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FORMULATION AND EVALUATION OF CUBOSOMES LOADED EMULGEL OF OXICONAZOLE NITRATE

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ABSTRACT
Dermatological conditions are known to be one of the most common medical conditions. Oxiconazole nitrate (OXN) is a potent anti-fungal drug which includes in azole derivatives (imidazole). But, Oxiconazole nitrate have poor solubility and comes under BCS class II. Also, it's short half-life (3-5 h) and the side effects limits its application. Hence in this study, OXN was designed into the nano formulation called cubosomes to increase its solubility and incorporated into emulgel base to curtail the adverse effects of OXN by the transdermal route and to provide dual release system. Emulgel is evolving system for the topical drug delivery, where two systems have been incorporated i.e, Emulsion and the gel. Even though, gels show various advantages it still has constriction in the delivery of hydrophobic drugs. So, in order to overcome this problem, the concept for emulgel was introduced.

KEYWORDS: Oxiconazole nitrate, cubosomes, Glyceryl monooleate, top-down approach, emulgel.

INTRODUCTION
It is well known that skin is an important body barrier towards external chemical, mechanical, physical, and microbial stresses, resulting in a protection against pathogens and water loss. Also, skin may be affected by many problematic disorders (e.g., rashes), infections of different nature (i.e., viral, bacterial, fungal, and parasitic), injuries caused by cuts or burns, and tumors etc. The treatment of skin disorders can be done with topical applications of drugs on the action site. In the past few decades, considerable attention has been focused on the development of novel drug delivery system (NDDS). The NDDS should ideally fulfil two prerequisites: Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment, Secondly; it should channel the active entity to the site of action.[1] Among the different pharmaceutical carriers, vesicles have become the vehicle of choice in drug delivery. Lipid vesicular carriers are extremely organized assemblies of bilayers of lipid that may be single or concentric in nature formed when the building blocks (amphipathic) of these bilayers encounter water.[2] Furthermore, the structural similarity between the lipid nanosystems and those of the skin represents one of the main advantage i.e., these allows the interaction between the nanosystem matrix and the stratum corneum therefore increases skin hydration and also the penetration of the carried active molecule.[3] Lipid-based nanosystems such as liposomes, niosomes, ethosomes, transferosomes, pharmacosomes and cubosomes have been proposed for cutaneous application. Liposomes have proved to be the good candidates for increasing the solubility of poorly soluble drugs, but the stability issue of liposomes remains an area which is surrounded by a number of problems due the formation of ice crystals in liposomes.[4] Comparing liposomes cubosomes, cubosomes offers simple production procedure and better chemico-physical stability. Cubosomes are distinct, sub-micron, nano-structured particles.[5] They are composed of bicontinuous cubic phase liquid crystals that consist of lipid bilayer separating two continuous but nonintersecting water regions, like honeycombed. Cubic phases were observed to have three structures: Diamond or D surface, primitive surface or P surface and Gyroid or G surface. Larsson revealed that the monoolein-water system forms the D-surface at high water levels and the G-surface at lower levels. Qiu and Caffrey later updated that the P-surface is formed only when a third component, such as caseins or amphiphilic block copolymers are added in to the system.[6]

Emulgel is emerging field for the topical drug delivery, where two systems have been incorporated i.e, Emulsion and the gel. Even though, gels show various advantages it still has limitation in the delivery of hydrophobic drugs. So to overcome this limitation the concept for emulgel was introduced.[7] Simply the Emulgel are emulsion in gel. Here, Emulsions are controlled release systems containing two immiscible phase in which one is dispersed into other with the use of emulsifying agent to stabilize the system. Emulsion are of oil-in-water or water-in-oil type, where the drug particle entrapped in

internal phase passes through the external phase and then slowly gets absorbed into the skin to provide controlled effect. Also, the gel contains the larger amount of aqueous or hydro alcoholic liquid in a cross linked network of colloidal solid particles where it captures small drug particles and maintain the controlled release of drug. Hence, emulgel is the approach using the benefits of both emulsion and gels, gaining the dual controlled release effect.[8]

MATERIALS AND METHODS

MATERIALS

OXN was collected from Yarrow chem products, Mumbai. Poloxamer 407 was procured from Research Lab Fine Chem Industries, Mumbai and Glyceryl monooleate was purchased from Kanton Laboratories, Kannur. All other chemicals used were of analytical grade and obtained commercially.

METHODS

Preformulation Studies

Prior to dosage form development, it is absolutely necessary to determine preformulation studies of candidate drug molecules. This helps the formulator to generate useful information that could prevent during the successful and productive development of an efficient dosage form. The preformulation studies conducted are solubility analysis, Melting point determination by capillary method, physical characterization like colour, odour etc., and compatibility studies (FTIR) of drug and excipients.

