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Research Article

Design and Characterization of Nicotine Polacrilex-Loaded Cubosomal Nanogel for Enhanced Topical Drug Delivery

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Abstract

The effective encapsulation of hydrophilic and lipophilic medications is made possible by cubosomes, which are nanostructured lipid carriers with a bicontinuous cubic liquid crystalline structure. Nicotine Polacrilex-loaded cubosomal Nanogel was designed and characterized in this study to improve topical drug delivery. Glyceryl monooleate (GMO) was used as the lipid and Poloxamer 407 as the stabilizer in the top-down method of creating cubosomes. The optimized cubosomal dispersion (NP3) demonstrated acceptable stability and nanoscale size with a zeta potential of -15.57 mV, a particle size of 134.6 nm, Drug content of nanogel of 91.22± 0.34% and a high entrapment efficiency of 90.71 ± 0.42%. A cubosomal Nanogel formulation was created by combining the optimized dispersion with Carbopol 934 gel base.

The produced gel had a smooth appearance, good homogeneity, a suitable viscosity (12358 ± 6.12 cps), an acceptable pH (6.52 ± 0.59), and a satisfactory spreadability (17.963 ± 0.842 g·cm/sec). Diffusion-controlled drug release was indicated by Franz diffusion cell in vitro drug release studies, which showed sustained release behavior for up to 6 hours after Higuchi diffusion kinetics (R^2 = 0.9799). Ultimately, the Nicotine Polacrilex-loaded cubosomal Nanogel showed promise as a topical drug delivery system with sustained release.

Keywords: Nicotine Polacrilex, Cubosomes, Topical drug delivery, Carbopol Nanogel, Sustained release

INTRODUCTION

The characteristic bicontinuous cubic liquid crystalline phase of cubosomes, which remain nanostructured lipid carriers, is created when exact amphiphilic lipids self-assemble with the aid of water and appropriate stabilizers. A lipid bilayer that divides two continuous but non-intersecting water channels makes up the three-dimensional periodic building of these nanoparticles. Hydrophilic, lipophilic, and amphiphilic medicinal molecules can be effectively encapsulated thanks to this exclusive internal architecture's enormous interfacial surface area.[1]

Studies on lipid phase behavior, which showed that lipids such phytantriol and glyceryl monooleate (GMO) formed persistent cubic phases ensuing hydration, gave rise to the idea of cubosomes. Subsequently, dispersion techniques made it possible to create nanoscale cubic particles that could be used in medicinal submissions since they were stabilized by polymers like Poloxamer 407. Cubosomes have garnered significant interest as cutting-edge drug delivery devices because of their bioadhesive properties and structural durability.[1]

For oral, topical, transdermal, ocular, and brain-targeted drug delivery submissions, cubosomes are promising carriers due to their highly ordered internal channels, which provide superior structural stability and sustained drug release appearances compared to conventional vesicular systems like liposomes. Additionally, their lipid composition improves compatibility with biological membranes, improving drug permeation and retention at the target site.[2]

When added to gel systems, often known as "cubogels," cubosomes have been shown to improve skin penetration and prolong the retention of antifungal and anti-inflammatory medications in topical formulations. In ocular drug delivery systems, where controlled drug release and extended residence duration are critical for healing efficiency, their bioadhesive and sustained-release qualities have also been utilized. Additionally, because cubosomal systems can improve drug permeability and bioavailability, they have been studied for brain-targeted oral delivery, especially in neurodegenerative diseases.[3]

By fusing the mechanical strength and patient acceptance of hydrogels with the structural benefits of cubic phases, the incorporation of cubosomes into hydrogel matrices has further increased their application potential. Still, studies that contrast cubosomal systems with other lipid-based carriers, such liposomes and nanoemulsions, emphasize how stable and effective they are at loading drugs.[4]

Cubosomes are a flexible and effective nanocarrier platform with great potential in contemporary medication delivery, according to the expanding body of research. Their significance in the production of pharmaceutical formulations is highlighted by their capacity to improve permeability, offer controlled release, protect labile medications, and increase solubility. [5]

MATERIAL AND METHODS

Materials

A free sample of Nicotine Polacrilex was acquired. We purchased Poloxamer 407 and Glyceryl Monooleate (GMO) from Sigma-Aldrich (USA). Triethanolamine and carbopol 934 were acquired from a licensed vendor. Every additional chemical and solvent employed in the research was of analytical quality. For the duration of the trial, distilled water was utilized.

