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Research Article

Formulation and Evaluation of Caffeine-Loaded Cubosomes Hydrogel for Topical Delivery

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Abstract

The goal of the current study was to create and assess a cubosomal hydrogel loaded with caffeine for long-term topical administration. Due to its hydrophilic nature, caffeine, which is widely utilized for its antioxidant, lipolytic, and skin-stimulating qualities, has limited skin permeability in traditional formulations. Glyceryl monooleate (GMO) and Poloxamer 407 were used in the top-down procedure to create cubosomes in order to get over this restriction. Particle size, polydispersity index (PDI), zeta potential, morphology, entrapment efficiency, and compatibility tests were assessed for the produced formulations. With a particle size of 280.4 nm, a PDI of 0.3461, and a zeta potential of −23.64 mV, F3 demonstrated the best qualities among the produced formulations, indicating satisfactory stability. F3's entrapment efficiency was determined to be 88.915 ± 0.148%. After being integrated into a Carbopol 934 hydrogel, the improved cubosomal dispersion was assessed for physicochemical characteristics. The gel had an appropriate pH of 6.72 ± 0.48, a viscosity of 13285 ± 6.12 cps, good spreadability, a consistent drug content of 95.382 ± 0.864%, and no grittiness. Caffeine was shown to be released continuously for up to 24 hours (82.756%), in-vitro drug release tests using Franz diffusion cells, which followed Higuchi diffusion kinetics. Formulation parameters did not significantly change throughout 90-day stability testing. Overall, the findings point to cubosomal hydrogel filled with caffeine as a potential method for improved and long-lasting topical medication administration.

Keywords: Caffeine; Cubosomes; Topical drug delivery; Carbopol hydrogel; Sustained release.

INTRODUCTION

The potential of topical drug delivery systems to decrease systemic adverse effects, enhance patient compliance, and produce localized therapeutic effects has drawn a lot of attention in recent years. However, inadequate medication penetration through the stratum corneum, the skin's main barrier, frequently limits the efficacy of traditional topical formulations. Novel nanocarrier-based technologies, like cubosomes, have been investigated for improved cutaneous and transdermal drug delivery in order to get around these restrictions[1].

Cubosomes are lipid-based nanostructured vesicular systems that self-assemble into bicontinuous cubic liquid crystalline phases. They are primarily made of amphiphilic lipids. These nanocarriers have special structural features, such as a high drug-loading capacity, a large interior surface area, and the capacity to encapsulate both lipophilic and hydrophilic medicines. Because it is biocompatible and can form stable cubic phases when stabilizers like Poloxamer 407 are present, glyceryl monooleate (GMO) is one of the most commonly utilized lipids for cubosome synthesis. Cubosomes' bioadhesive properties and nanometric size improve skin penetration and extend the duration of drug residence at the application location[2].

Caffeine is a methylxanthine derivative widely used in pharmaceutical and cosmetic formulations for its antioxidant, lipolytic, vasoconstrictive, and skin-stimulating properties. It is commonly incorporated in topical preparations for the treatment of cellulite, localized fat deposition, alopecia, and skin aging[3]. Despite its therapeutic benefits, the hydrophilic nature of caffeine and its limited skin permeability may reduce its topical efficacy when formulated in conventional dosage forms. Therefore, incorporation of caffeine into advanced nanocarrier systems like cubosomes can enhance its permeation, improve drug retention within the skin layers, and provide sustained drug release.

Hydrogels are three-dimensional networks of hydrophilic polymers that can hold a lot of water without losing their structural integrity. Because of its superior gelling, thickening, and bioadhesive qualities, carbopol 934 is a polymer that is frequently utilized in topical gel compositions. By combining the benefits of nanocarrier systems with the patient-friendly characteristics of gels, cubosomal dispersion can be incorporated into a

hydrogel basis to improve stability, ease of application, and drug release[4].

Given these advantages, the current study focused on the formulation and evaluation of caffeine-loaded cubosomes, as well as their inclusion into a carbopol-based hydrogel for topical distribution. The produced formulations were tested for entrapment efficiency, particle size, zeta potential, morphology, rheological characteristics, spreadability, drug content, and in-vitro drug release behavior. The goal was to create a stable and effective cubosomal hydrogel technology that could provide continuous caffeine release as well as increased topical distribution.

