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DESIGN AND EVALUATION OF PRONIOSOMAL FORMULATIONS CONTAINING POSACONAZOLE

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Abstract:

Posaconazole is a broad-spectrum triazole antifungal agent with poor aqueous solubility and limited bioavailability, which restricts its therapeutic effectiveness. The present study focuses on the design and evaluation of a proniosomal nanogel system for the prolonged release of posaconazole. Proniosomes were prepared using the coacervation phase separation technique with non-ionic surfactants, cholesterol, and lecithin, and subsequently incorporated into a nanogel matrix to enhance stability and extend drug release. The developed formulations were evaluated for vesicle size, drug entrapment efficiency, surface morphology, rheological properties, in-vitro drug release, and stability. The optimized proniosomal nanogel exhibited nanosized vesicles with high drug entrapment efficiency and good gel consistency, ensuring ease of application and prolonged residence time. In-vitro release studies demonstrated a sustained release profile of posaconazole over an extended period compared to conventional formulations. Morphological analysis confirmed uniform and spherical vesicle formation, while stability studies indicated minimal drug leakage and good physical stability. The findings suggest that proniosomal nanogel systems represent a promising strategy for prolonged delivery of posaconazole, potentially improving patient compliance and therapeutic efficacy.

Keywords: Posaconazole; Proniosomes; Nanogel; Sustained release; Antifungal therapy; Coacervation phase separation; Vesicular drug delivery

1. Introduction

Transdermal Therapeutic Drug Delivery System (TTDS)

Transdermal therapeutic drug delivery systems (TTDS) are designed to deliver drugs across the skin into the systemic circulation at a predetermined and controlled rate. TTDS offer several advantages over conventional dosage forms, including avoidance of first-pass hepatic metabolism, sustained drug release, improved bioavailability, reduced dosing frequency, and enhanced patient compliance. Additionally, transdermal systems provide steady plasma drug concentrations and minimize fluctuations associated with oral administration. Despite these advantages, the stratum corneum acts as a major barrier to drug permeation, limiting the transdermal delivery of many therapeutic agents. Therefore, advanced formulation strategies are required to enhance drug permeation across the skin and improve the therapeutic effectiveness of transdermal systems.

Vesicular Drug Delivery System

Vesicular drug delivery systems have emerged as an effective approach to overcome the limitations of conventional drug delivery systems. These systems consist of vesicles formed from amphiphilic molecules that encapsulate drugs within bilayered structures. Vesicular carriers such as liposomes, niosomes, proniosomes, transfersomes, and ethosomes have been widely investigated for transdermal applications. Vesicular systems

enhance drug stability, improve solubility of poorly water-soluble drugs, and facilitate controlled and sustained drug release. Proniosomes, in particular, are dry, free-flowing formulations that are converted into niosomes upon hydration, offering advantages such as improved physical stability, ease of handling, and reduced drug leakage. Due to these properties, proniosomal systems are considered suitable carriers for transdermal drug delivery.

MATERIALS

Various excipients play a crucial role in the successful formulation of proniosomal nanogel systems. Cholesterol is incorporated to improve membrane rigidity, stability, and reduce vesicle leakage. Span 60, a non-ionic surfactant with a high phase transition temperature, contributes to the formation of stable vesicles with high drug entrapment efficiency. Isopropyl myristate acts as a penetration enhancer, facilitating drug permeation through the skin by altering the lipid structure of the stratum corneum. Ethanol enhances drug solubility and vesicle flexibility, while glycerin and propylene glycol serve as humectants and co-solvents, improving hydration and drug permeation. Carbopol 934 is used as a gelling agent to provide appropriate viscosity and consistency to the nanogel system. Triethanolamine acts as a neutralizing agent to adjust the pH and promote gel formation, whereas methanol is employed as a solvent during formulation development to ensure uniform mixing of formulation components.

POSACONAZOLE:

Posaconazole is a second-generation triazole antifungal agent widely used in the prevention and treatment of invasive fungal infections. It exhibits broad-spectrum antifungal activity against various pathogenic fungi, including *Candida*, *Aspergillus*, and *Cryptococcus* species. Posaconazole acts by inhibiting the enzyme lanosterol 14-α-demethylase, which is essential for the synthesis of ergosterol, a key component of the fungal cell membrane. Inhibition of ergosterol synthesis leads to disruption of fungal cell membrane integrity and ultimately results in fungal cell death.

