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Quality-by-Design Assisted Development of Tioconazole-Loaded Lyotropic Liquid Crystalline Nanocarriers for Enhanced Solubility and Antifungal Efficacy

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Abstract: Tioconazole is a broad-spectrum imidazole antifungal drug widely used in the treatment of vaginal candidiasis and other fungal infections; however, its clinical performance is often limited by its poor aqueous solubility, as it belongs to Biopharmaceutics Classification System (BCS) class II, exhibiting low solubility and high permeability. This study develops Tioconazole-loaded liquid crystalline nanostructures (cubosomes) as an improved drug delivery technology to overcome current formulation limitations. Cubosomes were prepared using the emulsification method, employing glycerol monooleate as the lipid phase, which facilitates the formation of self-assembled bicontinuous cubic liquid crystalline structures capable of enhancing drug solubilization and controlled release. The developed cubosomal system aims to improve the solubility, stability, and bioavailability of Tioconazole, thereby enhancing its therapeutic efficacy in the management of vaginal yeast infections. The nanostructured lipid matrix provides a large internal surface area and unique three-dimensional architecture that enables efficient drug encapsulation and sustained drug release. Furthermore, the cubosomal formulation is expected to enhance drug permeation and localized antifungal activity at the site of infection. Considering that no advanced liquid crystalline formulation of Tioconazole is currently available in the market, the proposed system represents a promising strategy for improving the pharmacological performance of Tioconazole and may serve as a potential platform for the development of effective topical or intravaginal antifungal therapies.

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I. INTRODUCTION

Infections from cutaneous fungi are common globally. In all countries, many people have had fungal infections. Fungal contaminations can spread quickly and impair immune systems (1). Fungal skin infections are frequent dermatological issues today. Physicians can treat with solid, semisolid, or liquid dosages. Clear transparent gels are widely used in cosmetics and pharmaceuticals for dermatological disease and skin care. Clinicians and patients can choose from solids, semisolids, and liquids. The labile areas for superficial fungal manifestations are keratinized tissues, which include skin, nails, and hairs problemsassociated with conventional formulations but can also improve skin permeation of antifungal drugs, enhance the physicochemical and biological stability, protect the drugs from enzymatic metabolism and extend the half-life of drugs (3), Fungal infections can be life-threatening in normal people, secondary infections, and immunocompromised people (8). Bacterial vaginosis, candidiasis, and trichomoniasis, caused by bacteria, fungus, and protozoa, are the most common vaginal infections in women. They cause itching, discharge, and pain when urinating and/or during sexual activity, lowering self-esteem and quality of life (9)(10).

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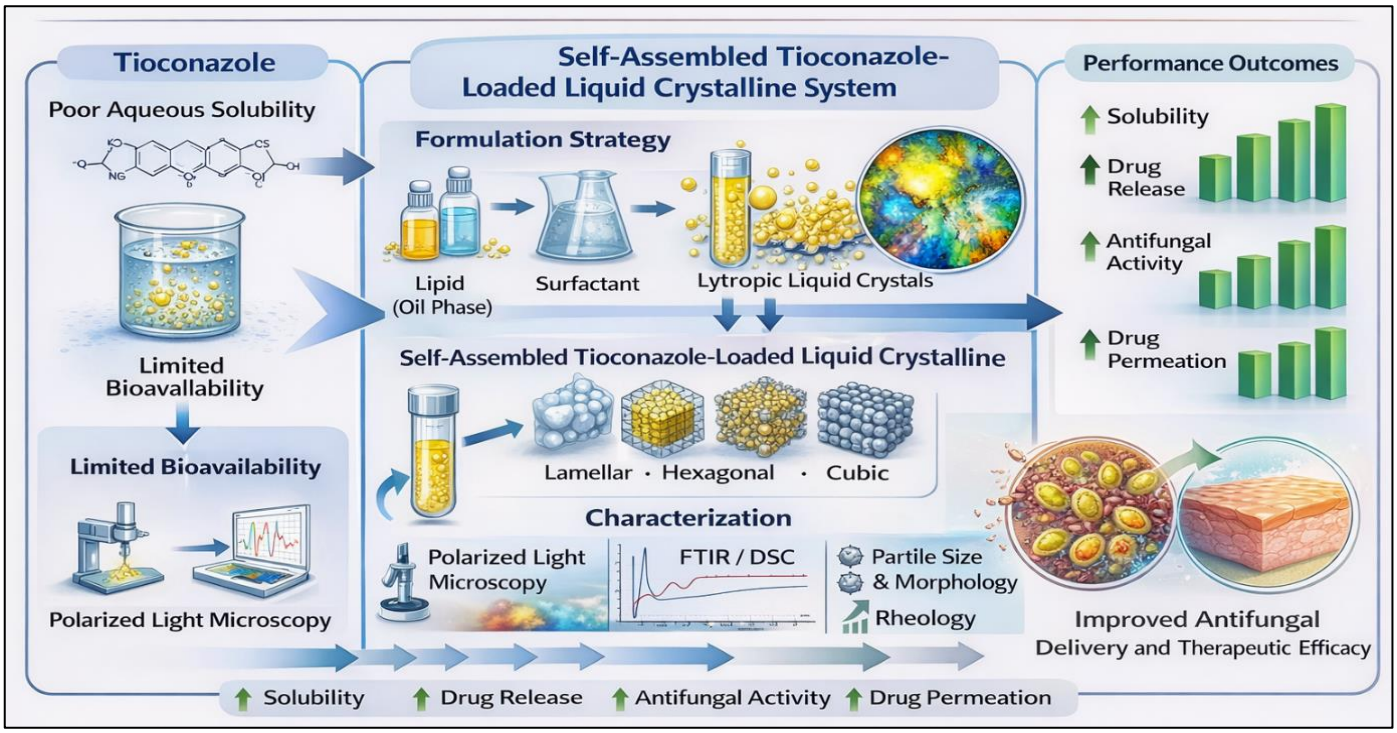

Fig 1 Graphical Abstract

II. MATERIALS AND METHODS

➢ *Materials*

Ticonazole as a drug and pluronic F-127 as a polymer was recived in sigma aldrich, Glycerol Mono-Oleate as a lipid was recieed in spell organic pvt Ltd.

➢ *Methods:*

- *Preparation of Ticonazole Loaded Cubosomes*

Tioconazole-loaded Cubosomes were made by hot emulsifying monoglycerides in water (41). GMO Glycerol Monooleate was used. At various concentrations, Pluronic F-127 and PVA were used as surfactants and stabilizers. After heating GMO to 45°C, Pluronic F-127 was added and agitated at 800 RPM on a magnetic stirrer until a clear surfactant solution formed in an oily mass. Tioconazole was mixed into this molten lipid mass until complete solubilization. Next, this lipidic mass was gently added to the preheated PVA-containing aqueous dispersion to form an emulsion. Stirred at comparable RPM, the heated emulsion cooled to normal temperature. Addition of pre-emulsion under continuous stirring (600 RPM) in additional water made up volume. Continuous churning created a stable Cubosome dispersion emulsion. After 20 min of centrifugation at 9500 rpm, the cubosomal dispersion was separated from unentrapped drug and excess lipid.

- *Experimental Design*

The trail batches of various concentration were performed before the applying of DoEsoftware and suitable batch were selected and apply in DoE Software.

Optimization of the Liquid Crystals of tioconazole was done with box-Behnken design (BBD) using three parameters at two levels. The selected optimization parameters were lipid concentration GMO (X1), the Pluronic F-127 amount (X2), and poly-vinyl alcohol PVA amount (X3) were considered as an independent parameter and the two dependent factors, particles size (Y1) and percentage entrapment efficiency (Y2) were considered.

- *Characterization of Ticonazole Loaded Cubosomes:*

✓ *Determination of λ Max*

Accurately 10 mg of drug was weighed and transferred into 10ml of volumetric flask and volume was made up to 10 ml by adding 0.1N HCl to make solution of 1000 µg/ml.From this solution 1ml was withdrawn and transferred into 10 ml volumetric flask andvolume was made up to 10ml by adding phosphate buffer 6.4 pH and make solution of100 µg/ml. Further from 100 µg/ml. solution 1ml was withdraw and transfer to 10 ml volumetric flask and volume was made 10ml with buffer and make solution 10µg/ml. The solution containing concentration of 100 µg/ml Tioconazole was scanned over thewavelength in range of 200-400nm on UV spectrophotometer.

✓ *Calibration Curve of Tioconazole*

The stock solution of Tioconazole was prepared using 10 mg of drug was transferred to1ml of 0.1N HCl. And further diluted with Phosphate buffer pH of 6.4 from the standardstock solution 0.2, 0.4, 0.6, 0.8 and 1ml were withdrawn and volume was made up to 10 ml with phosphate buffer 6.4 pH to give a concentration of 2, 4, 6, 8. and 10 µg/ml.absorbance of these solutions were measured against a blank 6.4 pH phosphate at 227 nm for Tioconazole. Then calibration curve was plotted.

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- *Physicochemical Characterization of Cubosomes*

✓ *Entrapment Efficiency:*

Entrapment Efficiency (%) of tioconazole-loaded Cubosomes was measured by centrifuging dispersion at 9600 rpm for 20 min. to separate free drug and nano-dispersion A 200 µL sample of the prepared dispersion with tioconazole-loaded Cubosomes was diluted with methanol to 2 mL and centrifuged at 9600 RPM using a Remi CM-12 centrifuge. The material was analyzed using a Shimadzu-1800 UV spectrometer at 227 nm (λ max) to calculate entrapment efficiency (%) using the method.

$$\text{Entrapment efficiency (\%)} = \frac{\text{Total drug} - \text{Unentrapped drug}}{\text{Total drug}} \times 100$$

✓ *Particle Size Determination:*

Particle size and polydispersity index of the Cubosomal emulsion was determined by using Litesizer-500 after suitable dilutions with distilled water.

