ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

FORMULATION AND EVALUATION OF TOPICAL CUBOSOMAL EMULGEL OF AN ANTIFUNGAL DRUG: ITRACONAZOLE

T N Purnima*, M Sunitha Reddy

Centre for Pharmaceutical Sciences, Institute of Science and Technology, JNTUH, Kukatpally, Hyderabad, Telangana, India

**Corresponding author: tnpurnima@icloud.com*

ABSTRACT

An antifungal drug Itraconazole is an azole derivative that belongs to BCS class II. Itraconazole with 14-α demethylase, a cytochrome P-450 enzyme obligatory to convert lanosterol to ergosterol; as ergosterol is an imperative component of the fungal cell wall. The present research work aims to extend the penetration of Itraconazole into deeper layers of skin by formulating cubosomes of Itraconazole into a topical emulgel that helps in enhancing the bioavailability by avoiding first-pass metabolism. Cubosomes were prepared by the Top-down approach (Emulsification method) employing GMO as a lipid phase vehicle, Pluronic F127 as a stabilizer, and distilled water as the aqueous phase. Itraconazole is an antifungal drug with 55% oral bioavailability. Consequential formulations were characterized by visual inspection, encapsulation efficiency, *in-vitro* drug release, particle size, zeta potential. Optimized formulation (F4) showed drug release of 89.76% within 9 hours, the particle size of 259.8 d.nm, and zeta potential of -34.4 mV. The optimized Cubosome formulation F4 was used for the Itraconazole emulgel using carbopol 974N, HPMC 15cps, and studied for pH, viscosity, drug content and *in vitro* drug release. Among all the preparations, formulation ITF7 was found to illustrate the utmost drug release of 86.93% at the closing stages of 20 hours and other evaluation parameters within specified limits. *In vitro* release kinetics exhibited sustained release and therefore the formulation ITF7 follows the Higuchi release mechanism and according to this model, the Itraconazole cubosomal emulgel formulation released the drug throughout non-Fickian super case-II transport ($n > 0.89$). This novel cubosomal, low-irritant gel would be a promising system for effectual topical drug delivery.

Keywords: Cubosomes, Itraconazole, GMO, Top-down approach, Emulgel.

1. INTRODUCTION

There is an enormous number of vesicular drug delivery systems that allocate drug targeting and the sustained or controlled release of conventional medicines. In such a scheme cubosomes are also an element of the vesicular drug delivery system or lipid-based colloidal system which was discovered in 1980. The term "Cubosomes" is defined as nano-structured, discrete and sub-micron particles of bicontinuous cubic liquid crystalline phases. The term "bicontinuous" refers to 2 distinct hydrophilic regions separated by the bilayer. Bicontinuous cubic crystalline resources have been a dynamic research topic because their structure lends itself well to controlled-release applications [1]. The cubosomes are honey-combed in a structure which is separating the 2 internal aqueous channels along with a large internal surface area. Cubosomes are nano-particles having a size range of 10-500nm. They are appearing like Dots, Slightly Spherical. Every single Dot corresponds to the presence of pore containing aqueous phase cubic phases in the lipid water system in X-ray scattering technique was first identified by Luzzati & Husson.

An antifungal drug Itraconazole is an azole derivative belongs to BCS class II. Itraconazole with 14-α demethylase, a cytochrome P-450 enzyme obligatory to convert lanosterol to ergosterol; as ergosterol is an imperative component of the fungal cell wall. Itraconazole has restricted solubility and the drug undergoes intensive hepatic metabolism that results in poor oral drug bioavailability (55%) of the drug and hinders its use for systemic treatment via gastro intestinal tract. The present research work aims to extend the penetration of Itraconazole into deeper layers of skin by formulating cubosomes of Itraconazole into a topical

emulgel that helps in enhancing the bioavailability by avoiding first-pass metabolism [2, 3]. Formulating Cubosomes as a nano sized particulate systems for topical delivery owing for the greatest advantages such as high drug payload due to high internal surface area and cubic liquid structure, encapsulating ability of hydrophobic, hydrophilic and amphiphilic molecules [4].

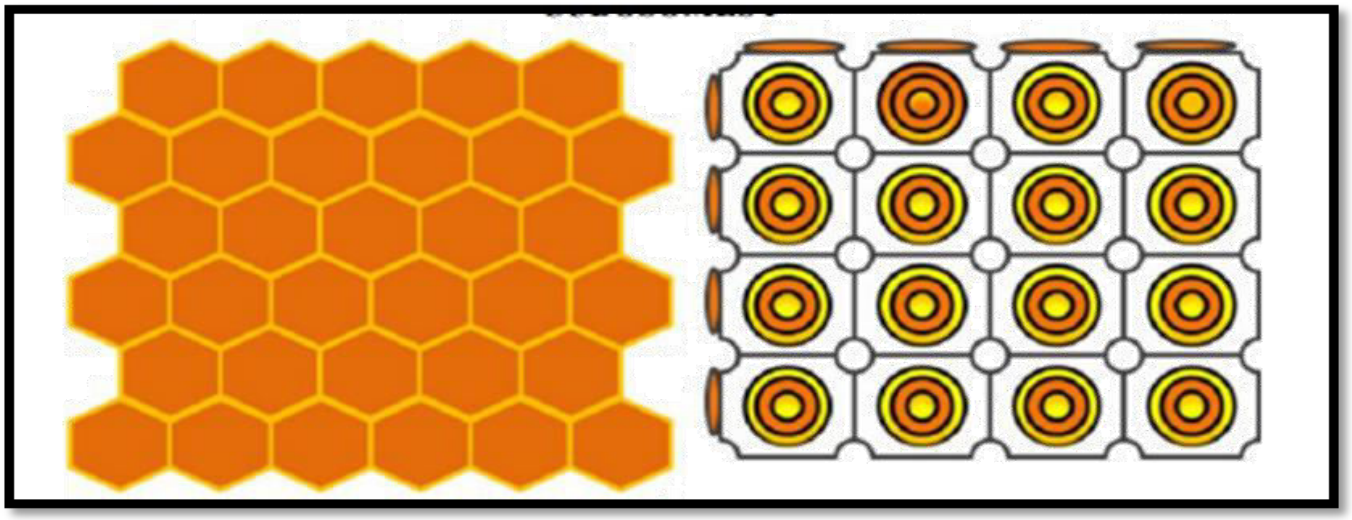

Fig. 1: Structure of Cubosomes shows the structures of primitive (P) cubic cubosomes which is similar to honeycomb

2. MATERIAL AND METHODS

2.1. Material

Itraconazole was a gift sample from LEE Pharma Pvt Ltd, Hyderabad, Telangana, India. Glyceryl monooleate (GMO) was purchased from Finar Chemicals (LR). Pluronic F127 was a kind gift from NATCO Pharma, Hyderabad. Carbopol 974N, HPMC 15cps were of commercial grade. All other reagents used were of analytical grade.

2.2. Calibration Curve of Itraconazole in Phosphate buffer pH 7.4

The calibration curve of Itraconazole was plotted by using phosphate buffer pH 7.4 as a solvent. 10mg of Itraconazole was weighed precisely and diluted with methanol in a 10ml volumetric flask and made up to the volume to give a concentration of 1000µg/ml. From this reserve solution 'A', 1ml was taken and diluted to 10ml using phosphate buffer pH 7.4 to give a concentration of 100µg/ml. From this reserve solution 'B', 1ml was taken and diluted to 10ml to give a concentration of 10µg/ml, similarly a range of concentrations of 20, 30, 40, 50µg/ml were prepared and the absorbance was measured at 285 nm against a blank using UV Spectrophotometer.