PRE-FORMULATION STUDIES

Preparation of standard curve of posaconazole:

A stock solution of posaconazole was prepared by dissolving 100mg of medication in little amount of methanol and made up 100ml with methanol. From this stock solution, different doses of posaconazole viz., 2, 4, 6, 8, 10 mg/ml was made by diluting with methanol and their absorbance was measured at 492nm using double beam spectrophotometer. A graph was created by taking concentration of posaconazole on X-axis &absorbance on Yaxis.

2. FORMULATION DEVELOPMENT

Proniosomes are dry, free-flowing formulations that serve as precursors to niosomal vesicles. They are typically prepared by combining the drug with non-ionic surfactants and cholesterol to form a uniform mixture. This mixture is then processed to produce a dry powder that remains stable during storage and handling. When required, the proniosomal powder can be hydrated with water or an appropriate buffer, which leads to the spontaneous formation of niosomal vesicles.

Preparation of Proniosomal gels of posoconazole were prepared by using different excipients concentrations. The gels were formulated by **Coaservation and phase separation method**.

Span 60 was used as a surfactant, cholesterol as a membrane stabilizer, and oleic acid, isopropyl myristate propylene glycol, and 0.1% glycerin as an aqueous phase to create the proniosomes. Phase separation and coacervation were the main methods utilized to prepare them. The formulation table is presented below. The surfactant mixture (span60 and cholesterol), the medication, ethanol and penetration enhancer were mixed and heated to 65±10℃ for 5min in a stoppered vessel. This results in a transparent liquid system. The aqueous phase was added and the mixture was warmed upto clarity. The mixture was cooled down by continuous mixing at room temperature, then set aside for 24hrs till the production of proniosomal gel.

Table No:1 Formulation Table of Posaconazole:

Appearance:

Visual inspection was used to verify the appearance. After gelling the clarity of the formulations, color, was determined by visual examination of the formulations under light, alternatively against white and black backdrop.

Physical evaluation of gels:

The prepared gel formulations were evaluated for physical appearance, pH, homogeneity, spread ability and viscosity by using conventional digital R/S plus Rheometer Brookfield Engineering Lab Inc.

Microscopic evaluation:

After being appropriately diluted, the niosomes are fixed on glass slides and examined under a 40X microscope for morphological analysis. The photomicrograph of the preparation also produced from the microscope by applying a digital SL camera.

Entrapment efficiency:

The trapping effectiveness of the drug into proniosomes the formulation was hydrate to create the matching niosomes. This was achieved by hydrating the proiosomal gel of 1gm using 10ml distilled water with usage of mechanical stirrer for 30min. the produced niosomes were treated to 30min of bath sonication. Immediately after hydration of proniosomes, the noisome dispersion was incubated in dialysis sac and dialysed against 100ml 40% v/v ethanol in water for 4 h. In order to achieve sink conditions, this dialysis fluid was used. The amount of free drug was determined by measuring the amount of drug present in the dialysis sac. By utilizing UV spectrophotometer at 492nm. The entrapment efficiency was estimated by following formula.

Formulation code	Surfactant	Cholesterol	Aqueous phase	Oleic acid	Isopropyl Myristate	Ethanol gm)	Drug (gm)
P1	4.5	0.5	4	1	0	5	0.3
P2	4	1	4	1	0	5	0.3
P3	3.5	1.5	4	1	0	5	0.3
P4	3	2	4	1	0	5	0.3
P5	4.5	0.5	4	0	1	5	0.3
P6	4	1	4	0	1	5	0.3
P7	3.5	1.5	4	0	1	5	0.3
P8	3	2	4	0	1	5	0.3

$$entrapment\ efficiency(\%) = [\frac{Ct - Cf}{Ct}] \times 100]$$

Where

Ct=Total concentration of the drug

Cf= concentration of free drug

Vesicle size analysis

Particle size and zeta potential of formulation was determined by using Malvern Zetasizer instrument v2.1.

In vitro permeation study

Franz diffusion cells were used to investigate the in vitro drug release of posaconazole from proniosomal formulation. The Invitro diffusion of the medication was accomplished through one end of the hollow glass tube. This served as a donor chamber. A beaker serving as a receptor compartment was filled with 10 milliliters of phosphate buffer saline 7.4 pH buffers. The rat skin membrane was evenly covered with a predetermined amount. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37±0.50C. The solutions of the receptor side were agitated by small magnetic bead and were rotated at a steady speed.