Preparation of OXN loaded cubosomes[9]

Oxiconazole nitrate cubosomes was prepared by top down method. Accurately weighed quantity of Glyceryl Monooleate (GMO) and poloxamer 407 was mixed and melted in a water bath at 60°C. To this mixture the drug OXN was added and stirred until the drug completely dissolves. Then to this solution add drop by drop preheated (up to 70°C) distilled water of suitable quantity by continuous stirring, after complete addition of water kept aside for one day to attained equilibration, there is a formation two phase system and it is disturbed by stirring. The composition of GMO and P-407 was based on observation of Daware *et al*, 2017. The whole system is then taken and subjected to bath sonication for 30 minutes. The prepared dispersions were stored at room temperature for 48 hrs, protected from light and later evaluations were carried out.

Table 1: Composition of OXN loaded Cubosomes.

FORMULATION CODE	GLYCERYL MONOOLEATE (%W/V)	POLOXAMER 407/PLURONIC F 407 (%W/V)	OXICONAZOLE NITRATE (gm)	DISTILLED WATER (% V/V)
F_1	4.8%	0.2%	1	100
F_2	4.6%	0.4%	1	100
F_3	4.4%	0.6%	1	100
F_4	4.2%	0.8%	1	100
F_5	4.00%	1.0%	1	100
F_6	3.8%	1.2%	1	100
F_7	3.6%	1.4%	1	100
F_8	3.4%	1.6%	1	100

Evaluation of OXN loaded cubosomes

1. Visual Inspection

The dispersions were visually assessed for optical appearance [e.g., colour, turbidity, homogeneity] about one week after preparation.

2. pH determination[9]

The pH of the cubosomes (F_1-F_8) was measured by direct immersion of the electrode of a pH meter (L1120 Elico Hyderabad) in the dispersion at room temperature.

3. Entrapment Efficiency (EE %)

Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the cubosomes. In order to determine entrapment efficiency (EE %), the total amount of OXN incorporated in 1 mL cubosomal dispersion was determined after the addition of 9.0mL methanol. The resultant solution was assayed for the total OXN content by UV spectrophotometer (SL 196 Shimadzu Corporation, Japan) at 228 nm using methanol as blank. The free drug concentration of drug was measured by diluting OXN loaded cubosomal dispersions in 10 mL of purified water, and 3 mL of these diluted samples were placed in centrifuge tubes and centrifuged at 8000rpm for 45 min at 4°C (REMI C-24BL). Free OXN contained in the filtrate was measured spectrophotometrically at 228 nm. The amount of entrapped OXN was calculated by subtracting the determined amount of OXN in the filtrate from the total amount of drug incorporated in 1mL cubosomal dispersion.[10] The EE % was calculated using the equation:

$$EE\ \% = \frac{C_t - C_f}{C_t} \times 100$$

Where,

C_t = Concentration of total Oxiconazole nitrate;

C_f = Concentration of free Oxiconazole nitrate.

4. Determination of Particle Size and Polydispersity Index (PI)

The particle size of the cubosomes was determined through dynamic light scattering (DLS, Malvern Zetasizer Ver7.13). DLS sometimes referred to as photon correlation spectroscopy, which is a non-invasive, well-established technique for measuring the size of molecules and particles typically in the submicron region.[11] Z-average (intensity weighed mean hydrodynamic size) was measured. Polydispersity (PI) of cubosomes samples was also measured.

5. High Resolution Transmission Electron Microscopy (HR-TEM)

Morphological analysis was carried out by HR-TEM. The samples were prepared by placing 5 µl droplet of the optimized dispersion onto a 300 mesh carbon coated copper grid, and allowing cubosomes to settle for 3-5 min. Excess fluid was then removed by wicking it off with an absorbent paper. The samples were then viewed on a JEOL Model- (JEM- 2100) 200KV TEM with point resolution of 0.23 nm, lattice resolution of 0.14 nm and magnification power of 1.5 M.[12]

6. Thermal Analysis Study

Thermal analysis of OXN, mixture of Glyceryl monooleate and Poloxamer 407, Cubosome physical mixture and OXN loaded cubosomes (F1) was carried out using differential scanning Calorimetry (DSC, Mettler Toledo, Database: STARe Default DB V16.10: METTLER). The calibration was done by using an aluminium standard. Samples were accurately weighed in to DSC aluminium pans having capacity of 40 uL and then sealed with aluminium lid. Empty pan used as a reference. Thermograms were obtained at a scanning rate of 10 K/min conducted over a temperature range of 30-200°C in the environment of liquid nitrogen. OXN cubosomes were freeze dried prior to DSC analysis.

