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Original Research Article

Fabrication & Evaluation of Ketoprofen Loaded Cubogel for Topical Sustained Delivery

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ABSTRACT

The present study is concerned with the development and characterization of a novel nanoparticulate system; cubosomes, of Ketoprofen loaded hydrogel to reduce the gastro intestinal effects with sustaining bioavailability. Cubosome dispersions were formulated by top-down technique using different concentrations of lipid phase monoolein, non ionic surfactant poloxamer 407 and water as aqueous phase. The prepared cubosomal dispersions were characterized regarding physical morphology, dimensional distribution by TEM, particle size by dynamic light scattering, entrapment efficiency and in vitro drug release. The optimum formulae were incorporated in a carbopol 934 based hydrogel to form cubosomal hydrogel (cubogel). The cubogel were characterized along with drug loaded plain gel regarding in physical examination, pH, % drug content, skin irritancy study, viscosity, spreadability studies, and in vitro drug release studies. Overall development of topical forms of ketoprofen is relevant due to its poor aqueous solubility and GI side effects. The ketoprofen-loaded cubosomes propose a promising system for treatment of arthritis simply through skin application.

Key Words: Cubosomes, Ketoprofen, Poloxamer 407, Hydrogel, Arthritis

INTRODUCTION

Arthritis treatment regimen aims to relieve patient pain and joints stiffness in order to improve patient ability to move. Patients suffering from rheumatoid arthritis need to use painkillers, like nonsteroidal anti-inflammatory drugs (NSAIDs) such as cyclo oxygenase inhibitor. [1] Ketoprofen a potent non-steroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions has pH dependent solubility and permeability. Ketoprofen has similar pharmacological actions as other prototypical NSAIDs; that are thought to be associated with the inhibition of prostaglandin synthesis. [2]

If you have arthritis in just a couple joints, you may not need to expose yourself to the risks of oral nonsteroidal anti-inflammatory drugs (NSAIDs) - such stomach upset or heart problems - to achieve some relief. A topical NSAID can be rubbed on the skin over sore joints to relieve pain. Topical NSAIDs have a moderate effect on pain relief, with efficacy similar to that of oral NSAIDs, with the advantage of a better risk: benefit ratio. [3]

Lipids have been widely used as main constituents in various drug delivery systems such as liposomes, SLNPs, and lipid based liquid crytstals. One way to increase the solubility of poorly soluble drugs is through the formation of self assembled lipid based cubic liquid crystals, such as cubosomes. Cubic-Phase Nanoparticles (CPnPs) or cubosomes are liquid crystalline nanoparticles with the

same unique properties of the bulk cubic phase. Their name, cubosomes, reflect to their dispersion particle shape which consists of cubic liquid crystalline phase consisting of a highly twisted bicontinuous structures, two congruent non-intersecting water channels separated by continuous lipid bilayer. [4]

A secondary vehicle is needed for loading cubosome into a suitable and convenient topical formulation. Bioabsorbable polymers such as hydrogel make the magic possible. Cubogels are the cubosomal dispersion of hydrogel. Due to the similar cubic phase structure between the cubosomes and the stratum corneum, the cubosomes have penetration enhancing effect on the skin as the lipid part of the particles mix with the lipids of the stratum corneum and consequently fluidize the stratum corneum .

In this regard, it would be a significant achievement to provide ketoprofen-based cubogel to form biocompatible and bioadhesive transdermal dosage form as well as the rapeutically effective nanocarriers leading to a significant decrease in ketoprofen side effects. The present study is concerned with the development of ketoprofen loaded cubogel to reduce the gastro intestinal effects with sustained bioavailability. [5,6]

MATERIALS AND METHODS

Ketoprofen and Poloxamer were obtained from Yarrow Chem Products, Mumbai. The purity of the samples compiled with USP-NF analytical specifications. Glyceryl Monooleate was procured from Otto Chemika-Biochemika reagents, Mumbai. All other chemicals used were of analytical grade and obtained commercially.

Methods

Preformulation Studies: The organoleptic properties of drug were studied and compared with pharmacopoeial specifications. Melting point of ketoprofen was determined by capillary method. The solubility study of ketoprofen was carried out in different solvents like DMSO, ethanol, phosphate buffer 7.4 and purified water.