At predefined time intervals, samples were removed and replenished by 5ml of phosphate buffer saline. The drug concentrations in the aliquot were analyzed for drug content using UV spectrophotometer at 492 nm against appropriate blank. The optimum formulation was taken and blended into gel.

Drug release kinetics

The release data obtained from various formulations were studied further for their fitness of data in different kinetic models like zero order, first order, Higuchi model and Korsemeyer peppa's model.

Spreadability

Spreadability of gel was tested by modified wooden block and glass slide apparatus. A measured amount of gel was placed on fixed glass slide, a movable pan with a glass slide attached to it and was moved over the fixed glass slide, such that the gel was sandwiched between two glass slides for 5 mins. S= M/T
Where S, is the spreadability in g/s, M is the mass in grams & T is the time in seconds.

Viscosity

Viscosity was tested by Brookfield viscometer (LVDV ProII), spindle S64 and the angular velocity was found to be raised from 5, 10, 50,100 rpm and the data were documented.

Drug content

Drug content was evaluated spectrophotometrically. After dissolving 50 mg of gel in methanol, the mixture was filtered. Methanol was added to bring the volume up to 10 milliliters. After appropriately diluting the resulting solution with methanol, absorbance was measured at 492 nm.

pH

pH was checked using pH meter. The data were recorded and filtered when the electrode was submerged in the formulation at room temperature.

3. RESULTS AND DISCUSSION

Compatibility studies

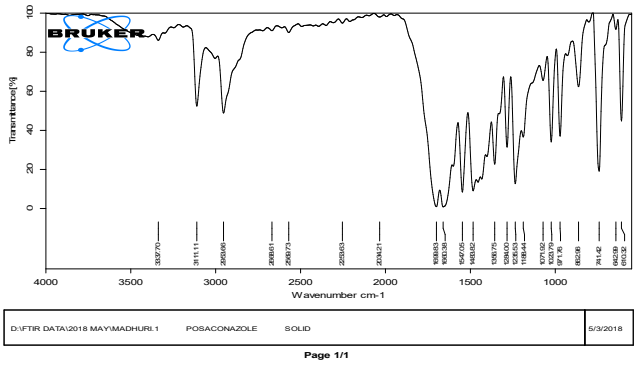


Figure 1: FTIR of Drug

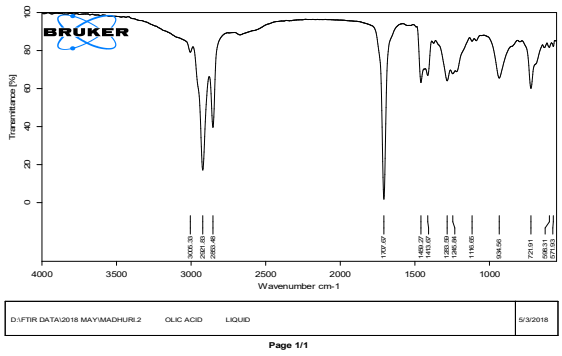


Figure 2: FTIR of drug with oleic acid

The peaks of the drug oleic acid combination and the pure drug did not significantly alter according to FTIR. Therefore, it can be extrapolated that there was no unique interaction seen between the medicine and the excipient.

