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Formulation and *In-Vitro* Evaluation of Posaconazole Loaded Transferosomal Gel

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ABSTRACT

Posaconazole is a broad-spectrum triazole antifungal approved for the prevention of invasive aspergillosis and candidiasis, although its effectiveness against rarer fungal infections is limited. To improve the transdermal delivery of Posaconazole and target the synovium while reducing toxicity, transferosomes were developed. The optimized formulation PF7, with a 70:30 (%w/w) ratio of soya lecithin to Tween-80, showed a high entrapment efficiency of 86.26% and an optimal drug release of 96.45%. FTIR analysis indicated no interactions between the drug and excipients, while in-vitro skin permeation studies demonstrated enhanced permeation and sustained drug deposition. Scanning electron microscopy (SEM) showed that the optimized posaconazole transferosomes were spherical and well-defined. The formulation PF7, containing 1.0 g, 1.5 g, and 2.0 g of Carbopol, identified the 1.5% w/w Carbopol transferosome gel as the optimized version, exhibiting a spreadability value of 3.6 cm and a pH of 6.72 ± 0.14. The actual drug content in the transferosomal gel was measured at 96.37 ± 0.18, indicating good content uniformity. The viscosity of the posaconazole transferosomal gel was recorded at 4500 cps, and the drug release percentage was found to be 97.18%. Stability studies showed that the transferosomal gels are more stable at lower temperatures. In conclusion, posaconazole transferosomal gels present a promising strategy by maintaining drug concentration at the target site for extended periods.

Keywords: Transferosomal gel, Posaconazole, thin film hydration method

INTRODUCTION

Posaconazole, a triazole antifungal agent, is clinically used to treat severe fungal infections, including Aspergillosis and Candidiasis. Posaconazole drug of BCS Class II compound (high permeability, low solubility)with dose 100 mg,35 hrs half-life and protein binding >98%.Posaconazole Formulations includes delayed-release tablets, oral suspension, and intravenous solutions. However, its conventional oral formulations are limited by poor absorption, first-pass metabolism, and side effects. Several advanced drug delivery systems, such as nanosuspensions, nanoemulgels, and ethosomal gels, have been explored to improve its bioavailability. Studies reveal that transferosomes, a type of deformable vesicular carrier, can penetrate the skin's stratum corneum more effectively than conventional vesicles. Despite these advancements, limited studies have focused on transferosomes for Posaconazole delivery. This study aims to bridge this gap by formulating a transferosomal gel for effective topical delivery.

The aim of this study is to formulate and evaluate a Posaconazole-loaded transferosomal gel to enhance transdermal delivery. This innovative approach seeks to overcome the limitations of conventional Posaconazole formulations, such as poor bioavailability, frequent dosing, and systemic side effects, by ensuring sustained drug release and targeted delivery.

The objectives of this study are to develop an analytical method for estimating Posaconazole in formulations, perform pre-formulation studies including drug-excipient compatibility, and prepare Posaconazole-loaded transferosomes using the thin-film hydration method. The study also aims to characterize the transferosomes, formulate a transferosomal gel, and evaluate its drug release, spreadability, viscosity, stability, and drug content. Additionally, the release kinetics and stability of the optimized formulation will be analyzed to ensure effective transdermal delivery.

This study presents a novel approach to deliver Posaconazole transdermally, aiming to improve patient compliance and therapeutic efficacy.

METHODOLOGY

PREFORMULATION STUDIES:

Preformulation maybe described as a phase of the research & development process where the formulation scientist characterizes the physical, chemical properties of API, in order to develop stable, safe and effective dosage forms. During this evaluation possible interaction with various inert ingredients intended for use in final dosage.

1.Organoleptic properties:

The colour, odour and taste of the drug were evaluated using descriptive terminology.

2. Solubility

The solubility of drug was studied in different solvents such as water, phosphate buffer 6.8,methanol,dimethyl formamide, dimethyl sulfoxide, by measuring how many parts of solvent is required for one part of solid.

3. Melting point

Melting point of Model drug was determined by capillary method. Fine powder of Model drug was filled in glass capillary tube (previously sealed on one end. The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt. Melting point of the drug was determined by using Scientec digital melting point apparatus.

4. Construction of standard curve of Posaconazole (UV method):

(i) Determination of maximum absorbance (λmax):

A 100µg/ml concentration of Posaconazole API was obtained by dissolving 10 mg in 10 ml of 6.8 pH phosphate buffer and absorbance was assessed using a UV-vis spectrophotometer within the 200–400 nm range.

(ii) Construction of standard curve of Posaconazole (UV method):

100 mg Posaconazole in 100 mL of pH 6.8 Phosphate buffer. Dilute 10 ml to 100 ml for a concentration of 100 µg/ml. Aliquots of 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, and 1 ml were pipetted into 10 ml volumetric flasks. The absorbance of each concentration was measured using the UV method at 244 nm.

5) FT-IR studies

FTIR (Fourier Transform Infrared) spectroscopy was conducted to assess the compatibility of Posaconazole with selected polymers and excipients. FTIR spectra were recorded using a PerkinElmer Spectrum Two in the range of 400–4000 cm^{-1} with a resolution of 4cm^{-1}.Samples were prepared as self-supporting disks (powder mixed with KBr) or as thin liquid films for liquid formulations. Spectra of the formulations were compared with those of the pure drug and excipient.

6.FORMULATION OF TRANSFERSOMES AND TRANSFEROSOMAL GEL:

- Preparation of transferosomes containing Posaconazole
- Preparation of topical Transferosome gel

1.Preparation of Transferosomes by Modified Hand shaking lipid film hydration technique:

Transferosomes were prepared using the thin film hydration method with posaconazole, soya lecithin, and varying concentrations of surfactants (Span-20, Tween 80), while keeping the drug amount constant at 100 mg. The components were dissolved in 10 ml of chloroform-methanol (1:1), and the solvent was evaporated by shaking above 43°C and then under vacuum. The lipid film was hydrated with phosphate buffer (pH 6.8) at 60 rpm for 1 hour, allowed to swell for 2 hours, and then sonicated for 30 minutes.

Table 1: Formulation of Posaconazole transferosomes

Formulation	Drug (mg)	Lecithin (mg)	Span 20 (mg)	Tween 80 (mg)	Chloroform (ml)	Methanol (ml)
F1	100	90	5	--	5	5
F2	100	80	10	--	5	5
F3	100	70	15	--	5	5
F4	100	60	20	---	5	5
F5	100	90	--	5	5	5
F6	100	80	--	10	5	5
F7	100	70	--	15	5	5
F8	100	60	---	20	5	5

2. Preparation of Posaconazole transferosome gel:

Carbopol gels were formulated for the topical delivery of transfersomes. A total of 1.50 g of carbopol 934 was dispersed in 100 mL of distilled water using a magnetic stirrer, hydrated for 24 hours, and then neutralized with triethanolamine to achieve a pH of 6.8, as measured by a pH meter.

Table 2: Composition of topical transferosomal gel formulation:

Formulation Code	Ingredients		
	Carbopol 934	**Propylene glycol**	**Methanol**
PF7	1.0g	10	10
PF7	1.5g	10	10
PF7	2.0g	10	10

7.CHARACTERIZATION OF POSACONAZOLE LOADED TRANSFERSOMES:

A. Particle Sizes, PDI, Zeta Potential:

The mean particle length and polydispersity index (PDI), that's a degree of the distribution of transfersomes, was decided the usage of dynamic light scattering and Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS.