✓ *Zeta Potential to Identify the Charges on Crystals:*

Zeta potential of the Cubosomes was determined by using Litesizer500 using omega cuvvet.

➢ *Solid State Characterization of Cubosomes:*

- *Fourier-Transform Infrared Spectroscopy (FTIR)*

The FT-IR spectroscopy (Shimadzu 8400S) of standard drug (Tioconazole, Glycerol Monooleate and poly-vinyl alcohol) was carried out using KBr pellet technique. Approximately 1-3 mg of sample was mixed with dry potassium bromide, and the sample were examined in transmission mode over a wave number range 4000-400 cm^{1}.The peak are visualized in Fig. which depicts the characteristic absorption of various functional group.

- *Differential Scanning Colorimetry (DSC)*

Differential scanning calorimetry analyses were conducted for both the pure drug and the improved formulation. We used a DSC instrument (DSC-1821e, Mettler-ToledoAG, Analytical, Schwerzenbach, Switzerland) to do the experiment. 5mg samples were put in aluminum pans (Al-Crucibles, 40 Al) and sealed. We used Differential Scanning Calorimetry (DSC-1821e, Mettler ToledoAG, Analytical, Schwerzenbach, Switzerland) to heat a pure sample of medication and formulation in a standard aluminum pan from 20°C to 140°C at a steady rate of 10°C per minute in a nitrogen atmosphere. We used dried nitrogen as a purge gas.

- *X-Ray Diffraction:*

XRD data was collected for pure drug and subsequent cubosomal liquid crystal formulation. A BrukerAXS, Inc. XRD equipment (Madison, WI, USA) was used to do the experiment. We used X-ray powder diffractometry to see how qualitative and quantitative analysis affected the crystallinity of the medication and excipients. We used a D2 Phaser2 ndgeneration-based diffractometer with a voltage of 30kV and a current of 10mA to record powder X-RD patterns.The scanning rate was 50 minutes, and it covered a range of diffraction angles (2θ) from 50 to 400.

- *Scanning Electron Microscopy (SEM)*

Scanning Electron Microscopy (SEM) – Scanning Electron Microscopy images were obtained for optimized batch of Cubosomes using SEM-EDAX: Jeol 6390LA/ OXFORD XMX N. Using 10 mA current the dried Liquid Crystals were gold coated bysputter cutter for a total duration of 4 minutes. After gold coating, sample was viewed at different magnifications at a voltage of 15.00 kV.

➢ *Preparation of Tioconazole Cubosomal Gel:*

Tioconazole-loaded Cubosomes were incorporated into a Carbopol-971 aqueous dispersion and stirred at 350 RPM to achieve a uniform distribution of Cubosomes within the aqueous system, resulting in a final formulation weight of 100 gm containing 0.2% w/w Tioconazole. Following the uniform dispersion of Cubosomes, 30µL of Triethanolamine was incorporated for the neutralization of Carbopol to create a gel.

- *Characterization of Cubosomal Gel:*

✓ *Gelling Temperature:*

The gelling temperature was ascertained by positioning the Cubosomes solution on a heated magnetic plate, swirling the solution with a magnetic bead at a constant speed of 52 rpm, and gradually elevating the temperature at a rate of 1°C/min.The temperature at which the magnetic bead ceases to spin was documented as the gelling temperature of the formulation.

✓ *Gelling Time:*

Gelling time refers to the duration required for the cubosome precursor dispersion to transform into a structured cubic phase gel upon hydration or temperature change. It indicates the efficiency of lipid self-assembly and polymer stabilization, influencing the stability, viscosity, and drug release behavior of the cubosomal formulation.

✓ *Viscosity Determination:*

The viscosity of the prepared formulation was measured using a Brookfield viscometer operated at 10 rpm. Approximately 10 mL of the final formulation was transferred into a narrow-mouth beaker and carefully positioned beneath the spindle of the viscometer to ensure proper immersion and accurate measurement of viscosity.

➢ *In-Vitro Drug Permeation:*

The in-vitro drug permeation study was conducted by using dialysis membrane. A pieceof about 2 cm^2 was cut and placed properly between the donor and the acceptor compartment. The acceptor compartment was filled with the phosphate buffer pH 6.4 and the temperature was maintained at 37 ± 0.2°c. One ml of Liquid Crystals (Cubosomes) gel containing 2 mg of the drug was kept over the membrane. Because oftemperature of the system the solution turned rapidly into gel and remained adhere to the system. The process was started and at predetermined time intervals (0.30,

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1, 2, 4, 6, 8, 10, and 12 hrs.) one ml of the solution from the reservoir compartment was removedand replaced with fresh buffer. This one ml solution was further diluted upto 9 ml by using phosphate buffer solution and the absorbance of this solution was taken at 227.40nm. Phosphate buffer pH 6.4 was used as blank.

➢ *Ex-Vivo Skin Permeation:*

The in-vitro drug permeation study was conducted by using Goat skin mucosa membrane. A piece of about 2 cm^2 was cut and placed properly between the donor and the acceptor compartment. The acceptor compartment was filled with the phosphate buffer pH 6.4 and the temperature was maintained at 37 ± 0.2 °c. One ml of Liquid crystals (Cubosomal) gel containing 2 mg of the drug was kept over the membrane. Because of temperature of the system the solution turned rapidly into gel and remainedadhere to the system. The process was started and at predetermined time intervals (0.30,1, 2, 4, 6, 8, 10, and 12 hrs.) one ml of the solution from the reservoir compartment was removed and replaced with fresh buffer. This one ml solution was further diluted upto 9 ml by using phosphate buffer solution and the absorbance of this solution was taken at 227.40 nm. Phosphate buffer pH 6.4 was used as blank.

➢ *Method Development for RP-HPLC:*

Plasma samples were analyzed using HPLC system (LabSolutions) software and diode array detectors. C-18 Shimpack C-18 X-Bridge column chromatographic separation was done at room temperature. The mobile phase, Ammonium Bicarbonate and Acetonitrile (70:30 v/v) with pH 7.6 adjusted with Glycerol Acetic acid (1% v/v), was pumped at 0.7 mL/min in an isocratic mode for 10 min. The concentration was measured at 220 nm after injecting 20 mL of sample using a Hamilton syringe. Tioconazole-loaded Liquid Crystals were pharmacokinetically analyzed using the pK solver (MS Excel add-in).

➢ *Pharmacokinetics Studies*

- *Animal and Dosing:*

Animals studies were approved by the institute animal ethics committee (IEAC) approval number DBCOP/IAEC/1426/22-23/P13 and conducted in accordance with the Committee for the purposed of Control and Supervision of Experiments on Animal (CPCSEA) guidelines. Female Sprague –Dawley rats weighing 200-250 g were suppliedby KUSUM lifescience, Nanded. Day prior to the beginning of the study, the 12 femalerats were randomly divided into two groups with six rats in each group, namely groupsA, and B. Group. Groups A received Cubosomal Gel of Tioconazole administered Vaginally equivalent to 18 mg/kg Tioconazole. Groups B with API Tioconazole at a constant dose. 0.5 ml blood was withdrawn from the retro-orbital venous plexus of ratsat predetermined time intervals of 1, 3, 6, 24,36 and 48 h. Plasma was separated from the blood immediately by centrifugation at 9500 rpm for15 min and stored at 4°C untilanalysis. Further 100 µL plasma was quantified by a modified RP-HPLC method for estimation of pharmacokinetic parameters. (Tmax(h), Cmax(mg/ml), $t_{1/2}$(h), MRT(h), $AUC_{0\text{-}12\ h}$(mg-h/ml)).

➢ *Stability Study:*

Accelerated stability investigation following ICH recommendations Q1A (R2) involved incubating optimal Tio-Loaded Cubosomes at regular (25 ± 2°C, 60 ± 5% RH) and accelerated conditions (40 ± 2°C, 75 ± 5% RH) for 3 months.Stability was determined by formulation appearance, particle size, and entrapment efficiency. Temperature and humidity were measured for 0, 1, and 3 months. This section outlines study technique and reports future results and discussions.