2.3. FTIR studies

FTIR spectra of pure drug and excipients, optimized emulgel formulation is taken and analyzed for presence of any incompatibility.

2.4. Formulation of Itraconazole Cubosomes

The method used for the preparation of cubosomes was the top-down method (Emulsification method). Precisely weighed quantity of Glyceryl monooleate and Pluronic F127 in different ratios were mixed and melted in a water bath at 60°C until Pluronic F127 completely dissolves in GMO. To the above solution Itraconazole was added and mixed well. To the obtained clear lipid solution added slowly preheated (60°C) distilled water drop by drop of appropriate quantity by uninterrupted stirring [4, 5]. After complete addition of lipid phase it was kept aside for one day to attain equilibration. There was a formation of a two-phase system and it was disturbed by stirring. The entire system was subjected to homogenization at 1200 rpm under room temperature for 2hr. The prepared dispersions were stored in closed glass vials at room temperature sheltered from direct sunlight and later valuation was carried out. The resultant was a white opaque dispersion without the presence of any aggregates. Various formulations were prepared in such an approach that each ml contains 10 mg of the drug.

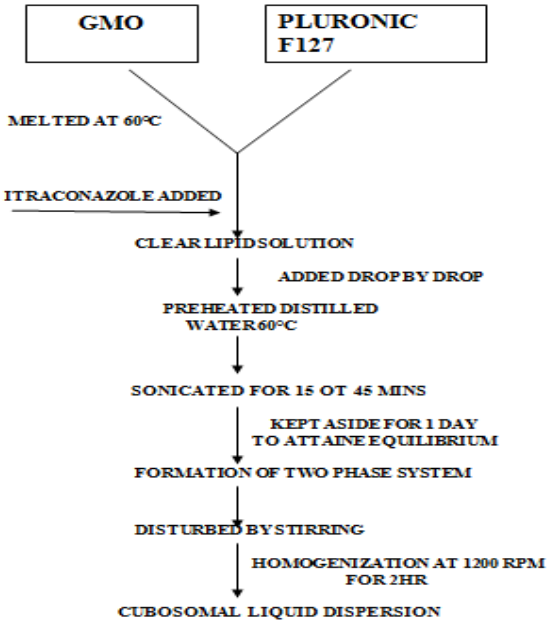

Fig. 2: Schematic representation of formulation of cubosomes

2.5. Formulation of Itraconazole Loaded Cubosomal Emulgel

Itraconazole cubosomal topical emulgels were prepared by a cold mechanical method using carbopol 974N and HPMC (15cps) as a gelling agent. The obligatory measure of the gelling agent was weighed. The weighed polymer was added to the beaker containing distilled water with slow and continuous stirring at 400-600 rpm. The entire mixture was stirred for 1hr continuously until it formed a clear gel. To the above formed clear gel, optimized cubosomal dispersion equivalent to 100 mg (10ml) Itraconazole was added and mixed properly. To bring the pH neutral Triethanolamine was added. Penetration enhancer, tween 80 was added with stirring. To the mixture glycerol was added to balance the viscosity. Methylparaben was added as a preservative. The prepared gel was held in reserve for 24h for complete polymer desolvation or swelling.

Table 1: Formulation of Itraconazole cubosomes

Formulation code	GMO (%w/v)	Pluronic F-127 (%w/w)	Drug (gm)	Water (up to 100%)
F1	1	1	1	100
F2	2.5	1	1	100
F3	5	1	1	100
F4	7.5	1	1	100
F5	10	1	1	100
F6	12.5	1	1	100
F7	15	1	1	100
F8	17.5	1	1	100

Table 2: formulation of Itraconazole loaded cubosomal emulgel

Formulation code	Cubosomal dispersion (ml)	HPMC 15 cps (%w/v)	Carbopol 974n (%w/v)	Glycerol (ml)	Tween 80 (ml)	Triethanolamine (ml)	Methylparaben (mg)	Water (up to 100%)
ITF1	10	1	-	0.25	0.5	0.12	2	100
ITF2	10	1.5	-	0.25	0.5	0.12	2	100
ITF3	10	2	-	0.25	0.5	0.12	2	100
ITF4	10	2.5	-	0.25	0.5	0.12	2	100
ITF5	10	-	1	0.25	0.5	0.12	2	100
ITF6	10	-	1.5	0.25	0.5	0.12	2	100
ITF7	10	-	2	0.25	0.5	0.12	2	100
ITF8	10	-	2.5	0.25	0.5	0.12	2	100

2.6. Characterization of Itraconazole Cubosomes

2.6.1. Visual Examination

The dispersions were visually assessed for visual appearance (*e.g.,* color, turbidity, homogeneity, presence of macroscopic particles), about one week after preparation. The visual assessment was used as a preliminary screen to rapidly exclude very poor dispersions from the auxiliary study. Well-dispersed samples of cubosomes contained no visible aggregates and possessed a milky white consistency [5].

2.6.2. Determination of Particle size/Particle size analysis

The particle size of cubosomes was resolute by dynamic light scattering technique using Zeta sizer Nano-series (Nano ZS, Malvern). Samples were diluted in particle-free purified water and measured at 25°C. Samples of aqueous dilution were sonicated for 5 min before measurement. Each value represents the average of 3measurements [6].

2.6.3. Zeta Potential

Zeta potential measurement utilizes the Electrophoretic light scattering method. Zeta potential of the prepared cubosomal dispersion was deliberated to determine the surface charge of the nano-particles which is important for predicting the long-term stability of the colloidal dispersion [6]. The high zeta potential values provide sufficient electric repulsion which in turn prevents particle aggregation. It is determined by using the Zeta sizer Nano-series (Nano ZS, Malvern).

2.6.4. Polydispersity index

PDI estimates the middling uniformity of a particle solution, and generously proportioned PDI values correspond to a larger size distribution in the particle sample. PDI was obtained by cumulative analysis of results from Zeta sizer Nano-series (Nano ZS90, Malvern) [6, 7].

2.6.5. Entrapment Efficiency (EE)

For the determination of entrapment efficiency, the cubosomes from the consequential dispersions were first separated by centrifugation. The separation of the (free) un-entrapped drug from the entrapped drug in the cubosome dispersion was achieved by centrifugation at 8000 rpm for 30 minutes. The ensuing solution was then separated and the supernatant liquid was collected. The supernatant was collected, then diluted appropriately and estimated using a UV visible spectro-photometer at 262 nm. The percent of encapsulation efficiency (%EE) was determined by the following equation:

% drug entrapment= {(Total amount of drug-untrapped drug)/ Total amount of drug} X100

2.6.6. In Vitro Drug Release Study

In vitro skin permeation studies were performed using a bi-chamber donor receiver compartment model (Franz diffusion cell). Studies were performed for all the formulations. The formulation was taken in the donor compartment and phosphate buffer pH 7.4 was taken in the receptor compartment. The cellophane membrane, formerly soaked overnight in the diffusion medium (phosphate buffer pH 7.4) was placed between the donor and receptor compartment. 10ml of Cubosomal formulation was placed on the dialysis membrane, which is in contact with the receptor medium. The entire system was placed on the thermostatically controlled magnetic stirrer with continuous stirring and the temperature of the medium was maintained at 37±0.5°C [8]. Samples were withdrawn from the receptor cell at specified time intervals. Each time instantaneously after the removal of the sample, the medium was compensated with fresh Phosphate buffer (pH 7.4). The cumulative amount of drug released from the cubosomes was calculated and plotted against time.