MATERIAL AND METHODS

Materials

Caffeine was received as a gift sample. Sigma-Aldrich (USA) supplied Glyceryl monooleate (GMO) and Poloxamer 407. Carbopol 934 and Triethanolamine were acquired from a reputable provider. The remaining chemicals and solvents utilized in the investigation were of analytical grade. Distilled water was utilized throughout the experiment.

Preparation of cubosomes

Caffeine-loaded cubosomes were created via the top-down technique. Glyceryl monooleate (GMO) and Poloxamer 407 were precisely weighed and melted together on a water bath at 60°C. Caffeine was dissolved separately in distilled water heated to 70ºC. The molten lipid-surfactant mixture was then introduced dropwise to the caffeine-containing aqueous phase while stirring continuously[5]. The dispersion was agitated for two hours to allow the complete development of cubosomes[6]. The resulting cubosomal dispersion was stored at room temperature, shielded from direct sunlight, and used in subsequent research.

Table 1: Formulation and Design of Cubosomes

Name	Glyceryl Monooleate GMO(g)	Poloxamer 407(g)	Caffeine (mg)	Water (up to ml)
F1	1	0.2	100	50
F2	1.25	0.2	100	50
F3	1.5	0.4	100	50
F4	1.75	0.4	100	50
F5	2	0.6	100	50
F6	2.25	0.6	100	50

Formulation of caffeine loaded Cubosomal Gel:

The cubosomal gel was made utilizing the direct dispersion method. A weighed amount of Carbopol 934 (2% w/w) was dissolved in distilled water and allowed to hydrate and swell for 12 hours. Triethanolamine was then progressively added to balance the pH and create a homogeneous gel. The produced gel base was then combined with the cubosomal dispersion in a 1:2 (w/w) dispersion-to-gel ratio to produce the final cubosomal gel[7].

Table 2: Formulation Design of Cubosomal gel

Sr.no	Ingredients	CG1
1	Caffeine Cubosomal Dispersion(ml)	10
2	Carbopol 934 (%w/v)	2
3	Triethanolamine (mL)	qs
4	Distilled water (mL)	qs

Calibration Curve of Caffeine

A standard stock solution of caffeine was made in distilled water. The stock solution was diluted to reach concentrations of 0, 2, 4, 6, 8, and 10 µg/mL. Each solution's absorbance was measured at 274 nm with a UV-Visible spectrophotometer, using distilled water as a blank. To create the calibration curve, a graph was constructed with concentration (µg/mL) on the X-axis and absorbance on the Y-axis.

Particle Size Analysis

The particle size and polydispersity index (PDI) of the caffeine-loaded cubosomal dispersion were measured using a particle size analyzer. One milliliter of the sample was diluted with 10 mL of distilled water, gently mixed, and analyzed. The particle size distribution and PDI were recorded [8].

Zeta Potential

The zeta potential of the cubosomal dispersion was measured using a Zetasizer. The diluted sample was placed in a zeta cell, and the surface charge was determined to evaluate the formulation's stability[8].

Transmission Electron Microscopy (TEM)

Transmission electron microscopy was used to investigate the morphological and structural properties of the caffeine-loaded cubosomal dispersion. For TEM investigation, the cubosomal dispersion was diluted 1:10 with distilled water. A drop of the diluted material was placed on a carbon-coated copper grid (200 mesh) and left to air dry. The form and size of the cubosomal particles were determined using bright-field imaging at various magnifications, as well as diffraction mode[9].

FTIR Spectral Analysis of Formulation

FTIR was employed for qualitative and quantitative analysis of the formulation. FTIR analysis enables identification of chemical bonds within organic and inorganic compounds by generating characteristic infrared absorption spectra. The obtained spectra provide a unique molecular fingerprint, which was used to identify functional groups and assess possible interactions between formulation components.

