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FORMULATION AND EVALUATION OF MICONAZOLE NITRATE AS A CUBOSOMAL TOPICAL GEL

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ABSTRACT

The aim of the present work was to formulate and evaluate sustained release formulation of Miconazole nitrate as cubosomal topical gel to improve the efficacy & bioavailability of Miconazole nitrate. Cubosomes were prepared by Top down approach employing GMO as lipid phase vehicle, Poloxamer 407 as stabilizer and distilled water as aqueous phase. Miconazole nitrate is an antifungal drug with 20% oral bioavailability. Resultant formulations were characterized by visual inspection, encapsulation efficiency, *in-vitro* drug release, particle size, zeta potential & SEM. Optimized formulation (M5) showed drug release of 71% in 6 hours, particle size of 88.7nm and zeta potential of +43.6 mV. The optimised cubosome formulation M5 was used for the Miconazole nitrate gel using carbopol 934, carbopol 940, HPMC K4M, HPMCK15M and studied for pH, viscosity, in vitro drug release. Among all the preparations formulation G2 was found to show the maximum drug release of 64.25% at end of 6 hour and other evaluation parameters within specified limits. *In vitro* release kinetics exhibited sustained release and followed non-fickian diffusion. This novel cubosomal, low-irritant gel would be a promising system for effective topical drug delivery.

Key words: Cubosomes, Miconazole nitrate, Lyotropic liquid crystal, Glyceryl monooleate, Top-down approach, Topical drug delivery.

INTRODUCTION

Miconazole nitrate is an antifungal drug that inhibits the enzyme cytochrome P450 CYP51 14α-demethylase. It is used in the treatment of Superficial Candidiasis, Dermatophysis and Pityriasis versicolor. The limited solubility of miconazole nitrate and the drug intensive hepatic transformation that results in poor oral drug bioavailability (25-30%) of the drug and hinders its use for systemic treatment via gastro intestinal tract. "Cubosomes" are discrete, sub micron nano structured particles of bicontinuous cubic liquid crystalline phases whose size ranges from 10-500 nm in diameter, they appear like dots square shaped, slightly spherical, each dot corresponds to the presence of pore size 5-10 nm, where "bicontinuous" refers to two distinct (continuous, but non-intersecting) hydrophilic regions separated by the bilayer. Cubosomes have great potential in formulating nano sized particulate systems for topical delivery owing to their best advantages such as high drug payload due to high internal surface area and cubic liquid structure, encapsulating ability of hydrophobic, hydrophilic and amphiphilic molecules. The purpose of the present study was to develop a Miconazole nitrate Cubosomal topical gel to increase the drug bioavailability by avoiding first pass metabolism and also to sustain the drug release. When compared to other vesicular structures like transferosomes, ethosomes are less suitable for percutaneous delivery because of their poor skin permeability, leakage of drug and aggregation. These problems can be overcome by using a new type of carrier system called "cubosomes".

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MATERIALS AND METHODS

Materials

Glyceryl monooleate (GMO) was gifted by Mohini Organics Pvt. Limited, Mumbai, India. Poloxamer 407 was a kind gift from Daewoong Pharmaceuticals, Hyderabad. Miconazole nitrate was a gift sample from NMR Drugs Pvt. Limited, Hyderabad, A.P, India. Carbopol 934, Carbopol 940, were gift samples from Loba Chemie, Mumbai, India. HPMC K4M and HPMC K15M were of commercial grade. All other reagents used were of analytical grade.

PREPARATION OF MICONAZOLE NITRATE LOADED CUBOSOMES

Preparation of Miconazole nitrate Cubosomes:

The method used for the preparation of cubosomes was top-down method. Varying concentrations of Glyceryl monooleate (5 to 50%) was heated along with Poloxamer407 (1 % weight corresponding to GMO conc.) on an electric water bath at a temperature of 40 to 45^{o}C until Pluronic F127 completely dissolves in GMO. To the above solution Miconazole nitrate (100mg) was added and mixed well. The clear lipid solution obtained was added drop by drop to distilled water and subjected to bath sonication for period of 15 to 45 minutes with intermittent shaking and stirring. The end result will be a white opaque dispersion without presence of any aggregates. Various formulations were prepared in such a manner such that each ml contains 20 mg of drug. The prepared dispersions were stored in closed glass vials at room temperature for 72 hours in a dark place and later evaluation was carried out.

Preparation of Miconazole nitrate Cubosomal Topical Gel

The topical gels are prepared in a similar manner to cubosome dispersions using the optimized concentration of GMO (along with Pluronic F127) from the above study as lipid phase & aqueous solution of gelling agent (Carbopol 940, 934, HPMCK4M&K15M B.P) as aqueous phase.

METHODS FOR OPTIMIZATION OF FORMULATION VARIABLES OF CUBOSOMES

1. Optimization of formulation variables

The effect of Poloxamer 407 concentration, GMO concentration and sonication time on formation of cubosomes were characterized by using optical electron microscopy.

CHARACTERIZATION OF CUBOSOMES

1. Vesicle shape and size analysis of cubosomes: Size and shape of the cubosomes were determined using optical microscopy and SEM (Hitachi S 3700N).

2. Particle size measurement: The average diameter of sonicated cubosomes was determined by laser diffraction technique using Horiba particle size analyzer.

3. Zeta potential

Zeta potential was determined using Zetasizer (Malvern Instruments). Measurements were performed on the same samples prepared for size analysis. Zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system.