Preparation of Cubosomes

The top-down approach was used to create cubosomes filled with nicotine Polacrilex. Poloxamer 407 and precisely weighed glyceryl monooleate (GMO) were melted together at 60 °C in a water bath. Distilled water that had been boiled to 70 °C was used to dissolve Nicotine Polacrilex individually. The aqueous phase containing Nicotine Polacrilex was then continuously stirred while the melted lipid-surfactant mixture was added dropwise [6]. For two hours, the dispersion was agitated to enable the cubosomes to fully develop. For later research, the resultant cubosomal dispersion was stored at room temperature and shielded from the sun.[7]

Table 1: Formulation Design of Cubosomes

Name	Glyceryl monooleate(g)	Poloxamer 407(g)	Drug(mg)	Water (up to)
NP1	2.5	0.3	100	50
NP2	2.0	0.3	100	50
NP3	1.5	0.3	100	50
NP4	2.5	0.25	100	50
NP5	2.0	0.25	100	50
NP6	1.5	0.25	100	50

Formulation Nicotine Polacrilex loaded Cubosomal Gel:

The direct dispersion method was used to prepare the cubosomal gel. For 12 hours, distilled water was used to dissolve a weighed amount of Carbopol 934 (2% w/w) so that it may hydrate and swell. The pH was then adjusted and a homogenous gel was produced by progressively adding triethanolamine. To create the final cubosomal gel, the prepared gel foundation was then combined with the cubosomal dispersion in a 1:2 (w/w) ratio of dispersion to gel.[8]

Table 2: Formulation Design of Cubosomal gel

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

Calibration Curve of Nicotine Polacrilex

Nicotine Polacrilex was made as a normal stock solution in distilled water. From this stock solution, appropriate dilutions were made to obtain concentrations of 0, 2, 4, 6, 8, and 10 µg/mL. A UV-visible spectrophotometer was used to test each solution's absorbance at 262 nm, using distilled water as a blank. A graph was plotted with concentration (µg/mL) on the X-axis and absorbance on the Y-axis to obtain the calibration curve.

Particle Size Analysis

A particle size analyzer was used to measure the synthesized Nicotine Polacrilex-loaded cubosomal dispersion's particle size and . After diluting one milliliter of the cubosomal dispersion with ten milliliters of distilled water, the mixture was gently stirred. After that, the diluted sample was moved to the sample cell and put within the instrument's sample holder unit. Values for the particle size distribution were noted appropriately.[9]

Zeta Potential

A Zeta Sizer (Malvern Instruments Ltd, Malvern, UK) was used to measure the produced Nicotine Polacrilex-loaded cubosomal dispersions' zeta potential. The surface charge of nanoparticles, which is essential for forecasting the long-term stability of colloidal dispersions, is indicated by the zeta potential. In order to prevent aggregation and preserve dispersion stability, high zeta potential values produce enough electrostatic repulsion between particles.[10]

FTIR Spectral Analysis of Formulation

The formulation was analyzed both qualitatively and quantitatively using Fourier Transform Infrared Spectroscopy (FTIR). By producing distinctive infrared absorption spectra, FTIR analysis makes it possible to identify the chemical bonds found in both organic and inorganic molecules. Functional groups were identified and potential interactions between formulation components were evaluated using the acquired spectra, which offer a distinct molecular fingerprint.