B. Determination of entrapment efficiency percentage:

Posaconazole entrapment in transfersomes was evaluated by diluting 1 g of gel in 10 mL phosphate buffer (pH 6.8), sonicating for 20 minutes, and centrifuging at 14,000 rpm for 30 minutes. The absorbance of a 0.5 mL supernatant was measured with a UV spectrophotometer.

8.EVALUATIONS OF TRANSFEROSOMAL GEL

1.Determination of pH:

1gm of gel formulation were dissolved in 10ml of distilled water (pH 7) was prepared. The pH of the gel was determined by using digital pH meter(Digi sun electronics), measured by bringing the probe of the pH meter in contact with the samples.

2.Spreadability: It was determined by modified wooden block and glass slide apparatus. A measured amount of gel was placed on fixed glass slide, the movable pan with a glass slide attached to it and was placed over the fixed glass slide, such that the gel was sandwiched between the two glass slides for 5min. The weight was continuously removed. Spreadability was determined using the formula.

$$S = Ml/T$$

Where,

S is the Spreadability in g/s,

Ml is the mass in grams & T is the time in seconds.

3.Determination of Viscosity:

Viscosities of the gels were determined by using Brookfield viscometer. Spindle type, S-64 at 100rpm.

4.Drug content:

1g of transfersomal gel was taken and the vesicles were lysed with 25 ml of methanol by sonication [citizen, India] for 15 min. Later this solution was centrifuged at 14000 rpm for 30 minutes. Then 10 ml of solution was diluted to 100 ml with phosphate buffer pH 6.8. Aliquots were withdrawn and drug content was calculated using UV (nicolet e100) spectrophotometer

$$\% \text{ Drug Content} = \frac{\text{Amount of Drug obtained after centrifugation}}{\text{Amount of drug taken}} \times 100$$

5.Scanning electron microscopy (SEM)

The morphology of the posaconazole transferosomal gel was studied using scanning electron microscopy (SEM).The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminium stub. The stubs were then coated with gold film under reduced pressure. The stub containing the coated samples was placed in the scanning electron microscope (Hitachi S3400N) chamber. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 5 kV. Microphotographs were taken on different magnification and higher magnification was used for surface morphology.

6.In-vitro diffusion drug release studies

In-vitro drug release studies from posaconazole transferosomal gel were performed by using Modified Franz diffusion cell on egg membrane in phosphate buffer solution (pH 6.8). Egg membrane was mounted horizontally on the receptor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was $2cm^2$ and capacity of receptor compartment was 30ml of phosphate buffer (pH 6.8) maintained at 37 ± 0.5^0C and stirred by a magnetic bar at 100rpm. Transfersomal gel formulation equivalent to 5mg drug was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals 5 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer (pH 6.8) to maintain sink conditions. The samples were analysed spectrophotometrically at λ max.

7.DATA ANALYSIS

Data Analysis Summary:

To study the release mechanism and rate of the dosage form, data were fitted to Zero Order, First Order, Higuchi Matrix, Peppas, and Hixson-Crowell models. The best-fit model was selected based on the R-value.

Zero Order Release

- Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented as:

$$\mathbf{Q = Q_0 + K_0 t}$$

- Where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero), and K_0 is the zero-order release constant.

- The plot made: cumulative % drug release vs. time (zero order kinetic model).

- Zero order drug release mechanism is mainly applicable to dosage forms like transdermal systems, coated forms, osmotic systems as well as matrix tablets with low soluble drugs.

First Order Release

- To study the first order release rate kinetics the release rate data were fitted into the following equation,

$$\mathbf{LogC = LogCo - kt / 2.303}$$

- Where C is the amount of drug released at time t, C_0 is the initial amount of drug in the solution and K_1 is the first order release constant[43].

- This model is applicable to study of hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

- **Higuchi Model**

✓ This model is based on the hypotheses that

(i) Initial drug concentration in the matrix is much higher than drug solubility;

(ii) Drug diffusion takes place only in one dimension (edge effect must be negligible);

(iii) Drug particles are much smaller than system thickness;

(iv) Matrix swelling and dissolution are negligible;

(v) Drug diffusivity is constant and

(vi) Perfect sink conditions are always attained in the release environment.

✓ Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

$$\mathbf{Q = Kt1/2}$$

Where, K is the constant reflecting the design variables of the system.

✓ This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

✓ The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$\mathbf{Q01/3 - Qt1/3 = K_{HC}\, t}$$

✓ Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation[45].

✓ This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

✓ When this model is used, it is assumed that the release is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix.

Korsmeyer-Peppas Model

✓ Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppa's model:

$$Mt/M\infty = Ktn$$

✓ Where Mt / M∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table for cylindrical shaped matrices.

This model is widely used when release mechanism is well known or when more than one type of Release phenomenon could be involved.

Table 3: Determination of the type of diffusion

Diffusion exponent (n)	Drug diffusion mechanism
<0.45	**Quasi Fickian**
0.45	**Fickian diffusion**
0.45<n<0.89	**Anomalous transport (Non Fickian transport)**
0.89-1	**Case II relaxation**
>1	**Super case II transport**

8.Stability Studies of transferosomes:

The optimized formulation was stored in sealed glass ampoules at refrigeration temperature (4±2ºC), room temperature (25±2ºC) and body temperature (37±2ºC) for a period of at least 3 months. The percentage entrapment of the drug and % drug content was determined . The percent drug lost was calculated taking the initial entrapment of drug as 100%.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES:

1.Organoleptic Characteristics:

TABLE 4: ORGANOLEPTIC PROPERTIES OF POSACONAZOLE (API)

Test	Description
State	Solid
Appearance	Amorphous powder
Colour	White
Odour	Free of odour

2.Solubility:

TABLE 5: SOLUBILITY OF POSACONAZOLE (API) IN VARIOUS SOLVENTS.

Solvents	Solubility in mg/ml
Water	0.001mg/ml±0.54
Methanol	0.25mg/ml±0.49
Dimethyl Formamide	0.45mg/ml±0.21
Dimethyl sulfoxide	0.5mg/ml ±0.32

Observations : The solubility of posaconazole is more in dimethyl sulfoxide & dimethyl formamide comparatively with methanol & water.

3. Melting Point determination:

TABLE 6: MELTING POINT DETERMINATION OF POSACONAZOLE(API)

Drug	Literature value	Melting point
Posaconazole	170-172 °C	**171°C±0.23**

All values expressed as mean ± SD, (n=3)

Observation: The melting point of posaconazole was observed to be 171ºC indicating the purity of drug sample.

