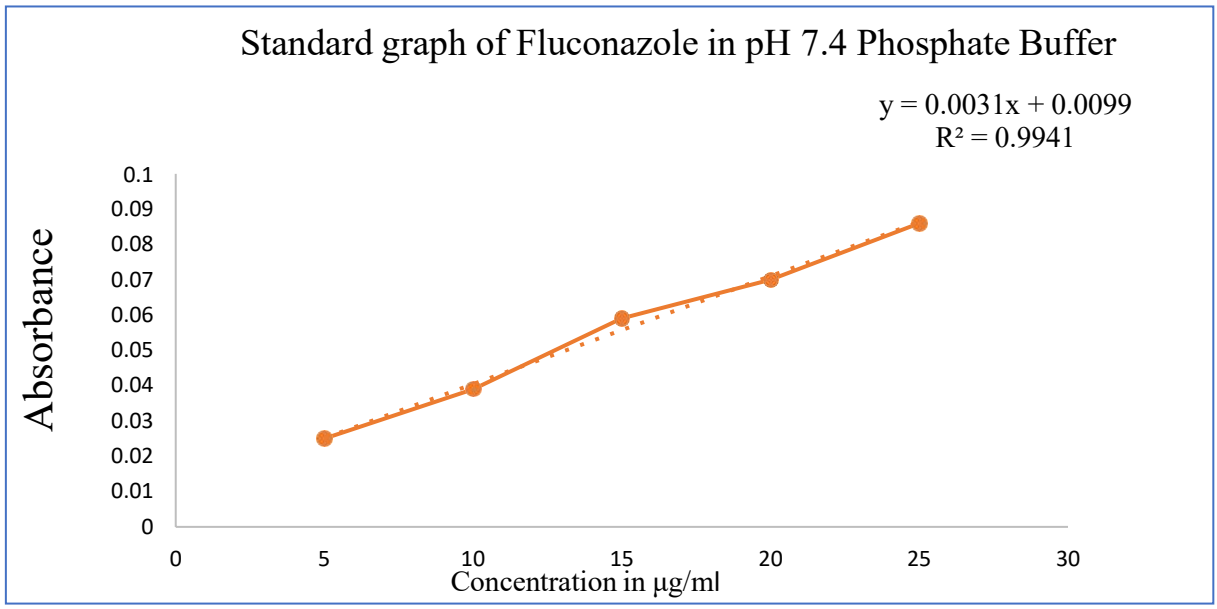


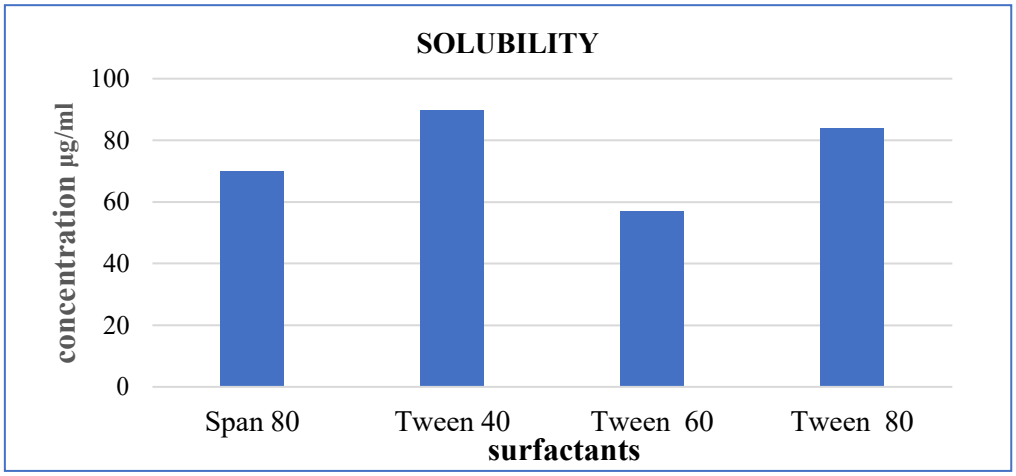
Fig 8: standard graph of Fluconazole in phosphate buffer

4.4 SOLUBILITY STUDIES OF FLUCONAZOLE IN VARIOUS SURFACTANTS

The solubility of Fluconazole was found to be highest in span 80 and tween 80.