Evaluation of Cubosomal Gel

Cubosomal Gel Appearance

The cubosomal gel's appearance was assessed visually for color, clarity/turbidity, homogeneity, and the presence of any apparent macroscopic particles[10, 11].

pH Determination

The pH of all cubosomal gel formulations was measured with a calibrated digital pH meter by immersing the electrode directly into the gel sample[10,12].

Drug Content

A precisely weighed 1 g of cubosomal gel was combined with 100 mL of a suitable solvent (water). The mixture was sonicated and then centrifuged. The resulting supernatant was analyzed for caffeine content using UV spectrophotometry[13].

Rheological Studies

Rheological behavior of the cubosomal gel was evaluated using a viscometer. Approximately 25 g of gel sample was poured in a beaker and allowed to equilibrate for 5 minutes prior to measurement. Readings were taken using a T-spindle rotating at 10 rpm. Measurements were recorded at decreasing spindle speeds, and each reading was performed in triplicate[12,14].

Spreadability Study

The spreadability of the cubosomal gel was determined using the glass slide method. A 0.1 g gel sample was properly weighed and placed in a 1 cm diameter circle on a glass slide before being covered with another glass slide. A weight of 250 g was applied to the upper slide for 5 minutes to compress the gel and achieve a homogeneous thickness. Following compression, an additional 250 g weight was added to the upper slide. The time it took (in seconds) for the two slides to separate was recorded as a measure of spreadability[15].

The spreadability was determined using the following equation:

$$S = \frac{m \times l}{t}$$

where
m= weight applied to the upper slide (g),
l= length of the glass slide (cm), and
t= time required for separation (s).

Homogeneity and Grittiness

A small quantity of the cubosomal gel was pressed gently between the thumb and index finger to assess homogeneity. The presence or absence of any coarse or particulate matter was noted to determine the uniformity of the gel. Similarly, the gel was evaluated for grittiness by tactile sensation, and the texture was recorded accordingly[16,17].

Entrapment Efficiency

Cubosome entrapment efficiency was assessed by measuring the amount of unencapsulated caffeine. A predefined volume of the cubosomal dispersion was transferred to a centrifuge tube and centrifuged for 30 minutes with the appropriate diluent[18]. Following centrifugation, the supernatant was collected and analyzed to quantify the free (unencapsulated) caffeine.

The following equation was used to compute the percentage entrapment efficiency:

$$\text{EE (\%)} = \frac{W_{\text{added drug}} - W_{\text{free drug}}}{W_{\text{added drug}}} \times 100$$

where $W_{\text{added drug}}$is the amount of caffeine added during formulation, and $W_{\text{free drug}}$is the amount of free caffeine present in the supernatant after centrifugation.

In-vitro Drug Release Studies

The caffeine-loaded cubosomal gel was tested for drug release in vitro using a Franz diffusion cell. A cellophane membrane served as the diffusion barrier between the donor and receptor compartments. The receptor compartment held 23 mL and was filled with phosphate-buffered saline (PBS, pH 7.4) as the diffusion medium along with a magnetic bead.

The assembly was placed on a magnetic stirrer and maintained at 37.0 ± 0.5 °C at 100 rpm. One gram of the gel formulation, which is equivalent to 0.5 mg of caffeine, was deposited in the donor compartment on the diffusion membrane surface. To maintain sink conditions, 1 mL samples were removed from the receptor compartment at regular intervals and promptly replaced with an equal volume of new diffusion medium. Air bubbles were carefully avoided beneath the diffusion membrane[19] .

The withdrawn samples were diluted appropriately and examined with UV spectrophotometry.

Stability Studies

Accelerated stability experiments for the improved caffeine cubosomal gel formulation (F3) were undertaken according to ICH recommendations at 30°C ± 2°C / 65% ± 5% RH with sample intervals of 0, 30, 60, and 90 days. The formulation was tested on a regular basis for pH, drug content, and in-vitro drug release[20].

RESULT AND DISCUSSION

The standard calibration curve showed a regression equation of y = 0.0509 x + 0.0176 with an R^2 value of 0.9959, indicating good linearity over the selected concentration range.