2.6.7. Light microscope

Light microscope (Fluorescence microscopy) was used to observe microscopically cubosome dispersion at a magnification of 45X.

2.7. Evaluation Of Cubosomal Emulgel

2.7.1. Physical appearance

The prepared cubosomal emulgel were inspected visually for their color, homogeneity and consistency.

2.7.2. pH determination

The pH of formulations was determined by using a digital pH meter by immersing the electrode in a gel formulation and pH was measured. The pH of each formulation was measured in triplicates and the average values were calculated. The pH meter was calibrated with standard buffer solutions (pH 4 & 7) [7, 8].

2.7.3. Clarity test

The formulations were visually checked for the presence of any macroscopic particles by using a black background.

2.7.4. Viscosity

The viscosity of formulations was determined by using Brookfield (DV Pro-II) viscometer with a small sample adaptor, spindle no.64.Speed was increased from 10 rpm to 100 rpm and viscosity was noted in cps [9].

2.7.5. Drug content

One gm of Itraconazole loaded cubosomal emulgel was transferred to a 50 ml volumetric flask and diluted with methanol. One ml of this solution was diluted to 25 ml

with ethanol [10]. The drug content was resolute by measuring the absorbance at 262 nm using UV- Visible spectrophotometer. The drug content of the drug loaded plain gel was also determined in the same approach.

Drug Content= (Absorbance/Slope) X dilution factor X (1/1000)

2.7.6. In vitro drug release study

In vitro drug release study was conducted in a similar manner as that of cubosome dispersion.

2.7.7. Kinetic Modeling

The optimized formulation was observed whether the pattern of drug release follows zero-order/first order/ Higuchi/Korse-Meyer Peppas model. Coefficient of correlation (r^2) values were calculated for the linear curves obtained by regression analysis of the plots [3, 11, 12].

3. RESULTS AND DISCUSSION

3.1. Calibration Curve of Itraconazole in Phosphate buffer pH 7.4

Table 3: Calibration Curve Data of Itraconazole in Phosphate buffer pH 7.4

Sample ID	Concentration (µg/ml)	Absorbance
10 ppm	10	0.181
20 ppm	20	0.314
30 ppm	30	0.493
40 ppm	40	0.665
50 ppm	50	0.799

3.2. FTIR studies

The compatibility study between drug and excipients all along with optimized formulation was performed by using IR spectrophotometer (Bruker alpha). The peaks were obtained as follows (table 4).

Table 4: FTIR peaks of Itraconazole and optimized formulation

Functional group	Observed wave number(cm^{-1})		Wave number range(cm^{-1})
	Itraconazole	Optimized cubosomal emulgel	
C=O	1699.0	-	1670-1820
C-Cl	672.5	678.2	600-800
C=C Aromatic stretching	1552.6	1557.7	1400-1600
C-H Bending	1451.1	1465.2	1350-1480
C-N Stretching	1185.1	1178.0	1080-1360
=C-H Bending	899.1	884.4	675-1000
C-F Stretching	1105.9	1110.9	1000-1400