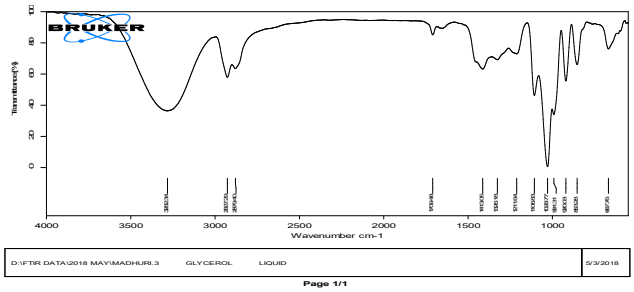


Figure 3: FTIR of drug with glycerol

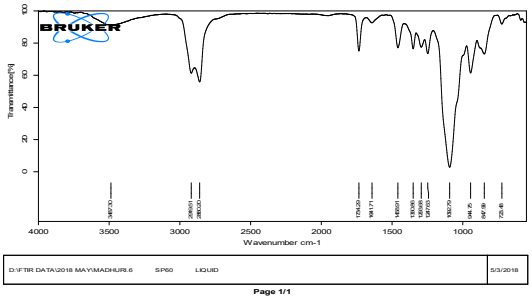
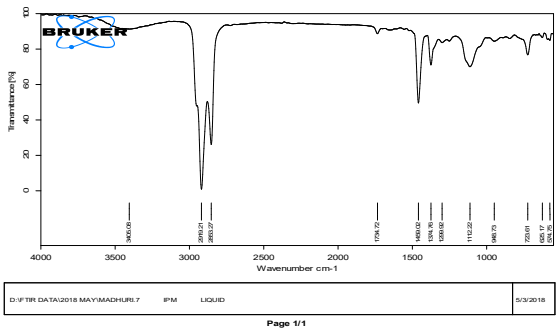


Figure 4: FTIR of drug with Span 60

From FTIR, there was no noteworthy change in the pinnacles of unadulterated drug & drug glycerol mixture and there was once no vast exchange in the peaks of pure drug and drug glycerol mixture. Along these lines it tends to be induced that there was no particular connection saw between the medication and the excipient.



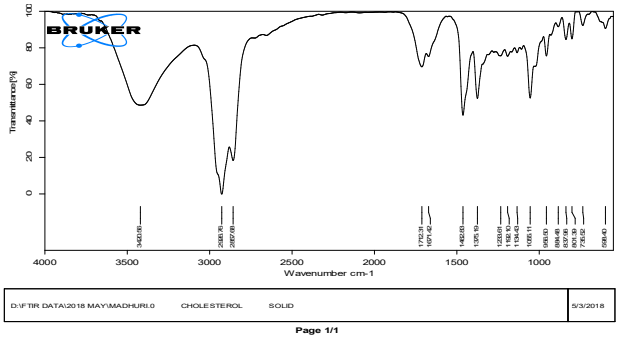


Figure 5: FTIR of drug with isopropyl myristate **Figure 6: FTIR of cholesterol**

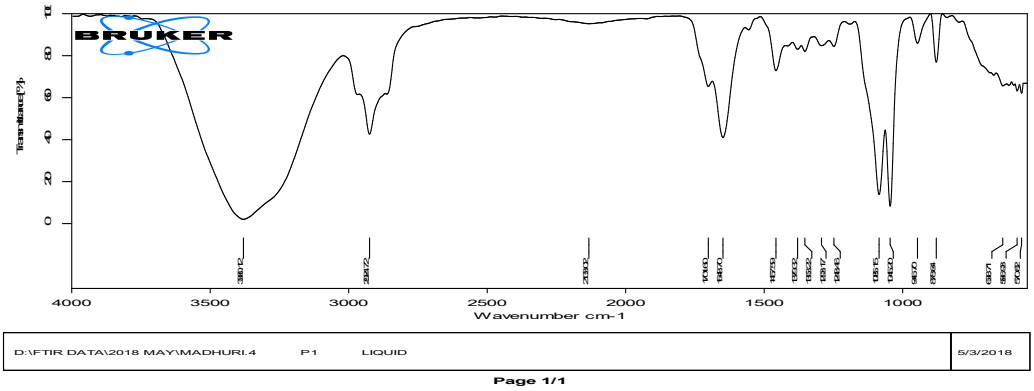


Figure 7: FTIR of P1(oleic acid (30% cholesterol P3)

Table: 2: Interpretation of FTIR graph of posaconazole Proniosomal gel

Group	Stretching	Zone	Drug	P3
C=O	Stretching	16001900	1701.60	1699.83
CH	Bend in plane	12001500	1356.75	1353.22
OH	Bending	12001500	1284.00	1293.17
CF	Stretching	10001400	1071.92	1085.15
NH	Rocking	700900	862.96	878.58