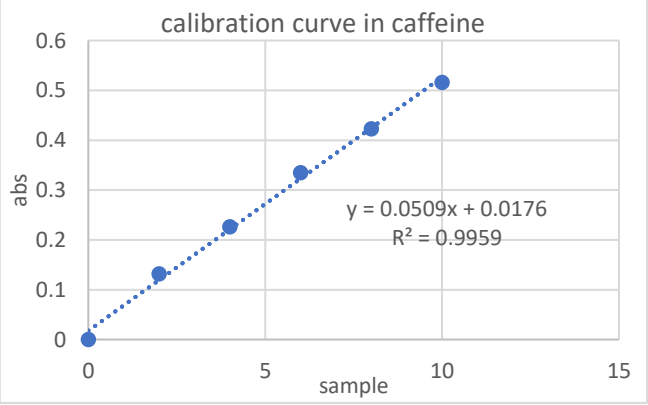


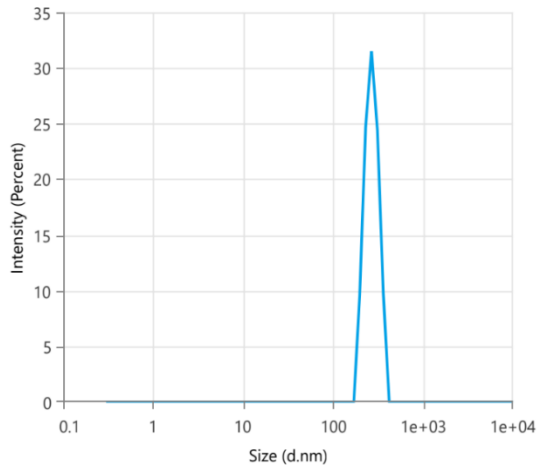
Figure 1: Plotting of calibration Curve by UV spectroscopy

Table 3: Preparation of Calibration Curve of Caffeine in Water

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.132
3	4	0.226
4	6	0.335
5	8	0.423
6	10	0.516

Particle Size:

Particle size analysis revealed that the optimized formulation exhibited a Z-average particle size of 280.4 nm. The polydispersity index (PDI) was found to be 0.3461, indicating moderate uniformity.

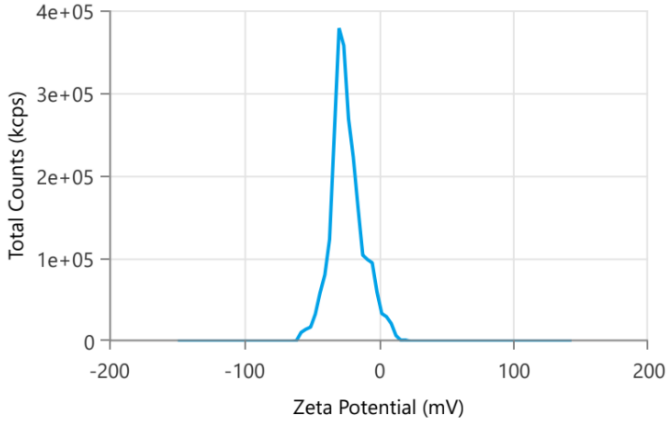


Name	Mean
Z-Average (nm)	280.4
Polydispersity Index (PI)	0.3461
Intercept	0.866
Fit Error	0.0007034
In Range (%)	93.53
Peak 1 Mean by Intensity ordered by area (nm)	271.1

Figure 2: Particle Size Analysis of F3

Zeta Potential:

The optimal formulation has a zeta potential of -23.64 mV, suggesting adequate electrostatic repulsion between particles and indicating acceptable stability of the cubosomal system.