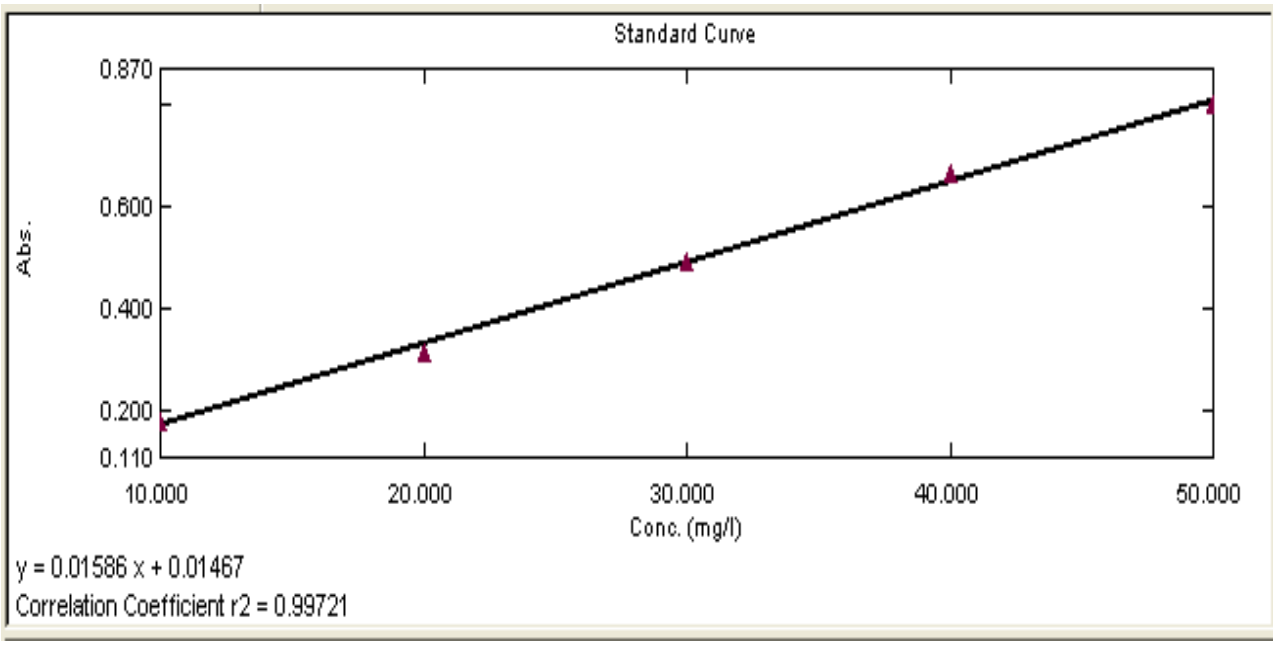

Fig. 3: Calibration Curve of Itraconazole In buffer pH 7.4

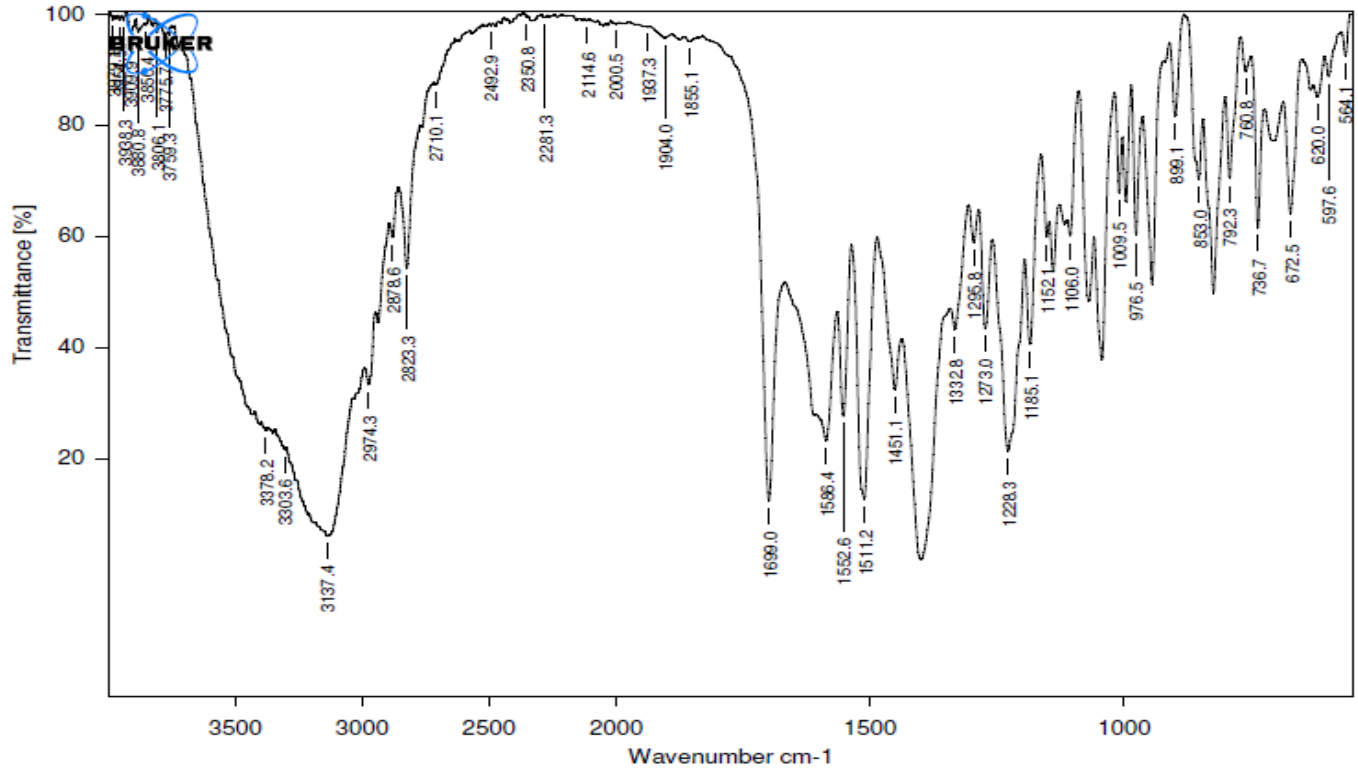

Fig. 4: FTIR Spectra of pure Itraconazole

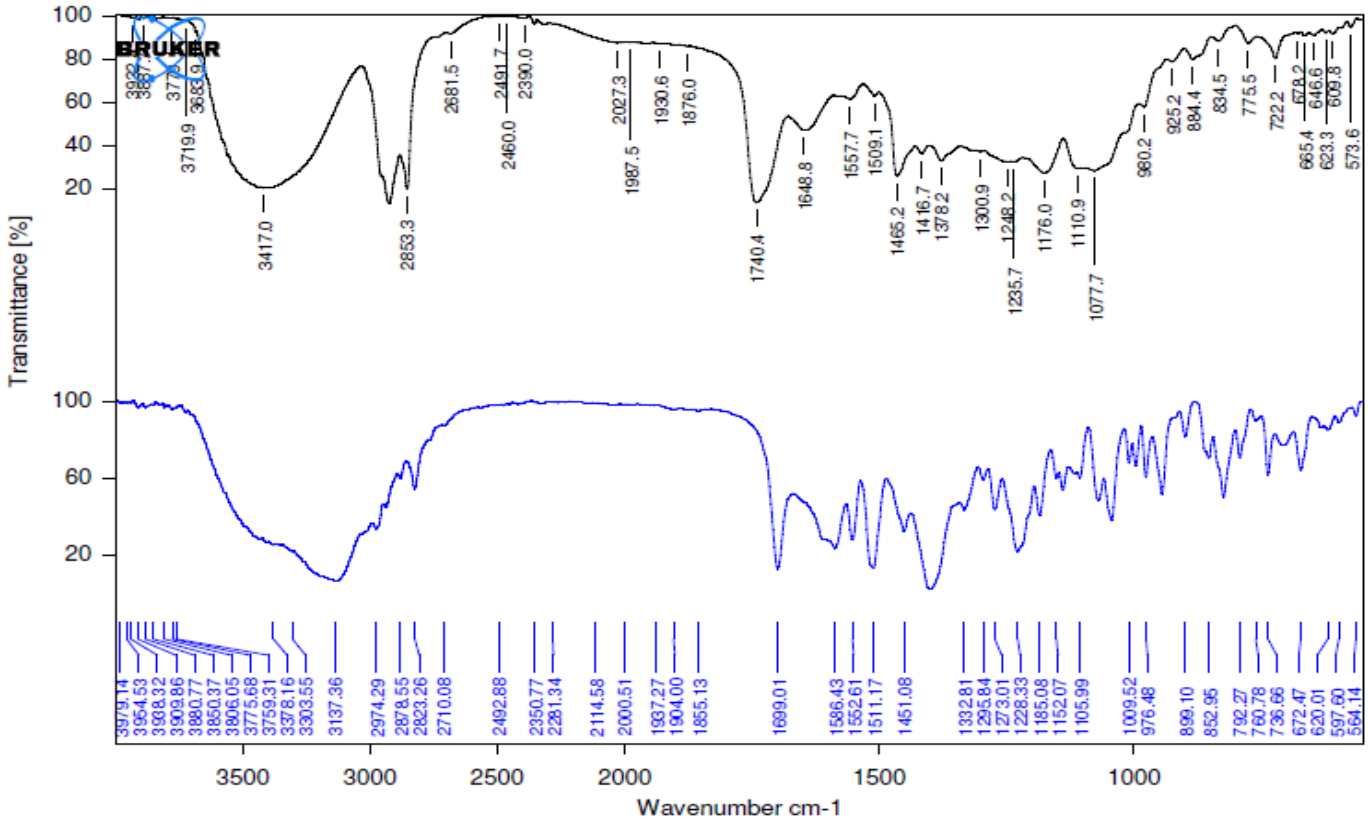

Fig. 5: FTIR Spectra of Optimized Formulation of Itraconazole Cubosomal Emulgel (ITF7)

3.3. Characterization Of Itraconazole Cubosomes

3.3.1. Visual Examination

The prepared cubosomal dispersion was visually assessed for optical appearance such as colour, turbidity presence of aggregates. The prepared Itraconazole cubosomal dispersions (F2-F7) were physically stable with homogeneous milky white appearance and no macroscopic particles, whereas, formulation F1 and F8 showed phase separation.

3.3.2. Particle size, Zeta Potential, Polydispersity index

The average particle size of the optimized formulation F4 was determined by using the Zeta sizer Nano-series (Nano ZS, Malvern) and was found to be 259.8 d.nm and PDI value was found to be 0.354 (fig. 6). The Zeta Potential was found to be -34.4 mV (fig. 7).

3.3.3. Entrapment Efficiency (EE)

Entrapment efficiency of cubosomes formulations were showed in (fig. 8). From the fig. 8, the entrapment efficiency was found to increase by increasing GMO concentration from 1 to 17.5% (w/v). So Formulation F4 was optimized based on high entrapment efficiency and optimum stability. The remaining formulations (F5-F8) were showing phase separation.