7. *In-vitro* drug Release Study

6 mL of cubosomal dispersion were placed inside the dialysis bag, tied at both ends and dipped in the dissolution media of pH 7.4 Phosphate Buffer solution at a temperature of 37±0.5°C. 5 millilitres of aliquot were withdrawn at particular time intervals and replaced by an equal volume of a fresh dissolution medium. After suitable dilution, the sample was determined spectrophotometrically (SL 196 Shimadzu Corporation, Japan) by measuring the absorbance at 228 nm. The concentration of test samples was calculated by using the regression equation of the calibration curve.[13] The percentage *in-vitro* drug release was calculated by using the formula:

$$\% \text{ Drug release} = \frac{\text{Cumulative amount of drug release}}{\text{Amount of drug release}} \times 100$$

Preparation of OXN cubosomes loaded emulgel[14]

OXN cubosomal emulgel were prepared by a cold mechanical method using carpobol 940 as a gelling agent. The weighed amount of gelling agent (2%W/V) was added to sufficient quantity of water and kept overnight for swelling and gelling. The carbopol mixture was stirred for 1 hour to form clear gel. To the above gel, optimized OXN loaded cubosomal dispersion equivalent to 100 mg (10ml) was added and properly mixed. To adjust the pH tri ethanol amine was added. To above mixture glycerol was added to balance the viscosity and methyl paraben was added as a preservative.

Table 2: Composition of OXN cubosomes loaded emulgel.

SL NO	INGREDIENTS	QUANTITY
1	OXN loaded cubosomes	Equivalent to 100 mg of OXN
2	Carbopol 940	2%W/V
3	TEA	0.12 ml
4	Glycerol	0.25 ml
5	Methyl paraben	0.03 mg

Preparation of OXN loaded emulgel[13]

The gel was prepared by dispersing Carbapol 940 in purified water with constant stirring and adjusted the pH using TEA. The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in distilled water. Propyl paraben were dissolved in propylene glycol whereas drug dissolved in methanol and both solutions mixed with aqueous phase. Both oily and aqueous phase were separately heated to 70-80°C. Then oil phase is added to aqueous phase by continuous stirring until cooled and mixed with gel in ratio of 1:1 to obtain emulgel.

Evaluation of emulgels

1. Physical Examination

The prepared cubosome loaded emulgel and plain emulgel were inspected visually for their colour, homogeneity and consistency.

2. pH Determination

The pH of the cubosomes loaded emulgel and plain emulgel was measured by direct immersion of the electrode of a pH meter (L1120 Elico Hyderabad) in the dispersion at room temperature. The measurement of pH of each formulation was done in triplicate and average values were calculated.[15]

3. Drug Content

1 gm of OXN cubosome emulgel and Plain emulgel was weighed and diluted with 50 ml of methanol in 50ml

volumetric flask. Five millilitres was pipetted out in 25 ml of volumetric flask and made up with methanol. Then the absorbance was measured using UV- Visible spectrophotometer (SL 196 Shimadzu Corporation, Japan) at 228 nm. Drug content was calculated using slope and intercept obtained by linear regression analysis of standard calibration curve.[16]

4. Rheological Evaluation

Viscosity of the formulations was determined at room temperature using a Brook field viscometer (DV-I Prime Brookefield Viscometer). The spindle was rotated at 10 rpm to 100 rpm and viscosities were observed.[9]

5. Spreadability Test

The spreadability of the formulations was measured by spreading of 0.5 g of the gel on a circle of 2 cm diameter pre-marked on a glass plate and then a second glass plate was employed. Half kilogram of weight was permitted to rest on the upper glass plate for 5 min (300 sec). The diameter of the circle after spreading of the gel was determined.[17]

6. *In-Vitro* drug release study

Studies were performed for OXN loaded cubosome emulgel and plain OXN emulgel. In vitro release studies were carried out using bi-chambered donor receiver compartment model (Franz diffusion cell) and this was placed on magnetic stirrer and temperature was adjusted to 37 ± 0.5° C. One end of the chamber was covered with dialysis membrane (cut-off molecular weight: 12000-14000), which was previously soaked for overnight in phosphate buffer pH 7.4. Phosphate buffer pH 7.4 was placed in the receptor cell. Accurately measured 2.5 ml of the formulation was spreaded 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 7.4. The samples were analysed by using a UV-Vis spectrophotometer (SL 196 Shimadzu Corporation, Japan) at 228nm.[18]

7. Mathematical modelling for drug release kinetics

Drug release kinetics was determined by the following kinetic equations such as zero order, first order, Higuchi model, Korsmeyer-Peppas model etc.