Table 8: Solubility of Fluconazole in different surfactants

Surfactants	Solubility µg/ml
Span 20	70.06±0.96
Span 80	89.6±0.82
Tween 40	57.02±1.04
Tween 80	83.99±0.78



Standard deviation n=3

Fig 9: Solubility of Fluconazole in various surfactants

4.5 EVALUATION OF NIOSOMES

4.5.1 Entrapment efficiency

F3 formulation showed highest entrapment efficiency of 90.6%

Table 9: Entrapment efficiency of formulations

Formulation	% Entrapment Efficiency
F1	75.71
F2	89.1
F3	**90.6**
F4	82.54
F5	85.11
F6	75.63
F7	88.54
F8	81.10
F9	79.81

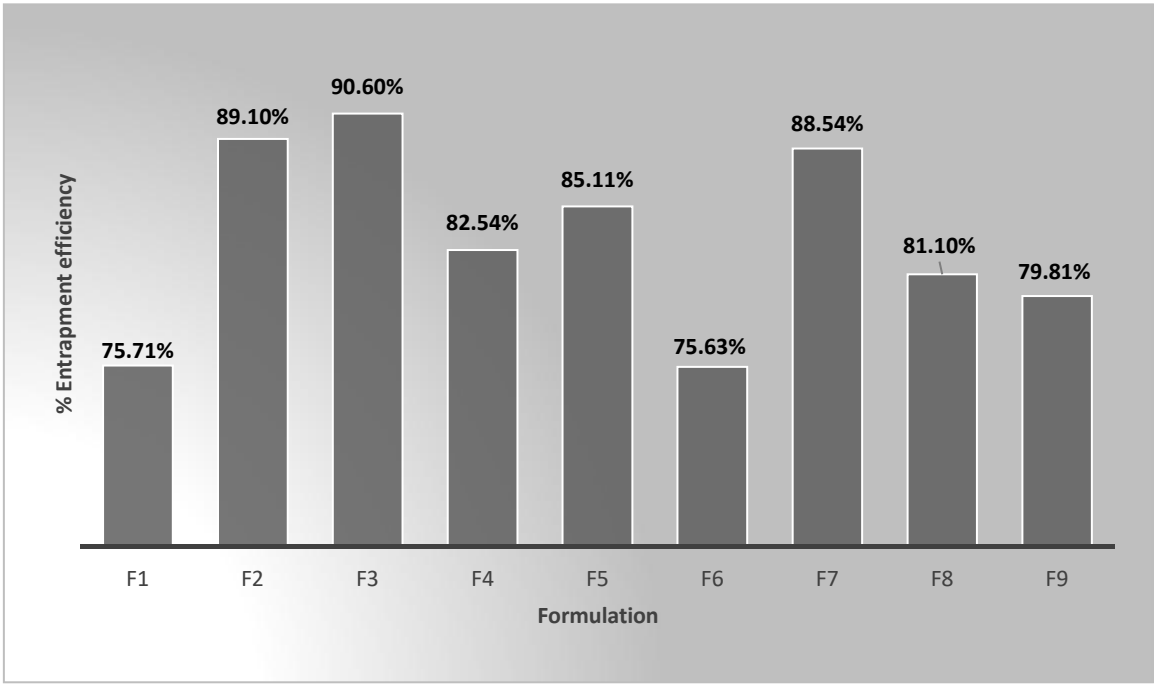


Fig 10: Entrapment efficiency

4.5.2 Charge & zeta potential

The zeta potential for F3 was found to be -52.2mV and the size was found to be 217.4nm.

Table 10: Zeta potential, Size and PDI of formulations

FORMULATION CODE	ZETA POTENTIAL (-MV)	SIZE	PDI
F1	-65	266	0.191
F2	-60	351.5	0.356
F3	**-52.2**	**217.4**	**0.228**
F4	-40.8	270.1	0.241
F5	-43.4	268	0.370
F6	-53.0	226.5	0.185
F7	-44.7	183.2	0.265
F8	-45.1	239.9	0.264
F9	-37.8	440	0.471