Table 5: Entrapment Efficiency (EE)

Formulation code	% Entrapment Efficiency (EE)
F1	76.80%
F2	85.60%
F3	90.89%
F4	95.40%
F5	97.62%
F6	98.71%
F7	99.81%
F8	99.70%

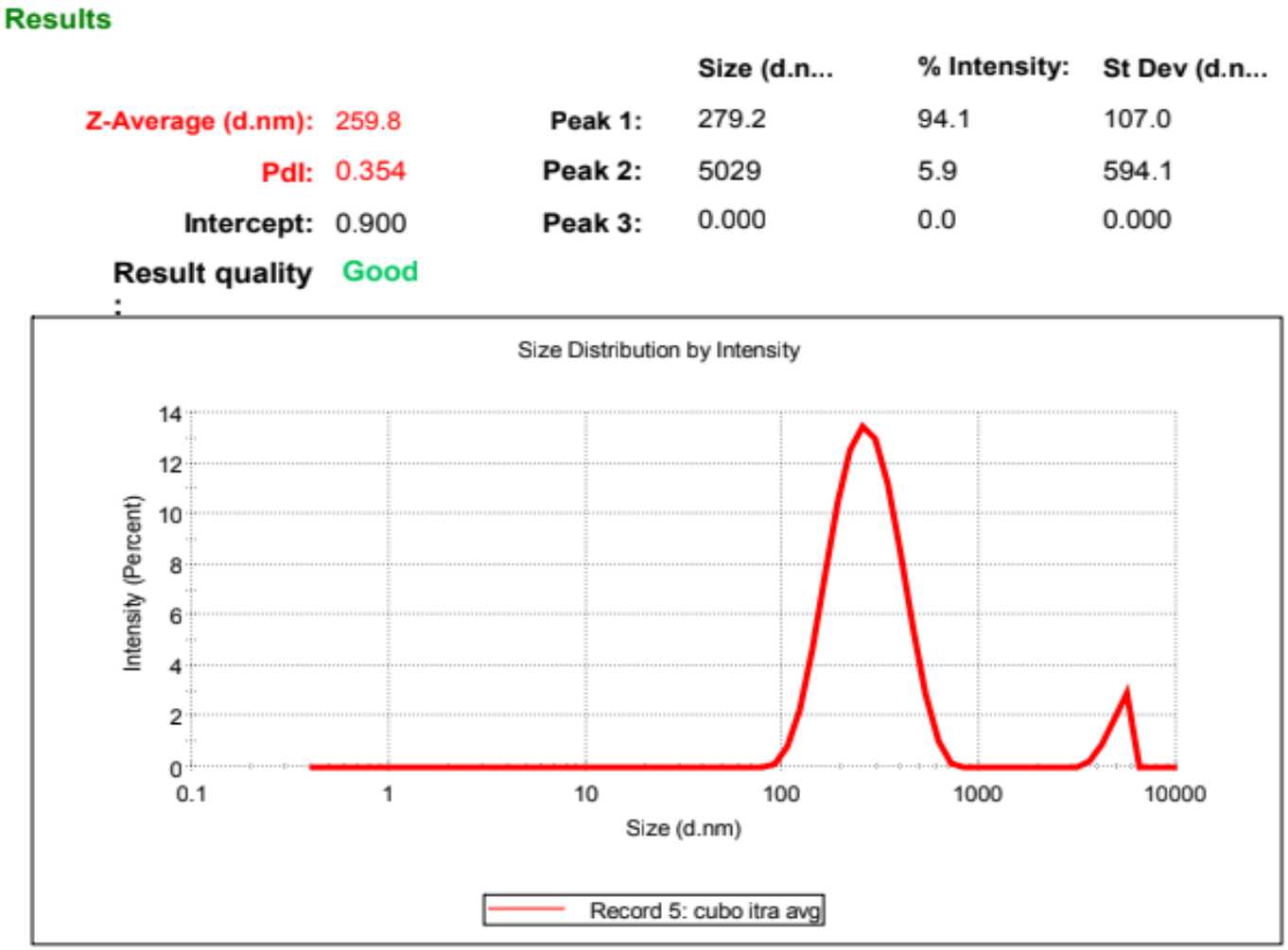

Fig. 6: Average particle size and PDI

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-34.4	Peak 1:	-41.4	58.6	4.83
Zeta Deviation (mV):	8.20	Peak 2:	-25.1	41.4	4.65
Conductivity (mS/cm):	0.0591	Peak 3:	0.268	0.0	0.00
Result quality :	Good				