4.UV-Spectroscopy-Analysis of Drug

1. Determination of λ max of posaconazole in phosphate buffer 6.8 by Uv spectroscopy:

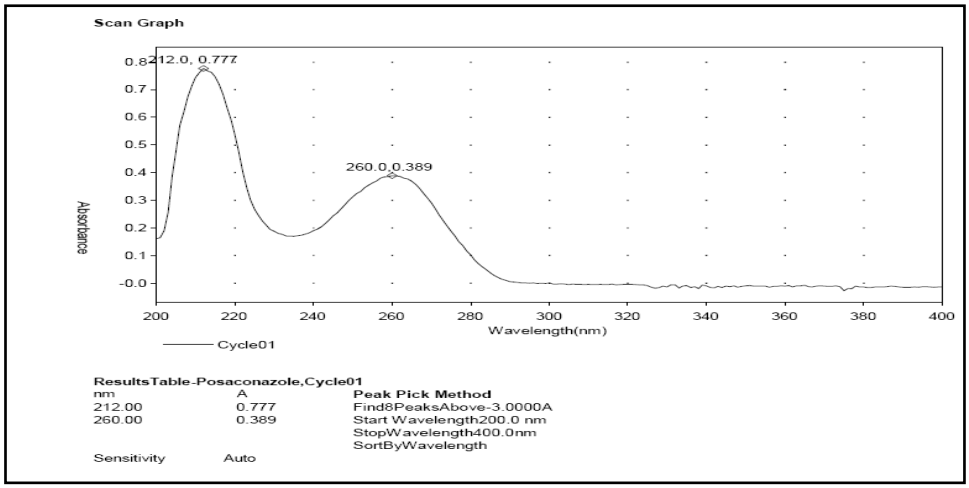

Fig 1: Wavelength Of Posaconazole In Simulated 6.8 pH Phosphate Buffer At 260nm

2.Calibration curve:

- The standard graph of posaconazole showed good linearity with R^2 of 0.9982, which indicates that it obeys "Beer- Lamberts" law.

Table 7: Calibration Curve data of Posaconazole in Phosphate Buffer pH6.8

S.no	Concentration (µg/ml)	Absorbance at 260nm
1	0	0
2	5	0.145+0.011
3	10	0.301+0.012
4	15	0.468+0.016
5	20	0.617+0.010
6	25	0.738+0.08

All values expressed as mean ± SD, (n=3)

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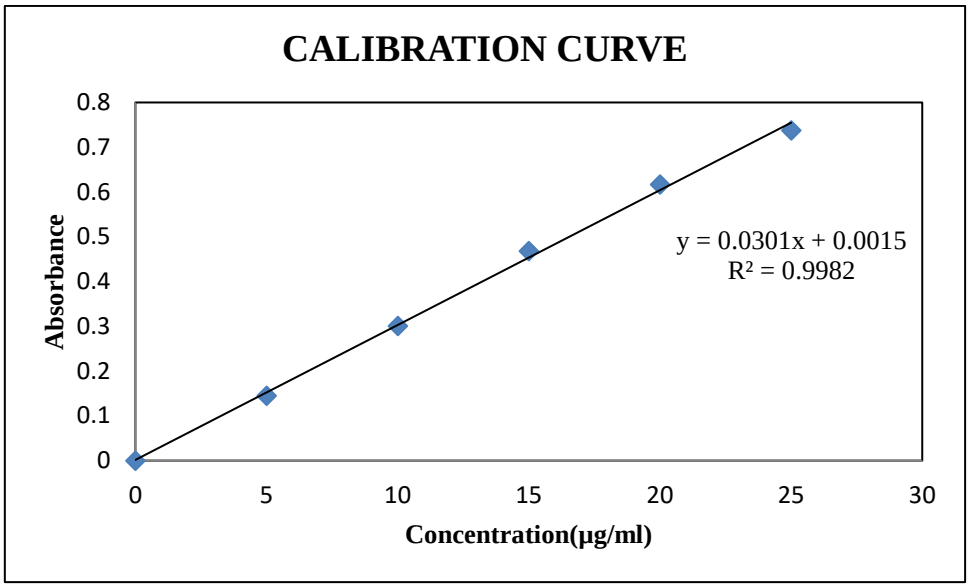

Fig.2: Standard Graph of Posaconazole in Phosphate Buffer pH 6.8

5.Drug excipient compatibility study (FTIR):

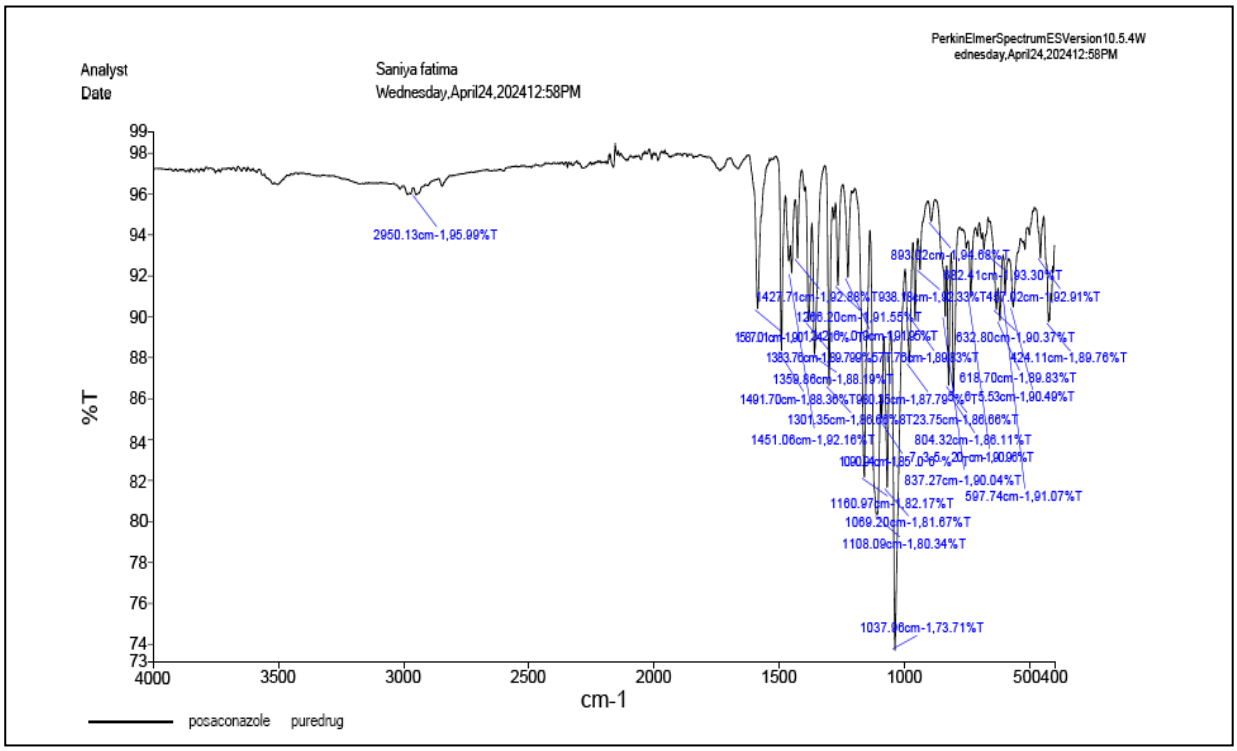

Fig 3 : FTIR spectra of Posaconazole pure drug

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 12, December 2024 ijppr.humanjournals.com ISSN: 2349-7203