Name	Mean
Zeta Potential (mV)	-23.64
Zeta Peak 1 Mean (mV)	-23.67
Zeta Peak 2 Mean (mV)	18.22
Conductivity (mS/cm)	0.1518
Wall Zeta Potential (mV)	-33.36
Zeta Deviation (mV)	12.21
Derived Mean Count Rate (kcps)	1.49E+05
Reference Beam Count Rate (kcps)	1413
Quality Factor	2.981

Figure 3: Zeta Potential of F3

TEM of Caffeine Loaded Cubosomes:

The TEM images of caffeine-loaded cubosomes show well-dispersed, nearly spherical nanoparticles with smooth surfaces, indicating uniform morphology. The individual cubosome particle observed at higher magnification (left, 20 nm scale) appears dense and structurally intact, suggesting efficient encapsulation of caffeine. The lower magnification image (right, 200 nm scale) demonstrates a relatively narrow size distribution and good dispersion without significant aggregation, which supports the stability of the cubosomal formulation. These features are consistent with effective preparation methods, confirming that the cubosomes are suitable for topical drug delivery applications.

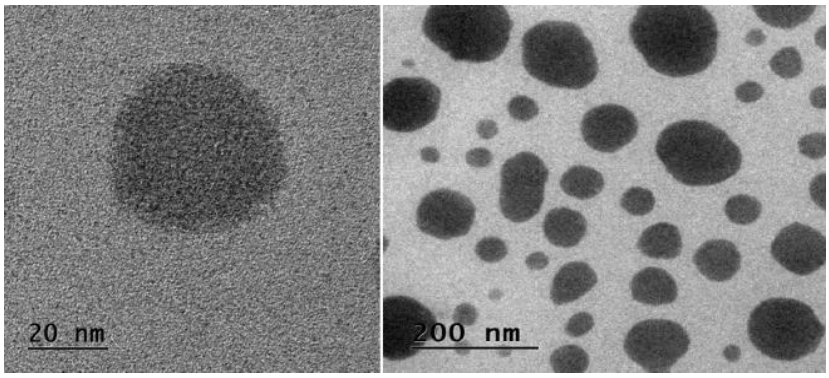


Figure 4: TEM images of caffeine-loaded cubosomes

FTIR Studies:

FTIR analysis confirms drug-excipient compatibility and demonstrates that caffeine remains chemically stable within the cubosomal gel formulation.