4. Entrapment Efficiency (EE):

Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the cubosomes. For the determination of entrapment efficiency, the un-entrapped drug was first separated by centrifugation at 15000 rpm for 30 minutes. The resulting solution was then separated and supernatant liquid was collected. The collected supernatant was then diluted appropriately and estimated using UV visible spectrophotometer at 272 nm. The percent of encapsulation efficiency (EE %) was determined by the following equation:

$$EE\% = \frac{[\text{Total drug}] - [\text{free drug}]}{\text{Total drug}} \times 100$$

5. *In vitro* drug release

Studies were performed for all the formulations. In vitro release studies were carried out using bichambered donor receiver compartment model (Franz diffusion cell) and this was placed on magnetic stirrer and temperature was adjusted to 37 ± 0.5^0 C. One end of the chamber was covered with Himedia dialysis membrane (cut-off molecular weight: 12000-14000), which was previously soaked in phosphate buffer pH 6.8. Phosphate buffer pH 6.8 was placed in the receptor cell. Accurately measured 2.5 ml of the formulation poured on a dialysis membrane, which was in contact with receptor medium Samples were withdrawn at specified time intervals and the medium was compensated with phosphate buffer pH 6.8. The samples were analyzed for drug using a UV-Vis spectrophotometer at 272nm.

EVALUATION OF TOPICAL GELS

A. FTIR: Spectra of drug along with gelling agents, optimized gel formulation is taken and analyzed for presence of any incompatibility.

B. pH: pH of formulations is determined by a digital pH meter by immersing the electrode in gel formulation and checking the pH.

C. Viscosity: A Brookefield DV Pro-II viscometer with small sample adaptor and spindle no.63 is used to determine viscosity for above formulations optimized by diffusion studies. Speed is increased from 10 rpm to 50 rpm and viscosity is noted in cps.

D. Drug content

1 g of the prepared gel is mixed with 100ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance is measured.

E. Diffusion Studies: Conducted in a manner similar to method used for cubosome dispersions.

F. Anti microbial activity: Antimicrobial efficiency studies were carried out to ascertain the biological activity of gel systems against microorganisms. This was determined in the agar diffusion medium employing Cup plate technique. Sterile solution of marketed cream (Micogel) was used as standard. The standard solution and the developed formulation (test solution) was taken into cups bored into sterile nutrient agar previously seeded with Candida albicans after allowing diffusion of solution for two hours. The plate was incubated for 24 hours at 37^0C. The zone of inhibition was compared with that of the standard. The optimized formulation was tested in triplicate.

G. Data fitting/Kinetic Modelling: The optimized formulation is 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.

H. Accelerated Stability Studies: Conducted as per ICH guidelines at 40oC±2oC/75%±5% RH for optimized gel formulation at sampling intervals of 0, 30,60 and 90 days respectively. The drug content, viscosity and pH are determined periodically.

RESULTS AND DISCUSSION

The main objective of the study is to develop Miconazole nitrate cubosomal gels using various concentrations of GMO, distilled water and gelling agents (Sodium alginate, Guar gum, Xantham gum and Carbopol 934 B.P) employing Pluronic F127 as stabilizer using Top Down Approach. Advantage of the method is simple technique and easy availability of raw materials.

A. FTIR Studies: The interaction study between the drug and excipients as well as optimized formulation was evaluated using IR spectrophotometer. Miconazole nitrate has characteristic absorption peaks C-cl at 684 cm^{-1},C=C at 1529 cm^{-1},C-O at 1207cm^{-1} and C-N at 1206 cm^{-1} . Similar peaks were observed in spectra of different combinations of excipients and in optimized formulation (Cubosomes and topical gels), along with absence of interfering peaks indicating there is no unwanted reaction between Miconazole nitrate and other excipients used in the study.

From the above Figures1,2 and Tables4,5 it can be inferred that there was no appearance or disappearance of any characteristic peaks. This shows that there was no interaction between the drug and excipients used in cubosomal topical gel preparation.

B. Optimization of formulation variables

a. Effect of poloxomer407 concentration on formation of cubosomes

The effect of varying the Poloxomer407 concentration was studied. It was found that 1% poloxomer407 concentration was the optimum concentration for cubosome formation and it showed the highest drug entrapment about 91.3%, highest drug release about 71.12%.

From the Figure 3, as poloxomer407 concentration increases there will be change in structure of cubosomes from cubic shape to rod like shape and also there will be decreases in entrapment efficiency and drug release of cubosomes formulation.

b. Effect of Glycerol Mono Oleate concentration on formation of cubosomes

The effect of GMO concentration were studied as shown in figure 4.

From the Figure 4, it was observed that Cubosomes were obtained by using GMO in the range of 5% to 50%. Below 5% and above 50% GMO spherical structures were obtained instead of cubic structures.

c. Effect of sonication time on the formation of cubosomes

The cubic structures were formed at 25-30 minutes. Below this sonication time large size cubic structures were formed and above this sonication time size of cubic structure were very small.

CHARACTERIZATION OF CUBOSOMES

1. Particle size of cubosomes

Particle size of cubosome dispersion was analysed by Horiba particle analyser.

From the Figure 6 it was found that the diameter (nm) of cubosomes was found to be in the range of 10 to 500 nm and the average particle size was found to be 88.7 nm.

2. Zeta potential of cubosomes

The zeta potential of the cubosomes was determined using Zetasizer and the value of the cubosomes was found to be +46.6 mV which indicates that cubosomes were stable.

3. Entrapment Efficiency

Entrapment efficiency of cubosomes formulations were showed in Figure 8.

From the above Figure 8 the entrapment efficiency was found to increase by increasing GMO concentration from 5 to 50 % (w/w). So Formulation M5 was optimized based on high entrapment efficiency and optimum stability. The remaining formulations (M6-M14) were showing phase separation.

4. Diffusion studies

Diffusion studies were performed for all formulations and formulation M5 was optimized. The drug release profiles of various formulations are given in Figure no 9 and 10.

From the above Figure 9 and 10 drug release was found to increase by increasing GMO concentration from 5 to 50 % (w/w), as the lipid concentration was increased, drug release was increased but phase separation was observed as seen in the remaining formulations. So Formulation M5 was optimized and it was formulated into topical gels.

From the above Figure 11 it was showed that at the end of 6 hours the optimized Miconazole Nitrate loaded cubosome formulation M5 was sustained over a period of 6 hours in 6.8pH phosphate buffer compared with crude Miconazole Nitrate powder. It was found that crude Miconazole Nitrate powder releases 13.21% only in 6 hours because of Miconazole Nitrate is insoluble in 6.8 pH phosphate buffer. The optimized cubosome formulation releases 71.38% in 6 hours and it was observed that Miconazole Nitrate highly soluble in GMO. The formulation M5 was optimized based on cubic structure, high entrapment efficiency and it was stable compared to other formulations. So Formulation M5 was optimized and it was formulated into topical gel.