8. Comparison of antifungal activity of Cubosome loaded emulgel with marketed formulation

The comparison was done by Kirby-Bauer Disc Diffusion method. Fungus *Candida albicans* was used. Formulated emulgel containing drug loaded cubosomes were impregnated in discs and it was aseptically transferred onto the inoculated agar plates and incubated for 2 days. Same procedure was followed for marketed formulation and OXN emulgel. The zone of inhibition obtained was calculated.[19]

RESULTS AND DISCUSSION

Pre formulation Studies

The organoleptic characters of drug were found to be within standard specifications. The melting point of drug was found to be 141.66 °C. Solubility profile showed OXN was soluble in methanol whereas sparingly soluble in chloroform and acetone and insoluble in water. Drug – excipient compatibility was studied by using FTIR. FTIR of OXN shows characteristics peaks at 753 cm^{-1} which indicated the presence of C – Cl stretching, a peak at 1330.93 cm^{-1} which indicated the presence of N-O stretching, a peak at 1476.56 cm^{-1} indicated the presence of C=N stretching, a peak at 1588.43 cm^{-1} indicated the presence of C=C (aromatic) stretching and peak at 3111.28 cm^{-1} indicated the presence of C-H (aromatic) stretching. Similar peaks were observed in spectra of combinations. It was observed that the excipients did not interfere with the major absorption peaks of the drug indicating chemical compatibility between the drug and excipients.

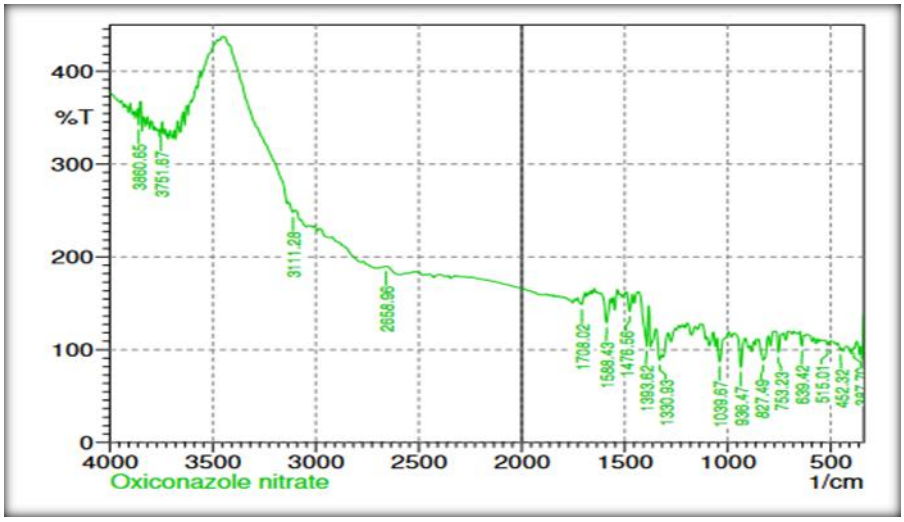

Fig. 1: FTIR Spectrum of OXN pure drug.

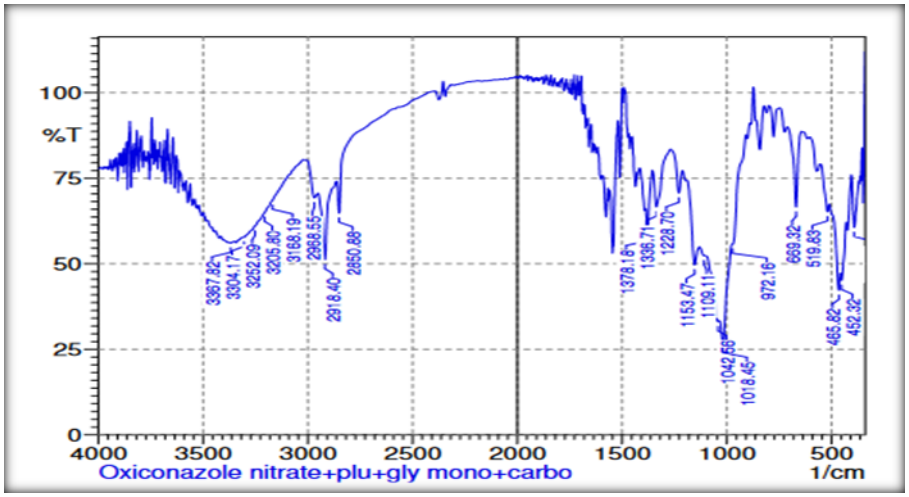

Fig. 2: FTIR Spectrum of OXN + Excipients.

Evaluation of OXN loaded cubosomes

1. Visual Inspection

The dispersion was visually assessed for optical appearance such as colour, turbidity and to check presence of aggregates. All the formulations were well dispersed and contain no visible aggregates. Formulations F_1 to F_8 possessed a milky white consistency.