III. RESULT AND DISCUSSION

➢ *UV Spectroscopy*

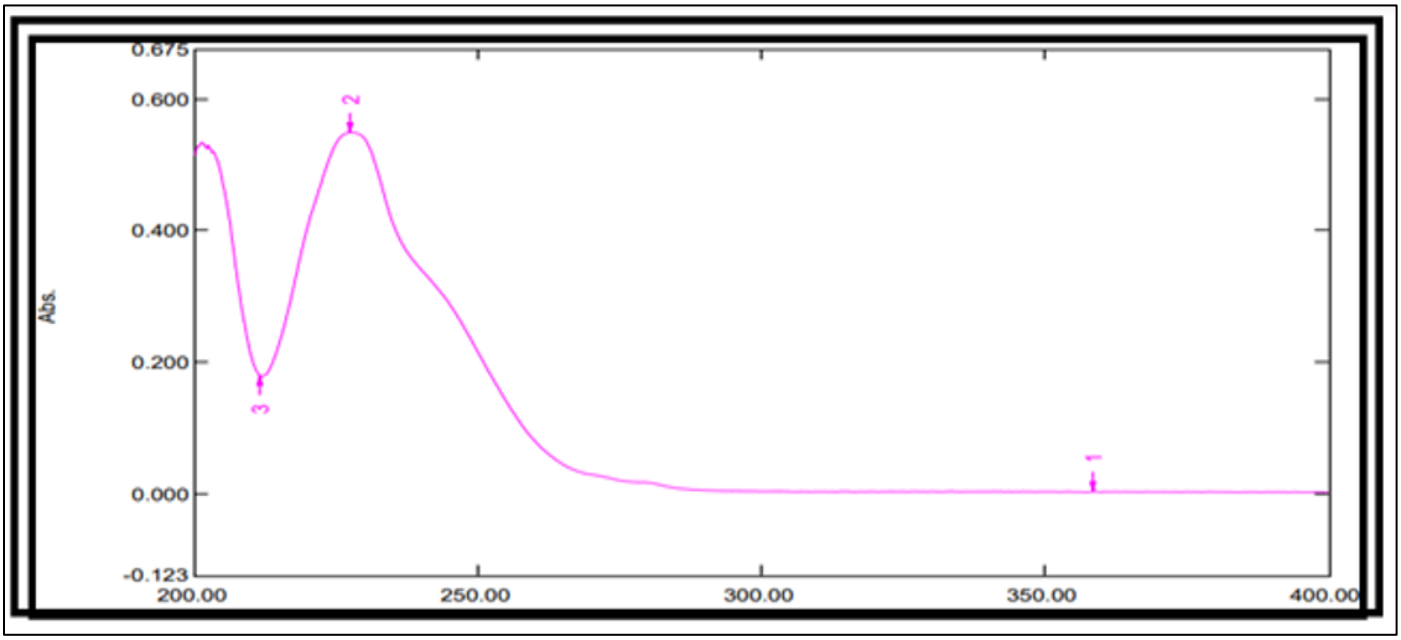

Fig 2 UV Spectrum of Tioconazole

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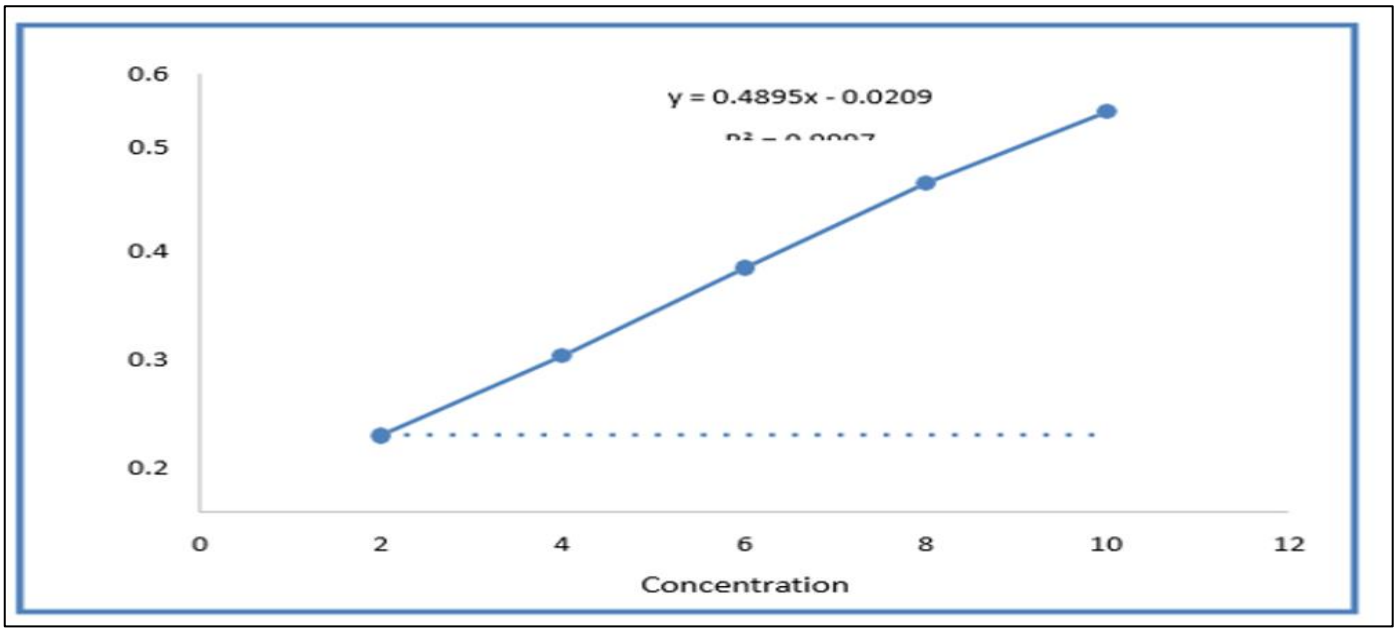

Fig 3 Calibration Curve of Ticonazole in Phosphate Buffer

➢ *Entrapment Efficiency*

- *Validation of Tioconazole Loaeded Cubosomes:*

This was done by preparing checkpoint batch from the overlay plot. Two checkpointbatches Batch-1 and Batch-2 were prepared and evaluated for particle size and % Entrapment efficiency as shown in table. When these actual values were comparedwith predicted values, the difference was found to be less than 5% of all the responses. (As shown in the table no.1)

Table 1 Predicted and Actual Response of Checkpoint Batch

Evaluationparameters	Batch-1			Batch-2		
	Predictedvalue	Actual value	% Error	Predictedvalue	Actualvalue	% Error
Y1: Particlesize	170.83	172.7	1.1	167.69	172.8	2.95
Y2: % Entrapmentefficiency	78.90	80.44	1.9	81.3	84.7	4.01

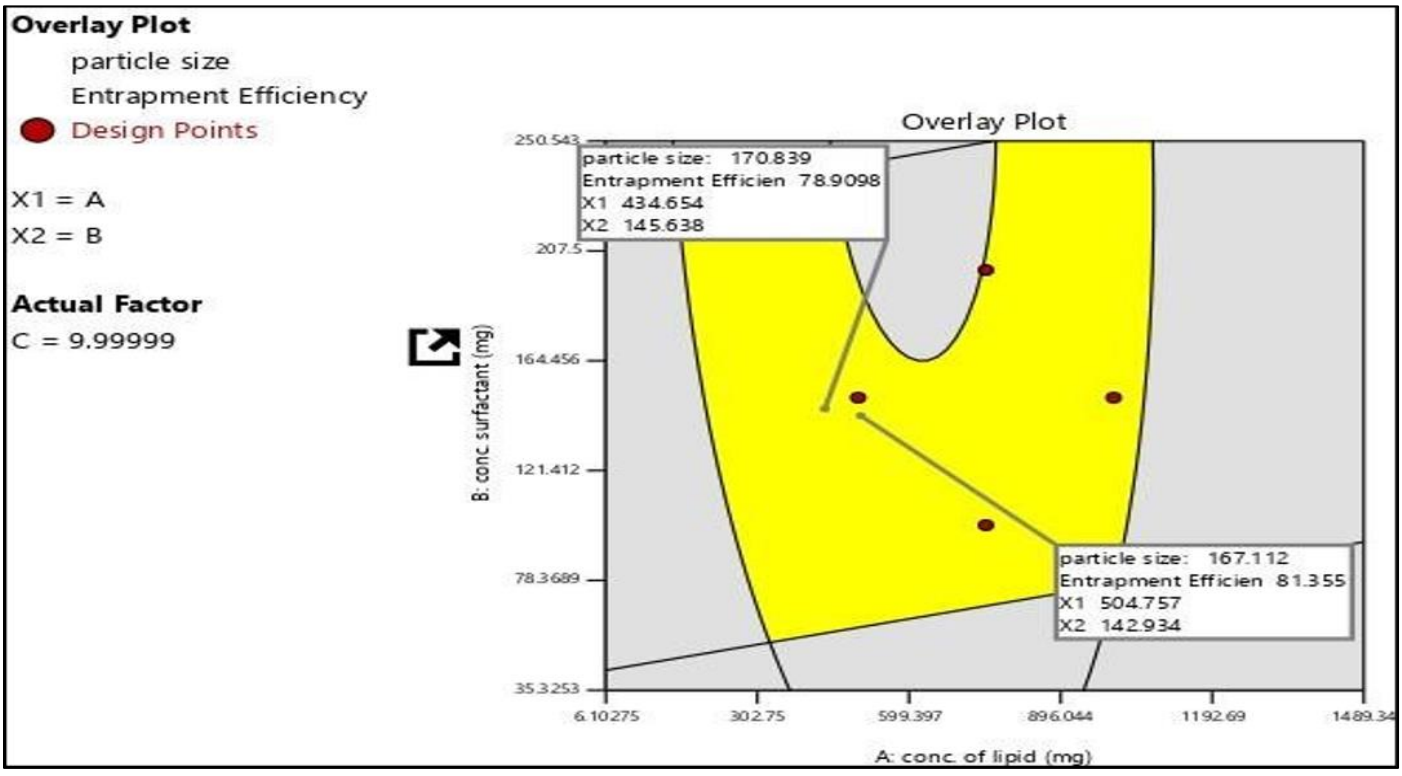

Fig 4 Overlay Plot for Response Variables

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- *Optimization of Tioconazole Cubosomes:*

The goal was to choose the optimal drug-excipient combination. Box-Behnken design was utilized for batch optimization and design. After designing and formulating 15 batches, batch F-13 was picked as the optimal batch and converted into gel based on desirability values.