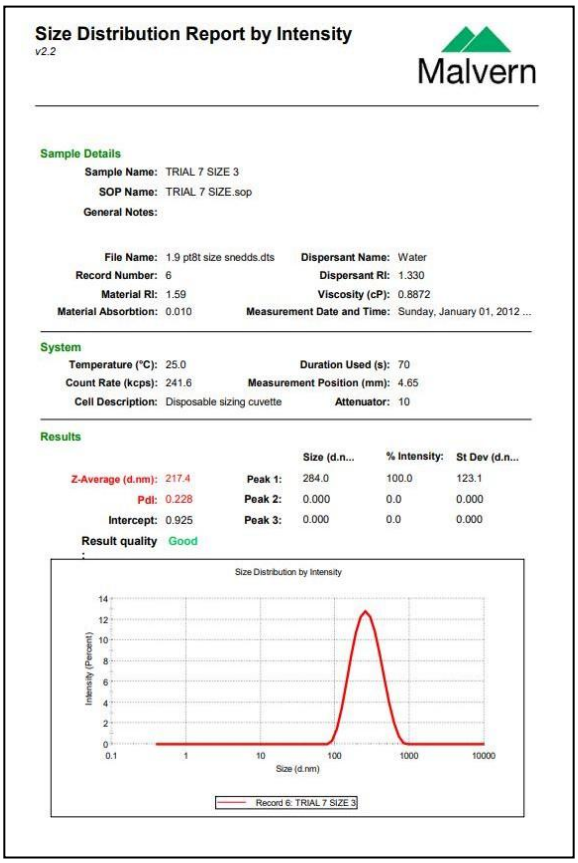


Fig 11: size distribution of F3 formulation

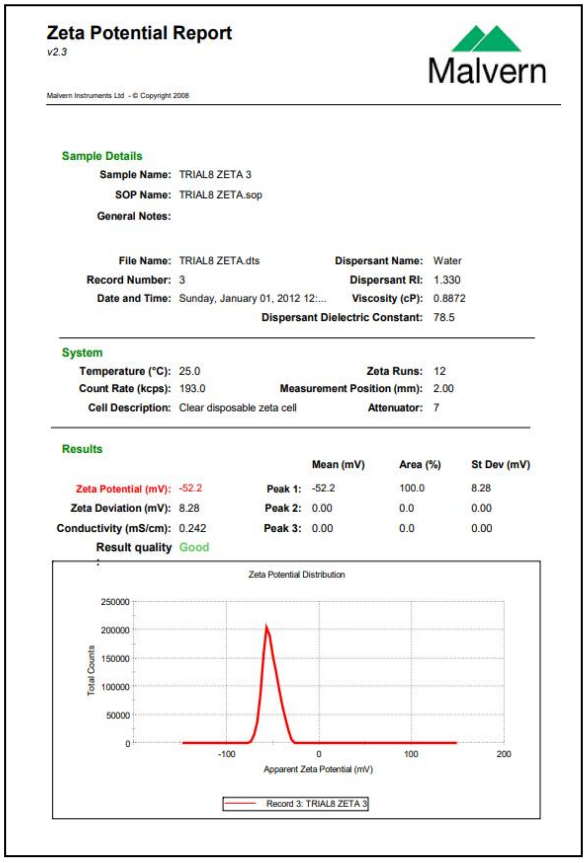


Fig 12: zeta potential of F3 formulation

4.5.3 *In vitro* drug release from Niosomes

F3 formulation showed highest drug release from prepared Fluconazole Niosomes.

Table 11: In-vitro drug release from formulations for 24 hrs

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	5.2±0.2	6.4±0.1	6.86±0.17	4.9±0.11	5.2±0.06	6.5±0.1	5.1±0.3	4.8±0.21	6.2±0.19
2	12.1±0.15	15.2±0.08	16.37±0.1	10.57±0.05	10.91±0.03	15.45±0.11	11.4±0.11	11.7±0.19	15.1±0.06
4	20.7±0.21	25.7±0.2	27.14±0.09	17.8±0.06	17.75±0.12	25.27±0.12	19.93±0.13	21.66±0.15	25.19±0.18
6	30.4±0.18	37.9±0.1	40.44±0.11	27.69±0.1	27.47±0.15	35.38±0.1	29.83±0.15	32.07±0.18	37.79±0.15
8	41.7±0.2	52.2±0.14	57.74±0.13	39.67±0.02	40.88±0.21	49.03±0.11	41.43±0.2	45.73±0.11	51.27±0.14
12	59.9±0.11	68.4±0.19	76.02±0.2	53.33±0.14	55.1±0.11	63.99±0.15	55.33±0.14	59.95±0.14	66.19±0.12
24	78.7±0.18	85.7±0.1	**94.91±0.14**	67.43±0.18	71.08±0.05	82.22±0.19	70.73±0.05	74.39±0.1	83.09±0.09