2. pH determination

The pH obtained for eight formulations is depicted in table given below:

Table 3: pH of cubosomal dispersion.

FORMULATION CODE	pH	FORMULATION CODE	pH
F_1	5.28	F_5	5.12
F_2	4.53	F_6	4.74
F_3	5.47	F_7	4.73
F_4	4.54	F_8	4.46

The pH of formulations (F_1-F_8) are within the range of 4.5-5.5 indicates suitable for application on skin.

3. Entrapment Efficiency (EE %)

The %EE of F_1 to F_4 was higher than %EE of F_5 to F_8. The low EE% values for F_5 to F_8 may be due to the extensive mobile character of the small OXN molecule, which does not associate with lipid bilayer or it was expected to be entrapped within the aqueous channels of cubosomes. These conditions might favour the leakage of drug from the aqueous channel to surrounding during preparation and centrifugation.[20]

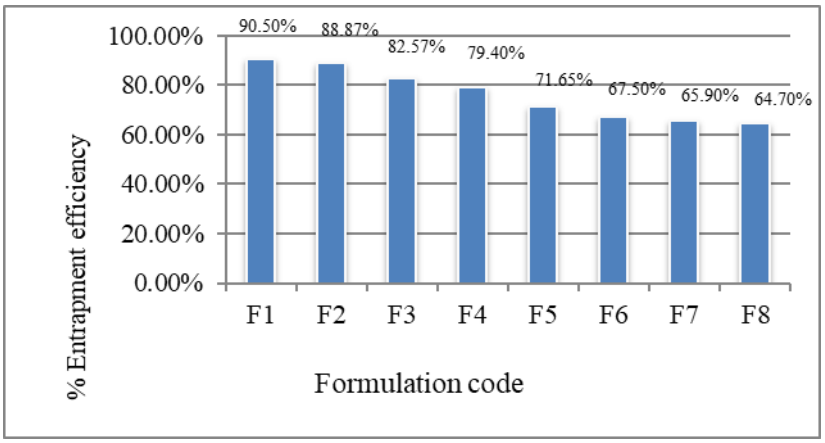

Fig 3: %EE of OXN-cubosomal dispersion.

4. Determination of Particle Size and Polydispersity Index (PI)

Upon reducing P-407 concentration larger cubosomal nanoparticles were formed and it may be due to condensed interfacial stability and insufficient amount of the surfactant leading to aggregation of nanoparticles.[3] Also, PDI values ranges from 0.1-0.3 which seemed to be acceptable and indicate homogeneous dispersion.[18]

5. High Resolution Transmission Electron Microscopy (HR-TEM)

The liquid cubosomes tended to form spherical nanoparticle.[21]

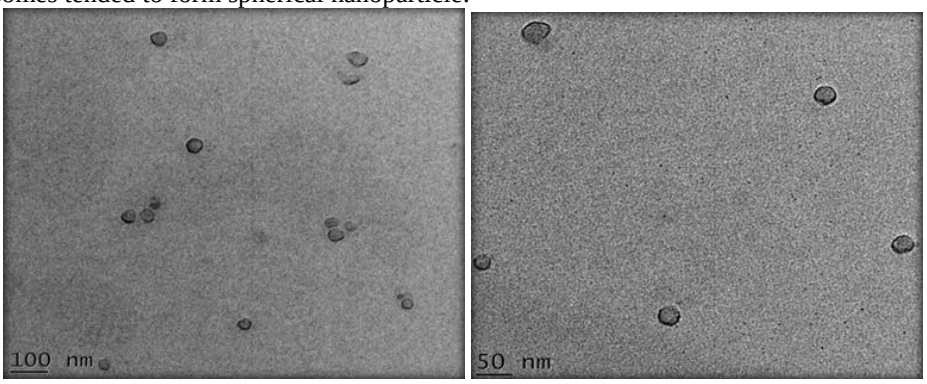

Fig. 4: TEM images of F1 formulation.