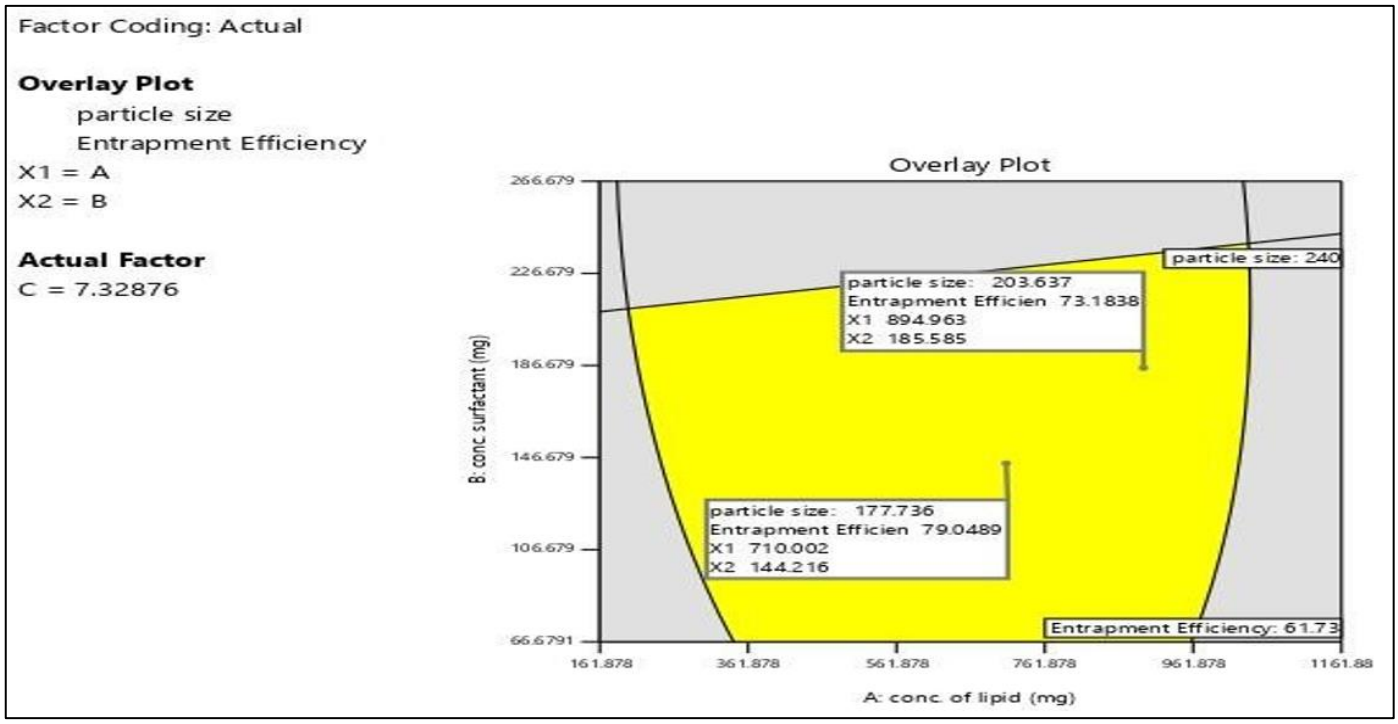

Fig 5 Overlay Plot for Optimized Batch F-13

- *Particle Size and PDI:*

The particle size of Cubosomes were found to be 178.64 nm. The particle size statistics show that the lipid and surfactant in the formulation. The PDI used as measure of unimodal size distribution was within the acceptable limits for all the formulation. ThePDI was found to be less than 0.5 hence homogeneous population.

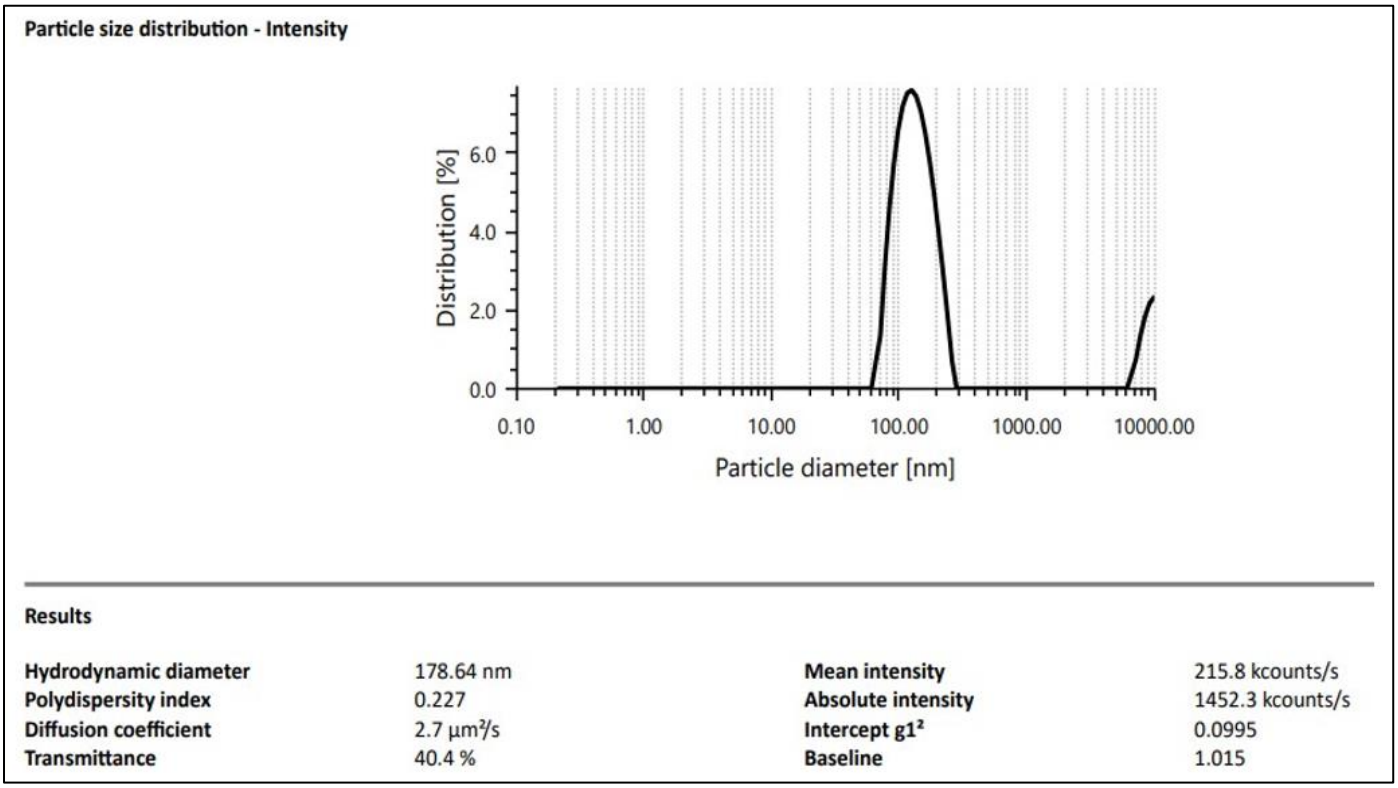

Fig 6 Particle Size and PDI

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➢ *FTIR Spectra of Lyophilized Optimize Batch:*