Compatibility study was carried out for pure drug, excipients, and drug: excipient mixture in the ratio of 1:1. The effect of the excipient on the major absorption peaks of ketoprofen was observed to determine the compatibility of the drug and excipients.

Method validation for ketoprofen in ph 7.4 by uv-visible spectrophotometer:

The calibration curve for ketoprofen in pH 6.4 phosphate buffer was plotted by using double beam UV-visible spectrophotometer (Shimadzu Co. Ltd., Japan). The stock solution was scanned in the 200-400nm UV region. The absorbance maximum (λmax) was noted for ketoprofen. The linear regression analysis was carried out for the concentration range of 4-20 µg /ml in triplicate. Accuracy was determined from mean recovery obtained from three different concentration level of ketoprofen solution. [7-9]

Preparation of Ketoprofen Loaded Cubosomes by Top-Down Technique

Accurately weighed quantity of Glyceryl monooleate and Poloxamer 407 in different ratios were mixed and melted in a water bath at 60^0C. To the above mixture accurately weighed Ketoprofen drug was added and mixed well. The clear lipid solution obtained was added slowly by drop by drop to preheated (60 ^{0}C) distilled water of suitable quantity by continuous stirring. After complete addition of lipid phase it was kept aside for one day to attain equilibration. There is a formation of two phase system and it is disturbed by stirring. The whole system is taken and subjected for homogenization at 1200 rpm for 2hr under room temperature. The prepared dispersions were stored in closed glass vials at room temperature protected from direct sunlight and later evaluation was carried out. [10]

Table 1: Formulation of Ketoprofen loaded cubosomal dispersions

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ketoprofen(mg/)	200	200	200	200	200	200	200	200
Glyceryl Monooleate (%w/w)	5	7.5	10.0	12.5	15.0	17.5	20.0	22.5
Poloxamer 407(%w/w)	0.5	0.5	0.5	0.5	1.0	1.0	1.0	1.0
Distilled water(ml)	94.50	91.69	88.57	86.40	83.37	80.77	78.16	75.57

Characterization and Evaluations of Ketoprofen Cubosome

1. Visual Examination

The dispersions were visually assessed for optical appearance [e.g., colour, turbidity, homogeneity, presence of macroscopic particles], about one week after preparation. The visual assessment was used as an initial screen to rapidly exclude very poor dispersions from further study. A well dispersed sample contained no visible aggregates and possessed a milky white consistency.

2. Particle Size Analysis

The particle size of cubosomes was determined by dynamic light scattering technique using Horiba particle size analyzer. Samples were diluted in particle-free purified water and measured at 25^0C. Each value represents the average of 3 measurements.

3. Zeta potential

Zeta potential of the prepared cubosomal dispersion was studied to determine the surface charge of the nanoparticles which is important for predicting the long term stability of the colloidal dispersion. The high zeta potential values provide sufficient electric repulsion which in turn prevents particles aggregation. It is also determined by dynamic light scattering technique using Horiba particle size analyzer. Electrophoretic light scattering method was utilized for zeta potential measurement.

4. Polydispersity index

PDI is used to estimate the average uniformity of a particle solution, and larger PDI values correspond to a larger size distribution in the particle sample. PDI was obtained by cumulative analysis of results from Horiba particle size analyser using Malvern software.

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

TEM observations were performed to know the morphology of liquid crystals formulations following negative staining with sodium phosphotungstate solution (0.2% w/v). The grid was allowed to air dry, and samples were viewed under transmission electron microscope (TEM, Jeol/JEM 2100, Tokyo, Japan). The experiment was conducted at room temperature, and micrograph was taken at a suitable magnification power.

6. Entrapment Efficiency (EE)

For the determination of entrapment efficiency, the cubosomes from the resulting dispersions were first separated by centrifugation. The separation of the free (nonentrapped) drug from the entrapped drug in the cubosome dispersion was achieved by centrifugation at 8000 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 260 nm.

The percent of encapsulation efficiency (%EE) was determined by the following equation:

$$\% \text{ of EE} = C_t - C_f / C_t \times 100$$

where,

C_t is equal to total drug concentration and C_f is equal to free drug concentration.