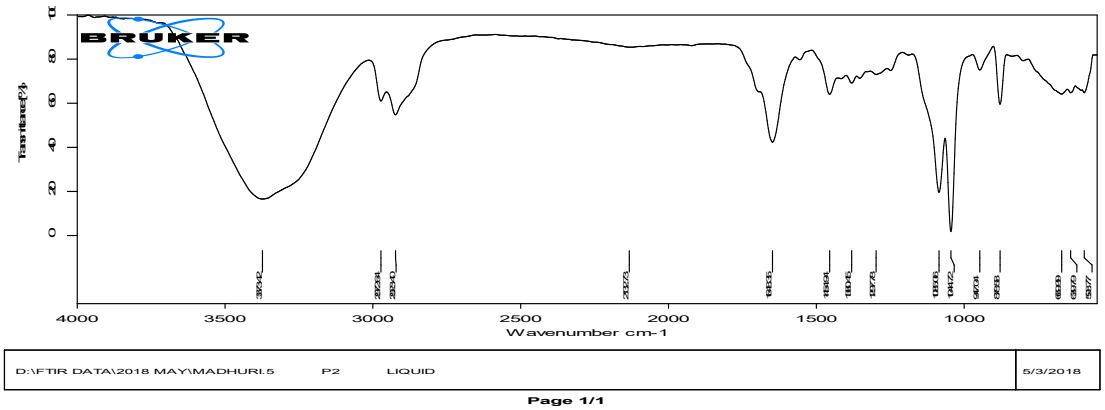


Figure 8: FTIR of P2 (P7 IPM (30% cholesterol))

Table 3: Interpretation of FTIR graph of posaconazole Proniosomal gel

Group	Stretching	Zone	Drug	P2
C=O	Stretching	16001900	1660.38	1648.35
OH	Bending	12001500	1284.00	1297.78
CF	Stretch	10001400	1071.92	1085.06

CH	Rocking	600900	642.99	639.79
NH	Rocking	700900	862.96	878.64

Appearance:

The physical appearance of the gel was observed by eyes. The pH of all formulations was found in ranged from 6.5-7.1 given in table 2 and that pH suitable to skin pH.

Microscopic determination

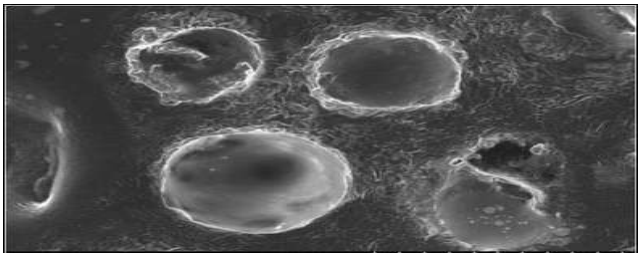


FIG:9 SEM photograph of proniosomes

After hydration of proniosomes by using phosphate buffer the niosomal suspension was formed which was seen under the microscope. The photomicrographs of all formulations are shown in fig. 1 the SEM picture showed that proniosomes are seen as bountiful, round fit as a fiddle and smooth and size in Nano measurements.

Entrapment Efficiency

Table 4 : Entrapment Efficiency

Formulation code	P1	P2	P3	P4	P5	P6	P7	P8
%Entrapment Efficiency	12.26	45.34	72.52	52.43	55.69	39.47	63.34	22.33

Where

P1 – P4 (oleic acid formulations),

P5 – P8 (Isopropyl myristate formulations)

Figure 10: Capture proficiency of proniosomes

Percentage entrapment of Posaconazole proniosomes was once located to be in the vary of 6372%. The entrapment effectivity was once located to be greater for P3 method (72%). Amounts of oleic acid, LDL cholesterol used for Proniosomes practise regarded to have an impact on the entrapment efficiency. Of all the elements examined, the attention of ethanol was once discovered to affect the entrapment effectivity to a full size extent (comparing to IPM (63%). The proportion entrapment effectivity of one of a kind proniosomal formulations was once discovered to be in between degrees of 12.26 to 72.52%

Invitro tranquilize discharge

Rate medicate discharge for Optimized plan (P3) from different proniosomes formulations with different cholesterol concentration is shown in table 12was 74.21% in 8hrs.Therefore P3 has been selected for formulating the proniosomes when compared to proniosomes l formulation with IPM.