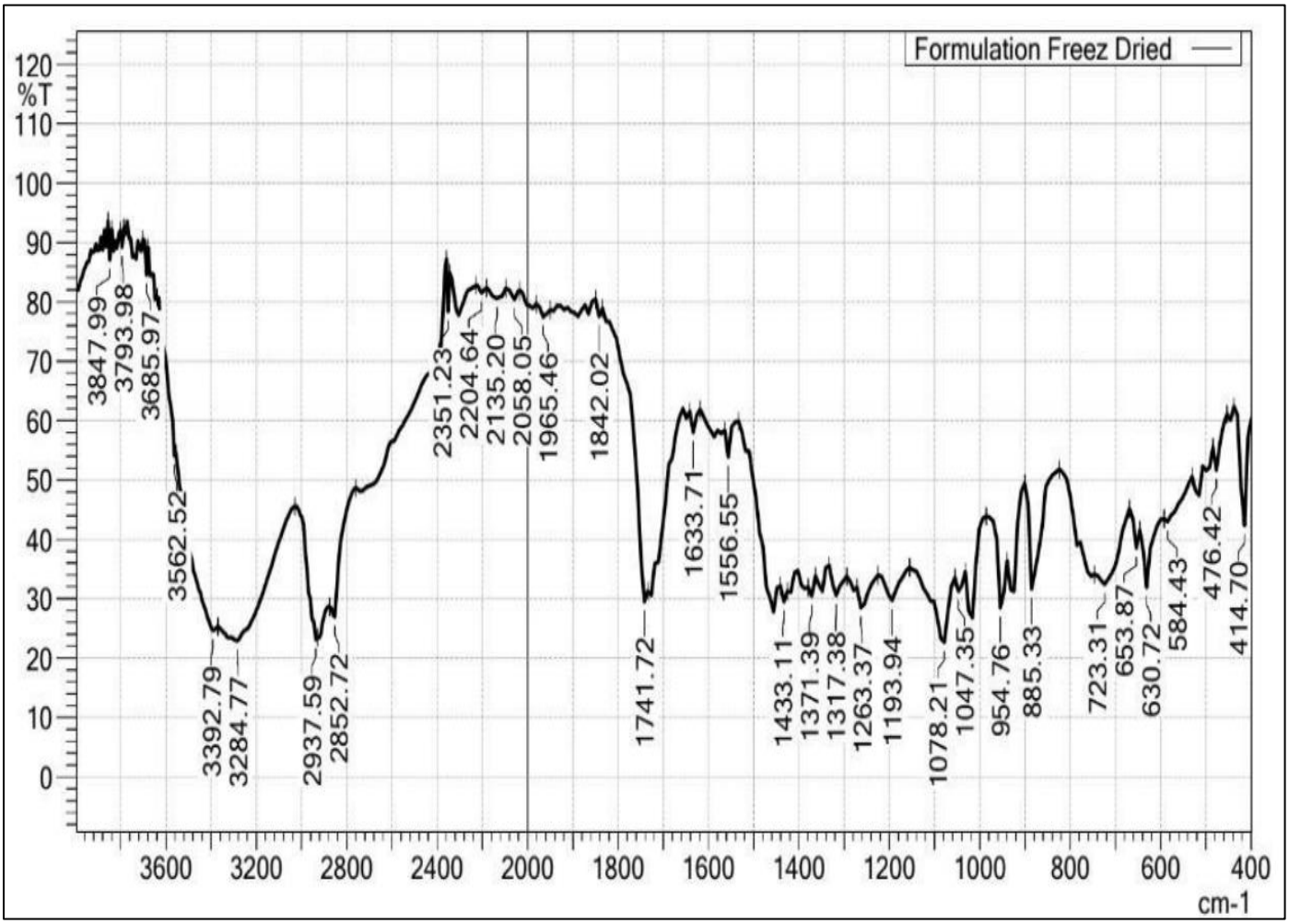

Fig 7 FTIR Spectra of Freeze-Dried Formulation

➢ *X-RAY Differaction (XRD):*

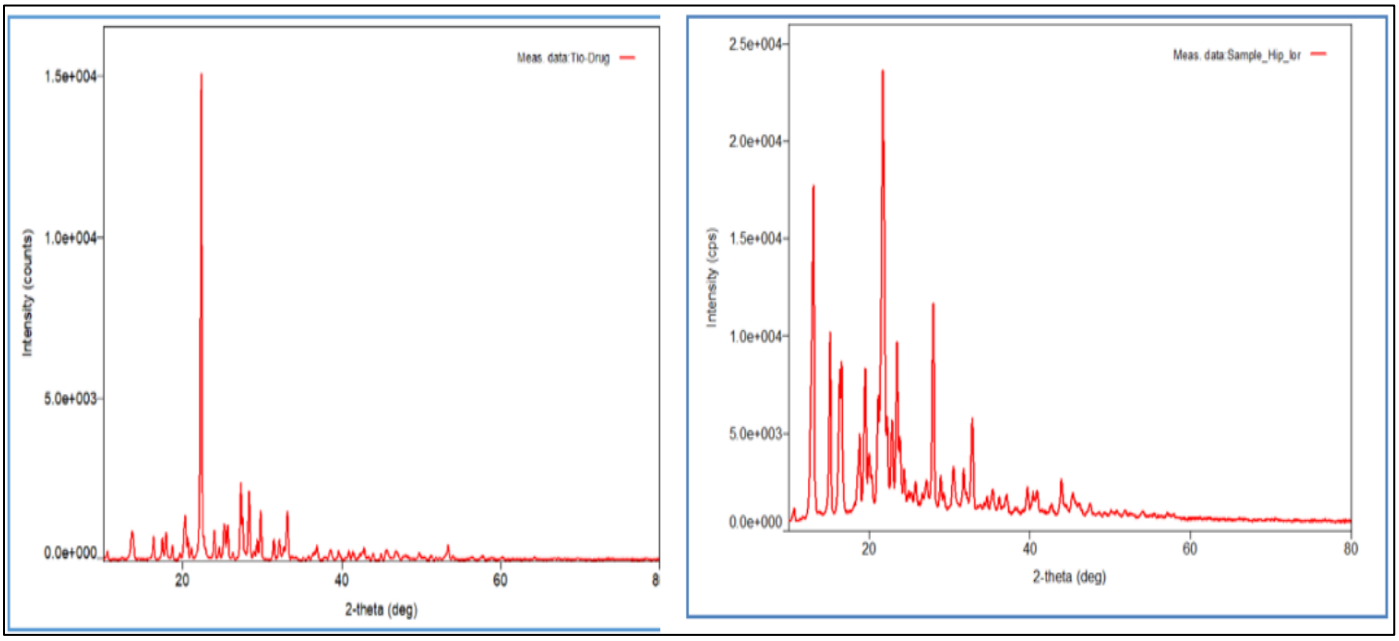

Fig 8 X-Ray Diffraction of A) Tioconazole and B) Cubosomes Formulation

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➢ *Differential Scanning Calorimetry (DSC):*

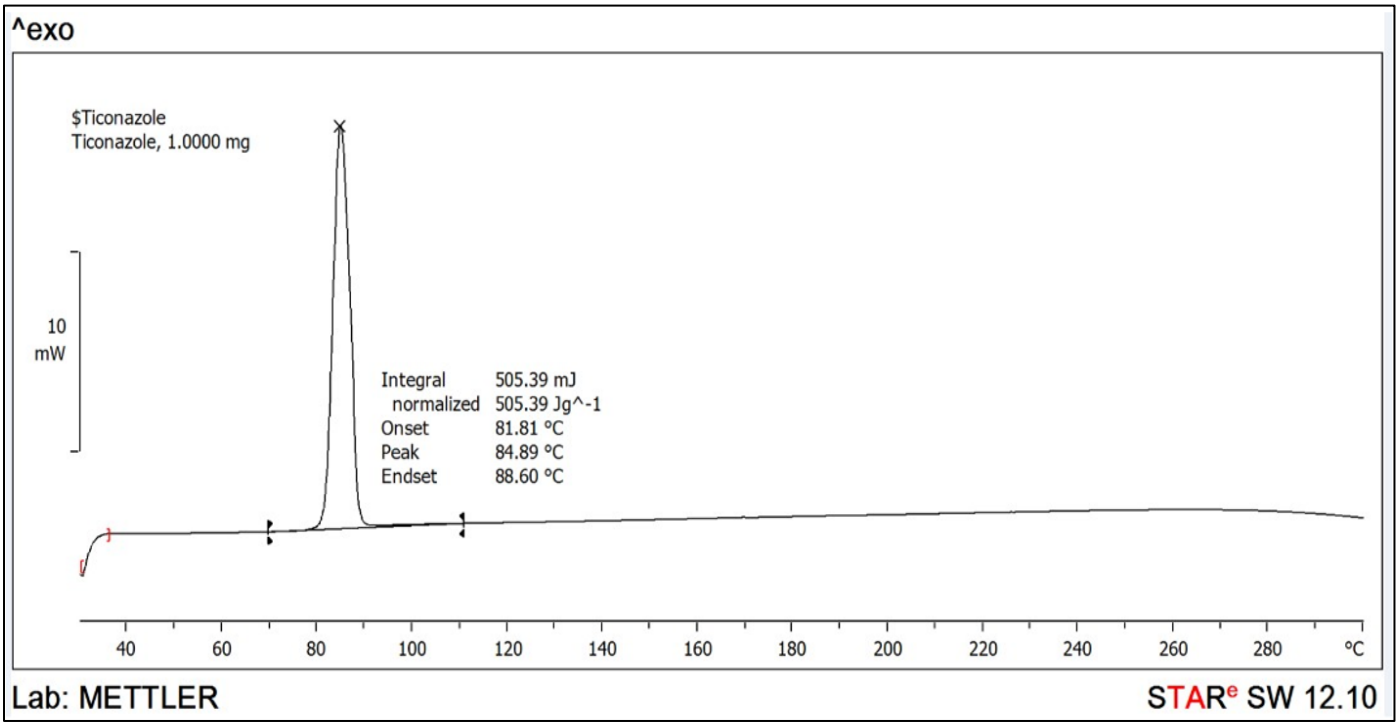

Fig 9 DSC of Tioconazole

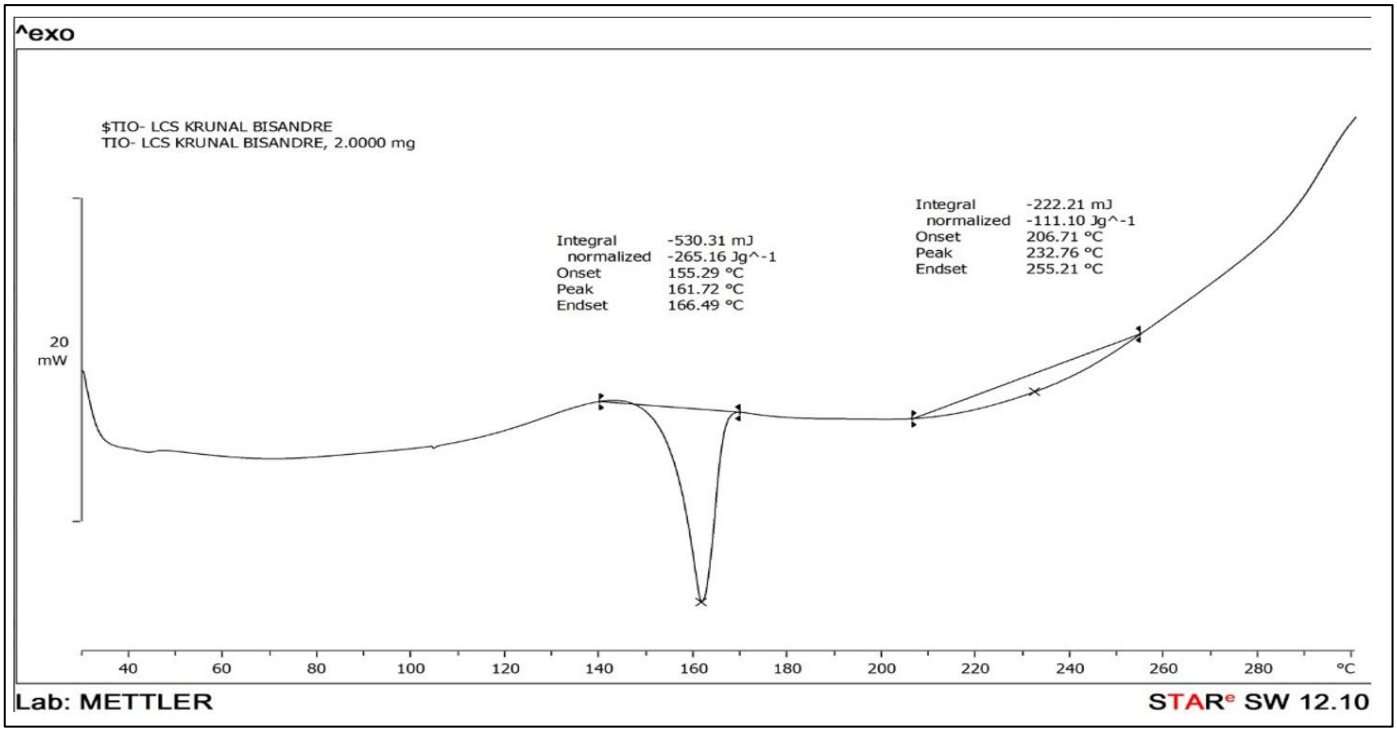

Fig 10 DSC of Liquid Crystals (Cubosomes)

DSC study demonstrated that Tioconazole showed the presence of exotherms at 84-89°C implying crystallinity's melting exotherms of Tioconazole with sharp peak indicating crystalline form. Where, tioconazole loaded Cubosomes showed the sharp endothermic peak at 161.72°C which showed the crystalline nature of formulation (As shown in figure no.9 and 10)

➢ *Scanning Electron Microscopy:*

Shape analysis and surface morphology of Tioconazole Liquid Crystals (Cubosomes) optimize batch was carried out by SEM. The photograph revealed that the surface was smooth of prepare liquid crystals (Cubosomes) formulation was in cubic shape.