EVALUATION OF CUBOSOMAL TOPICAL GELS

Physical parameters

A. Homogenicity: It was evaluated by visual observations. All formulations were found to be homogenous and clear.

A. pH: The pH was found to range from 5.84 to 7.35 which are close to skin pH.

C. Viscosity: The viscosities of formulations G2 was shown in Table 6.

D. Drug content: Drug content was found to be in the range of 91% to 98%.

E. Diffusion studies: Diffusion results of prepared gels are showed below.

The results of in vitro drug release studies of Miconazole nitrate cubosomal topical gels were formulated using increasing Carbopol940 concentration from 0.05% to 0.3%. Sustained drug release at end of 6 hour was obtained with G2.

The results of in vitro drug release studies of Miconazole nitrate cubosomal topical gels were formulated using increasing Carbopol934 concentration from 0.05% to 0.3%. Sustained drug release at end of 6 hour was obtained with G6.

The results of in vitro drug release studies of Miconazole nitrate cubosomal topical gels were formulated using increasing HPMCK4M concentration from 0.1% to 0.35%. Highest drug release at end of 6 hour was obtained with G11 (0.1% HPMCK4M).

The results of in vitro drug release studies of Miconazole nitrate cubosomal topical gels were formulated using increasing HPMCK15M concentration from 0.1% to 0.35%. Highest drug release at end of 6 hour was obtained with G16 (0.1% HPMCK15M).

F. Anti microbial study: Microbial studies were performed and the optimized formulations showed antifungal activity when tested by the cup-plate technique using Micogel as standard solution. Antimicrobial activities are shown in Figure 16. From Figure 16 and Table 7, Formulation G2 shows19mm inhibition which is high when comapared to the zone of inhibition of marketed Micogel 18mm.

G. Kinetic modelling:

The optimized cubosomal gel G2 was studied for release kinetics and it was shown in below Table 8. It follows Non-fickian kinetics.

H. Stability studies: pH, Drug content and drug release values are analyzed periodically as per ICH guidelines through accelerated stability studies for optimized gel formulation G2 was shown in Table 8.

The formulation G2 was optimized based on cubic structure, high drug release and it was stable compared to other formulations. So Formulation G2 was optimized.

Table 1: Formulation of cubosomes for optimization of poloxamer 407 concentration

Formulation code	Monooleine (%W/V)	Poloxomer 407 (%W/W)	Miconazole nitrate (mg)	Water (up to 100%)
P1	15	1	100	100
P2	15	2	100	100
P3	15	3	100	100
P4	15	4	100	100
P5	15	5	100	100

Table 2: Formulation of cubosomes using GMO

Formulation code	Monooleine (%W/V)	Poloxomer 407 (%W/W)	Miconazole nitrate (mg)	Water (%w/v up to100%)
M1	1	1	100	100
M2	2.5	1	100	100
M3	5	1	100	100
F4	10	1	100	100
M5	15	1	100	100
M6	20	1	100	100
M7	25	1	100	100
M8	30	1	100	100
M9	35	1	100	100
M10	40	1	100	100
M11	45	1	100	100
M12	50	1	100	100
M13	55	1	100	100
M14	60	1	100	100

Table 3: Formulation of Miconazole nitrate cubosomal topical gels

Formulation code	Cubosome Dispersion (ml)	Carbopo l934 (gm)	Carbopo l934 (gm)	HPMCK4M	HPMCK15M	Glycerol (ml)	Methyl Paraben (mg)	Triethonolamine (ml)	Tween 80 (ml)	Water (ml upto 100%)
G1	5	0.05	-	-	-	0.25	2	0.125	0.5	5
G2	5	0.1	-	-	-	0.25	2	0.125	0.5	5
G3	5	0.15	-	-	-	0.25	2	0.125	0.5	5
G4	5	0.2	-	-	-	0.25	2	0.125	0.5	5
G5	5	0.3	-	-	-	0.25	2	0.125	0.5	5
G6	5	-	0.05	-	-	0.25	2	0.125	0.5	5
G7	5	-	0.1	-	-	0.25	2	0.125	0.5	5
G8	5	-	0.15	-	-	0.25	2	0.125	0.5	5
G9	5	-	0.2	-	-	0.25	2	0.125	0.5	5
G10	5	-	0.3	-	-	0.25	2	0.125	0.5	5
G11	5	-	-	0.1	-	0.25	2	0.125	0.5	5
G12	5	-	-	0.2	-	0.25	2	0.125	0.5	5
G13	5	-	-	0.25	-	0.25	2	0.125	0.5	5
G14	5	-	-	0.3	-	0.25	2	0.125	0.5	5
G15	5	-	-	0.35	-	0.25	2	0.125	0.5	5
G16	5	-	-	-	0.1	0.25	2	0.125	0.5	5
G17	5	-	-	-	0.2	0.25	2	0.125	0.5	5
G18	5	-	-	-	0.25	0.25	2	0.125	0.5	5
G19	5	-	-	-	0.3	0.25	2	0.125	0.5	5
G20	5	-	-	-	0.35	0.25	2	0.125	0.5	5

Table 4: FTIR of Miconazole nitrate pure drug

Functional Group	Reported Value (cm^{-1})	Observed value (cm^{-1})
C-cl	785-540	684.75
C=C	1600-1475	1529.6
C-0	1300-1000	1207.48
C-N	1350-1000	1206

Table 5: FTIR of Miconazole nitrate cubosomal gel:

Functional Group	Reported Value (cm^{-1})	Observed value (cm^{-1})
C-cl	785-540	648.1
C=C	1600-1475	1537.22
C-0	1300-1000	1251.84
C-N	1350-1000	1209

Table 6: Viscosities in cps of MN cubosomal topical gel G2 formulation at different rpm