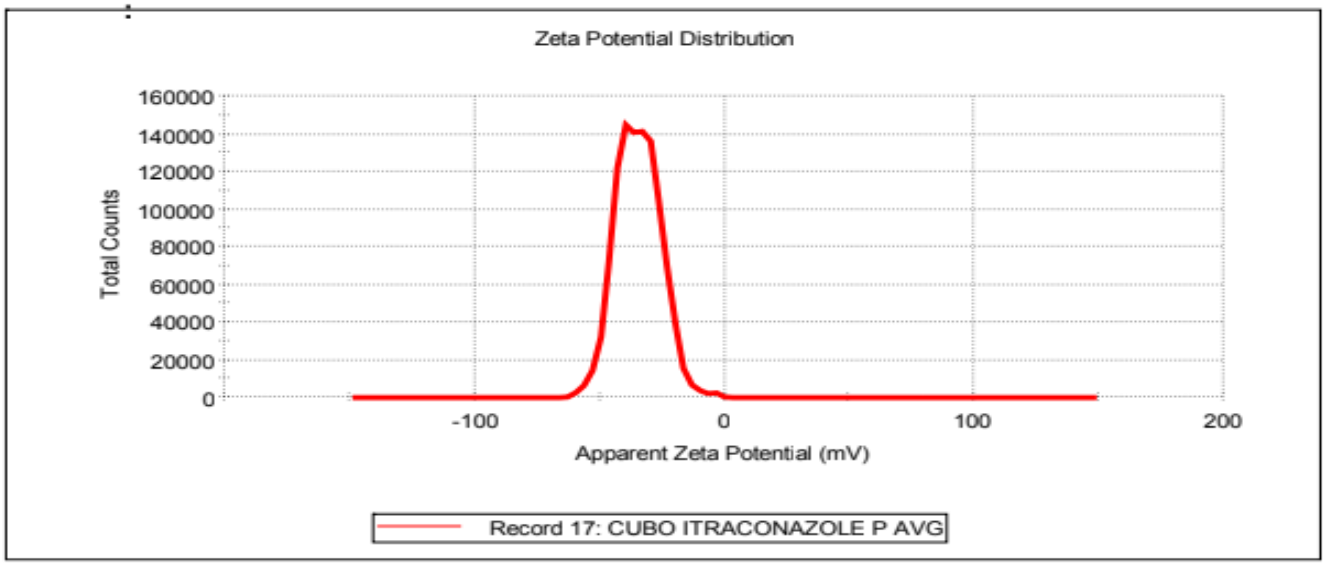

Fig. 7: Zeta Potential

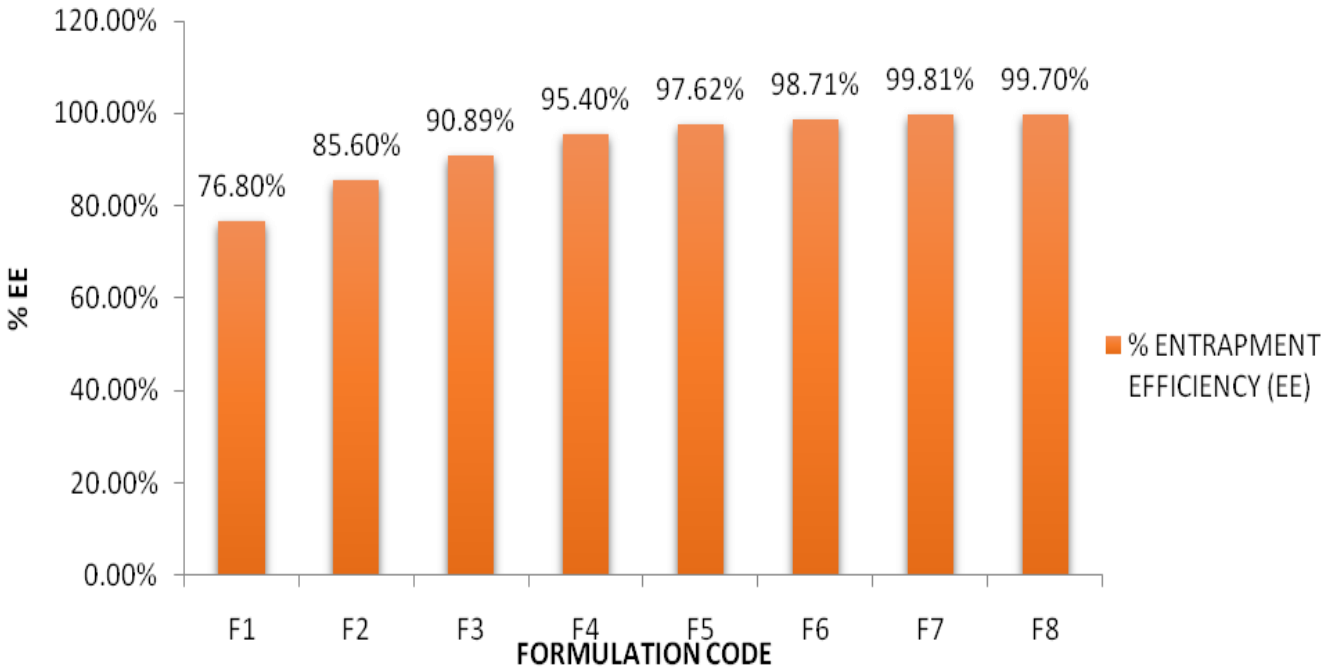

Fig. 8: Entrapment efficiency of cubosomes

3.3.4. *In Vitro Drug Release Study*

From the Fig. 9, it was showed that at the end of 8 hours the Itraconazole loaded cubosome F4 formulations showed maximum drug release was sustained over a period of 8 hours in 7.4pH phosphate buffer. The optimized cubosome formulation F4 releases 89.7% in 8 hours and it was observed that Itraconazole is highly soluble in GMO. The formulation F4 was optimized based on cubic structure, high entrapment efficiency and it was stable compared to other formulations. So Formulation F4 was optimized and it was formulated into topical emulgel.

3.3.5. *Light microscope*

Formation of cubosomes is definite by observing under Fluorescence microscopy at 45X magnification (fig.10).

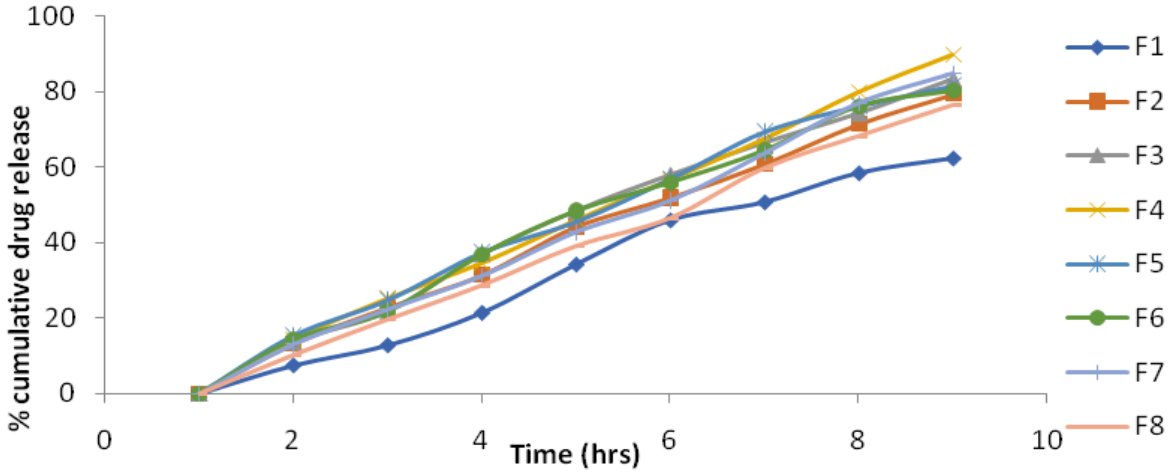

Fig. 9: *In-vitro* Drug Release Studies Of Itraconazole Cubosomes (F1-F8)

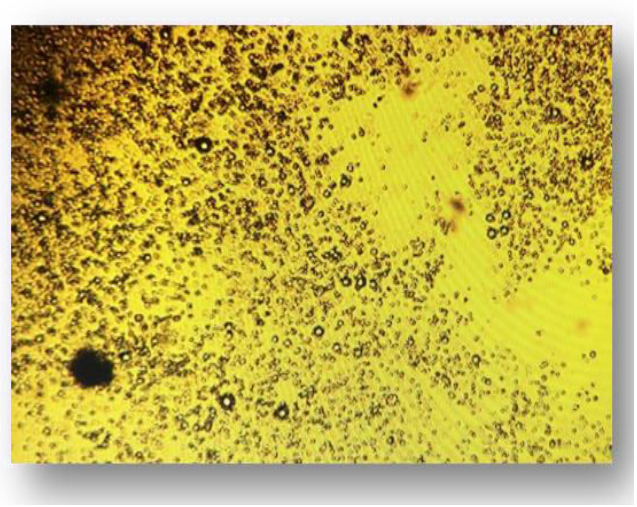

Fig. 10: Cubosome Dispersion under Fluorescence microscopy

3.4. Evaluation Of Cubosomal Emulgel

3.4.1. *Physical appearance*

The cubosomal emulgel were inspected visually and were found to be consistent, viscous with a smooth and homogenous appearance. Emulgel appeared white in color with gel consistency.

3.4.2. *pH determination*

The pH of the formulation is determined by using a digital pH meter. The pH was found to range from 5.9 to 7.4 which are close to skin pH (table 6).

Table 6: pH Determination

Formulation code	pH
ITF1	6.8
ITF2	5.9
ITF3	7.1
ITF4	6.9
ITF5	7.4
ITF6	7.1
ITF7	7.0
ITF8	6.8
Plain Emulgel	6.9

3.4.3. *Clarity test*

The formulations were visually checked for clarity. The prepared cubosomal emulgel was found be clear and thus passes the clarity test.

3.4.4. *Viscosity*

The viscosity of the cubogel and plain gel was shown in table 7; it was found that diminish in the viscosity as the rpm was amplified.

3.4.5. Drug content

The percentage drug content of drug loaded plain carbopol 974N emulgel, as well as cubosome enriched emulgel was found to be 95.12% and 90.44% as shown in table 8.