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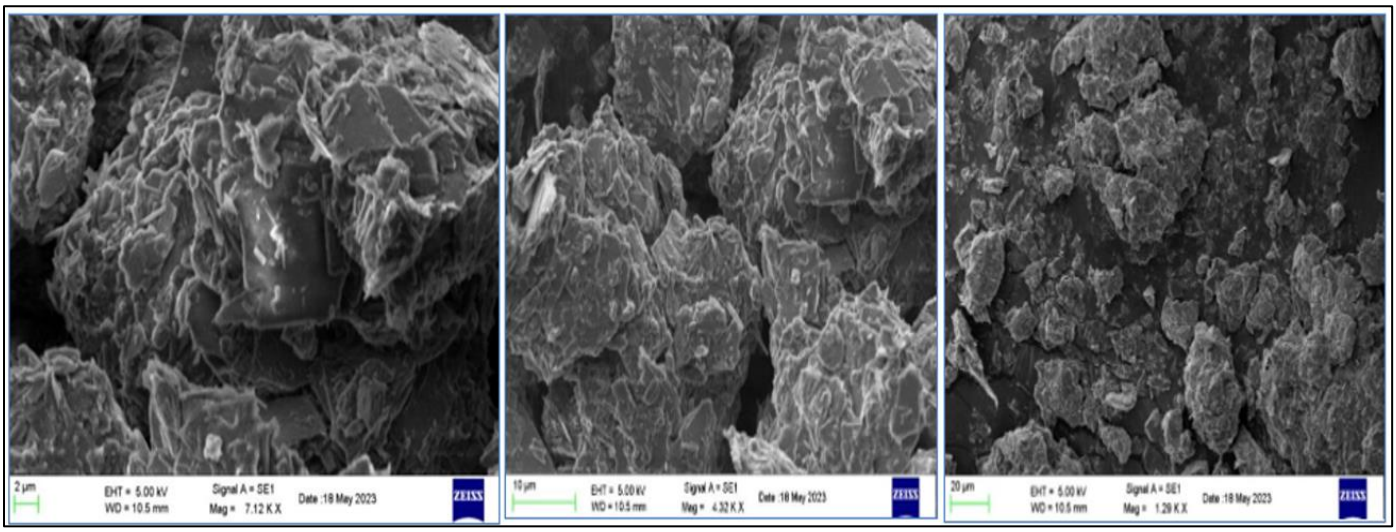

Fig 11 SEM Image of Cubosomes

Table 2 Result of Cubosomes Gel

Sr. No.	Parameter	Result
1	Gelling Temperature	27 ℃ - 32 ℃
2	Gelling Time	57 Sec.
3	Viscosity Determination	22,800 cP.

➢ *In-Vitro* Drug Release Kinetic Study:

In-vitro drug release from the optimized formulation batch is best described by Higuchiplot release profile since the plot shows highest R^2 value for linearity. Higuchi release signifies that the drug release rate is independent of the concentration of Tioconazole inside the Liquid Crystals. The drug releases at a constant rate for prolong period of time at predetermined time intervals and maintains the therapeutic concentration.

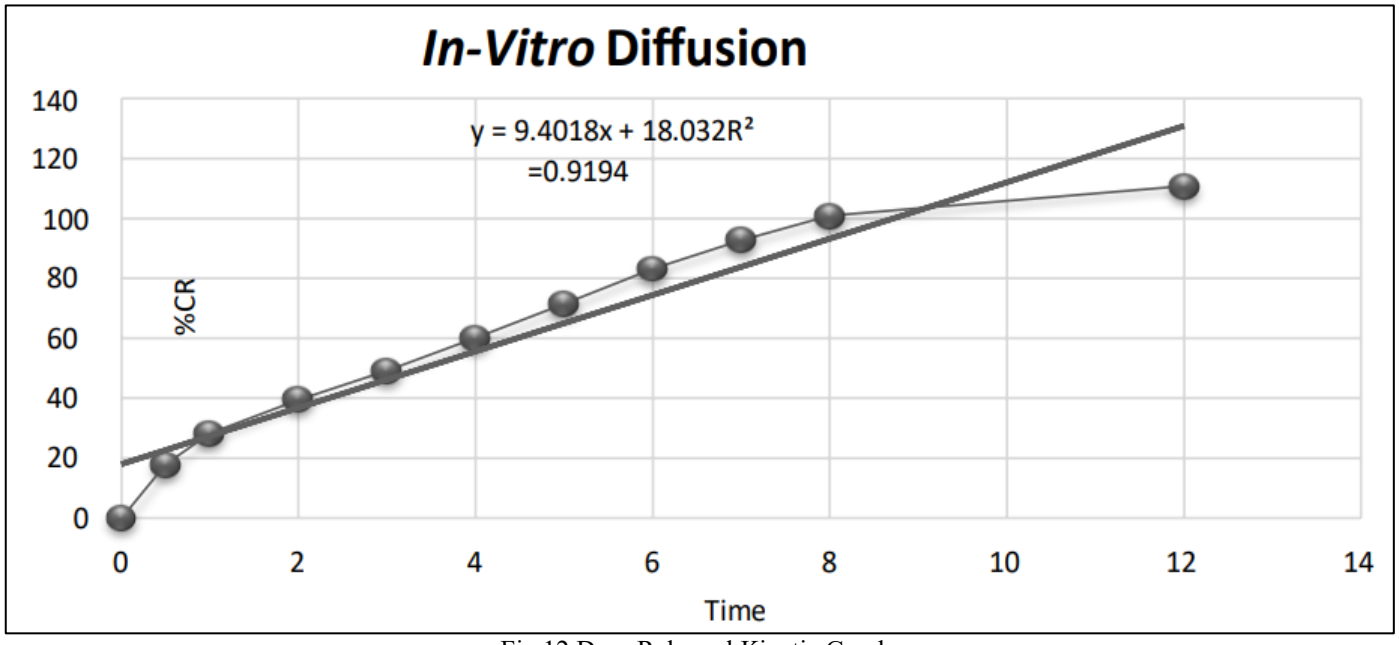

Fig 12 Drug Released Kinetic Graph.

Table 3 In-Vitro Kinetic Study of Cubosomal Gel

Model	*In-Vitro* kinetic study of Cubosomal Gel				
	Zero Order	First Order	Hixson-Crowell	Higuchi	Korsmeyer Peppas
R^2	0.9194	0.5021	0.5977	0.9783	0.525
Slope	9.40	0.11	0.28	38.62	0.96
Intercept	18.03	1.09	2.28	24.74	1.12

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➢ *Ex- Vivo Permeation Study:*

The Ex-vivo drug permeation from the optimized formulation could be best explained by Higuchi model. It showed increase in drug release in initial 8 hour then showed sustained drug released up to 12 hours, the drug released from liquid crystals fitted intoHiguchi equation, where R^2 value was found to be 0.9822 it describes drug release as adiffusion process based on Fick's law which is square root of time dependent. Drug release mechanism following Higuchi model signifies that there is constant diffusivity and sink conditions are perfectly maintained in the release media.