Rpm	Viscosity(cps)
10	8614
20	7301
50	4198
100	3136

Table 7: Antimicrobial activity of Miconazole nitrate cubosomal topical gel G2 comparing with Marketed Micogel cream

Organism	Formulation	Zone of inhibition
Candida albicans	G2	19mm
Candida albicans	Micogel	18mm

Table 8: Stability studies of optimized gel G2 formulation

Time in days	pH	Drug content	% Drug release
0	6.9	96.32	64.25
30	6.5	95.14	63.48
60	6.4	64.21	62.56
90	6.2	91.87	61.27

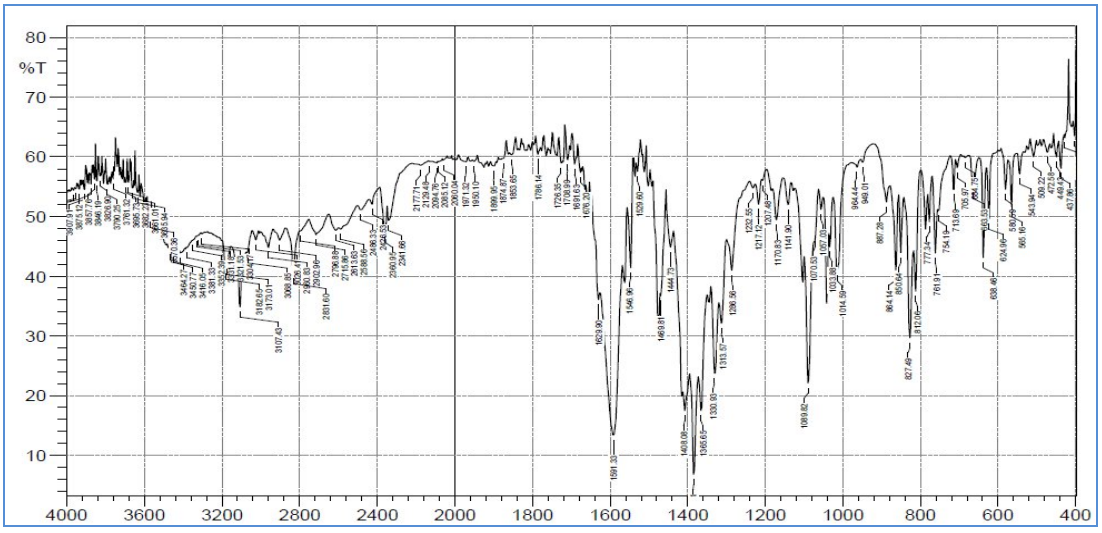


Figure 1: FTIR of Miconazole nitrate pure drug

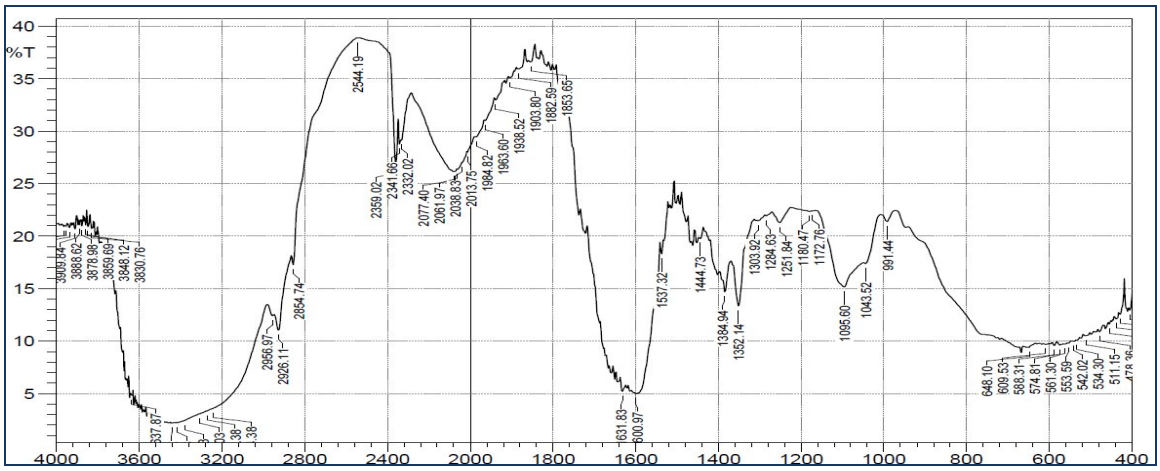


Figure 2: FTIR of Miconazole nitrate cubosomal gel:

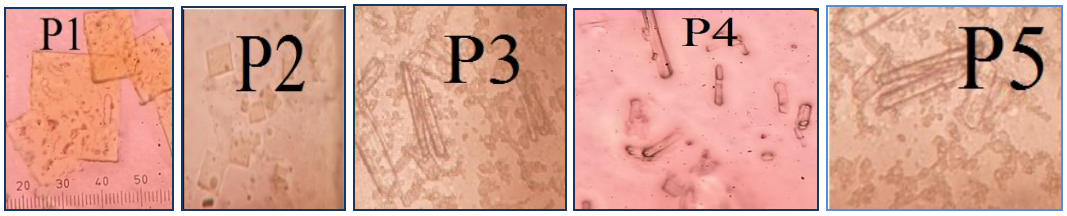
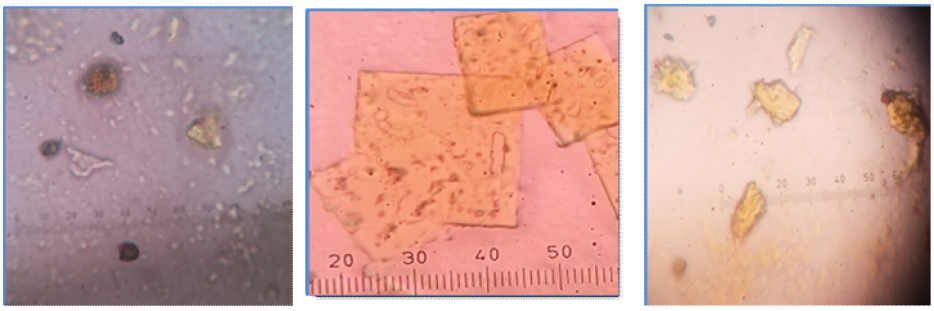
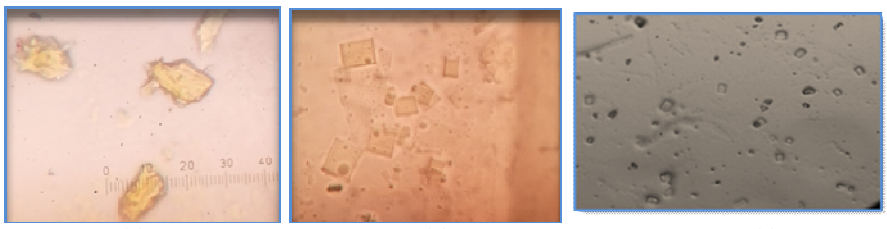