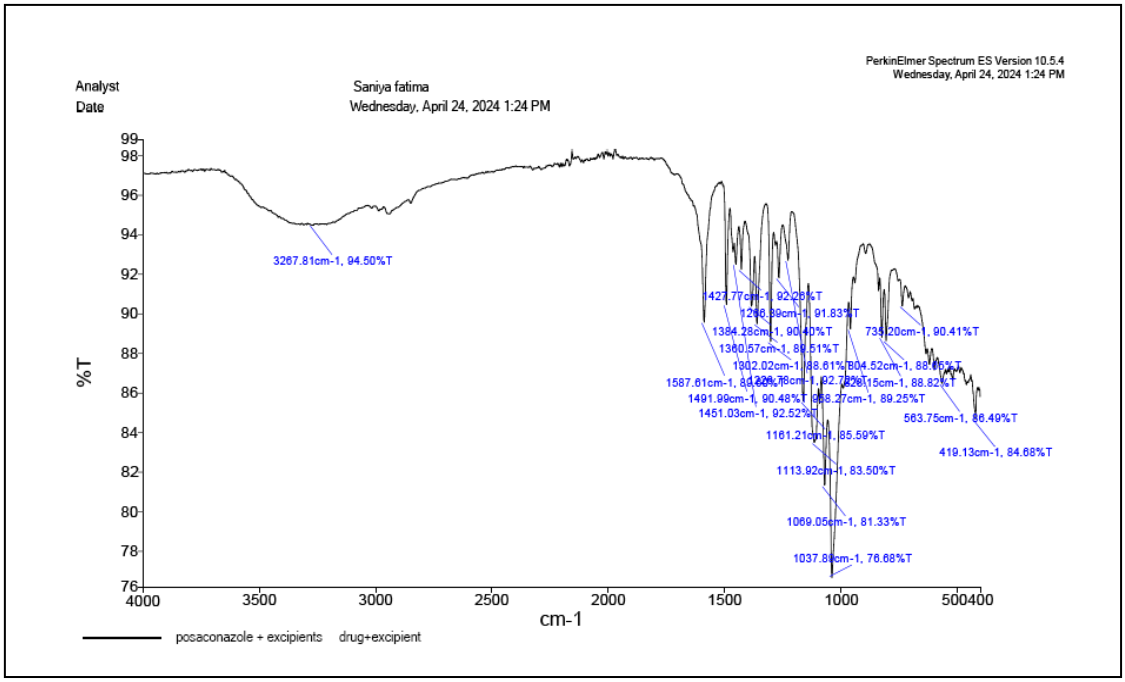

Fig 4 : FTIR Spectra of Posaconazole with all excipients

Table 8: FTIR Interpretation table

Characteristic peak	LITERATURE VALUES	OBSERVED VALUES		
		Pure drug	Excipients	
			Soya lecithin	Carbopol
O-H	3300-2500	2950.13	2951.71	2985.14
C –O	1210-1160	1160.97	1161.46	1161.63
C ═O	1870-1540	1587.01	1587.01	1587.38
C-F	1400-1000	1383.76	1384.30	1383.53

The FTIR Spectrophotometric studies found no indication of drug-excipient interaction.

6.CHARACTERISATION OF PREPARED POSACONAZOLE TRANSFEROSOMES

Table 9: Particle Size, PDI, Zeta potential, Entrapment Efficiency, and Drug Content of all formulations

Formulation	Particle size (nm)	PDI	Zeta potential (mV)	Entrapment Efficiency (%)	Drug content (%)
PF1	159.4	0.271	-17.4	81.24±0.18	92.35±0.12
PF2	169.7	0.296	-16.2	82.10±0.14	91.47±0.27
PF3	157.4	0.276	-19.6	84.26±0.25	93.26±0.16
PF4	164.7	0.289	-18.9	82.11±0.12	92.45±0.24
PF5	176.1	0.291	-21.0	84.28±0.36	94.22±0.19
PF6	197.3	0.341	-19.8	80.41±0.27	94.17±0.21
PF7	**151.6**	**0.257**	**-22.18**	**86.26±0.20**	**96.45±0.36**
PF8	187.4	0.302	-17.2	84.28±0.22	94.24±0.23

All values expressed as mean ± SD, (n=3)

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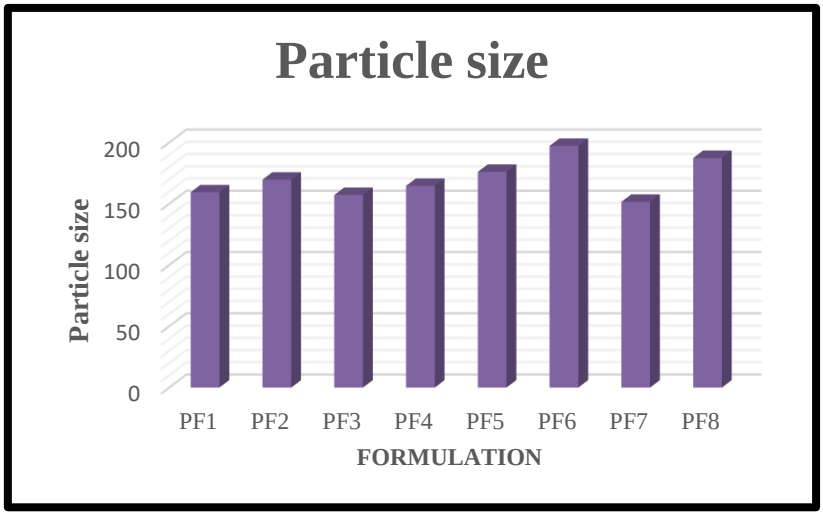