7. In Vitro Drug Release Study

Studies were performed for all the formulations. In vitro skin permeation studies were performed using bi chamber donor receiver compartment model (Franz diffusion cell). The formulation was taken in the donor compartment and phosphate buffer pH 7.4 was taken in the receptor compartment. The cellophane membrane, previously soaked overnight in the diffusion medium (phosphate buffer pH 7.4) was placed between the donor and receptor

compartment. Cubosomal formulation (10 ml) was placed on the dialysis membrane, which is in contact with the receptor medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer with continuous stirring and the temperature of the medium was maintained at 37±0.5^{0}C. Samples were withdrawn from the receptor cell at specified time intervals of 1, 2, 3, 4, 5, 6, 7, 8 and 12 hours. Each time immediately after the removal of the sample, the medium was compensated with fresh Phosphate buffer (pH 7.4). The cumulative amount of drug from cubosomes permeated through synthetic membrane was plotted against time. [11,12]

Preparation of Ketoprofen Loaded Cubosome Based Hydrogel

Ketoprofen cubosomal topical gels were prepared by cold mechanical method using carbopol 940 as gelling agent. The required quantity of carbopol 940 was weighed. Weighed polymer was added slowly in the beaker containing distilled water (40ml) with continuous stirring at 400-600 rpm. The mixture was stirred continuously for 1h until it forms a clear gel. To this optimized cubosomal dispersion equivalent to 200 mg ketoprofen was added and mixed proparly.Triethanolamine (0.5%) was added to bring the pH neutral. Penetration enhancer propylene glycol was added with stirring. Then glycerol was added to the gel to balance its viscosity. Methylparaben was added as preservative. The final quantity was made up to 100gm with distilled water. The prepared gel was kept for 24h for complete polymer desolvation.

Table 2: Formulation of Optimized Cubosome Loaded Hydrogel

Ingredients	Quantity
Ketoprofen cubosome dispersion	Equivalent to 200 mg ketoprofen
Carbopol	2% w/w
Propylene glycol	3 ml
Glycerol	0.25 ml
Methyl praben	0.075 mg
Triethanolamine	qs
Distilled water	qs

Preparation of Ketoprofen loaded plain hydrogel

Ketoprofen loaded plain gel were preapared by cold mechanical method using carbopol 934 as gelling agent. The required quantity of carbopol 934 was weighed. Weighed polymer was added slowly in the beaker containing distilled water (40ml) with continuous stirring at 400-600 rpm. The mixture was stirred continuously for 1h until it forms a clear gel. Accurately weighed ketoprofen was dissolved in ethanol & the ethanolic solution of drug was added slowly with stirring (400-600 rpm) in the previously prepared polymer gel. Triethanolamine (0.5%) was added to bring the pH neutral. Penetration enhancer oleic acid and propylene glycol was added with stirring. Then glycerol was added to the gel to balance its viscosity. Methylparaben was added as a preservative. The final quantity was made up to 100gm with distilled water. The prepared gel was kept for 24h for complete polymer desolvation.

Evaluations of Optimized Cubosome Loaded Hyrogel (Cubogel

1. **Physical examination**
   Should have a pleasant appearance with respect to color, consistency etc. The prepared cubogel and plain gels were inspected visually for their colour, homogeneity and consistency.
2. **Determination of pH**
   pH of formulations were determined by using digital pH meter by immersing the electrode in gel formulation and pH was measured. The measurement of pH of each formulation was done in triplicate and average values were calculated. The pH meter was calibrated with standard buffer solutions (pH 4 & 7).
3. **Skin Irritancy Test**
   Skin irritation test was performed for the gel formulations on human volunteers to find out any irritation problems which could make it unsuitable for topical use. About 1 g of final formulation to be tested was applied to the sensitive part of the skin (like wrist portion of the hand). The site of application was inspected for irritancy, erythema and oedema.

4. **Drug Content**
   1.0 gm of ketoprofen loaded cubogel was transferred to 50 ml volumetric flask and was diluted with ethanol. 1 ml of this solution was further diluted to 25 ml with ethanol. The drug content was determined by measuring the absorbance at 260 nm using UV- Visible spectrophotometer. The drug content of the drug loaded plain gel was also determined in the same manner.
5. **Viscosity**
   Viscosity of formulations was determined by using Brookfield (DV Pro-II) viscometer with small sample adaptor, spindle no.64.Speed was increased from 10 rpm to 100 rpm and viscosity was noted in cps.
6. **Spreadability studies**
   Spreadability of semisolid formulations that is, the ability of a cream or gel to evenly spread on the skin, plays an important role in the administration of standard dose of a medicated formulation to the skin and the efficacy of a topical therapy. The flow properties of the formulation can affect the spreadability and residence time of the formulation at the application site.