6. Thermal Analysis Study

DSC thermogram of OXN shows sharp endothermic peak at 144.61°C. In thermogram of P-407 and GMO the peaks appeared at 54.00°C. Change in the position or disappearance of drug or excipients thermal events often suggestive that there is interaction between various components of a system, but FTIR confirms there is no interaction. Hence this data gave the information that the compound is not in crystalline form.[11]

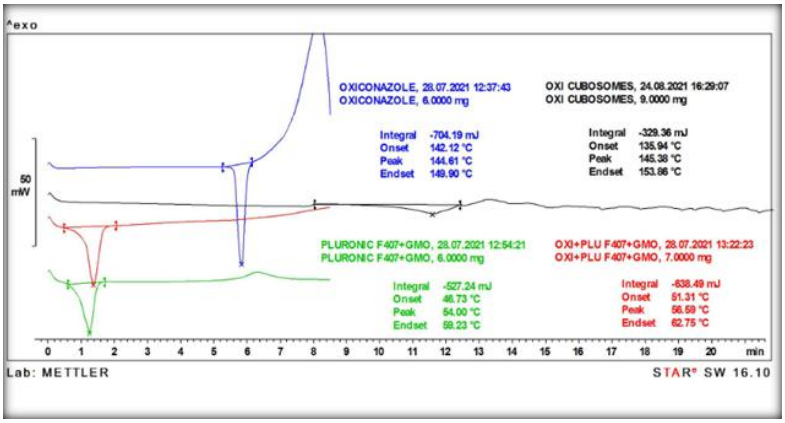

Fig. 5: DSC Thermogram of (a) OXN, (b) GMO+P-407, (c) Physical mixture containing OXN+GMO+P-407 and (d) OXN- Cubosomes.

7. In-*vitro* drug Release Study

During *in-vitro* study it was noticed that formulations F_5-F_8 released at faster rate for 2-3 hours and decreases its rate for next 24 hours, while formulations F_1-F_4 was released slowly at 2-3 hours and follows constant release up to 24 hours. The reason is not quite clear, but might be related to the ability of P-407 to partially solubilize the hydrobhobic drug.[12] F_1 shows highest drug release of 94% in 24 hrs.

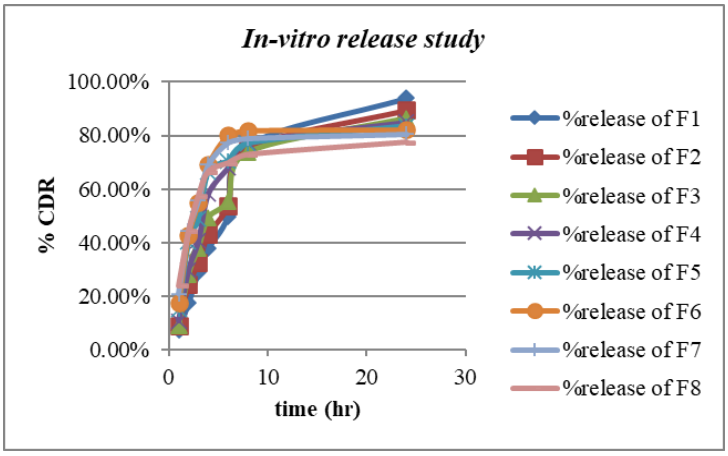

Fig. 6: *In-vitro* release study of formulations F_1-F_8.

EVALUATION OF OXN LOADED CUBOSOMES EMULGEL(G_1) AND OXN EMULGEL(G_2)

1 Physical Examination

Optimized cubosome loaded emulgel (G1) and drug loaded plain emulgel (G2) were consistent, viscous with a smooth and homogenous appearance. Both emulgels were appeared as a white in colour.

2 pH Determination

Here, the pH of both formulations are within the range of 4.5-5.5 indicates suitable for application on skin.

Table 4: pH of OXN cubosome emulgel and pH of OXN emulgel.

SL NO	pH OF OXN CUBOSOME EMULGEL	pH of OXN EMULGEL
1	5.19	5.23
2	5.20	5.41
3	5.19	5.50
Average	5.19	5.38

3. Drug Content

The percentage drug content of drug loaded plain emulgel, as well as cubosome loaded emulgel was found to be 91.54% and 93.24% respectively.

Table 5: Drug content of G_1 and G_2

SL NO	FORMULATION CODE	DRUG CONTENT%
1	OXN cubosome loaded emulgel	93.24%
2	OXN emulgel	91.54%

4. Rheological Evaluation

On viscosity determination, it was found that decrease in the viscosity as the rpm was increased.

Table 6: Viscosity of G_1 and G_2

SL NO	RPM	VISCOCITY OF OXN-CUBOSOME LOADED EMULGEL (G_1) (cps)	VISCOCITY OF OXN EMULGEL(G_2) (cps)
1	10	6431	5905
2	20	5782	5645
3	50	5042	4520
4	100	4325	4258

5. Spreadability Test

OXN loaded cubosome emulgel have much more spreadability than the plain OXN emulgel.

Table 7: Spreadability test for G_1 and G_2.