Figure 5: Particles size for PF1 –PF 8

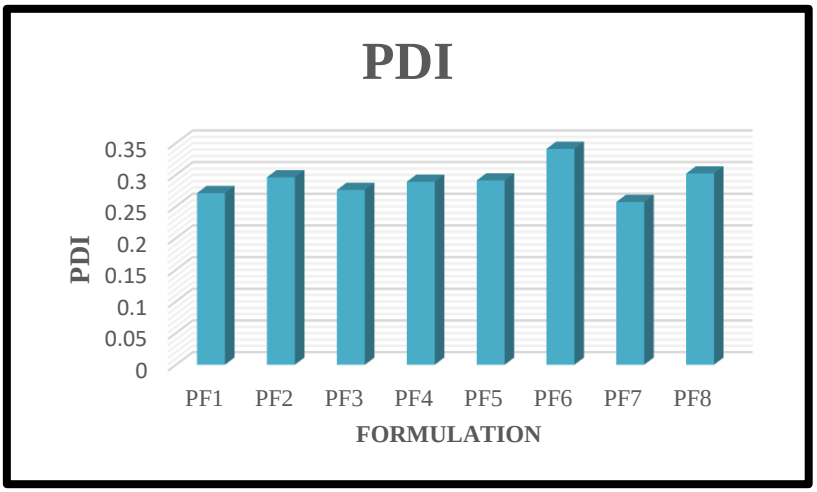

Fig 6 :PDI for PF1 –PF 8

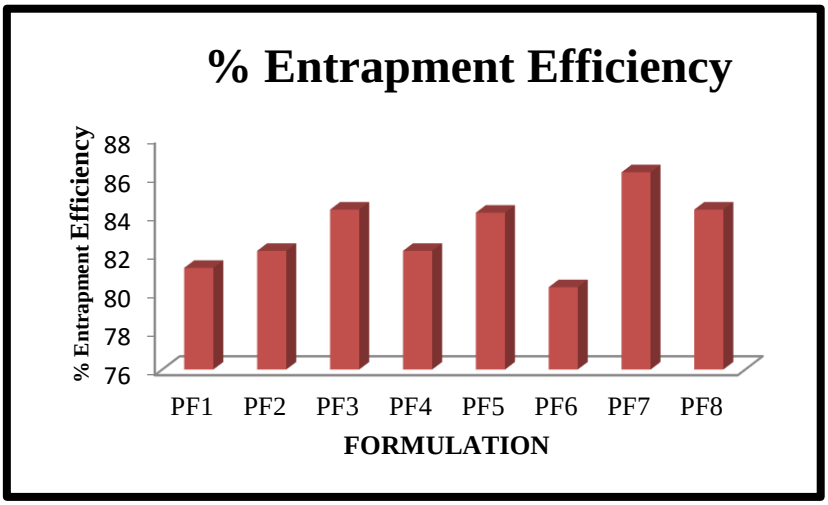

Fig 7: % Entrapment efficiency for PF1 –PF 8

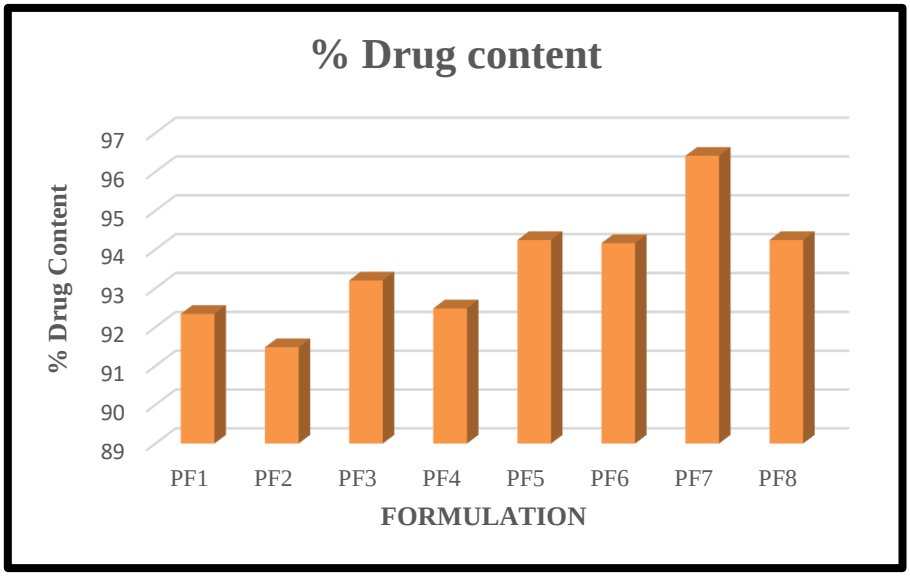

Fig 8: %Drug content for PF1 –PF8

7.In-vitro drug release study

Table 10: *In-Vitro* drug release of transferosomal gel (PF1to PF8)

Time (hr)	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8
0	0	0	0	0	0	0	0	0
1	17.20±0.8	12.46±0.14	13.21±0.6	21.17±0.1	10.8±0.10	18.37±0.4	12.4±0.2	19.8±0.1
2	22.04±0.12	26.42±0.4	21.26±0.4	28.54±0.2	16.88±0.11	27.14±0.1	24.21±0.12	29.5±0.4
3	34.47±0.3	31.27±0.18	36.4±0.1	32.16±0.1	24.36±0.3	38.26±0.8	30.9±0.5	39.2±0.1
4	41.61±0.2	36.59±0.15	42.26±0.4	40.29±0.5	29.8±0.1	43.27±0.2	37.26±0.6	49.6±0.2
5	48.81±0.2	40.28±0.14	45.28±0.2	46.41±0.3	36.72±0.4	49.17±0.6	42.51±0.2	56.8±0.4
6	52.31±0.2	45.17±0.8	52.51±0.8	49.24±0.2	42.81±0.2	57.24±0.4	46.26±0.1	65.7±0.1
8	59.45±0.6	51.78±0.4	59.29±0.5	53.2±0.4	50.2±0.4	68.34±0.4	54.34±0.1	77.42±0.4
12	67.24±0.4	60.43±0.1	67.75±0.4	59.19±0.1	66.43±0.1	76.19±0.21	66.42±0.6	84.14±0.6
24	80.24±0.7	84±0.9	84.8±0.2	74.28±0.1	76.14±0.2	88.35±0.14	96.18±0.4	89.46±0.2

All values expressed as mean ± SD, (n=3)

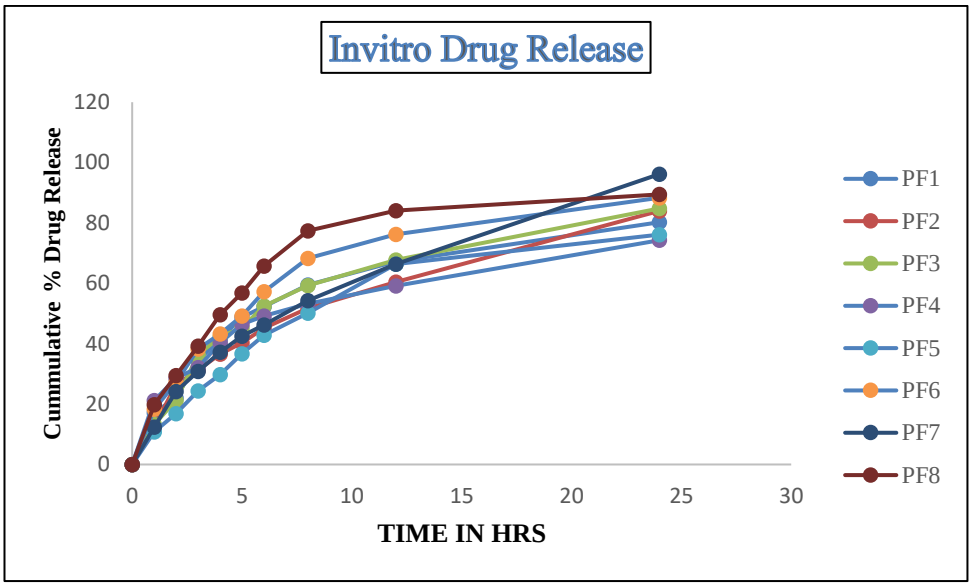

Fig 9: In-Vitro drug release of transferosomal gel (PF1to PF8)

8.CHARACTERISATION OF OPTIMIZED FORMULATION

1.Surface morphology of optimized formulation:

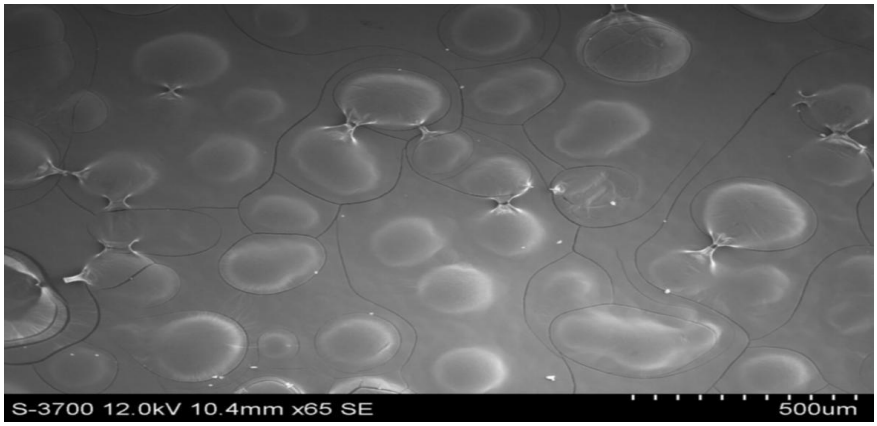

Fig 10: SEM analysis of optimized formulation (PF7)