Table 7: Viscosity of Optimized Cubosomal Emulgel ITF7

rpm	Viscosity of cubo emulgel (cps)	Viscosity of drug loaded plain emulgel (cps)
10	8412	7013
20	7620	6204
50	5959	4503
100	4230	3520

Table 8: Percentage Drug Content

Formulation code	Drug content %
ITF7	95.12%
Drug loaded plain emulgel	90.44%

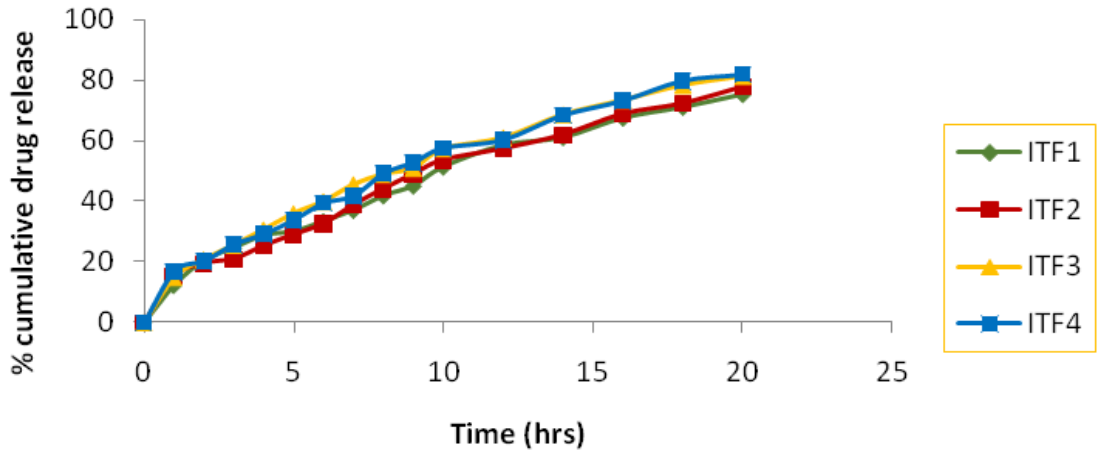

Fig. 11: Drug release profile of Itraconazole cubosomal emulgel using HPMC 15cps (ITF1 to ITF4)

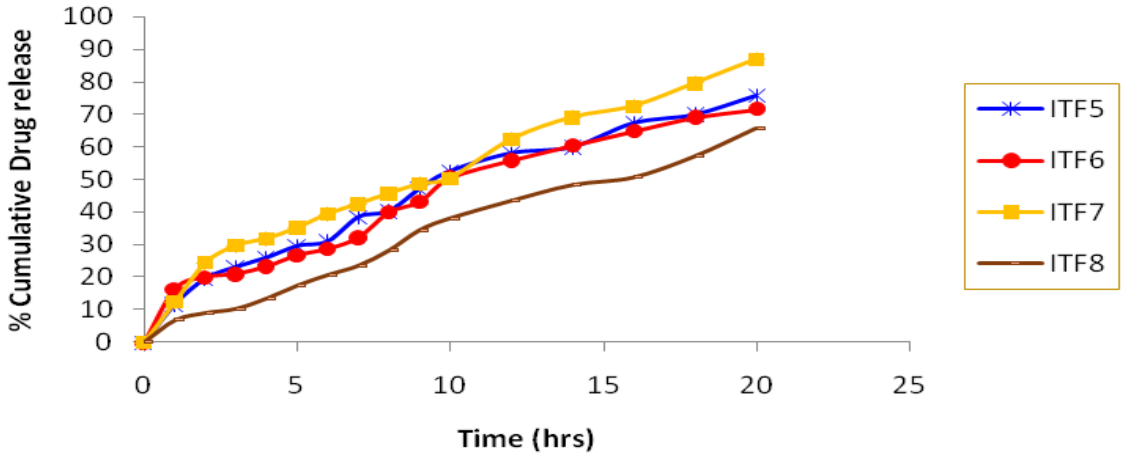

Fig. 12: Drug release profile of Itraconazole cubosomal emulgel using Carbopol 974N (ITF5 to ITF8)

3.4.6. In-vitro drug release study

The optimized formulation F4 was developed into emulgel using polymer Carbopol 974N and HPMC 15cps in the concentration 1, 1.5, 2, and 2.5%.The formu-lation ITF7 containing 2% carbopol 974N shows the majority drug release of 86.93% at the end of 20 hours. Thus ITF7 was considered as optimized emulgel and further kinetics studies have been conducted.

Time (hrs)	% Cumulative drug release ± SD (Mean ± SD, n=3)							
	ITF1	ITF2	ITF3	ITF4	ITF5	ITF6	ITF7	ITF8
0	0	0	0	0	0	0	0	0
1	12.26±0.3	15.26±1.2	14.98±0.1	16.73±0.6	11.72±1.2	16.38±0.1	12.35±0.3	6.7±0.4
2	20.47±1.2	19.52±0.5	20.79±0.8	20.14±1.1	19.60±0.5	20.02±0.7	24.4±0.4	8.91±0.1
3	24.62±06	20.99±0.4	25.63±0.6	25.62±1.5	23.16±0.2	20.98±0.2	29.7±0.7	10.22±1.1
4	28.74±1.7	25.39±0.1	30.71±0.2	29.04±1.7	26.03±0.7	23.3±0.2	31.82±1.1	13.4±1.5
5	30.01±0.2	29.04±1.1	36.05±0.3	33.71±0.6	29.58±0.9	26.74±0.4	35.2±1.5	17.38±1.9
6	33.41±0.8	32.67±1.5	40.02±1.1	39.25±0.1	31.02±0.1	28.7±0.9	39.41±1.9	20.65±0.8
7	37.05±0.4	38.91±1.6	45.62±1.8	41.62±0.7	38.5±0.3	32.21±0.3	42.5±0.2	23.5±0.2
8	41.82±1.1	44.23±0.7	49.01±1.7	49.06±0.4	40.30±0.5	39.92±1.1	45.71±0.7	28.2±0.4
9	45.06±1.7	49.07±0.8	50.98±1.1	52.70±0.3	47.23±0.4	43.15±02	48.62±1.1	34.45±0.9
10	51.31±0.5	53.72±0.2	57.42±0.1	57.45±0.3	52.63±1.1	50.45±1.5	50.41±1.5	38.1±0.7
12	58.47±0.9	57.45±0.7	61.07±0.3	60.14±0.5	58.17±1.4	55.82±1.7	62.33±1.8	43.5±0.1
14	61.06±0.1	62.03±0.4	68.68±0.7	68.24±0.7	60.02±1.8	60.41±1.6	69.1±1.9	48.36±1.2
16	67.48±1.4	68.91±0.4	73.46±0.4	73.05±1.1	67.4±0.7	64.82±1.1	72.56±0.8	50.7±1.6
18	71.03±0.5	72.38±1.1	78.43±0.4	79.62±1.6	70.01±0.9	69.03±0.2	79.6±0.3	57.21±0.4
20	75.24±1.8	77.81±0.3	81.35±0.6	81.72±1.2	75.81±0.4	71.46±0.8	86.93±0.7	65.8±0.7