SL NO	FORMULATION CODE	TIME (Sec)	SPREADABILITY (g.cm/sec)
1	G_1	300 Sec	12.5
2	G_2	300 Sec	9.9

6. *In-Vitro* drug release study

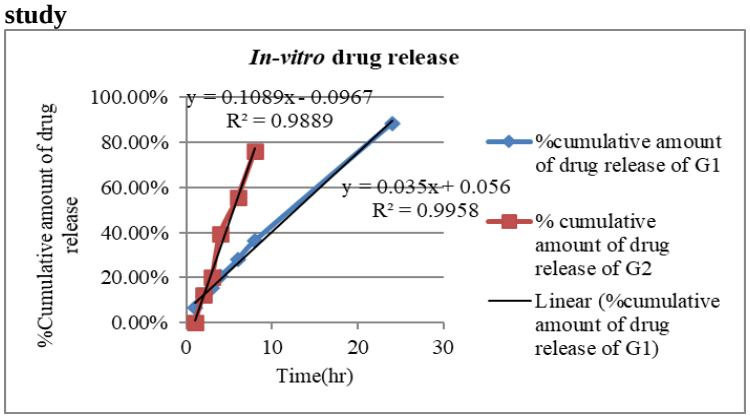

Fig. 6: %Cumulative amount of drug release of G_1 and G_2

The cubosomal dispersion shows high release rate than the cubosomal emulgel. While comparing, G_1 with G_2, G_2 has been released at higher rate than G_1. G_2 released its 94.03% of drug at 8 hours itself, while G_1 takes 24 hours to release its 88% drug. This indicates that the formulation G_1 follows sustained drug release than G_2. This might be due to the longer diffusion path that the drug has followed. First the drug has to diffuse from the cubic liquid crystals into the vehicle and from there onto the skin.[22]

7. Mathematical modelling for drug release kinetics

Table 8: Kinetic study of cubosome emulgel (G_1) and plain emulgel (G_2).

Formulation code	Drug release kinetics				
	Zero order	First order	Higuchi model	Korsmeyer Peppas plot	
	R^2	R^2	R^2	n value	R^2
OXN cubosome emulgel(G_1)	0.995	0.981	0.981	0.8161	0.999
OXN Plain emulgel (G_2)	0.988	0.939	0.984	1.033	0.980

From the above data it was found that R^2 values of zero order release was higher than the first order release.[23] So G_1 and G_2 follows zero order kinetics with regression coefficient value of 0.995 and 0.988 respectively.

8. Comparison of antifungal activity of Cubosome loaded emulgel with marketed formulation

Table 9: Antifungal activity of $G_1$and G_2 with marketed formulation.

Organism	Formulation	Zone of inhibition (mm)
Candida albicans	G_1	34mm
	Marketed formulation	32mm
	G_2	21mm

From the study, G_1 was showed higher zone of inhibition than the marketed gel (standard).

CONCLUSION

Eight cubosomal dispersions were made by top-down technique using Glyceryl monooleate as a lipid and pluronic F 407 as a stabilizer. FTIR confirmed that there is no incompatibility between the drug and excipients. Characterisations like particle size analysis, zeta potential, Polydispersity index and entrapment efficiency was done to ensure the size, stability, homogeneity and amount of drug incorporated in the cubosomes. TEM analysis and DSC confirms the morphology and physical state of optimized formulation. *In-vitro* release study showed controlled release for 24 hours. Based on evaluation criteria the best formulation (F_1) was incorporated into emulgel base, and plain OXN emulgel was used for comparative study. Evaluations for both formulations were done and *in-vitro* study suggested that OXN – cubosome emulgel have sustained release comparing to plain emulgel. Antifungal assay was done to compare the antifungal activity of OXN-cubosome emulgel, plain emulgel and marketed formulation. Finally, it concludes that OXN-cubosome loaded emulgel application by transdermal route has the potential to sustain the drug release for 24 hours and have good antifungal activity.