   Spreadability was determined using the formula, **S=M L/t**

   Where, M is the weight (g) placed to the upper slide, L is the increase in diameter, and t is time (sec).
7. **In vitro drug release study**
   Studies were performed for all the gel formulations in ph 7.4 buffer in a manner similar to method used for cubosomal dispersions.
8. **Kinetic modeling**
   The optimized cubosomal gel formulation and plain gel were studied for release kinetics. Coefficient of correlation values were calculated for the linear curves obtained by regression analysis of the plots.
9. **Accelerated Stability Studies**
   Accelerated stability studies for optimized gel formulation (G1) were conducted as per ICH guidelines at 40°C ± 2°C/75% ± 5% RH and at25°C ±2°C/60%±5% RH at sampling intervals of 30, 60 and 90 days respectively. The drug content and pH are determined periodically. [13,14]

RESULTS AND DISCUSSION

Preformulation Studies

The organoleptic properties of the drug were found to be within the standard specification. Melting point was found to be 94^0C. The solubility profile shows, in DMSO, Ethanol, and phosphate buffer drug was freely soluble and in distilled water slightly soluble.

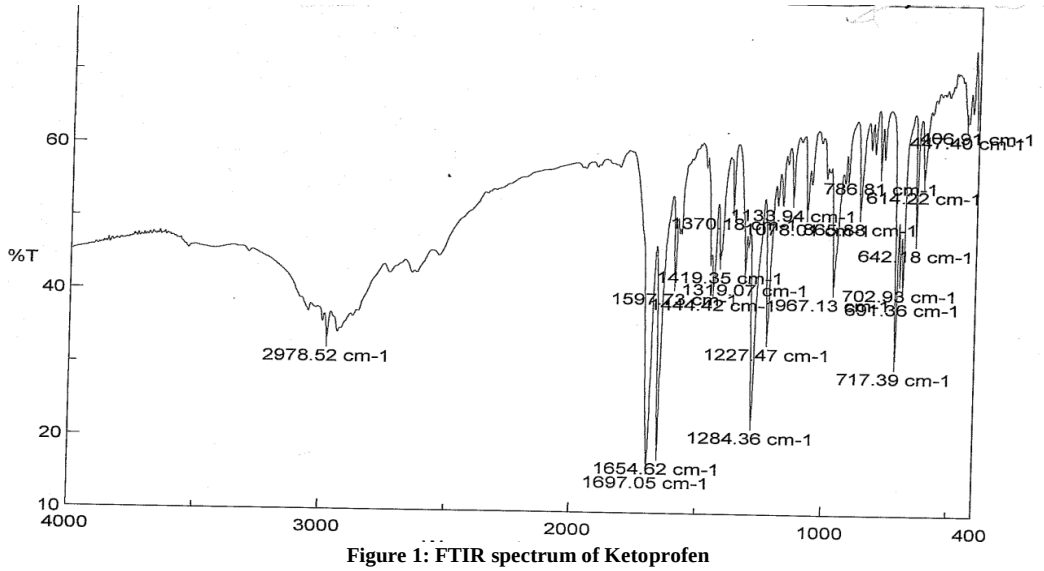

Figure 1: FTIR spectrum of Ketoprofen

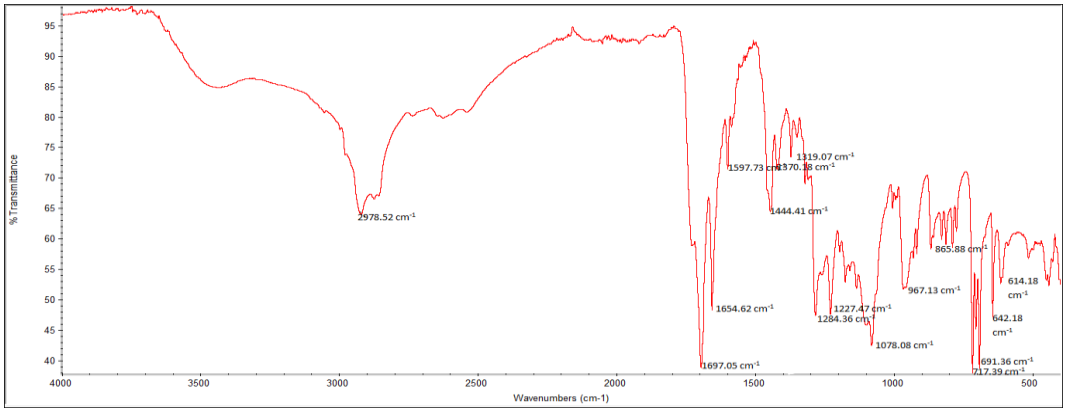

Figure 2: FTIR spectrum of physical mixture of Ketoprofen + Glyceryl monooleate + Poloxamer 407+ Carbopol 934

From drug-excipient compatibility studies, the chemical compatibility was assured by carrying out FTIR special analysis of drug with excipients and by comparing the peaks. Ketoprofen has characteristic absorption peaks Methyl –CH asymmetric stretching at 2978.72 cm $^{-1}$, Carbonyl and C=O streching of ketone at 1697.05 & 1654.62 cm $^{-1}$. 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.