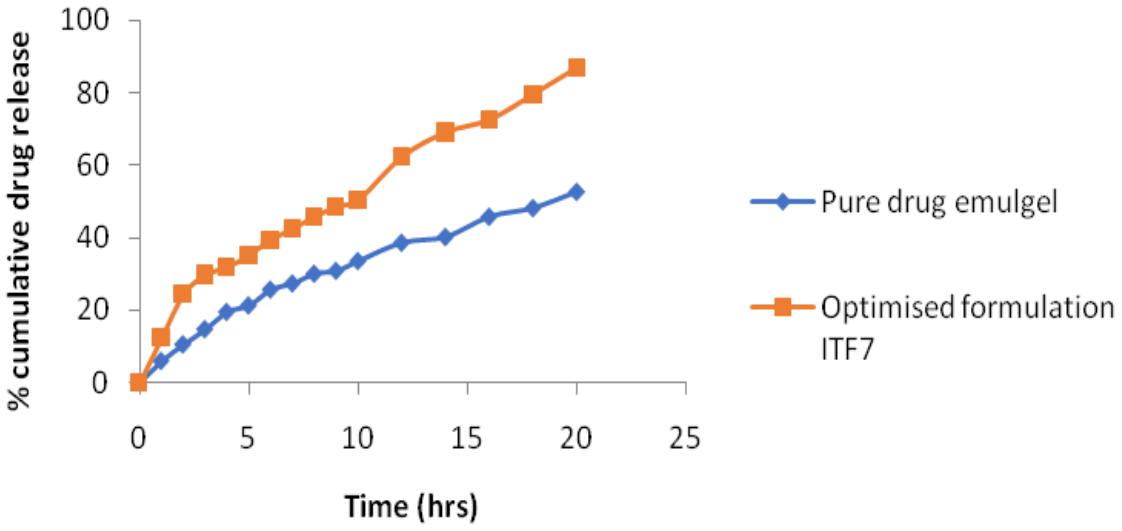

Fig. 13: percentage drug release of pure drug emulgel and optimized formulation ITF7

3.4.7. Drug Release Kinetic Data of ITF7

The optimized formulation ITF7 was equipped in distinct kinetic models, *i.e.* zero order, first order, Higuchi, and Korsmeyer-Peppas equation for best interpretation.

The optimized formulation ITF7 shows R^2 value 0.980 as the value is near to '1' it was confirmed that the formulation follows the Higuchi release mechanism and according to this model, the Itraconazole cubosomal formulation released the drug throughout non-Fickian super case-II transport (n > 0.89) (fig. 14).

Table 9: Drug Release Kinetic Data of ITF7

Drug Release Kinetics (R^2 value)				
Formulation code	**Zero order**	**First order**	**Higuchi**	**Korsmeyer-peppas**
ITF7	0.968	0.961	0.980	0.714

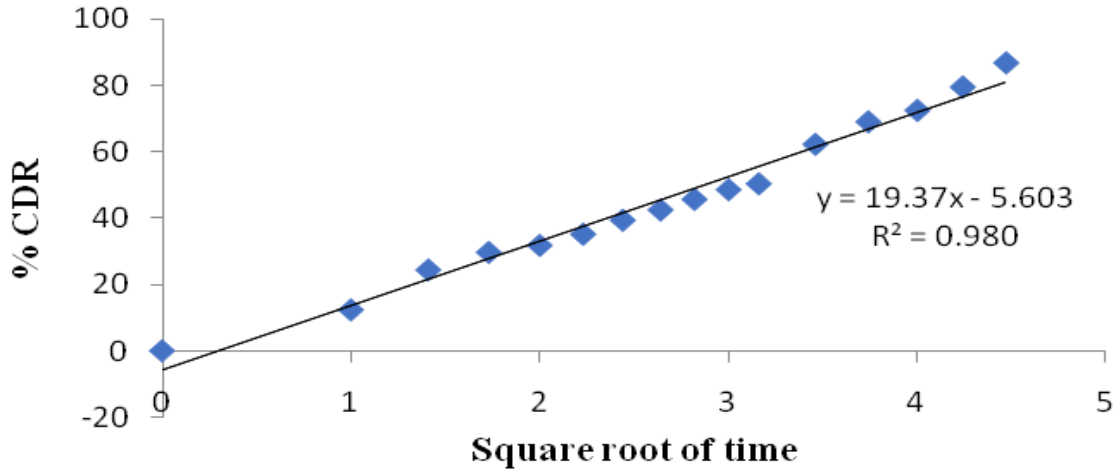

Fig. 14: Higuchi Release Graph

4. SUMMARY AND CONCLUSION

Cubosomes can be created by a simple combination of biologically compatible lipids (GMO) and water and are thus well appropriate for pharmaceutical and body tissue. The ability to form cubosomes during manufacture offers superior flexibility for product improvement. The cubosomal topical gels deserve consideration due to its unique liquid crystalline structure and ease of preparation. Cubosomes are unique dosage forms formed by GMO when added to water. Since it is a lipid that tends to detach in the aqueous phase Pluronic F127 is used as a stabilizer to avoid aggregation. Itraconazole drug has low solubility and formulated into cubosomes to sustain the drug release it was formulated to topical gels. Cubosome formulation prepared by GMO (7.5%), pluronic F127 (1%) was considered as an optimized formulation that shows adequate entrapment efficiency (95.40%), and drug release (89.76%). As GMO concentration increases entrapment efficiency and drug release are increased but the prepared formulations are not steady, the phase separation has occurred. To sustained the drug release the optimized cubosome formulation F4 was formulated into emulgel using carbopol 974N & HPMC 15cps. Dealing with other aspects, Preparations containing Carbopol 974N show higher drug release (86.93%) at closing stages of 20 hours in pH 7.4 buffer and stable than other formulations. The formulation ITF7 follows the Higuchi release mechanism and according to this model, the Itraconazole cubosomal formulation released the drug throughout non-Fickian super case-II transport ($n > 0.89$). The nature of cubosome dispersion was observed microscopically.

The above research specifies cubosomal effectiveness as a controlled release drug carrier. The Prolonged-release is achieved when they are formulated as topical gels maintaining the cubosome structure. Although they possess advantageous characteristics, there is still an extensive way to go before their clinical relevance.

5. ACKNOWLEDGEMENTS

The authors acknowledge Centre for pharmaceutical science, JNTUH for their support in completion of present study.

Conflict of Interest

None declared.

6. REFERENCES

1. Maheshwari R, Chaturvedi S, Jain N. *Indian journal of pharmaceutical sciences*, 2007; **69(1):**101.
2. Bansal S, Kashyap CP, Aggarwal G, Harikumar SL. *Int J Res Pharm Chem*, 2012; **2**:704-713.

3. Dhadwal avantika. *Journal of drug delivery and therapeutics*, 2020; **10(1):**1123-1130.
4. Samia M, et al. *Journal of Advanced Pharmacy Research*, 2019; **3(2):**68-82.
5. Karthika V T, Sheri PF, et al. *International Journal of Research and Review*, 2018; **5(8)**:149-159.
6. Dr Sunitha reddy M, Bhagyalakshmi N, et al. *World journal of pharmacy and pharmaceutical sciences,* 2018; **7(12):**862-880.
7. S. Indira, Venkatesh B, et al. *Journal of Global Trends in Pharmaceutical Sciences*, 2014; **5(4)**:2037-2047.
8. Jyoti K, Bhushan A, et al. *World Journal of Pharma ceutical Research*, 2017; **6(10)**:567-588.
9. Daware S U, Saudagar R B. *European Journal of Biomedical and Pharmaceutical Sciences*, 2017; **4(11)**:321-331.
10. Barhate D, Bavaskar K. R, Saoji Y. S, Potdar M, Gholap T. N. *Int J of Pharma Research and Development,* 2009; **1(10)**:1-7.
11. Ghada A, Nadia M, et al. *European Journal of Pharmaceutics and Biopharmaceutics*, 2014; **86:**178-189.
12. Gaurav G, Shruti S, et al. *Bentham science publications*, 2018; **12(2)**:121-129.