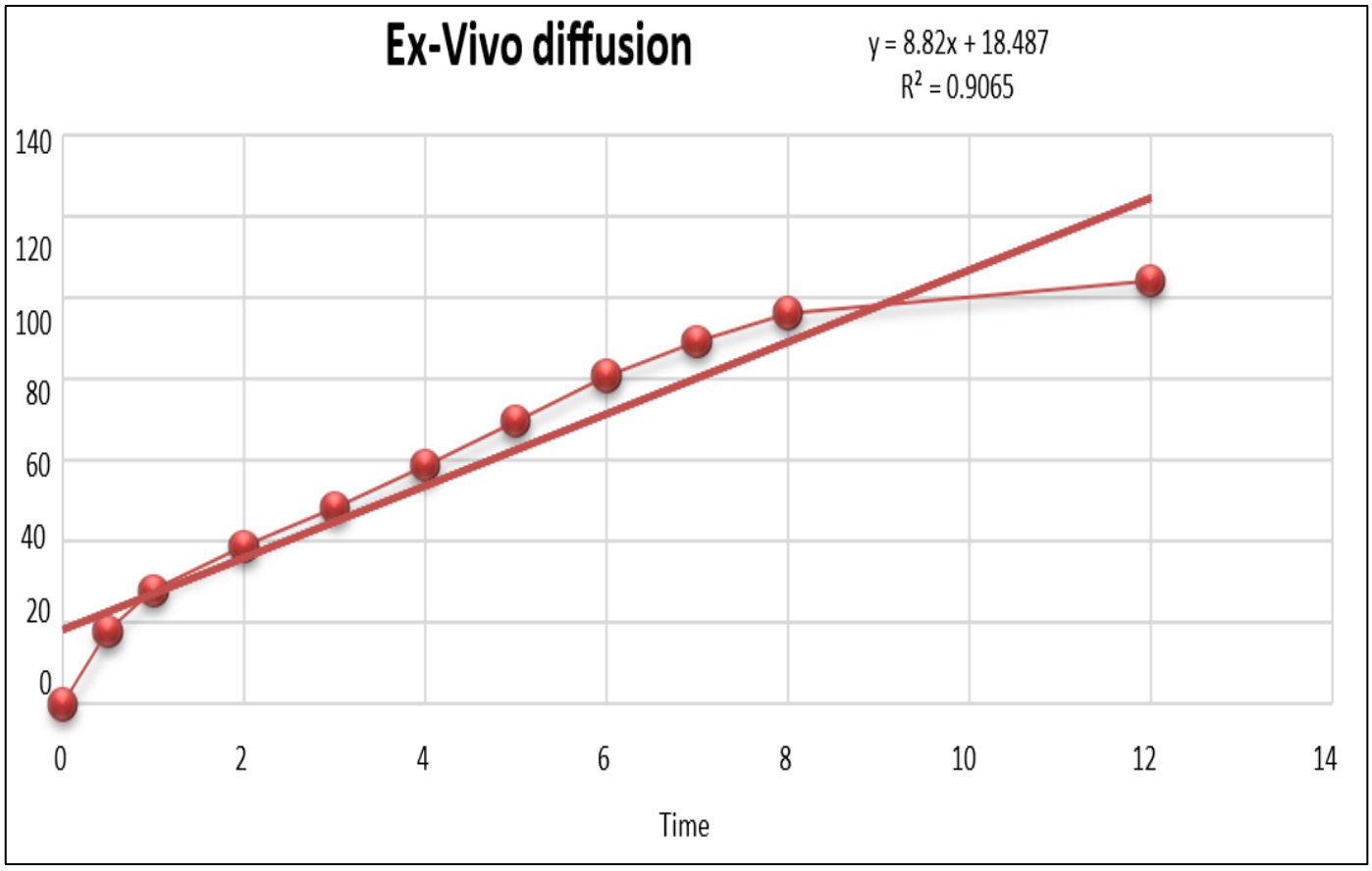

Fig 13 Ex-Vivo Diffusion

Table 4 Ex- Vivo Permeation Study

Model	Ex-vivo permeation kinetic study of optimized batch				
	Zero Order	First Order	Hixson-Crowell	Higuchi	Korsmeyer Peppas
R^2	0.9065	0.4927	0.5833	0.9822	0.5164
Slope	8.82	0.11	0.27	33.03	0.94
Intercept	18.48	1.09	2.28	4.12	1.12

➢ *Development of Method for RP-HPLC:*

- *Chromatographic Condition:*

The chromatographic condition for HPLC method development, Coloumn C-18 Shimpack. Mobile phase was used ammonium bicarbonate:Acetonitrile ratio of 70:30 with flow rate of 0.7 ml/min. for run time of 10 min and observed at 220nm.

Table 5 Chromatographic Condition

Coloumn	C-18 Shimpack
Mobile Phase A	Buffer (Ammonium Bicarbonate 7.6 pH of 25 mM)
Mobile Phase B	Acetonitrile
Flow Rate	0.7 ml/min
Wavelength	220 nm.
Injection Volume	20 µL
Run Time	10 Min.
Ratio	Ammonium Bicarbonate: ACN (70:30)

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- *Developed Method for HPLC:*

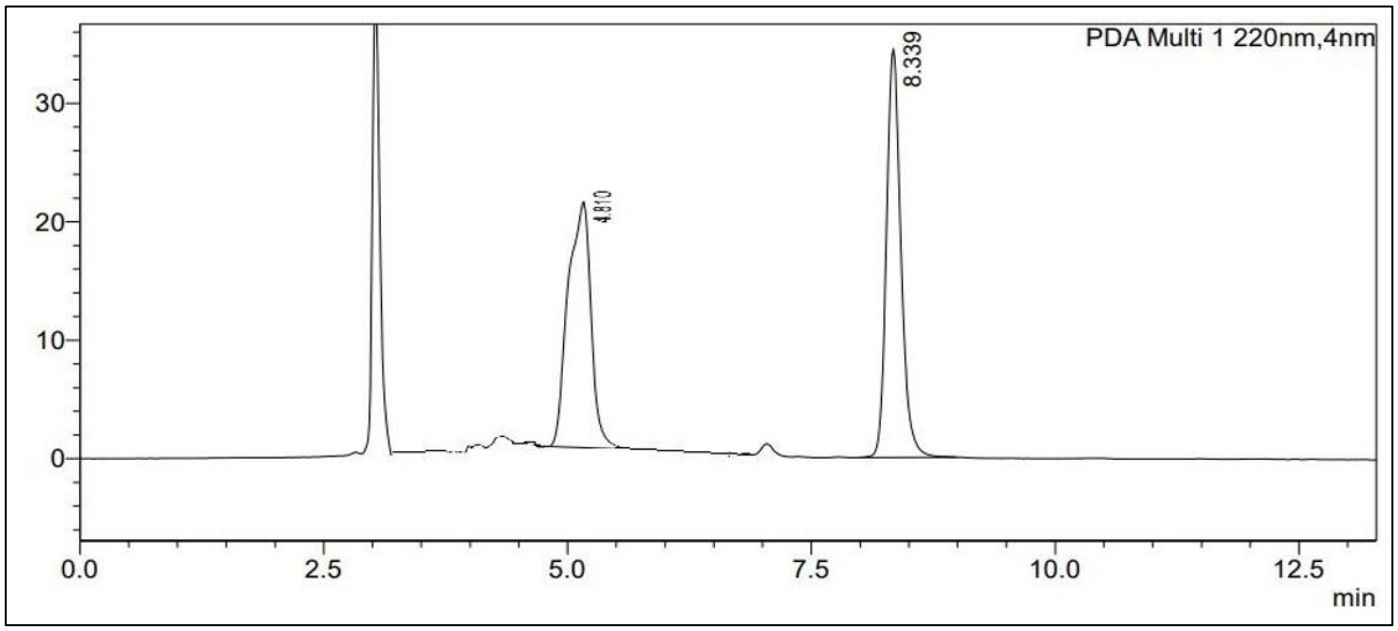

Fig 14 Represents Tioconazole Chromatogram at 220nm.

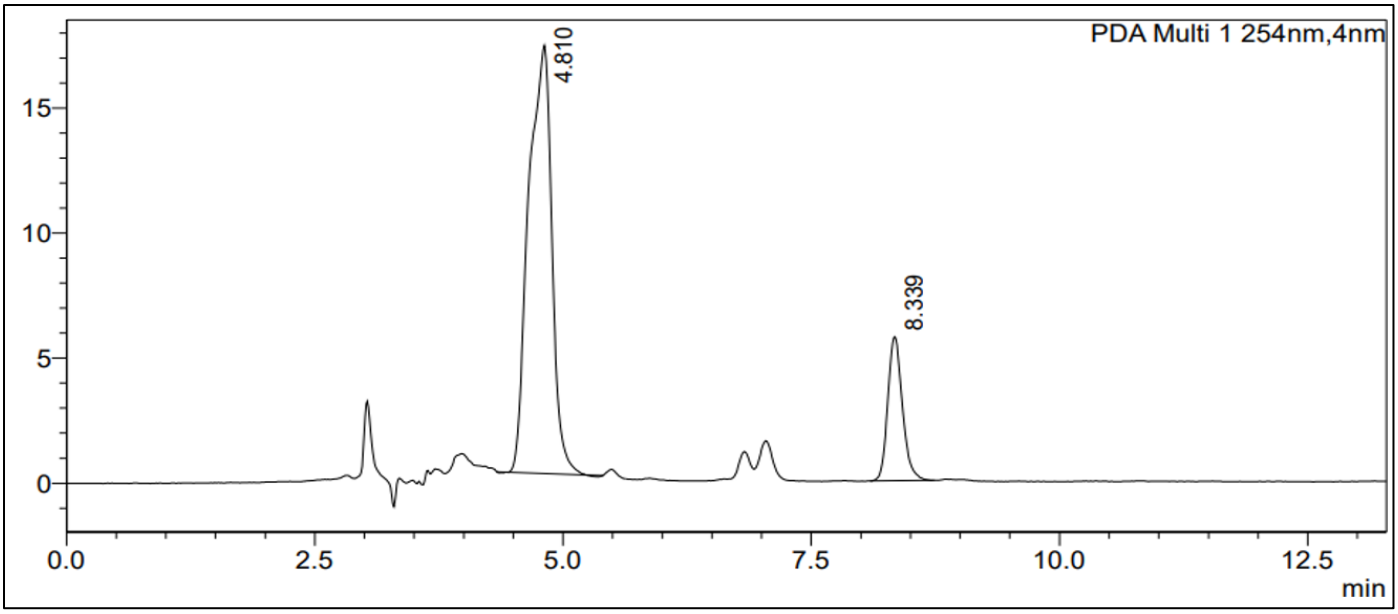

Fig 15 Represent Internal Standard Chromatogram of Afatinib Dimaleate at 254nm.

Above chromatogram comprised of Ammonium Bicarbonate: ACN that is 70:30 flow rate of 0.7ml/min the solvent peak observed at 3min. and internal standard peak at 4.8min. And Drug peak is obtained at 8.3 min with Area of 236689 and 356346. Tailingfactor 1.1, Height of 13455 and 34399 with resolution of 5.5.