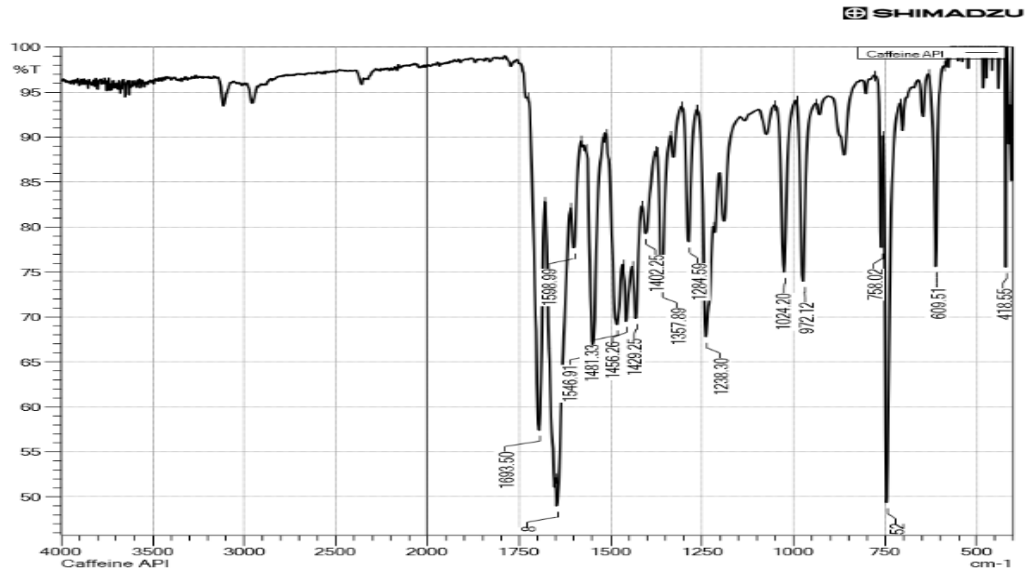


Figure 5: FTIR Spectrum of Caffeine

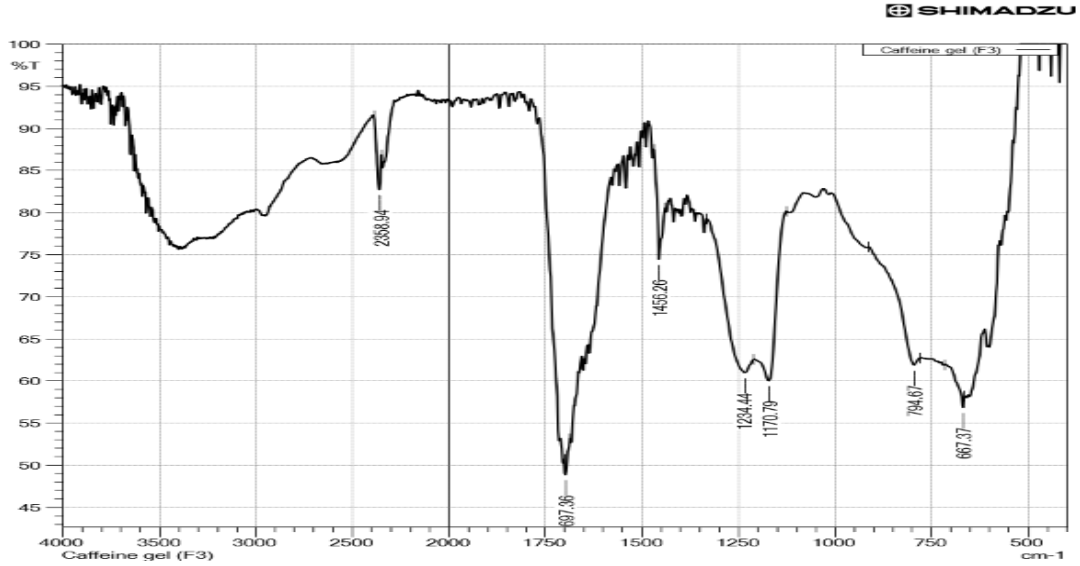


Figure 6: FTIR Spectrum of Caffeine Loaded Cubosomal Gel

Visual Examination & Visual Appearance of Caffeine Loaded Cubosomal Gel (CG1)

The prepared caffeine-loaded cubosomal gels were visually examined for consistency and appearance. Batch F3 showed a smooth, homogeneous texture with no visible lumps and was selected for further studies. CG1 (C934-2%) formed a milky white gel.

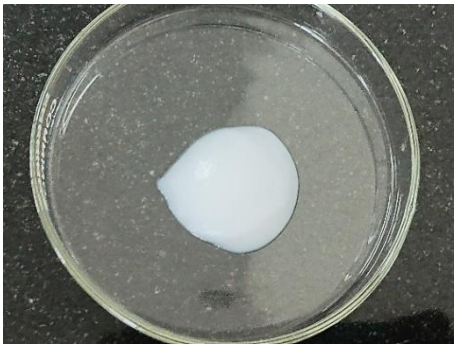


Figure 7: Visual Appearance of Caffeine Loaded Cubosomal Gel

pH Determination:

The pH of formulation F3 was found to be 6.72 ± 0.48, which lies within the physiologically acceptable range for topical gel formulations.

Drug Content:

The caffeine gel formulations had a drug concentration of 95.382 ± 0.864%. The formulation's percentage drug content was within acceptable limits, indicating that caffeine was distributed uniformly in the gel matrix and that the production procedure was suitable.

Rheological Studies:

The viscosity of formulation F3 was found to be 13285 ± 6.12 cps, indicating suitable consistency for topical application.

Spreadability Study:

The spreadability of formulation F3 was determined to be 17.963 ± 0.842 gcm/sec, demonstrating good spreadability characteristics.

Homogeneity And Grittiness:

The formulation F3 was evaluated for homogeneity and grittiness. The results indicated that F3 was homogeneous in nature and showed no signs of grittiness.

Percentage Drug Entrapment:

The proportion of drug entrapment in all formulations ranged from 57.842 ± 0.158% to 88.915 ± 0.148%. The findings show that concentration has a substantial effect on the entrapment efficiency of caffeine-loaded cubosomes. An increase in concentration resulted in improved drug entrapment. Among all the formulations, F3 exhibited the highest entrapment efficiency (88.915 ± 0.148%). Based on the entrapment efficiency results, formulation F3 was selected as the optimized batch for further evaluation studies.