Invitro kinetic analysis:

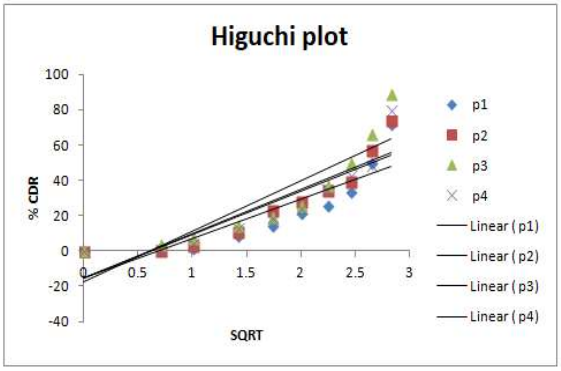
The drug launch records is geared up into a variety of pharmacokinetic parameters such as zero order, first order, higuchi, korsemeyerpeppas fashions.

Table 5: Cumulative % drug release of proniosomal gel of all formulation

Formulation	0.5	1	2	3	4	5	6	7	8
P1	0.7143	1.2857	8.5714	14.123	21.2857	25.7143	33.4286	49.7143	71.631
P2	0.8571	3.4285	11.1429	23.513	28.4286	34.2857	39.4286	57.431	74.072
P3	3.4285	7.4285	14.5714	18.941	25.4286	37.1429	50.1429	66.2857	88.5714
P4	1.1428	4.2857	12.8571	18.7143	24.1429	35.1429	42.5714	48.4286	79.5714
P5	2.8571	3.163	10.8571	15.8571	20.1429	24.8571	28.2857	29.4286	57.7143
P6	1.2857	2.5714	11.4286	19.1429	24.1429	26.7143	28.2857	41.961	68.7143
P7	0.5714	5.5714	14.8571	22.523	26.4286	32.2857	35.8571	47.8571	73.2857
P8	0.1429	2.4285	8.42857	13.5714	19.8571	28.1429	33.8571	40.8571	70.2857

Invitro kinetic analysis

Initially at 0.5hrs the higher amount of drug release was 3.428 and 2.857 by P3 and p5 formulations.50% of the drug was released at 6hrs with P3 formulation and all the other formulations released 50% of drug at 7th hour. The drug release of P1 to P8 at 8th hour are 71.63, 74.072, 88.57, 79.57, 68.71, 73.28, 70.28 respectively from the above table the optimized formulation was selected as P3 with high initial drug release and at 8th hour highest drug release. The above information is fitted into various motor boundaries, for example, zero order, first order,Huguchi and korsemeyerpeppas models and different plots were plotted.