Analytical method validation of fluconazole in pH 7.4 phosphate

The absorbance maximum (λmax) of ketoprofen was found to be 260 nm in pH 7.4 phosphate buffer. The calibration curve was found to be linear for concentration range of 4-20 µg/ml at 260 nm with significant higher value of correlation coefficient, R2 =0.994.

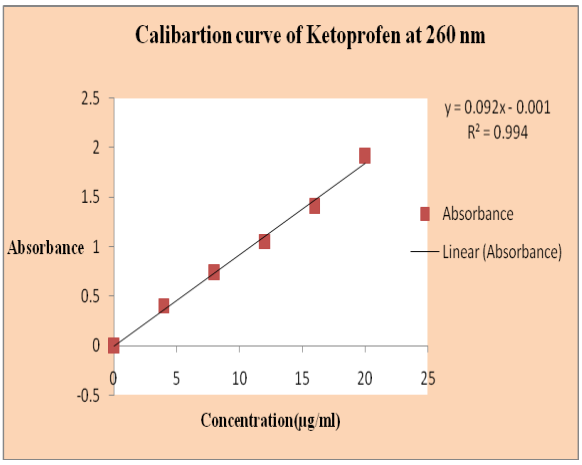

Figure 3: Calibration curve of Ketoprofen in phosphate buffer 7.4 at 260 nm

Characterization of cubosomal dispersion

1. Visual Examination

The dispersion was visually assessed for optical appearance such as color, turbidity presence of aggregates. A well dispersed sample contains no visible aggregates and possessed a milky white consistency.

2. Particle Size

The particle and zeta potential of cubosomes determined by dynamic light scattering technique using Horiba particle analyzer. Particle size measurement was done to confirm that particles of the dispersion are all of cubosomal range (10-500nm). The result showed that as the GMO content increases, the particle size decreases. From figure 4, it was found that the diameter of cubosomes was found to be in the range of 10-500nm and the average particle size was found to be 61.1nm.

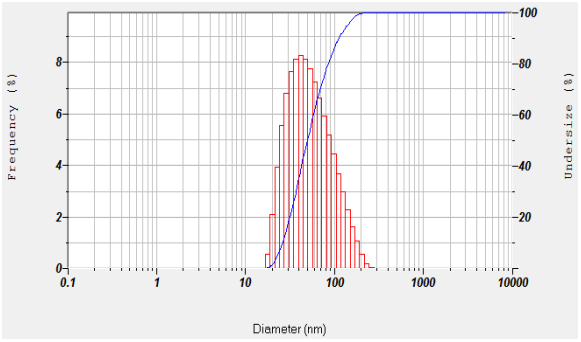

Figure 4: Size distribution of optimized formulation F5

3. **Zeta potential**

Zeta potential is an indication of the stability of the colloidal systems and indicates charge present on the particles of the colloidal systems. Zeta potential of at

least +- 30 mv was normally required to achieve a reasonably stable dispersion. The high zeta value provides sufficient electric repulsion which intern prevents aggregation. From the figure 5, the zeta potential was found to be -46.7 mv, which indicates that cubosomes were stable.

