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Curcumin cubosomal emulgel: Mechanistic approach to improved fungal cell membrane targeting

Hasanpasha N Sholapur[1]*, Yashaswini R[2], Vineeta V Nagathan[2], Fatima Sanjeri Dasankoppa[2], Kamladevi T Kshatriya[2], Arunkumar G Ramesh[3], Mahesh M[2] and Revati D Sagare[2]

[1]Department of Pharmacognosy, [2]Department of Pharmaceutics, KLE College of Pharmacy, Vidyanagar, Hubli 580031, Karnataka, India

[3]Department of Regulatory Affairs, JSS Academy of Higher Education and Research, Mauritius, Droopnath Ramohul Avenue, Bonne Terre, Vacoas, Republic of Mauritius

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Fungal infections, mainly caused by *Candida* and *Aspergillus spp*, are the most common dermatological issue globally. Current treatments face poor absorption and increased resistance. Curcumin from *Curcuma longa* offers effective and safe alternatives that reduce ergosterol production and cause fungal cell death, but is hindered by low bioavailability and photodegradation. A novel approach is developed to enhance curcumin's stability and efficacy. This study aims to develop a novel topical herbal cubosomal emulgel to enhance drug stability, bioavailability, protect against photodegradation, and achieve antifungal activity through controlled and targeted release. Topical herbal cubosomes formulated using curcumin, glyceryl monooleate (GMO), Pluronic F127, and distilled water. The characterisation covered particle length, zeta potential, and morphology analysis by field emission scanning electron microscopy (FESEM). The optimised curcumin-loaded cubosomal dispersion was incorporated into an emulgel with carbopol 940 940 and chitosan using a cold method, then evaluated and optimised using Design of Experiments. (DOE). The F3 (GMO 9%) formulation was optimised based on characterisation and entrapment efficiency. Drug release studies showed the Carbopol 940-based formulation (C1) had an enhanced release rate of 87.8% within 8 hours. Further optimisation with Design of Experiments (DOE) demonstrated the cubosomal emulgel's controlled release of 82.3% over 8 hours. Zone of Inhibition (ZOI) tests against *Aspergillus niger* revealed that the cubosomal emulgel preserved curcumin's photodegradation, unlike pure curcumin. Curcumin photodegradation is effectively prevented by the developed cubosomal emulgel formulation, which also exhibits a controlled drug-release profile.

Keywords: Antifungal activity, Cubosome, Curcumin, Nanoparticles, Photodegradation

IPC code; Int. cl. (2021.01)− A61K 36/00, A61K 36/906, A61P 31/00, A61P 31/10

Introduction

Fungal infections, caused by yeasts and molds, are common dermatological conditions affecting skin and mucous membranes. It is expected that around forty million humans globally are affected by these infections. Superficial infections affect the skin, hair, and nails. Subcutaneous infections are mainly found within the tissues or dermis; they can also move deep into the epidermis and can even be invasive in nature. Most fungal infections are caused by *Candida, Cryptococcus*, and *Aspergillus spp*. Treatment for deep-seated fungal infections, such as invasive Candidiasis, can be more difficult to treat because of the poor absorption potential of medicine released from general topical formulations, which prevents them from reaching the target site[1-3].

When the current state of fungal diseases & antifungal medications is taken into consideration, it may be seen that resistance to the antifungal medications in use has increased. Thus, there is a need to find and create novel, effective, and secure antifungal medications from sources, such as herbal treatments[4-5].

Herbal medicines have a long history and were used for various therapeutic purposes in ancient Indian, Chinese, Egyptian, and Greek medicine. 80% of the world's population gets their primary medical treatment from medicinal plants. They are widely accessible, less expensive, have fewer side effects, and are thought to be safer than the majority of contemporary synthetic pharmaceuticals. Study suggested that phytochemicals are a more effective

*Correspondent author
Email: hasanpashasholapur@gmail.com

source of medicine to combat infections brought on by strong and increasingly common resistance to the application of synthetic antifungal, less toxic antimicrobial agents are required[6-7].

Curcumin is a primary phytochemical of the rhizome *Curcuma longa* L. (Zingiberaceae family), often known as turmeric. Curcumin chemically is diferuloylmethane (1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-three,5-dione). It is a lipophilic polyphenol, a pigment with a yellow-orange colour. This polyphenolic compound, because of its biological activities, has received tremendous attention from researchers. Curcumin's antimicrobial, antioxidant, antibacterial, anti-inflammatory, and anticancer qualities are among its medicinal qualities. Curcumin at its minimum inhibitory concentration (MIC) creates a hydrophobic bond with the fungal cellular membrane, which leads to a marked reduction in ergosterol production. Cell wall depletion and ions seep out (potassium and hydrons), which ultimately causes cell death. It is, however, unstable in inorganic solutions, insoluble in water, and reveals low bioavailability, photosensitivity, insufficient absorption, and brief excretion. As a result, numerous strategies like the usage of adjuvants and drug transport devices, nanocarriers have been employed to cope with the Curcumin issues. Among the nanocarriers, cubosomes, which solubilizes and protect from degradation till it reaches the target area, wherein it achieves controlled release[8-9].

Cubosomes are a class of nanoparticles that range in size from 100 to 500 nm, which are discrete, sub-micron, bicontinuous cubic liquid crystalline phases. Because of their structure, they have been a subject of intense scientific interest for targeted controlled release of bioactive medication applications. It can encapsulate various therapeutic compounds with amphiphilic, hydrophobic, and hydrophilic in nature, and the characteristics offer a promising method for improved bioavailability of medications with low water solubility. The lipid which acts as a permeation enhancer when cubosomes pass through the layers of skin and to increase the stability this nanoparticle cubosomal dispersion is incorporated in emulgel[8,10].