Figure 3: Different types of cubosomes formed using poloxomer 407



(a) **(b)** **(c)**

Figure 4: Structure of cubosomes (a) below 5% GMO concentration, (b) 5-50% GMO concentration, (c) above 50% GMO concentration



(a) **(b)** **(c)**

Figure 5: Structure of cubosomes (a) 5-20 minutes sonication time, (b) 25-45 minutes sonication time, (c) above 50 minutes sonication time

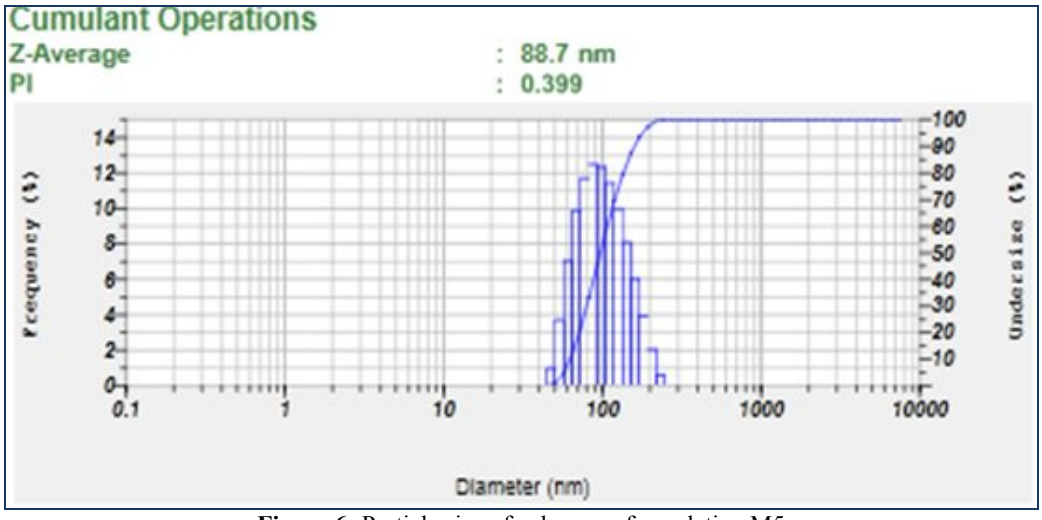


Figure 6: Particle size of cubosome formulation M5