Table 3: Zeta Potential of Ketoprofen Cubosome Dispersion

Formulation code	Zeta potential (mv)
F1	- 26.7±0.001
F2	-39.5±0.003
F3	-33.2±0.002
F4	-33.1±0.001
F5	-46.7±0.004
F6	-20.5±0.002
F7	-24.9±0.001
F8	-26.7±0.003

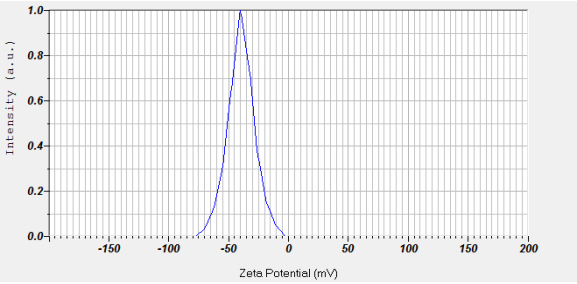

Figure 5: Zeta potential of optimized cubosome F5

4. Polydispersity index

PDI values of all formulation were determined using DLS technique using Horiba particle size analyzer. . The optimized formulation showed a low PDI of 0.443 with uniform particle size distribution.

5. High resolution - Transmission electron microscopy (HR-TEM)

To confirm the formation of cubic structures in the prepared dispersions, the morphology was examined using TEM, and the obtained photomicrographs are presented in figure 6. The transmission electron micrographs show that the prepared cubosomes are in the nano-size, which confirms the results of particle size measurement. Micrographs show that the particles are slightly spherical or cube shape and well separated from each other.

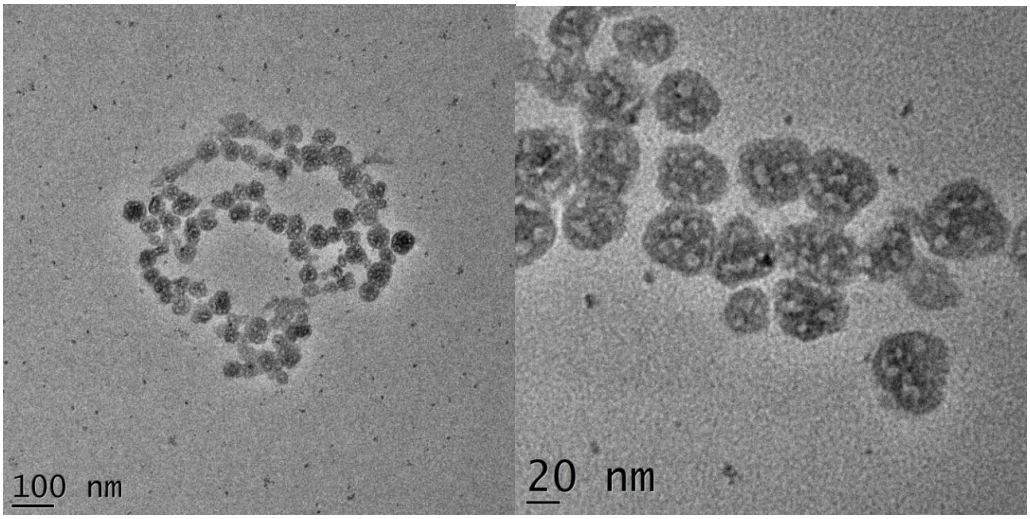

Figure 6: Typical TEM images of Ketoprofen loaded cubosome F5

6. Entrapment efficiency

Drug EE was determined in order to make sure that the added amount of Ketoprofen is present in the cubosome dispersion. The EE of all batches is in the range of 59.02- 86.45 as shown in **table 4** the highest EE was found in the batch F5,consisted of 15% of GMO and 1% poloxamer 407. The EE of ketoprofen into cubic nanoparticles was dependent on the concentration of GMO and poloxamer 407. The result showed that the EE increased, as the amount of lipid and surfactant increased. Increasing the amount of lipid resulted in faster solidification of the cubosomal nanoparticles, due to increased viscosity of the medium. Moreover this would prevent

drug diffusion to the external phase of the medium.