Evaluation of Cubosomal Gel

Appearance of Cubosomal Gel

The cubosomal gel's color, homogeneity, clarity/turbidity, and presence of any discernible macroscopic particles were all visually assessed.[10,11]

pH Determination

A calibrated digital pH meter was used to measure the pH of each cubosomal gel formulation by submerging the electrode into the gel sample.[11,12]

Drug Content

100 mL of an appropriate solvent (water) was combined with 1 g of the cubosomal gel that had been precisely weighed. After being sonicated, the liquid was centrifuged. UV spectrophotometry was used to determine the amount of Nicotine Polacrilex in the resultant supernatant. [13,14]

Rheological Studies

A viscometer was used to assess the cubosomal gel's rheological behavior. Before being measured, about 25 g of the gel sample was put in a beaker and given five minutes to equilibrate. T-spindle revolving at 10 rpm was used to take readings. Three duplicate readings of each measurement were taken at progressively lower spindle speeds.[13,15]

Spreadability Study

The glass slide method was used to assess the cubosomal gel's spreadability. A glass slide was covered with another glass slide after a precisely weighed 0.1 g of gel was positioned inside a circle with a diameter of 1 cm. To compress the gel and achieve a consistent thickness, a 250 g weight was applied to the upper slide for five minutes. An extra 250 g weight was fastened to the upper slide following compression. As an indicator of spreadability, the amount of time (in seconds) needed for the two slides to separate was noted.[16]

Spreadability was calculated 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

To test for homogeneity, a tiny amount of the cubosomal gel was gently pushed between the thumb and index finger. To assess the gel's homogeneity, the existence or lack of any coarse or particle materials was recorded. In a similar manner, the gel's grittiness was assessed by tactile perception, and the resulting texture was noted.[17,18]

Entrapment Efficiency

The entrapment efficiency of cubosomes was determined by estimating the amount of unencapsulated Nicotine Polacrilex. A predetermined volume of the cubosomal dispersion was transferred into a centrifuge tube and centrifuged for 30 minutes using a suitable diluent. After centrifugation, the supernatant was collected and analyzed to quantify the free (unencapsulated) Nicotine Polacrilex

The percentage entrapment efficiency was calculated using the following equation:

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

where $W_{\text{added drug}}$ is the amount of Nicotine Polacrilex added during formulation, and $W_{\text{free drug}}$ is the amount of free Nicotine Polacrilex present in the supernatant after centrifugation.[18,19]

In-vitro Drug Release Studies

In-vitro drug release studies of the Nicotine Polacrilex - loaded cubosomal gel was performed using a Franz diffusion cell. A cellophane membrane was used as the diffusion barrier between the donor and receptor compartments. The receptor compartment had a capacity of 23 mL and was filled with phosphate-buffered saline (PBS, pH 7.4) as the diffusion medium along with a magnetic bead.[20]

The entire assembly was placed on a magnetic stirrer and maintained at a stirring speed of 100 rpm and a temperature of 37.0 ± 0.5 °C. One gram of the gel formulation, equivalent to 0.5 mg of Nicotine Polacrilex, was placed in the donor compartment on the surface of the diffusion membrane. At predetermined time intervals, 1 mL samples were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh diffusion medium to maintain sink conditions. Care was taken to avoid the formation of air bubbles beneath the diffusion membrane.[21] The withdrawn samples were suitably diluted and analyzed using UV spectrophotometry.

RESULT AND DISCUSSION

Table 3: Preparation of Calibration Curve of Nicotine Polacrilex

Serial number	Conc. (µg/ml)	Absorbance
1.	0	0
2.	2	0.122
3.	4	0.236
4.	6	0.355
5.	8	0.468
6.	10	0.579

The calibration curve Nicotine Polacrilex was constructed using concentrations ranging from 2 to 10 µg/mL in distilled water. The absorbance was measured at a λmax of 262 nm using a UV spectrophotometer. The standard calibration curve showed a regression equation of y = 0.0579x + 0.0039 with an R^2 value of 0.9998, indicating good linearity over the selected concentration range.

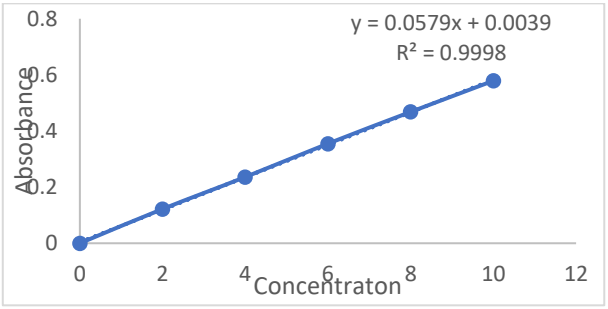


Figure 1: Calibration curve of Nicotine Polacrilex

Evaluation of Nicotine Polacrilex Loaded Cubosomes:

Table 4: Percentage Drug Entrapment

Sr. No.	Formulation Code	% Entrapment Efficiency
1	NP1	74.82 ± 0.93
2	NP2	77.98 ± 0.62
3	NP3	90.71 ± 0.42
4	NP4	82.15 ± 0.57
5	NP5	85.74 ± 0.49
6	NP6	81.90 ± 0.62

The percentage drug entrapment of all formulations was found to be in the range of 53.689 ± 0.140% to 89.915 ± 0.148%. The results indicate that concentration had a significant influence on the entrapment efficiency of Nicotine polacrilex-loaded cubosomes. An increase in concentration resulted in improved drug entrapment. Among all the formulations, NP3 exhibited the highest entrapment efficiency (89.915 ± 0.148%). Based on the entrapment efficiency results, formulation NP3 was selected as the optimized batch for further evaluation studies.

Particle Size:

The particle size analysis revealed that the optimized formulation exhibited a Z-average particle size of 134.6 nm. The polydispersity index (PDI) was found to be 1, indicating moderate uniformity in particle size distribution.

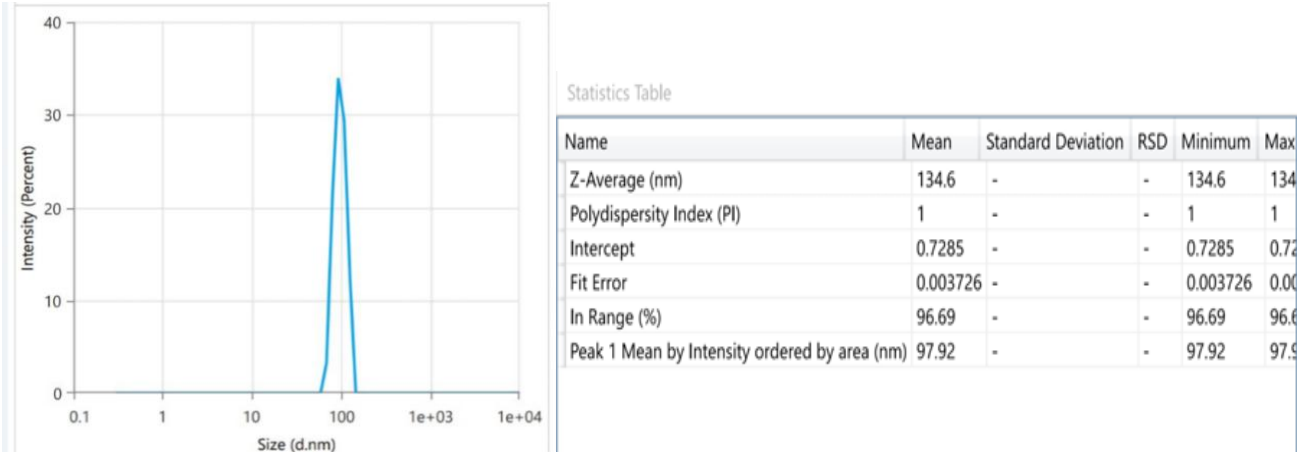
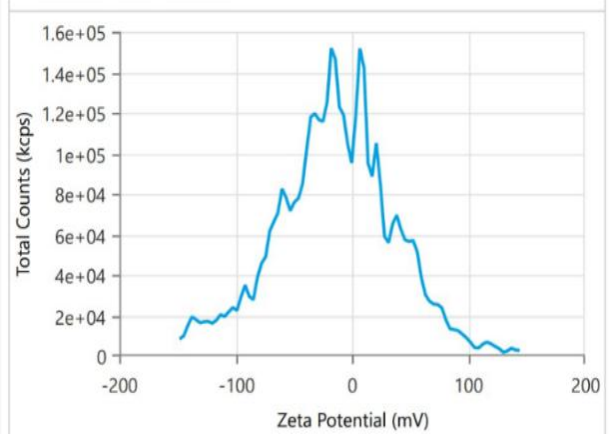


Figure 2: Particle size Analysis of NP3

Zeta Potential:

The optimized formulation exhibited a zeta potential value of -15.57 mV, suggesting adequate electrostatic repulsion between particles and indicating acceptable stability of the cubosomal system.