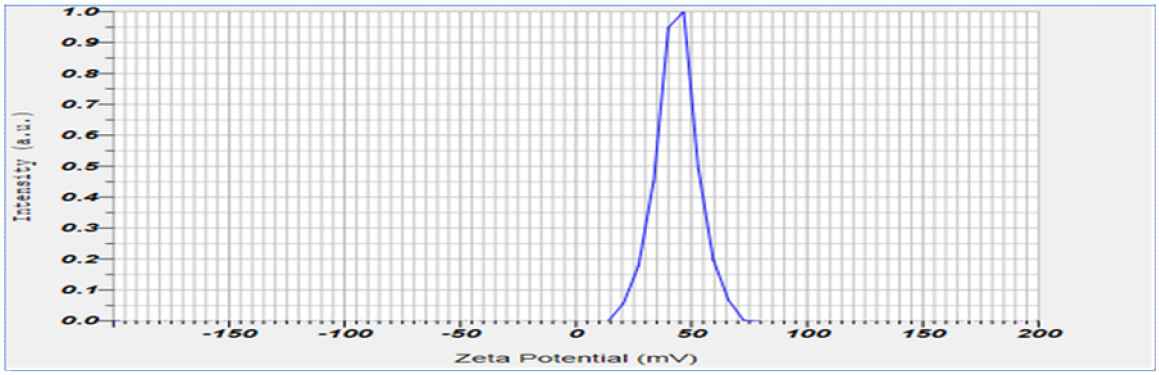


Figure 7: Zeta potential of cubosome formulation M5

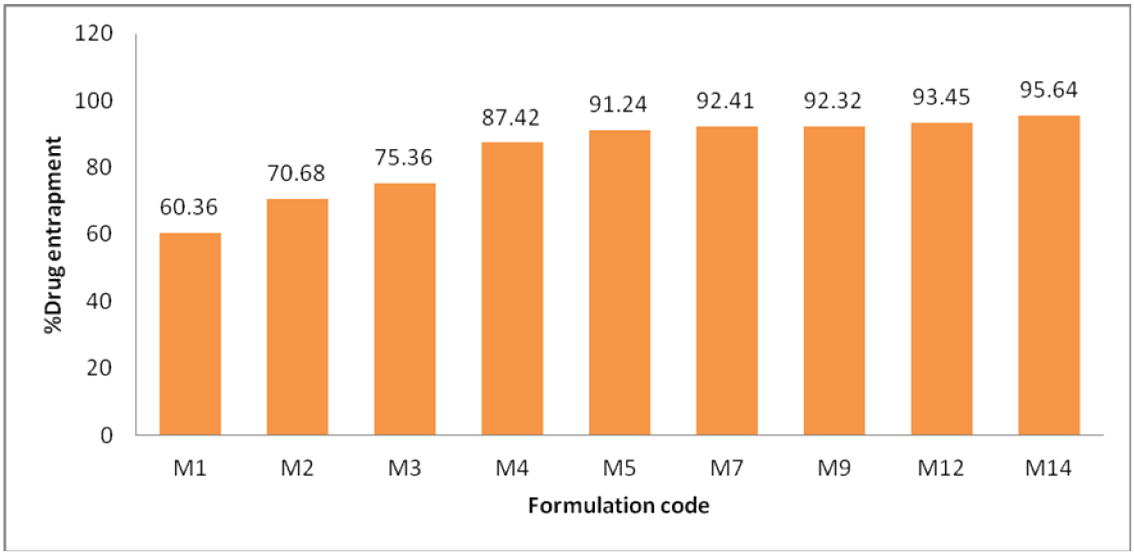


Figure 8: Entrapment efficiency of cubosomes

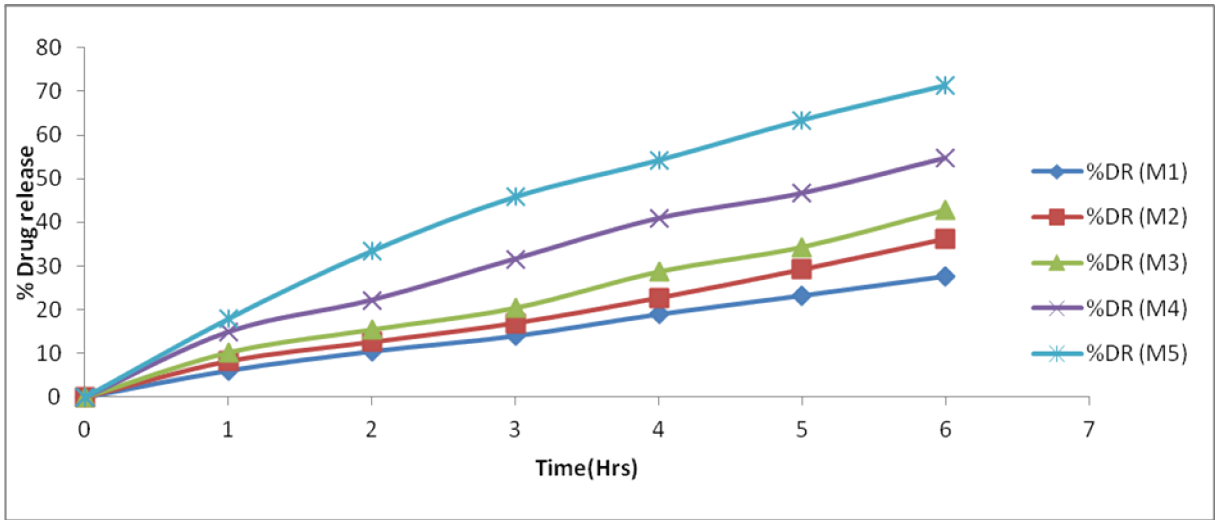


Figure 9: In vitro diffusion profile of Miconazole Nitrate cubosomes M1-M5 in 6.8pH phosphate buffer

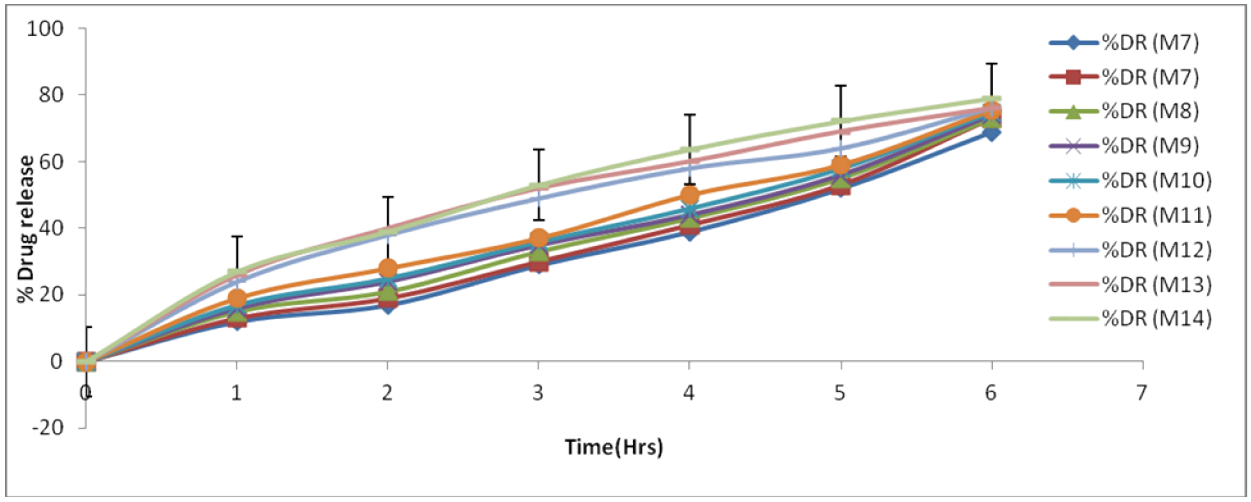


Figure 10: In vitro diffusion profile of Miconazole Nitrate cubosomesF6-F14 in 6.8pH phosphate buffer