REFERENCES

1. Seema M. Jadhav, Pournima Morey, Mrs. Manisha Karpe, Vilasrao Kadam. Novel vesicular system. Journal of Applied Pharmaceutical Science, 2012; 02(01): 193-202.
2. Akshay Rajabhau Barkate, Dhanashri Naghnath Gadekar. Cubosomes: The Novel Drug Delivery System. World Journal of Pharmaceutical Research, 2020; 9(8): 1170-1185.
3. Maddalena Sguizzato, Elisabetta Esposito and Rita Cortesi. Lipid-Based Nanosystems as a Tool to Overcome Skin Barrier. International journal of molecular science, 2021; 22: 8319. https://doi.org/10.3390/ijms22158319.
4. Saurabh Bansal, Chandan Prasad Kashyap, Geeta Aggarwal and SL Harikumar. A comparative review on vesicular drug delivery system and stability issues. International journal of research in pharmacy and chemistry, 2012; 2(3): 704-713.
5. Anbarasan. B, Fatima Grace, Shanmuganathan S. An overview of cubosomes-smart drug delivery system.Sri Ramachandra Journal of Medicine, 2015; 8(1): 1-4.
6. B. Aubine Molly*1and N. L. Prasanthi. Cubic Liquid Crystalline Nanoparticles (Cubosomes): A Novel Carrier For Drug Delivery. IJPSR, 2019; 10(3): 973-984.
7. Panwar A, Upadhyay N, Bairagi M, Gujar S, Darwhekar G, Jain D. Emulgel: a review. Asian J Pharm Life Sci., 2011; 2231: 4423.
8. Sreevidya V.S. An Overview on Emulgel. International Journal of Pharmacy and Pharmaceutical Research, 2019; 9(1): 92-97.
9. S.U. Daware, and R.B Saudagar. Formulation and evaluation of cubosomes loaded emulgel of fluconazole. European journal of Biomedical and pharmaceutical sciences, 2017; 4(11): 321-331.
10. Ananda Kumar Chettupalli, Madhubabu Ananthula, Padmanabha Rao Amarachinta, Vasudha Bakshi, Vinod Kumar Yadha. Design, Formulation, In-vitro and Ex-vivo Evaluation of Atazanavir loaded Cubosomal Gel. Biointerface Research in Applied Chemistry, 2021; 11(4): 12037-12054.

11. Di Bei, Tao Zhang, James B. Murowchick, and Bi-Botti C. Youan. Formulation of Dacarbazine-loaded Cubosomes. Part III. Physicochemical Characterization. American Association of Pharmaceutical Scientists, 2010; 11(3): 1243-1249. DOI: 10.1208/s12249-010-9496-7.
12. Dina Fathalla, Eman M K Youssef, and Ghareb M. Soliman. Liposomal and ethosomal gels for the topical delivery of anthralin: Preparation, comparative evaluation and clinical assessment in psoriatic patients. Pharmaceutics MDPI, 2020; 12: 446.
13. A.P Gadad, Amol Prakash Magdum, PM Dandagi, Uday Bolmal. Formation and characterisation of oxiconazole-loaded emulgel for topical application. Indian journal of health sciences and biomedical research, 2017; 10(3): 303-310.
14. T N Purnima, M Sunitha Reddy. Formulation and evaluation of topical cubosomal emulgel of an antifungal drug: Itraconazole. Journal of advanced scientific research, 2021; 12(2): 263-275.
15. Cuihua Chang, Thomas G. Meikle, Calum J. Drummond, Yanjun Yang and Charlotte E. Conn. Comparison of cubosomes and liposomes for the encapsulation and delivery of curcumin. Royal society of chemistry, 2021; 17: 3306-3313.
16. Anju, V, S., Dr. M, A, Kuriachan. Formulation & Evaluation of TBF-HCl loaded microsponge based gel for topical sustained delivery. International journal of Pharmacy & Pharmaceutical Research, 2017; 10(20): 69-93.
17. Milla Gabriela Belarmino Dantas, 1 Silvio Alan Gonçalves Bomfim Reis, Camila Mahara Dias Damasceno. Development and Evaluation of Stability of a Gel Formulation Containing the Monoterpene Borneol. The Scientific World Journal, 2016, Article ID 7394685, 1-4, http://dx.doi.org/10.1155/2016/7394685.
18. B.Venkatesh, S.Indira, Dr. Prathima Srinivas. Formulation and evaluation of miconazole nitrate as cubosomal topical gel. Journal of Global Trends in Pharmaceutical Sciences, 2014; 5(4): 2037-2047.
19. Sah SK, Badola AS, Mukhopadhyay S. Development and evaluation of tioconazole loaded emulgel. International Journal of Applied Pharmaceutics, 2017; 9: 83-90.
20. Mohammed Nasr, Karima Ghorab Ahmed Abdelazem. Invitro and in vivo evaluation of cubosomes containing 5-flurouracil for liver targeting. Acta Pharmaceutica sinica B., 2015; 5(1): 79-88.
21. Di Bei, Jacob M. Marszalek, Bi Botti Youan. Formulation of decarbazine loaded cubosomes- Part II: influence of Process Parameters. AAPS PharmSciTech., 2009; 10(3): 1043-1047.
22. Karthika V T, Sheri P.S, Dr. M.A Kuriachan. Fabrication and evaluation of ketoprofen loaded cubogel for topical sustained delivery. International Journal of Research and Review, 2018; 5(8): 149-159.
23. Suvakanta Dash, Padala Narasimha Murhy, Lilakanta Nath, and Prasanta Chowdary. Kinetic Modelling on Drug Release from Controlled Drug Delivery Systems. Acta Poloniae Pharmaceutica-Drug Research, 2010; 67(3): 217-223.