Table 6 Linearity of Tioconazole and Afatinib Dimaleate (I.S) in HPLC:

Calibration standard (µg/ml)	AUC Tioconazole /AUC of Afatinib Dimaleate
0.05	0.0080
0.1	0.0183
0.25	0.0526
0.5	0.0774
1.0	0.1487
2.5	0.3894
5.0	0.7819
10	1.5036

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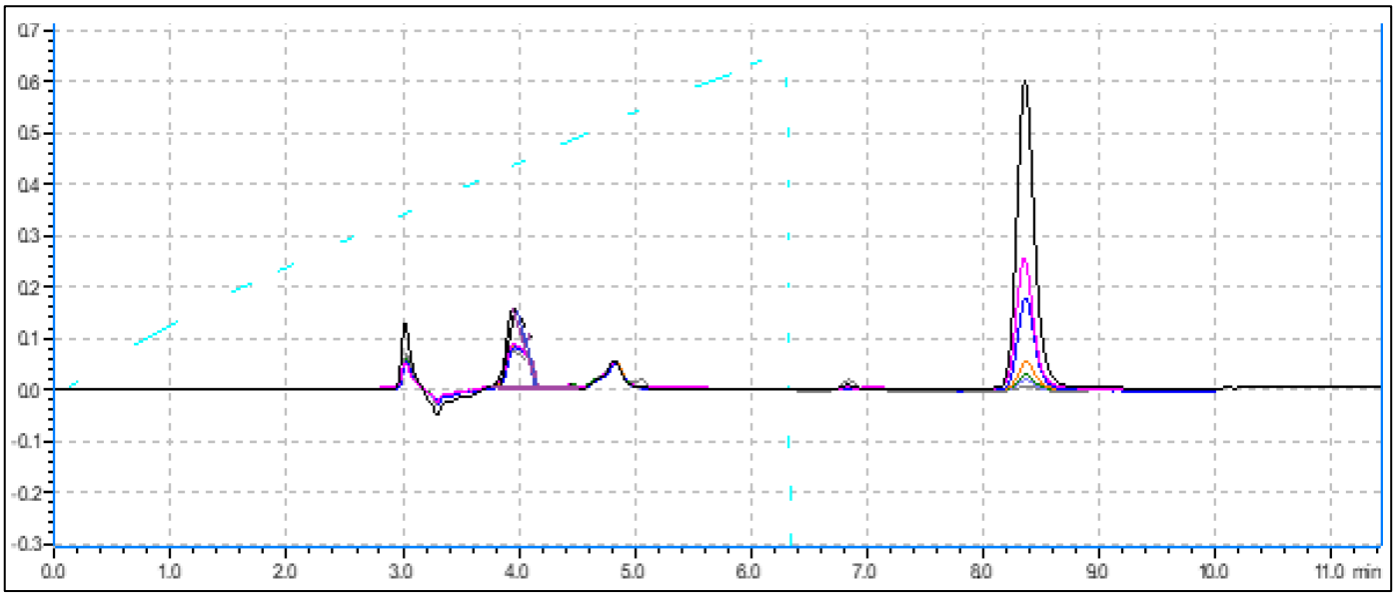

Fig 16 Overlay Plot of Tioconazole in HPLC

➢ *Pharmacokinetic Study:*

The Non compartmental analyses and the linear trapezoidal technique were used to determine the pharmacokinetic parameters. The result showed that Tioconazole loaded Liquid crystals had higher AUC and Cmax Value that Tioconazole (pure), indicating a significant increase in tioconazole in liquid crystals. Tmax, half-life (t1/2), and MRT were more in liquid crystals, indicating a considerable increase in Tioconazole vaginalabsorption.

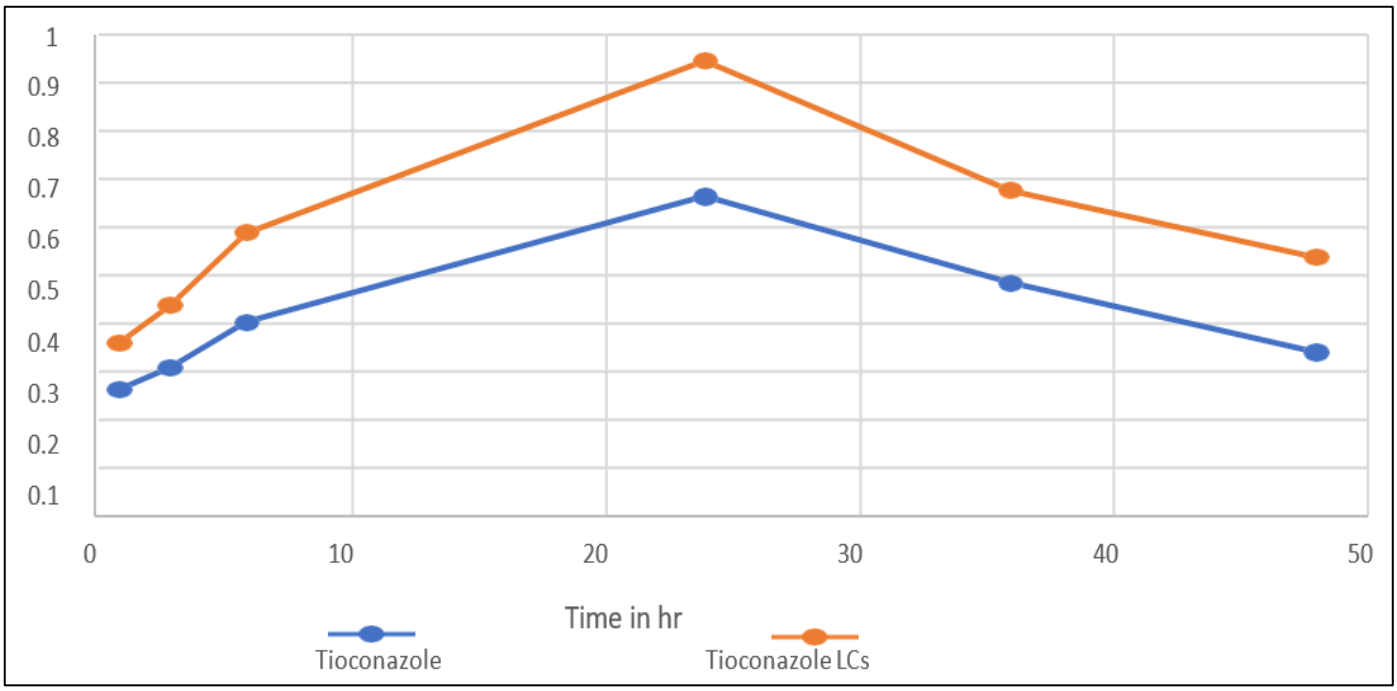

Fig 17 Pharmacokinetic Parameter for Tioconazole and Tioconazole Loaded Cubosomes

➢ *Stability Study:*

Table 7 Stability Study of Optimize Batch

Time (month)	25 ± 2 °C and 60 ± 5% RH			40 ± 2 °C and 75 ± 5% RH		
	Change inPhysical apperance	Particle size (nm)	Entrapment efficiency (%)	Change inPhysical apperance	Particle size (nm)	Entrapment efficiency (%)
0	No	178	78.63%	No	178	78.63%
1	No	180	80.00%	No	180	79.30%
3	No	182.33	89.00%	No	181.6	77.23%

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Accelerated stability study of the prepare formulation was perform in terms of physical appearance, Particle size, and drug entrapment efficiency upto storage in different condition as per ICH guidelines Q1A. The formulation was observed at different intervals as mentioned above, No significant changes in physical appearance of Tioconazole loaded Cubosomes was observed at both the regular and accelerated condition of temperature and humidity a little increase in particle size and decrease in entrapment efficiency was recorded after a 3 month of storage at both condition. The changes were slightly in accelerated condition then the regular condition. It can be conclude that optimized formulation was satisfactorily stable during the entireperiod (As shown Table No.7).

IV. CONCLUSION

Tioconazole loaded liquid crystals (Cubosomes) were formulated by using Emulsification method To solve the problem low solubility and bioavailability of Tioconazole. The formulation of cubosomes using Tioconazole as API and Glyerol monooleate as Lipid and their optimization done by using Box-behnkem experimental design expert software the optimize Batch-13 shows the minimum particle size of 178 nm, polydispersity index 0.355 and zeta potential -25.7 mV. As well as Entrapment Efficiency 78.63 %. FTIR spectroscopy suggest that Tioconazole is compatible with other excipient like GMO and Pluronic F-127.SEM analysis indicates the presence of cubic shape particle structure. It shows maximum solubility in phosphate Buffer 6.4 pHthat is in mg/ml. In vitro-Ex vivo Diffusion showed an significant increase and display sustained drug release behavior lasting for 12 hr. The melting exothermic peak of the does not observed in thermogram of Tioconazole loaded Liquid Crystals (Cubosomes). X-Ray diffractogram of Tio-loaded Liquid crystals shows high diffraction peak 2 theta value at 20°C indicates initial crystalline state and in formulation. The stable Cubosomes with good entrapment efficiency (>75%) and the particlesize (178 nm) were successfully optimized using Box-Behnkem design. Cubosomes demonstrated cubic shape morphology and smooth surface. In vitro - Ex vivo showed asustain released property of Cubosomes (12h). The pharmacokinetic result showedincrease in bioavailability of Batch-13. Moreover, significant increase in half-life and mean residence time confirm the long-term retention of Batch-13 Cubosomes. Solubility and Bioavailability enhancement along with long term retention of TCZ Cubosomes definitely improved the treatment efficiency of vaginal candidiasis as wellas relief patient.

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