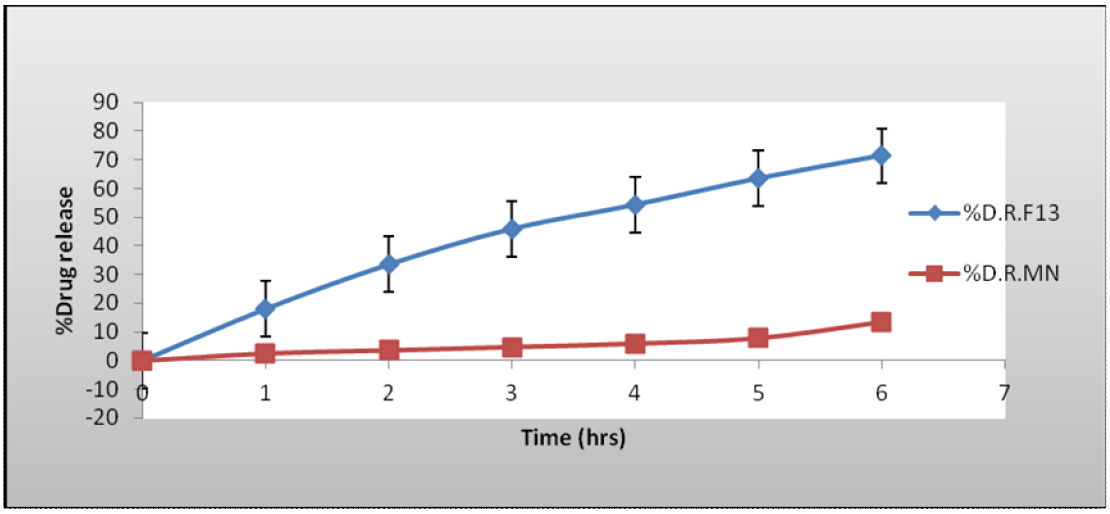


Figure 11: In vitro diffusion profile of Miconazole Nitrate crude drug and optimized Miconazole Nitrate cubosome formulation in 6.8pH phosphate buffer

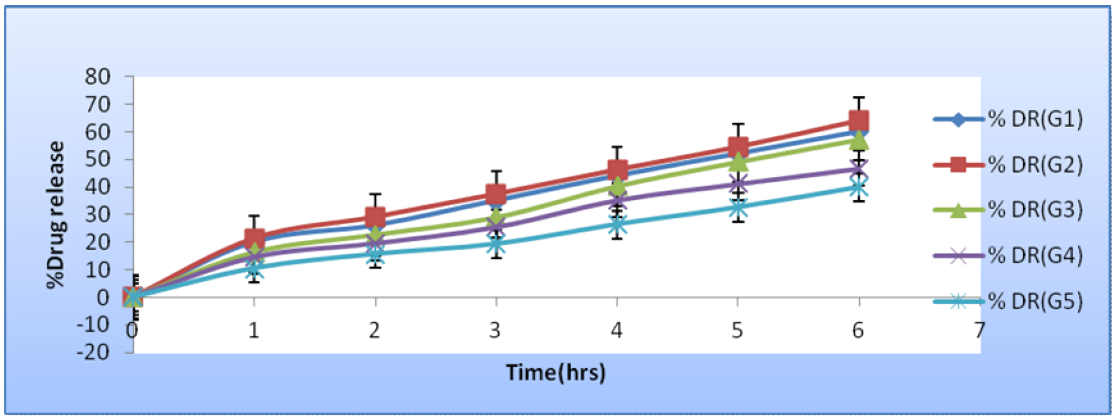


Figure12: *In Vitro* diffusion profile of Miconazole Nitrate Cubosomal Topical Gel using Carbopol 940 G1 to G5 in 6.8 pH phosphate buffer

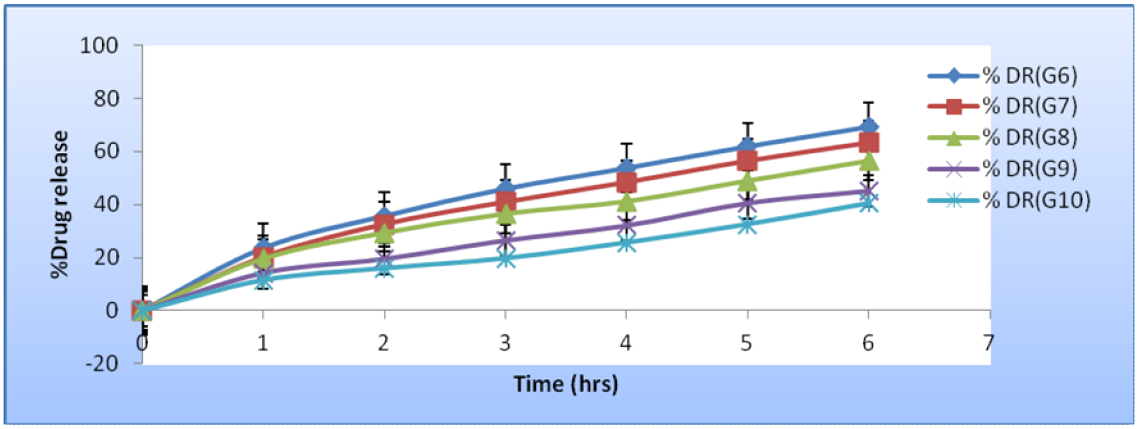


Figure 13: *In Vitro* diffusion profile of Miconazole Nitrate Cubosomal topical gel Gel using Carbopol 934 G6 to G10 in 6.8 pH phosphate buffer

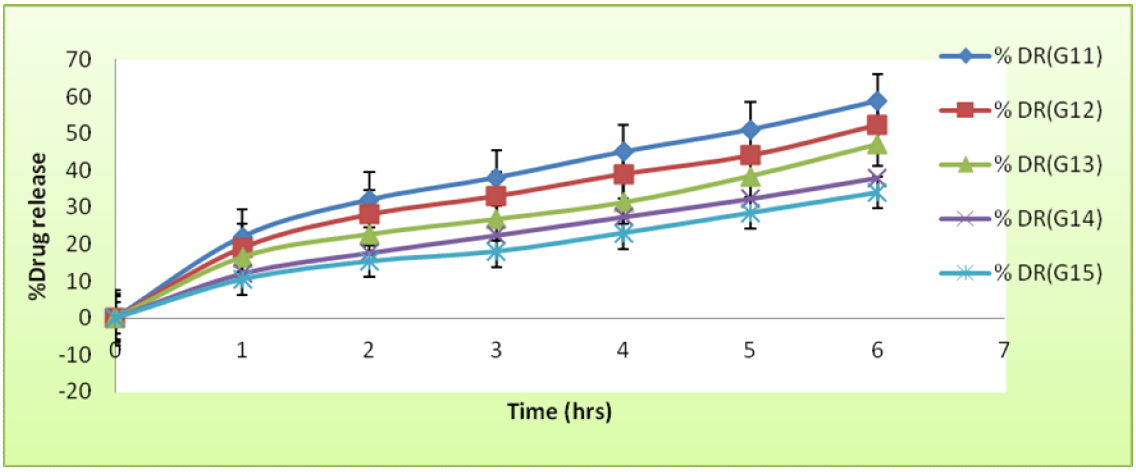


Figure 14*: In Vitro* diffusion profile of Miconazole Nitrate Cubosomal Topical Gel using HPMCK4M G11 to G15 in 6.8 pH phosphate buffer