Standard deviation n=3

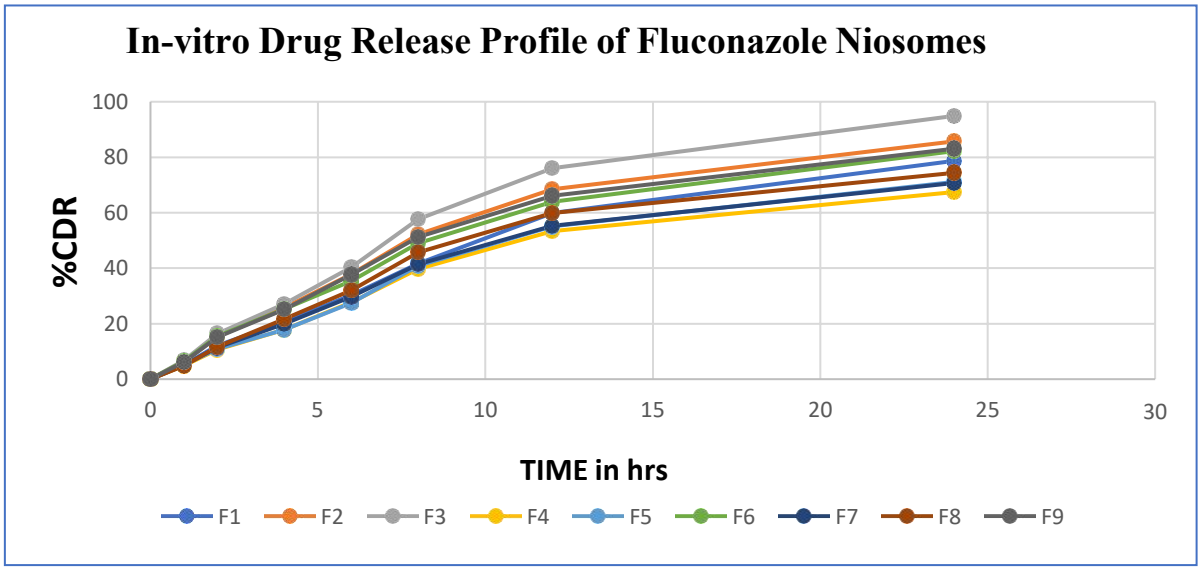


Fig 13 *In Vitro* Drug Release Profile of Fluconazole Niosomes

4.6 EVALUATION OF NIOSOMAL GEL

4.6.1 Physical Appearance

Niosomal gels were visually evaluated for odour, colour, homogeneity, phase separation, and grittiness.

4.6.2 Clarity, viscosity, and pH determination and %Drug content

The gel was found to be transparent, white, and viscous without any lumps and particles. The formulation had a good amount of Spreadability. The pH level was found to be 6.85.

Fig 14: Niosomal gel

Table 12: Result of Clarity, pH, Extrudability, Viscosity and %Drug content of the gel

FORMULATION	CLARITY	pH	Viscosity(cps)	%Drug Content
F3	GOOD	6.85±0.42	1728	93.14

Standard deviation n=3

4.6.3 *In Vitro* Release Study

In vitro diffusion studies were conducted using a Franz diffusion cell apparatus to assess the diffusion characteristics of the substance.

Table 13 *In Vitro* Drug Diffusion profile of prepared Fluconazole Niosomal gel

Time in hr	%Cumulative Drug Release
0	0
1	7.52±0.02
2	16.2±0.019
4	28.01±0.17
6	41.21±0.021
8	55.65±0.03
12	73.85±0.01
24	95.27±0.028