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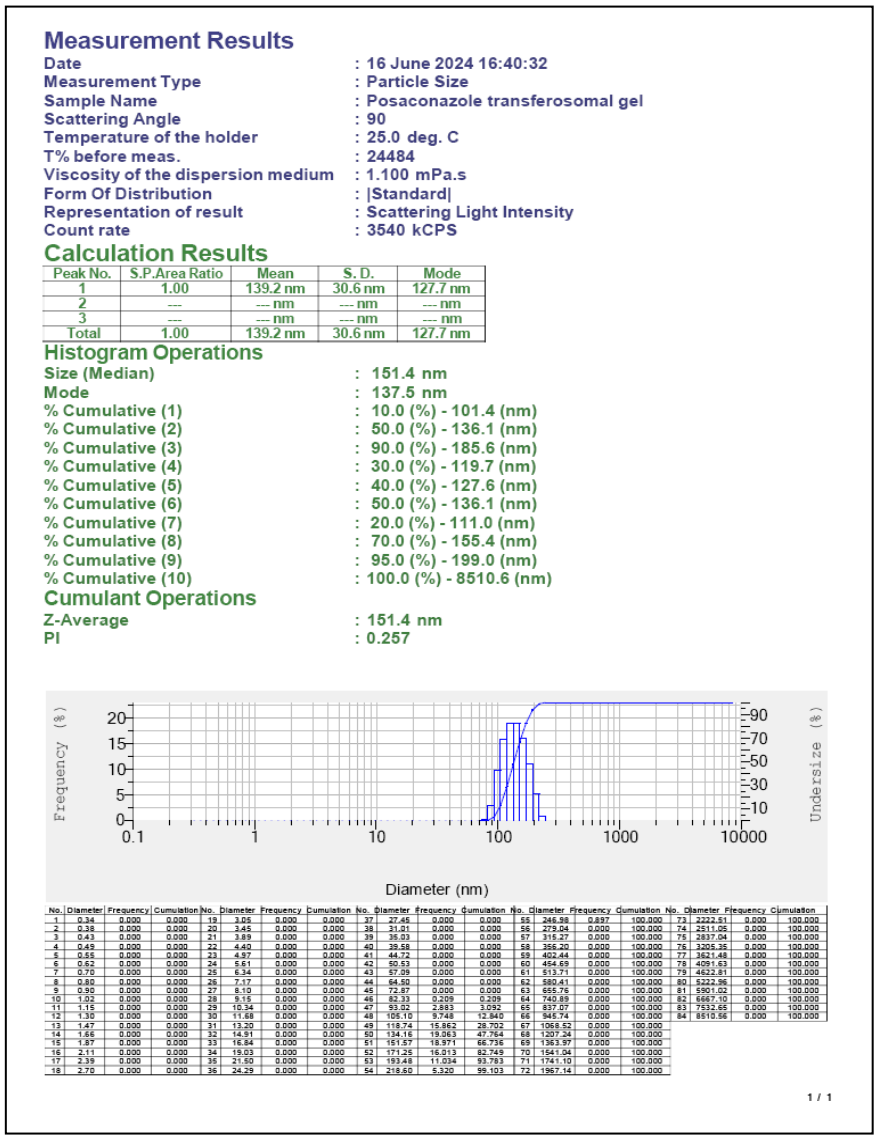
Volume 30, Issue 12, December 2024 ijppr.humanjournals.com ISSN: 2349-7203

2. Particle size & (PDI) analysis:



Measurement Results

Date	: 16 June 2024 16:40:32
Measurement Type	: Particle Size
Sample Name	: Posaconazole transferosomal gel
Scattering Angle	: 90
Temperature of the holder	: 25.0 deg. C
T% before meas.	: 24484
Viscosity of the dispersion medium	: 1.100 mPa.s
Form Of Distribution	: |Standard|
Representation of result	: Scattering Light Intensity
Count rate	: 3540 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	139.2 nm	30.6 nm	127.7 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	139.2 nm	30.6 nm	127.7 nm

Histogram Operations

Size (Median)	: 151.4 nm
Mode	: 137.5 nm
% Cumulative (1)	: 10.0 (%) - 101.4 (nm)
% Cumulative (2)	: 50.0 (%) - 136.1 (nm)
% Cumulative (3)	: 90.0 (%) - 185.6 (nm)
% Cumulative (4)	: 30.0 (%) - 119.7 (nm)
% Cumulative (5)	: 40.0 (%) - 127.6 (nm)
% Cumulative (6)	: 50.0 (%) - 136.1 (nm)
% Cumulative (7)	: 20.0 (%) - 111.0 (nm)
% Cumulative (8)	: 70.0 (%) - 155.4 (nm)
% Cumulative (9)	: 95.0 (%) - 199.0 (nm)
% Cumulative (10)	: 100.0 (%) - 8510.6 (nm)

Cumulant Operations

Z-Average	: 151.4 nm
PI	: 0.257

No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation
1	0.34	0.000	0.000	19	3.05	0.000	0.000	37	27.45	0.000	0.000	55	246.98	0.897	100.000	73	2222.61	0.000	100.000
2	0.38	0.000	0.000	20	3.45	0.000	0.000	38	31.01	0.000	0.000	56	279.04	0.000	100.000	74	2511.05	0.000	100.000
3	0.43	0.000	0.000	21	3.89	0.000	0.000	39	35.03	0.000	0.000	57	315.27	0.000	100.000	75	2837.04	0.000	100.000
4	0.49	0.000	0.000	22	4.40	0.000	0.000	40	39.58	0.000	0.000	58	356.20	0.000	100.000	76	3205.35	0.000	100.000
5	0.55	0.000	0.000	23	4.97	0.000	0.000	41	44.72	0.000	0.000	59	402.44	0.000	100.000	77	3621.48	0.000	100.000
6	0.62	0.000	0.000	24	5.61	0.000	0.000	42	50.53	0.000	0.000	60	454.69	0.000	100.000	78	4091.63	0.000	100.000
7	0.70	0.000	0.000	25	6.34	0.000	0.000	43	57.09	0.000	0.000	61	513.71	0.000	100.000	79	4622.81	0.000	100.000
8	0.80	0.000	0.000	26	7.17	0.000	0.000	44	64.50	0.000	0.000	62	580.41	0.000	100.000	80	5222.96	0.000	100.000
9	0.90	0.000	0.000	27	8.10	0.000	0.000	45	72.87	0.000	0.000	63	655.76	0.000	100.000	81	5901.02	0.000	100.000
10	1.02	0.000	0.000	28	9.15	0.000	0.000	46	82.33	0.209	0.209	64	740.89	0.000	100.000	82	6667.10	0.000	100.000
11	1.15	0.000	0.000	29	10.34	0.000	0.000	47	93.02	2.883	3.092	65	837.07	0.000	100.000	83	7532.65	0.000	100.000
12	1.30	0.000	0.000	30	11.68	0.000	0.000	48	105.10	9.748	12.840	66	946.74	0.000	100.000	84	8510.56	0.000	100.000
13	1.47	0.000	0.000	31	13.20	0.000	0.000	49	118.74	15.862	28.702	67	1069.52	0.000	100.000				
14	1.66	0.000	0.000	32	14.91	0.000	0.000	50	134.16	19.063	47.764	68	1207.34	0.000	100.000				
15	1.87	0.000	0.000	33	16.84	0.000	0.000	51	151.57	18.971	66.736	69	1363.97	0.000	100.000				
16	2.11	0.000	0.000	34	19.03	0.000	0.000	52	171.25	16.013	82.749	70	1541.04	0.000	100.000				
17	2.39	0.000	0.000	35	21.50	0.000	0.000	53	193.48	11.034	93.783	71	1741.10	0.000	100.000				
18	2.70	0.000	0.000	36	24.29	0.000	0.000	54	218.60	5.320	99.103	72	1967.14	0.000	100.000				