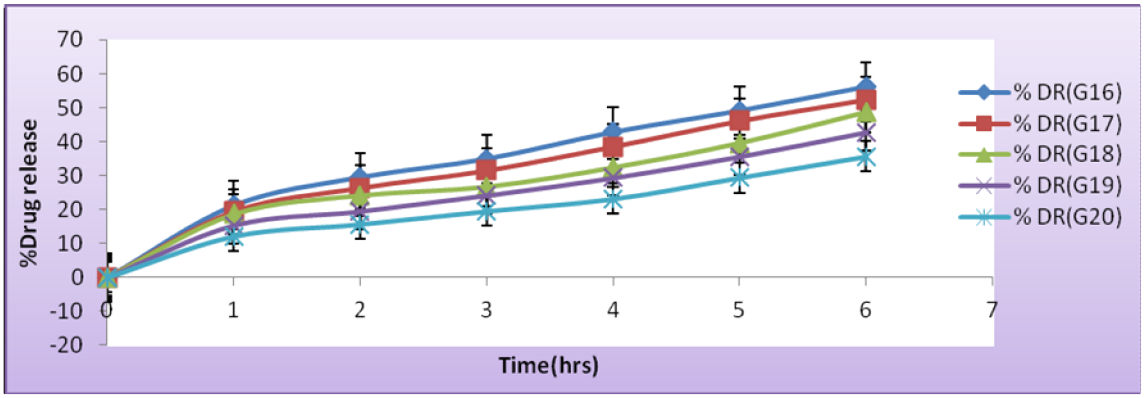


Figure 15: *In Vitro* diffusion profile of Miconazole Nitrate Cubosomal Topical Gel using HPMCK15M G16 to G20 in 6.8 pH phosphate buffer

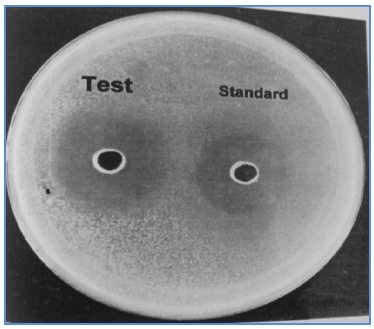
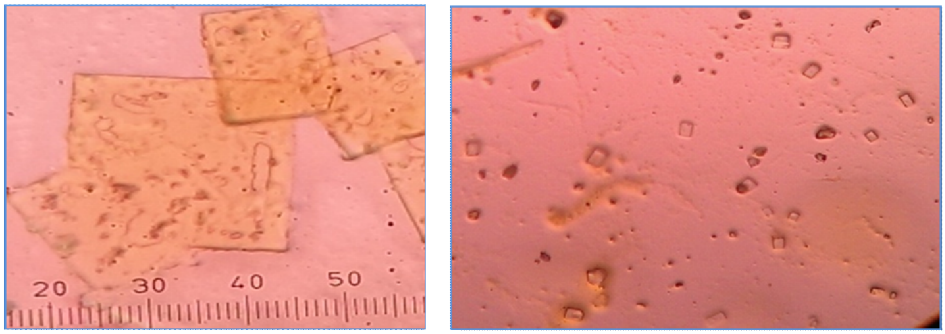


Figure 16: Antimicrobial activity of Miconazole nitrate cubosomal topical gel G2 comparing with Marketed Micogel cream

Figure 17: the optimized cubosomal topical gel G2



(a) **(b)**

Figure 18: Microscopic structure of (a) optimized cubosome formulation F2 (b) optimized cubosomal gel formulation G2

SUMMARY

The cubosomal topical gels deserve attention due to its unique liquid crystalline structure and ease of preparation. Advantages such as high degree of biocompatibility possessed by GMO, capability of accommodating various drugs irrespective of hydrophilic or hydrophobic nature, sustained release action lead to investigation in formulation of liquid crystalline drug delivery vehicles through various routes of administration. Cubosomes are one such dosage forms formed by GMO when added to water. Since it is a lipid and tends to separate in aqueous phase poloxamer407 is used as a stabilizer to prevent aggregation. Miconazole nitrate drug has low solubility and formulated into cubosomes in order to sustain the drug release it was formulated to topical gels. Cubosome formulation prepared by GMO (15%), poloxamer407 (1%) shows good cubic structure, satisfactory entrapment efficiency (91.24) and drug release (71.38%). As GMO concentration increases entrapment efficiency and drug release are increased but the prepared formulations are not stable, the phase separation will occurred. To sustained the drug release the optimized cubosome formulation F5 was formulated into gel using carbopol 940, carbopol 934,HPMC K4M & HPMC K15M.Dealing with other aspects, Preparations containing Carbopol940 show good cubic structure higher drug release(64.12%) at end of 6 hours in pH 6.4 buffer and stable than other formulations. The nature of cubosome dispersion and topical gel formulation are observed microscopically. The difference is shown in below Figure 18.

CONCLUSION

Cubosomes can be formed by simple combination of biologically compatible lipids (GMO) and water and are thus well suited for pharmaceutical and body tissue. The ability to form cubosomes during manufacture offers enhanced flexibility for product development. The above research specifies cubosomal utility as controlled release drug carrier. Prolonged release is achieved when they are formulated as topical gels maintaining the cubosome structure. Although they possess advantageous characteristics, there is still a long way to go before their clinical application.

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