Standard deviation n=3

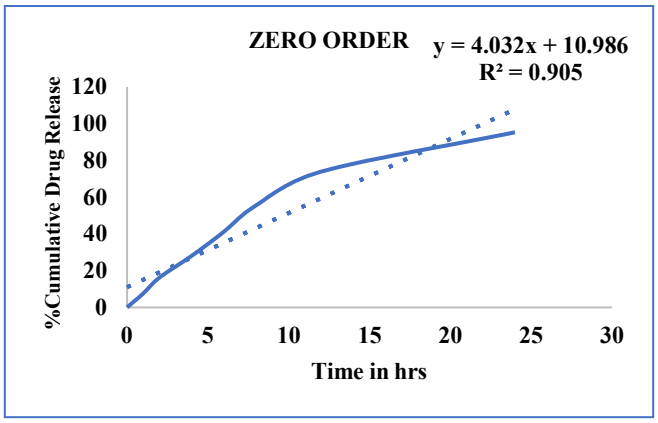


Fig 15: zero order kinetics

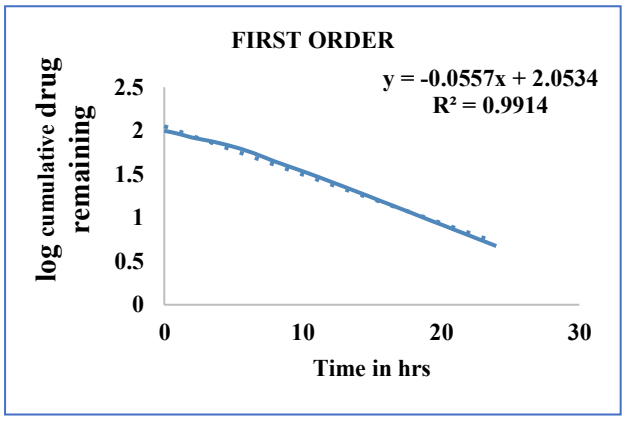


Fig 16: First order plot

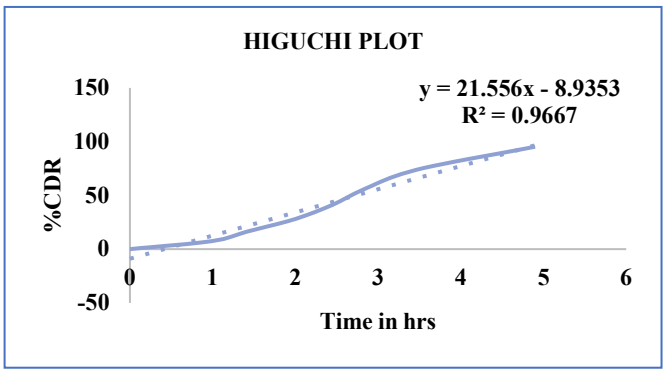


Fig 17: Higuchi plot

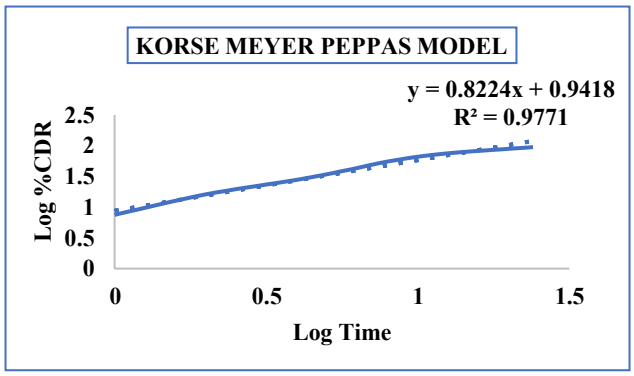


Fig 18: Korsmeyer peppas model

4.6.4 Calculation of Release Kinetics for Fluconazole Niosomal gel

The release kinetics for the formulations was plotted against time to fit zero-order, first-order, Higuchi kinetic model and Korsmeyer Peppas equations. The regression value and 'n' values were acquired from the plots.

Table 14: Release kinetics for optimised formulation F3

KINETIC MODEL	R^2
Zero order	0.905
First order	0.9924
Higuchi model	0.9667
Korsmeyer-Peppas model	0.9771

4.6.5 STABILITY-STUDIES

Stability studies conducted for optimized Niosomal gel at two temperatures i.e., 4±0.2°C and at 25-28±2°C for 3 months.

Table 15: stability studies of optimised gel formulation

Characteristic	1 month		2 months		3 months	
Temperature	4±0.2°C	25±2°C	4±0.2°C	25±2°C	4±0.2°C	25±2°C
Size in nm	231.6	240.2	247.5	280.7	277.8	366.4
Zeta in mV	45.4	37.9	45.3	37.8	37.1	31.9
%EE	86.3%	87.1%	86.5%	84.1%	83.2%	81.3%
pH	6.7±0.3	6.75±0.2	6.5±0.2	6.45±0.1	6.4±0.2	6.3±0.3
Drug release in %	93.89±0.08	93.49±0.05	93.02±0.09	92.98±0.1	92.58±0.12	92.28±0.19

Standard deviation n=3

5. CONCLUSION

In this research, Fluconazole Niosomes were optimised and incorporated in the gel. Fluconazole Niosomes were prepared by sonication method and incorporated into the gel using a mechanical stirrer. The optimised niosomal formulation F3 showed highest entrapment efficiency 90.6%. The size and charge of the Niosomes were within the range in all the formulations. Highest drug release from the Niosomes was shown by F3 formulation 94.91%. The formulated gel had a pH like that of the skin. The *in vitro* drug release of the prepared gel was 95.27%.

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