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Fig. 11: Average Particle Size & PDI of Optimized Formulation (PF7)

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3.Zeta Potential:

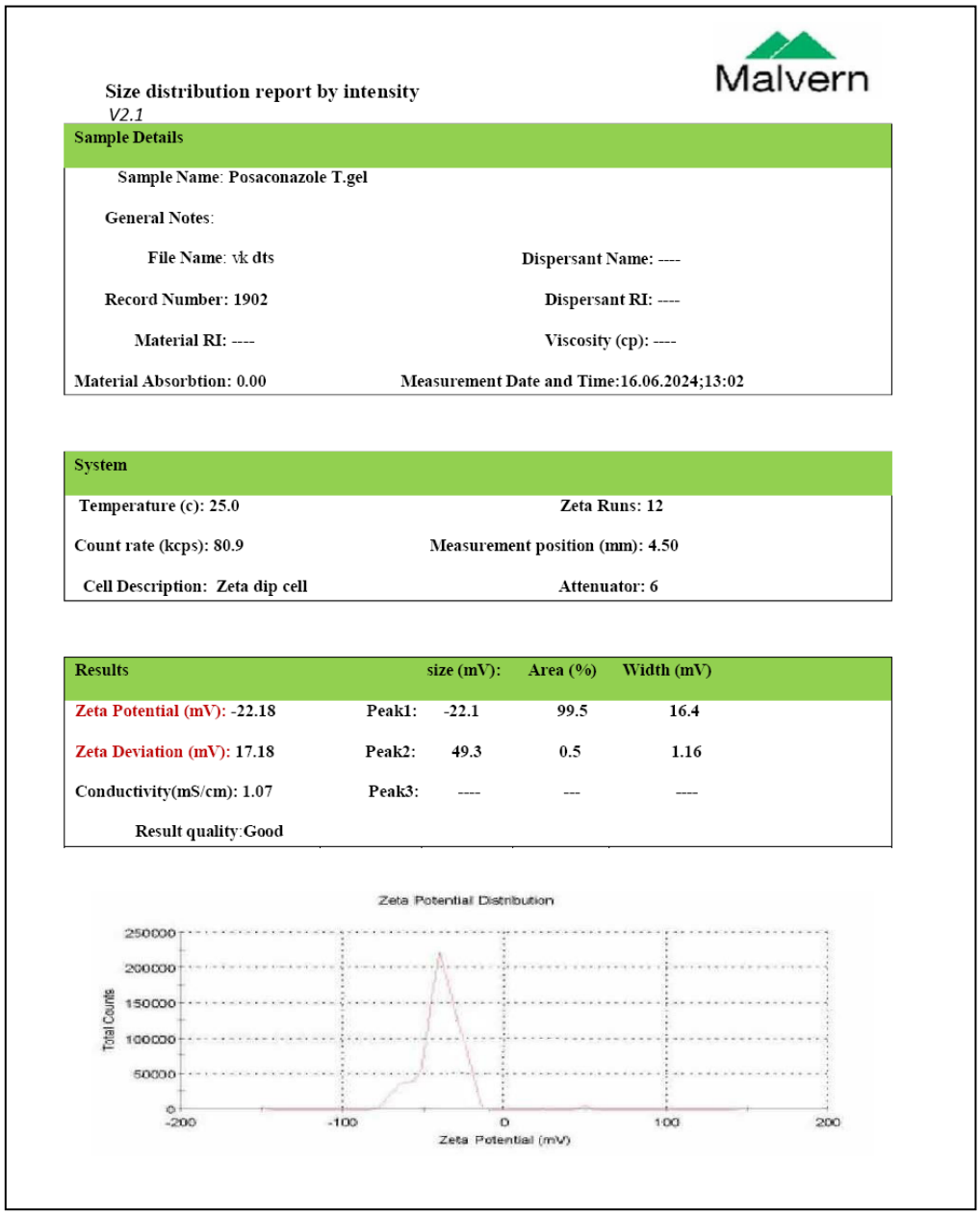

Fig 12: Zeta Potential of optimized formulation (PF7)

9. CHARACTERISATION OF TRANSFEROSOMAL GEL

Table 11: Gel evaluation parameters of PF7 formulation

Formulation PF7 optimized Carbopol 934 gel	PH	Viscosity(cps)	Spreadability (Gm.cm/sec)*	Extrudability	% Drug content	Skin Irritation Test
1.0g	6.48±0.22	3600	3.4±0.21	+	92.19±0.24	No
1.5g	6.72±0.14	4500	3.6±0.19	+	96.37±0.18	No
2.0g	6.42±0.21	4000	3.4±0.22	++	94.18±0.22	No

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Table 12 *IN-VITRO* DIFFUSION STUDIES OF TRANSFEROSOMAL GEL:

Time(hr)	Pf7 optimised 1.0g Carbopol gel	Pf7 optimised 1.5g Carbopol gel	Pf7 optimised 2.0g Carbopol gel
0	0	0	0
1	31.14	16.26	22.32
2	42.74	24.37	34.24
3	56.48	35.61	46.38
4	69.51	43.28	57.34
5	82.36	50.26	66.51
6	91.17	56.37	81.67
8	--	67.15	94.12
10	--	78.34	--
12	--	97.18	--

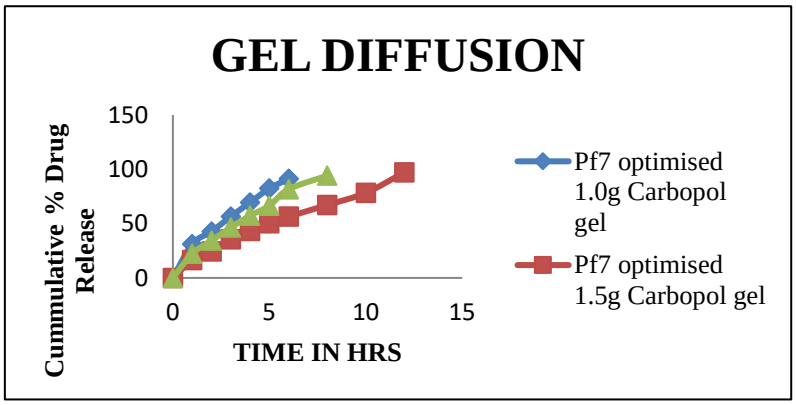

Fig.13: In –vitro diffusion studies for Transfersome gel with different concentrations of Carbopol 934

The 1.5g carbopol 934 gel improved by PF7 has the maximum drug release (97.18% for 24 hours), the best homogeneity, the highest drug content, and the right viscosity. It was therefore regarded as an optimum formulation.