Table 4: Percentage Entrapment Efficiency of Caffeine in Different Formulations

Formulation Code	% Entrapment Efficiency
F1	57.842 ± 0.158
F2	61.374 ± 0.132
F3	88.915 ± 0.148
F4	70.925 ± 0.165
F5	76.312 ± 0.149
F6	82.456 ± 0.176

***In-vitro* Drug Release:**

The in-vitro drug release of F3 showed a sustained release, reaching 82.756 ± 0.193% at 24 hours.

Table 5: In-Vitro Drug Release of Caffeine loaded Cubosomal Gel from Formulation F3

Sr. No.	Time (hr)	% Drug Release of F3
1	0	0
2	0.5	8.124 ± 0.338
3	1	19.486 ± 0.284
4	2	23.915 ± 0.602
5	4	32.774 ± 0.451
6	6	44.658 ± 0.517
7	8	52.983 ± 0.671
8	12	60.214 ± 0.884
9	24	82.756 ± 0.193

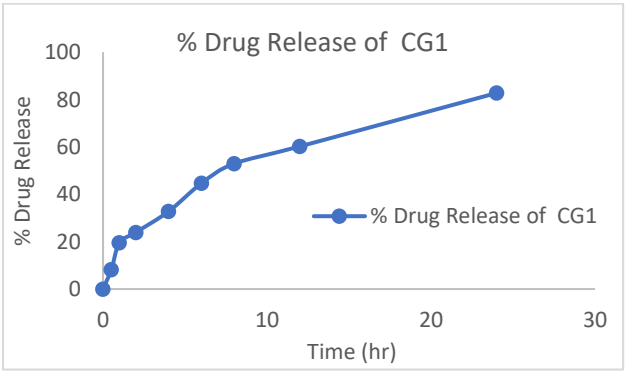


Figure 8: % Drug Release of Caffeine Loaded Cubosomal Gel

Zero order Kinetics:

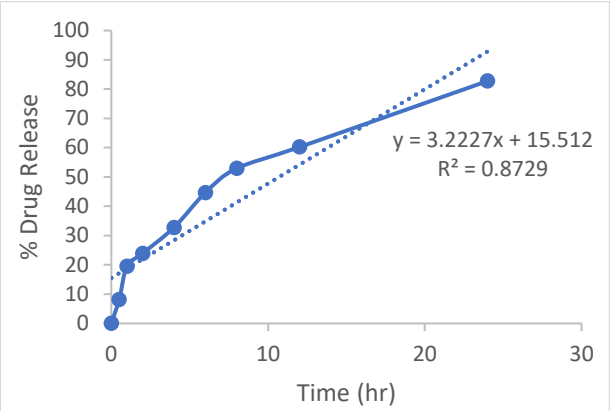


Figure 9: Zero order Kinetics

First order Kinetics:

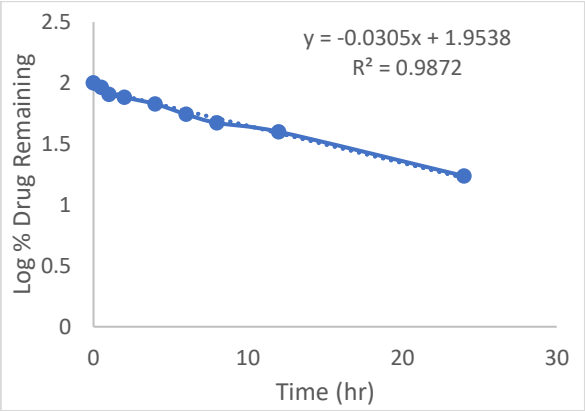


Figure 10: First order Kinetics

Higuchi's Model:

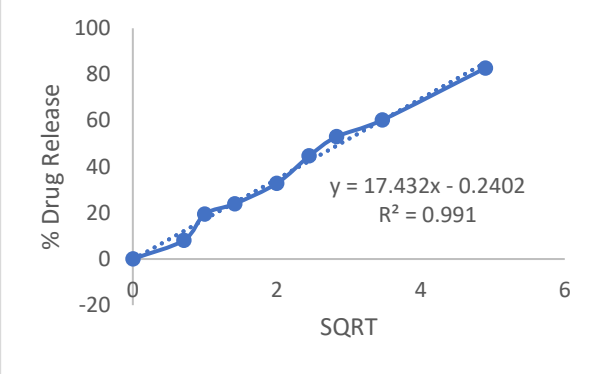


Figure 11: Higuchi's Model

Korsmeyer-Peppas Model:

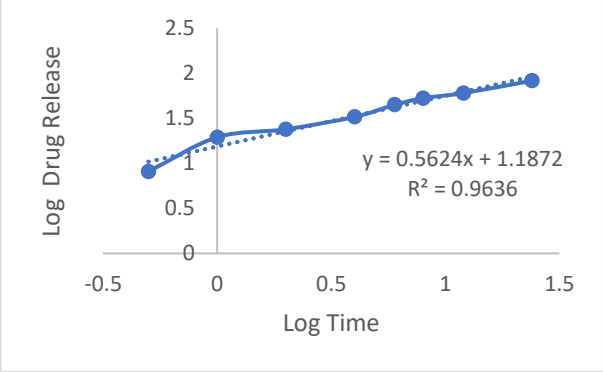


Figure 12: Korsmeyer-Peppas Model

Drug Release Kinetics of Formulation F2

The F2 release kinetics were assessed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, with correlation coefficients (R^2) of 0.8729, 0.9872, 0.991, and 0.9636, respectively, indicating that the drug release largely followed the Higuchi diffusion mechanism.

Table 6: Kinetic Equation Parameter of CG1

Formulation	Zero order	First Order	Higuchi model	Korsemeyer's model
CG1	0.8729	0.9872	0.991	0.9636

Stability Studies:

The cubosomal gel remained stable over 90 days, with minimal changes in pH (6.5–6.72), drug content (91.024-95.382%), and drug release (81-82.756%), indicating good formulation stability.

Table 7: Stability Study of Cubosomal Gel

Time	pH	Drug content	Drug release
0	6.72 ± 0.48	95.382 ± 0.864%	82.756 ± 0.193
30	6.5±0.98	94.17±0.468%	81.45
60	6.5±0.76	93.42±0.795%	82±0.452
90	6.7±0.2	91.024±0.756%	81±0.75

CONCLUSION:

The current study aims to create and analyze caffeine-loaded cubosomes before incorporating them into a Carbopol-based hydrogel for long-term topical administration. The results show that cubosomes made from glyceryl monooleate (GMO) and stabilized with Poloxamer 407 were successfully created using the top-down technique.

Among the prepared batches, formulation F3 showed comparatively higher entrapment efficiency (88.915 ± 0.148%), nanosized particle distribution (280.4 nm), acceptable polydispersity index, and a zeta potential (-23.64 mV) indicative of physical stability. These findings suggest that lipid concentration plays a significant role in drug entrapment and release behavior.

The improved cubosomal dispersion was successfully integrated into a Carbopol 934 hydrogel base. the resulting gel demonstrated acceptable physicochemical properties, including appropriate pH (6.72 ± 0.48), satisfactory viscosity, good spreadability, uniform drug content, and absence of grittiness, indicating suitability for topical application.

In-vitro drug release studies revealed sustained release of caffeine over 24 hours, with release kinetics best fitting the Higuchi model, suggesting diffusion-controlled drug release from the gel matrix. Stability studies conducted over 90 days under accelerated conditions showed no significant changes in pH, drug content, or release profile, indicating reasonable formulation stability during the study period.

Overall, the findings support that incorporation of caffeine into a cubosomal hydrogel system may enhance drug retention and provide sustained topical delivery compared to conventional gel systems. However, further studies such as ex-vivo skin permeation, in-vivo evaluation, and long-term stability studies are required to confirm its clinical applicability.

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Informed Consent Statement: Not applicable.

Ethical Approval: Not applicable.

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