Table 4: Percentage Drug Entrapment Efficiency of Ketoprofen Cubosomes

Formulation code	Drug entrapment efficiency (EE%)
F1	59.32±0.12
F2	74.12±0.23
F3	77.01±0.21
F4	80.14±0.15
F5	86.45±0.16
F6	57.72±0.17
F7	59.16±0.18
F8	60.38±0.19

7. Diffusion study

Diffusion studies were performed for all formulations and formulation F5 was optimized. Drug release was found to be decreased with increasing poloxamer 407 concentration and increased with increasing the GMO concentration from 5 to 22.5%. Cumulative percentage drug release profile of various formulations was shown in the figure 7

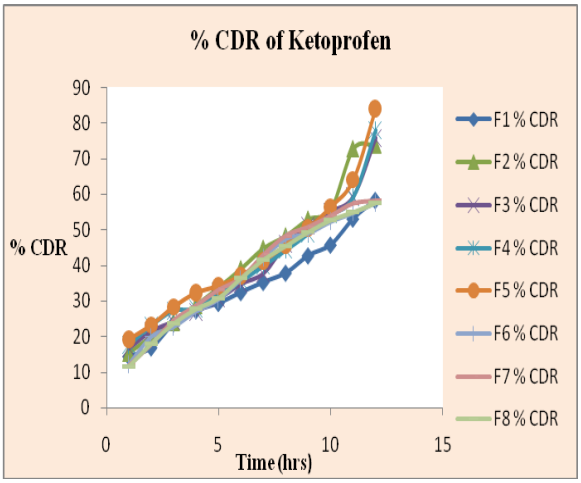

Figure 7: In vitro diffusion profile of Ketoprofen cubosomes F1-F8

Evaluations of optimized cubosome loaded hyrogel (cubogel)

1. Physical examination

Optimized cubosome loaded hydrogel (G1) and drug loaded plain gel (G2) were consistent, viscous with a smooth and homogenous appearance. Cubogel appeared white in colour and plain gel in transparent consistency.

2. Determination of pH

The pH of the formulations was found to be 5.4 for cubogel and 5.31 for drug loaded plain gel. However, the normal skin pH is varied from 4- 7. So the formulations that have this range of pH, they are accepted.

3. Viscosity

The viscosity of the cubogel and plain gel was shown in **table 5** from the figure it was found decrease in the viscosity as the rpm was increased.

Table 5: Viscosity of cubogel & drug loaded plain gel

Rpm	Viscosity of cubogel (cps)	Viscosity of drug loaded plain gel (cps)
10	6300±0.12	5600±0.001
20	5893±0.14	5020±0.003
50	5020±0.11	4325±0.004
100	4065±0.13	3800±0.006

4. Spreadability study

Spreadability studies were carried out for optimized cubosome based gel formulation and compared with the drug loaded plain gel. Spreadability of the formulations is shown in Table 6 cubogel had much more spreadability than the drug loaded plain gel.

Table 6: Spreadability of cubosome based gel and drug loaded plain gel

Formulation code	Time (sec)	Spreadability(g.cm/sec)
Cubogel(G1)	300	10.5± 0.01
Drug loaded plain gel(G2)	300	9.83± 0.03

5. Skin irritancy test

Cubogel and drug loaded plain gel were tested for skin irritancy. No formulation showed irritation, oedema and erythema when applied on skin.

6. Drug content

The percentage drug content of drug loaded plain carbopol 934 gel, as well as cubosome enriched gel was found to be 92.12 and 90.44% as shown in Table 7

Table 7: Percentage drug content of prepared formulations

Formulation code	Drug content %
Cubogel (G1)	90.44±0.02
Drug loaded plain hydrogel (G2)	92.12±0.03

7. In vitro drug release study

The in vitro drug release studies were carried out using Franz diffusion cell for 12 hrs. Figure 8 shows the in vitro drug release study of cubosome based gel

formulation and drug loaded plain gel using Franz diffusion cell. The percentage of cumulative drug released from the formulations were tabulated in Table 8

Table 8: Percentage cumulative drug release data for formulations G1-G2

Time (hrs)	Cubogel (G1)	Drug loaded plain gel(G2)
1	20.47±0.03	24.19±0.13
2	36.21±0.02	34.73±0.15
3	39.70±0.01	48.41±0.17
4	42.14±0.02	57.03±0.12
5	47.00±0.04	69.79±0.13
6	58.61±0.03	87.23±0.15
7	61.39±0.02	91.67±0.16
8	67.79±0.01	-
9	76.26±0.04	-
10	84.31±0.02	-
11	86.94±0.01	-
12	89.04±0.03	-