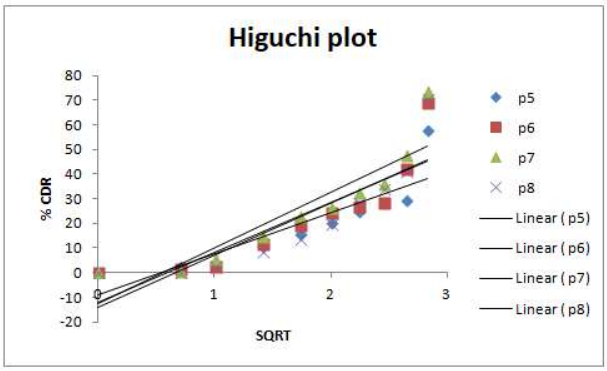


Figure 11: Higuchi plot of P1 to P4

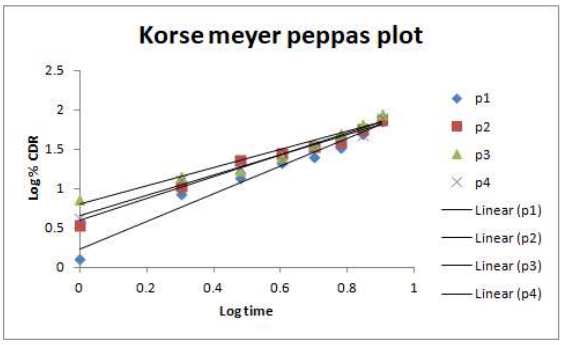


Figure 12: Higuchi plot of P5 to P8

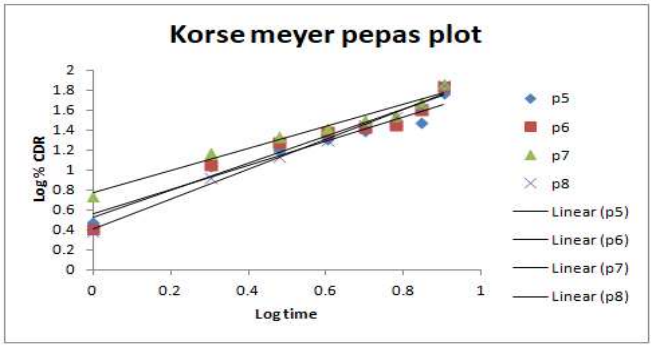


Figure 13: Korse Meyers peppas plot of P1 to P4

Figure 14: Korse Meyers peppas plot of P5 to P8

Table 6: In vitro medicate discharge energy of posaconazole gel or suspension

S.No	Zero order	First order	Higuchi	Korsemeyerpeppas	
	R^2	R^2	R^2	R^2	N
P1	0.934	0.801	0.760	0.971	1.304
P2	0.963	0.863	0.840	0.989	1.451
P3	0.939	0.752	0.797	0.976	1.110
P4	0.930	0.766	0.800	0.986	1.407
P5	0.886	0.792	0.846	0.972	1.064
P6	0.888	0.764	0.780	0.972	1.364
P7	0.927	0.805	0.825	0.928	1.501
P8	0.911	0.809	0.774	0.760	1.963

From the above tables it was observed that the release kinetics showed higher release 88.57% (P3) for oleic acid with 30% cholesterol formulation in comparison to other formulations of proniosomal suspension with permeation enhancers. The P3 produced 88.57% at the end of 8thhour. Here in current study faster release with quicker onset of action is required. In vitro drug launch of proniosomal gel with oleic acid (P3) IPM (P7) produced 88.57% and 73.28% inside eight hrs respectively.

Table 7: Invitro skin permeation studies

Formulation	0 h	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
P3	0	3.4285	7.4285	14.5714	18.941	5.4286	37.1429	50.1429	66.2857	88.5714
Posanol	0	2.234	5.023	13.992	16.662	23.224	35.442	49.033	65.223	86.542

Cumulative %drug release of proniosomal gel/suspension and marketed formulation (posanol suspension)

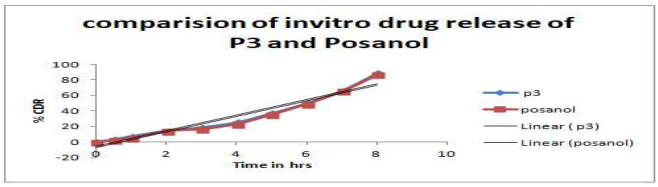


Figure 15: Comparison of Invitro drug release of P3 and Posanol

From the above table and figure it was concluded that among all the formulations P1P8. Formulations gave 71.631%, 74.072%, 88.57%, 79.57%, 57.71%, 68.71%, 73.28%, and 70.28% of drug release respectively. When compared to posanol marketed formulation 86.54% which is relatively low than the P3 prepared proniosomal gel.

Zeta potential

The estimation of zeta potential was seen as17.95Mv for enhanced (p3) detailing as appeared in above figure. It demonstrates arranged proniosomes have adequate surface charge to forestall collection of the vesicles.

Vesicle size measurement

The average sizes of proniosomes were found to be 170.98±0.006nm. And poly dispersity index (PI) is 0.702±0.02. As the optimum polydispersity index of the proniosomes must be 0.70.8 and the size ranges from 74.4nm to 200nm. So the formulation P3 showed the value of 0.702±0.02 PDI and 170.98±0.006nm and it was selected as optimized formulation.

pH determination:

The optimum pH of proniosomes is in the range of 6.8 - 7.4 pH. pH of the P3 formulation showed 7.2pH and it was selected as optimized formulation.

Antifungalstudies:

The chosen formulations demonstrated antifungal effectiveness when tested using the cup plate technique with posanol as the reference solution, according to antifungal research. When compared to the commercialized Posanol's zone of inhibition, which was 21 mm, Formulation P3 had a high inhibition of 23 mm.

4. SUMMARY

Proniosomal gel was formulated and evaluated for antifungal therapy. The co-acervation phase separation method was used to prepared topical proniosomal gel by using different grades of Excipients, and cholestrol was utilized in this study which prolong the release of drug and to improve poor skin penetration and residence of the topical antifungal drugs. Sustained and prolonged release makes the delivery system more reliable and more acceptable to the patients and increases patient compliance. Developed carbopol gel had potential to act as controlled release drug carrier which prolonged the drug release for number of hours. Overall, these findings indicate that topical proniosomal gel will be encouraging drug delivery method for Posaconazole

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