Name	Mean	Standard Deviation	RSD	Minimum	Maximum
Zeta Potential (mV)	-15.57	-	-	-15.57	-15.57
Zeta Peak 1 Mean (mV)	-138.1	-	-	-138.1	-138.1
Zeta Peak 2 Mean (mV)	-125.4	-	-	-125.4	-125.4
Conductivity (mS/cm)	0.2421	-	-	0.2421	0.2421
Wall Zeta Potential (mV)	-5.356	-	-	-5.356	-5.356
Zeta Deviation (mV)	53.33	-	-	53.33	53.33
Derived Mean Count Rate (kcps)	1897	-	-	1897	1897
Reference Beam Count Rate (kcps)	1437	-	-	1437	1437
Quality Factor	1.027	-	-	1.027	1.027

Figure 3: Zeta Potential of NP3

Visual Examination & Visual Appearance of Nicotine Polacrilex Loaded Cubosomal Gel (CG1):

The prepared Nicotine Polacrilex-loaded cubosomal gels were visually examined for consistency and appearance. Batch NP3 showed a smooth, homogeneous texture with no visible lumps and was selected for further studies. CG1 (C934 - 2%) formed a milky white gel.

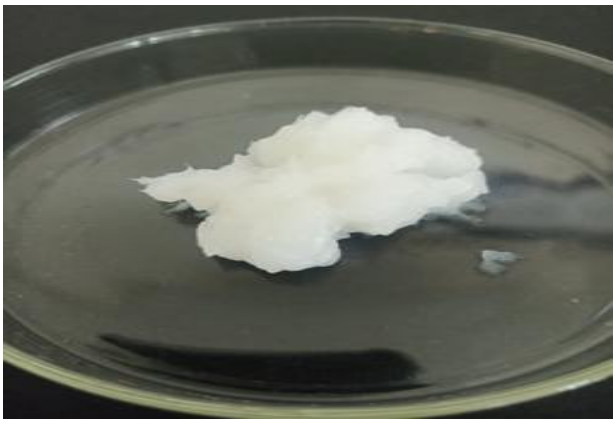


Figure 4: Visual Appearance of NP3

pH Determination:

The pH of formulation NP3 was found to be 6.52 ± 0.59, which lies within the physiologically acceptable range for topical gel formulations.

Drug Content:

The drug content of nicotine polacrilex nanogel formulation was to found be 91.22± 0.34% this value falls within the acceptable limits indicating satisfactory uniformity of the formulations. The results conforms that nicotine polacrilex was uniformly distributed throughout the gel matrix.

Rheological Studies:

The viscosity of formulation NP3 was found to be 12358 ± 6.12 cps, indicating suitable consistency for topical application.

Spreadability Study:

The spreadability of formulation NP3 was determined to be 17.963 ± 0.842 gcm/sec, demonstrating good spreadability characteristics.

Homogeneity And Grittiness:

The formulation NP3 was evaluated for homogeneity and grittiness. The results indicated that NP3 was homogeneous in nature and showed no signs of grittiness.

FTIR Studies:

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

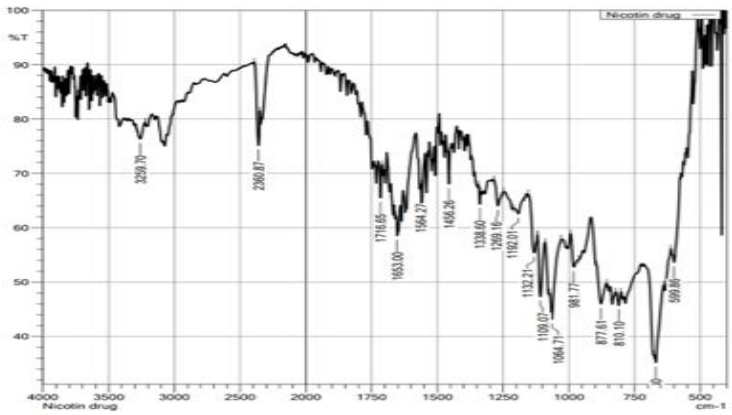


Figure 5: FTIR of Nicotine Polacrilex

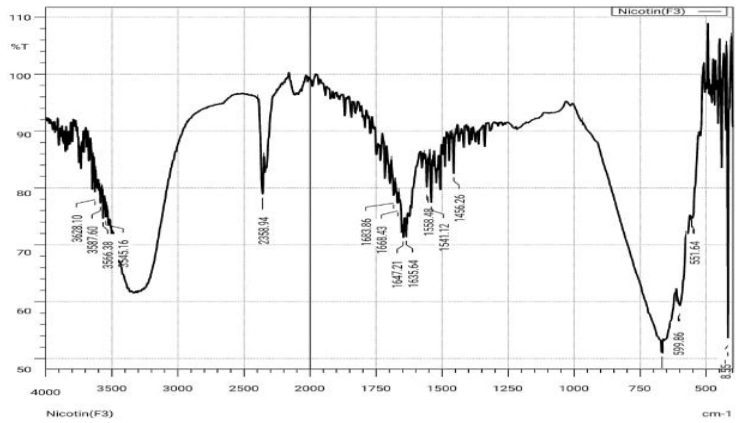


Figure 6: FTIR of formulation of NP3

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

The in-vitro drug release of NP3 showed a sustained release, reaching 60.88 % at 6 hours.

Table 5: % Drug Release of Nicotine Polacrilex Loaded Cubosomal Gel

Time (hr)	% Drug Release of NP3
0	0
1	21.63
2	31.16
3	36.93
4	44.13
5	52.28
6	60.88

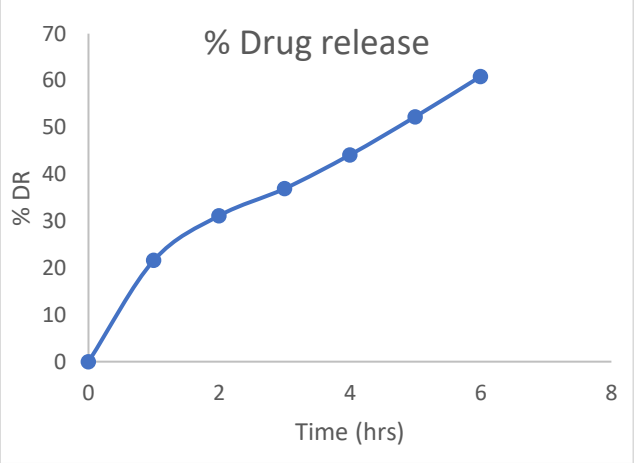


Figure 7: %Drug Release of Nicotine Polacrilex Loaded Cubosomal gel

Zero order Kinetics:

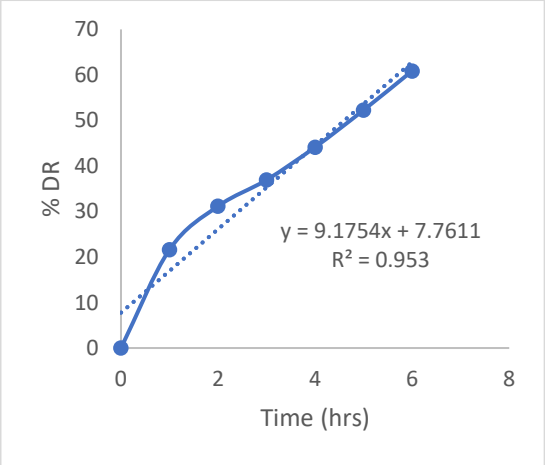


Figure 8: Zero order Kinetics

First order Kinetics:

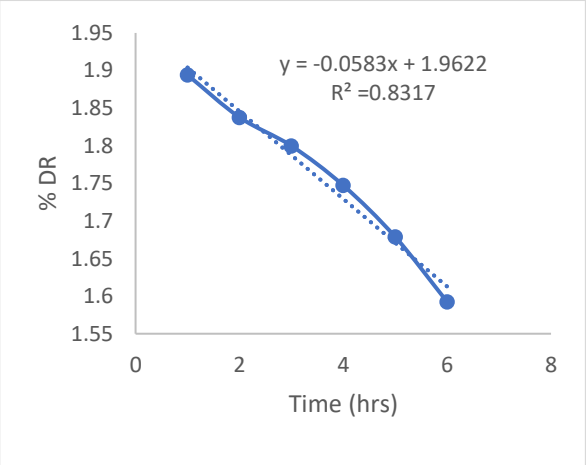


Figure 9: First order Kinetics

Higuchi's Model:

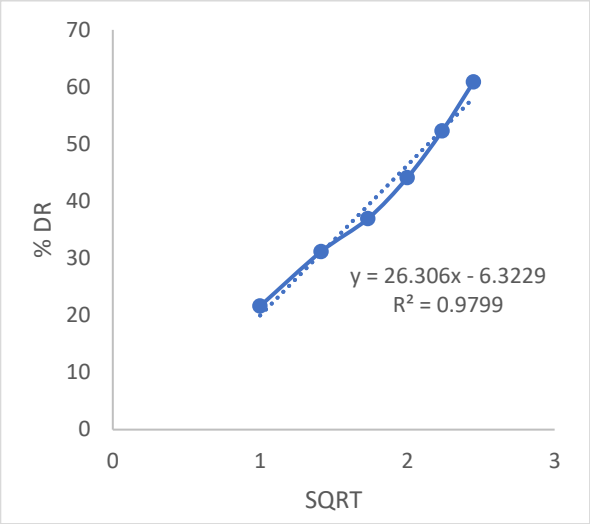


Figure 10: Higuchi's Model

Korsmeyer-Peppas Model:

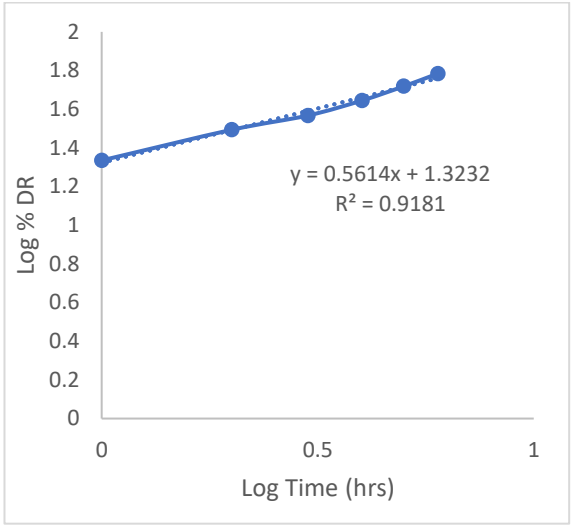


Figure 11: Korsmeyer-Peppas Model

Drug Release Kinetics of Formulation NP3

The release kinetics of NP3 were evaluated using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, with correlation coefficients (R^2) of 0.953, 0.8317, 0.9799, and 0.9181, respectively, indicating that the drug release predominantly followed the Higuchi diffusion mechanism.

Table 6: Kinetic Equation Parameter of CG1

Formulation	Zero order	First Order	Higuchi model	Korsemeyer's model
NP3	0.953	0.8317	0.9799	0.9181

CONCLUSION:

The top-down method was used in this study to successfully formulate Nicotine Polacrilex-loaded cubosomes using glyceryl monooleate and stabilize them with Poloxamer 407. Batch NP3 outperformed all other formulations due to its acceptable zeta potential, appropriate nanoscale particle size, and high entrapment efficiency, all of which indicated stable cubosomal dispersion.

To create a topical cubosomal gel, the optimized cubosomal system was successfully integrated into Carbopol 934 hydrogel. The formulation was suitable for topical application due to its favorable physicochemical characteristics, which included the right pH, viscosity, Drug content, homogeneity, and spreadability. According to the Higuchi model, sustained and diffusion-controlled drug release behavior was validated by in vitro release studies.

The developed cubosomal Nanogel system can be regarded as a promising strategy for long-term topical delivery of Nicotine Polacrilex, potentially enhancing patient compliance and therapeutic efficacy, based on the results obtained.

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Informed Consent Statement: Not applicable

Ethical Approval: Not applicable

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