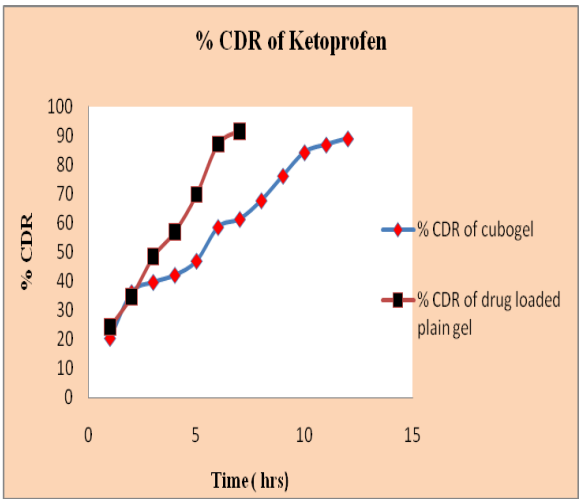

Figure 8: Comparison of percentage cumulative drug release profile of G1 & G2

The optimized cubosome (F5) loaded hydrogel formulation (G1) shows 89.92% drug diffusion (% cumulative drug release [% CDR]) after 12 hr. The result of % CDR shows that loading into a secondary vehicle such as hydrogel had a profound effect on the drug release, i.e. optimized formulation(F5) had drug release of 84% when it was loaded into hydrogel , release increased. The optimum sustained release of drug was shown by formulation G1.

Ketoprofen loaded plain gel showed a percentage cumulative drug release of 91.67 within 7 hrs. From these results it was evident that Ketoprofen loaded cubogel, sustained the release of drug when compared to drug loaded plain gels. The drug release of cubosome enriched gels showed a slower release when compared to plain gel formulation. This may be due to the longer diffusion path the drug has to follow. First the drug has to diffuse from the cubic liquid crystals into the vehicle and from there onto the skin.

8. Kinetic modeling

The optimized cubogel and drug loaded plain gel formulations were studied for release kinetics as shown in table. From the above data it was found that R^2 values of zero order release was higher than the first order release (G2). So the optimized cubosome loaded hydrogel (G1) and drug loaded plain gel follows zero order kinetics with regression coefficient value of 0.9817 and 0.9908 respectively.

Table 9: Kinetic study of cubogel and drug loaded plain gel

Formulation code	Drug release kinetics				
	Zero order R^2	First order R^2	Higuchi R^2	Peppas R^2	
				n values	R^2 value
Cubogel (G1)	0.9817	0.9454	0.973	0.5764	0.9307
Drug loaded plain gel(G2)	0.9908	0.9183	0.9733	0.7082	0.9867

9. Stability studies

pH, drug content , zeta potential and drug release values were analyzed periodically as per ICH guidelines for cubogel formulation G1 as shown in table.

The results obtained from the stability studies showed that the cubogel formulation G1 showed only a slight decrease in the drug content of Ketoprofen at 40^0C after 3 month of storage. The in vitro drug release also slightly decreased after the stability period. This may be due to the decrease in the relative drug content. There was no change in the appearance of the formulation and observed only a slight difference in pH. Zeta potential was slightly increased after one month. From the stability studies it was confirmed that the

formulation of cubosome based gel remained stable at 40^0C and 75% relative humidity.

Table: 10 Stability studies of optimized cubogel formulation G1

Parameters	Before stability studies	After 3 month stability studies
Appearance	Smooth, homogenous & white in colour	Smooth, homogenous & white in colour
pH	5.4	5.36
Drug content (%)	90.44	89.65
% CDR	89.04	88.67
Zeta potential	- 46.7	- 49.8

CONCLUSION

In the present study, cubogel containing Ketoprofen was successfully developed for arthritis. Results in this study shows that the formulation of cubosome dispersion containing Ketoprofen in cubic liquid crystalline nanoparticles provides sustained release of ketoprofen hence avoiding the GI side effects. It was observed that the novel cubic vesicles were able to enhance the drug payload, offered good entrapment efficiency and enhanced drug permeability. In vitro study revealed that cubosomes formulation F5 containing 1% poloxamer 407 and GMO concentration of 15% showed better release, good entrapment efficiency and better stability. Optimized cubosomal formulation was incorporated into carbopol 943 gel base to form cubogel. The study altogether indicated that ketoprofen loaded cubogel can serve as a potential topical gel to treat the arthritis conditions.

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