10. DRUG RELEASE KINETICS

Table 13: Release kinetics of optimized formulation

Time(hr)	cumulative % drug release	sqr time	log % cdr	log time	% Drug remaining	log % Drug remaining
0	0	0	0	0	100	2.00
1	16.26	1	1.21	0	83.74	1.92
2	24.37	1.41	1.39	0.30	75.63	1.88
3	35.61	1.73	1.55	0.48	64.39	1.81
4	43.28	2	1.64	0.60	56.72	1.75
5	50.26	2.24	1.70	0.70	49.74	1.70
6	56.37	2.45	1.75	0.78	43.63	1.64
8	67.15	2.83	1.83	0.90	32.85	1.52
10	78.34	3.16	1.89	1	21.66	1.34
12	97.18	3.46	1.99	1.08	2.82	0.45

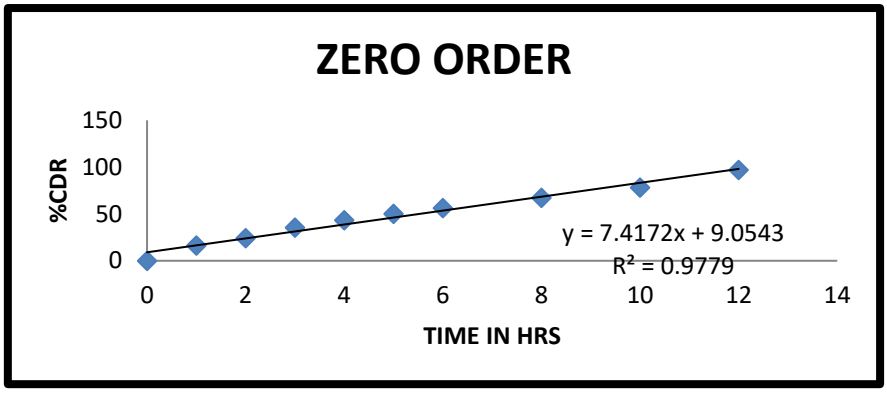

Fig 14:Zero order release kinetic

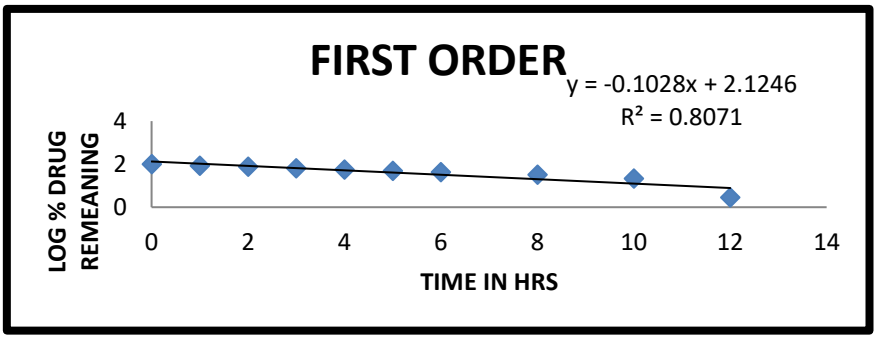

Fig 15:First order release kinetic

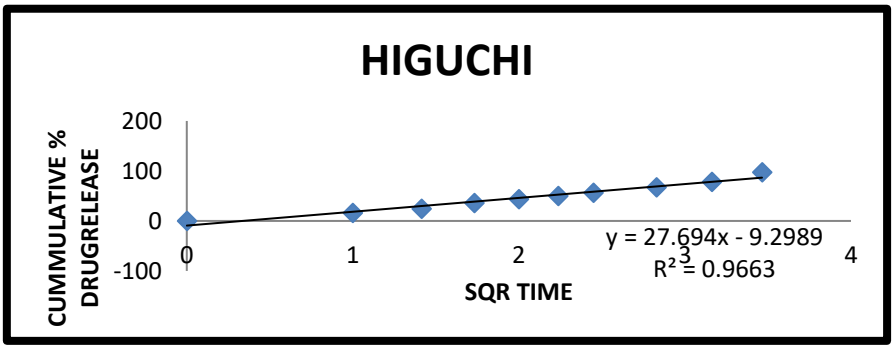

Fig 16:Higuchi release kinetic

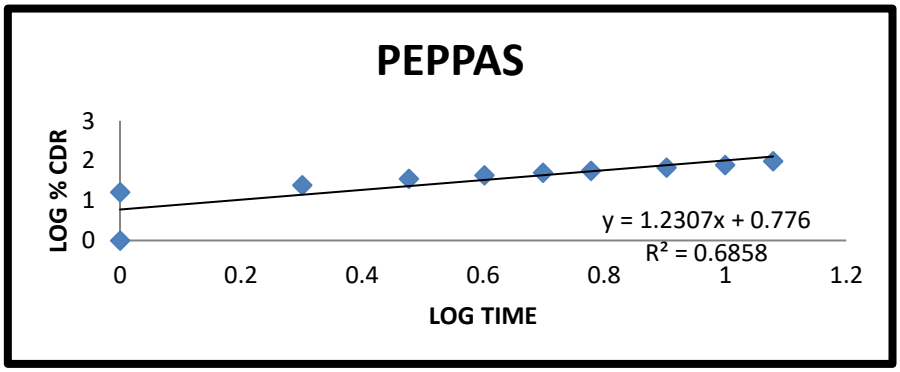

Fig 17: Peppas release kinetic

The drug release kinetics was studied with invitro drug permeation data for optimized formulation Pf7 optimized 1.5g carbopol 934transferosomal gel and was analysed for the drug release mechanism. The best fit model for selected formulation Pf7 were found to be **Higuchi kinetics** with correlation coefficient value (0.966).

12.STABILITY STUDIES .

Table 14: Stability studies of Pf7 optimized 1.5g Carbopol 934 transferosome gel

Number of Days	% Entrapment Efficiency at temperatures		% Drug Content at temperatures	
	4±2ºC	25±2ºC	4±2ºC	25±2ºC
15	88.21	88.21	96.41	96.41
30	88.10	88.14	95.64	95.00
45	87.48	87.51	94.23	94.20
90	87.24	87.24	94.45	94.13

The stability studies found that transferosomes have minimal drug loss and high drug retention at refrigerated conditions. Higher temperatures resulted in less drug entrapment and content retention over three months. The higher drug leakage at elevated temperatures may be due to lipid degradation and phase transition phenomenon. Therefore, formulation storage should be lower to minimize drug loss and enhance drug stability.

CONCLUSION

The work was carried out to prepare posaconazole transfersome gel to achieve sustain release effect at site of administration. The wavelength absorption maxima of Posaconazole in 6.8pH phosphate buffer were found to be 260nm.The FTIR spectra revealed that there was no interaction between the drug and excipients. Total eight formulations were formulated and optimized PF7 showed highest entrapment efficiency 86.26% also cumulative % drug release 96.45%. SEM of optimized Posaconazole Transferosomes appeared as spherical, well identified. Optimised Transfersome formulation were prepared by hand shaking modified thin film hydration technique and were incorporated into carbopol gel. The Formulation Pf7 containing 1.0g, 1.5g, 2.0g carbopol. Among these PF7 formulation with Carbopol 1.5%w/w transferosomal gel is the optimised transferosmal gel and showed Spreadability value 3.6 cm, pH value 6.72 ±0.14. The actual drug content of the Transferosomal gel was found to be 96.37 ±0.18, which represents good content uniformity. The viscosity of Posaconazole Transferosomal gel is found to 4500cps. The percentage drug release for Posaconazole Transferosomal gel is 97.18 %.Stability studies showed that Transferosomal gel is more stable at 4˚C when compared to other temperatures. Based on the above data, it was confirmed that prepared Posaconazole, transfersomal gels can be considered as one of the promising approach to reduce the dosing frequency and to maintain drug concentration at the desired site for longer time.

FUTURE SCOPE:

- Conducting extensive clinical trials to validate the safety and effectiveness of the gel in larger populations.

- Conducting long-term stability studies under various environmental conditions to ensure the formulation remains effective over time.

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