Emulgel that combines emulsion and gel with additional beneficial properties such as greaseless, readily spreadable, easily removable, thixotropic, emollient, non-staining, long shelf life, bio-friendly, clear, and visually appealing, better in terms of patient acceptability and ease of usage, is a few of the advantageous qualities of emulgels for use in dermatology. Gels have many benefits, but one significant drawback is their inability to distribute hydrophobic medications. To get over this restriction, emulgels are made and applied, enabling even a hydrophobic medicinal moiety to benefit from the special qualities of gels[11-12].

This study focuses on developing a novel delivery system for antifungal agents by formulating Curcumin cubosomes using the top-down method. The cubosomal dispersion created is then incorporated into an emulgel, which is designed to enhance the stability of the drug, bioavailability, and resistance to photodegradation, thereby ensuring controlled and targeted release. The characterisation of the prepared nanoparticles includes analysing the particle size and zeta potential using a Zetasizer and examining the surface morphology through Field Emission Scanning Electron Microscopy (FESEM). The emulgel is prepared using a cold method and subsequently evaluated and optimised using Design of Experiments (DOE). This novel approach aims to improve the therapeutic efficacy and stability of antifungal treatments.

Materials and Methods

Materials

In this study, various materials were sourced to develop and test a novel antifungal delivery system. Glycerol monooleate (GMO) was provided as a gift sample by Mohini Pharmaceuticals, Mumbai, Maharashtra, India. Curcumin with a 95% purity (HPLC grade) from SD Fine-Chem Limited, Tarapur, Maharashtra, India. The fungal strains used for testing included *Candida albicans* (ATCC no. 96901) and *Aspergillus niger* (ATCC no. 10581), both obtained from NCIM Pune, Maharashtra, India. Poloxomer-407 from Sigma Aldrich. Carbopol 940 940, Chitosan, Tween 80, Potassium hydroxide, Benzalkonium chloride, Triethanolamine, and potato dextrose broth. All reagents used in the study were of analytical grade, ensuring high-quality and reliable results in the formulation and testing processes.

Pre-formulation studies

Determination of λ max of curcumin

The absorption maxima of pure curcumin were determined by dissolving curcumin in methanol. A sample with a concentration of 10 µg/mL was prepared and scanned using a UV-Visible

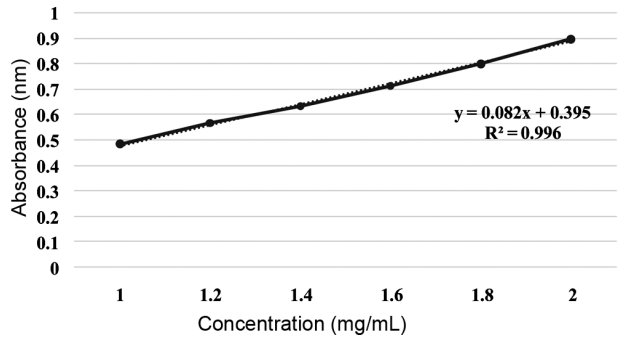

Fig. 1 — Standard calibration graph of curcumin absorbance (nm) Vs concentration (mg/mL).

spectrophotometer (Shimadzu 1800) across a wavelength range of 200 to 800 nm, with methanol serving as the blank[13].

Calibration curve of curcumin in methanol

10 mg of curcumin was precisely weighed and transferred to a 100 mL volumetric flask, where it was dissolved in methanol to obtain a 100 µg/mL concentration, labelled as SS1. From SS1, 10 mL was pipetted and further diluted to 100 mL with methanol to obtain a 10 µg/mL concentration. This solution, SS2, was then diluted by taking 1, 1.2, 1.4, 1.6, 1.8, and 2 mL aliquots up to 10 mL, and their UV absorbance was observed. The absorbance of these solutions was measured spectrophotometrically (Shimadzu 1800) at 429 nm using methanol as the blank. The absorbance values were plotted against the concentrations to obtain the standard calibration curve in Fig. 1, from which the calibration equation and regression coefficient were determined[14].

Antifungal studies-determination of Minimum inhibitory concentration (MIC study)

The sample was prepared by dissolving 2000 µg of curcumin in 5 mL of DMSO to achieve a concentration of 400 µg/mL. Further serial dilutions of the sample were made from 1000 µg/mL to 62.5 µg/mL using potato dextrose broth in sterilised test tubes. Standardised inoculums of the tested fungal strains *Candida albicans* (ATCC no. 96901) and *Aspergillus niger* (ATCC no. 10581), with turbidity adjusted to approximately 0.5 and McFarland standard (1 × 10^8 cfu/mL), were used. 10 µL of these inoculums were placed in each test tube. Positive, negative, and drug controls (Itraconazole 8 mg/mL) were prepared for reference. The test tubes were incubated at 27±2°C for 3 days. After incubation, the growth was observed to determine the MIC results[15].

Compatibility studies

Compatibility studies were conducted using Fourier Transform Infrared Spectroscopy (FTIR) Shimadzu 1800 and Differential Scanning Calorimetry (DSC). FTIR was employed to identify any potential chemical interactions between the drug and the excipients by analysing the characteristic functional groups and their possible shifts or changes. DSC was used to assess the thermal behaviour of the drug and excipients, providing information on their melting points and indicating incompatibility. These studies are essential to ensure that the components of the formulation are compatible. The peaks are shown in Figs. 2,3, and 4[16].

Formulation of curcumin-loaded cubosomes

Cubosomal dispersions of curcumin were prepared using a top-down technique. An accurately weighed amount of glyceryl monooleate (GMO) was melted in a water bath at 60°C, and poloxamer 407 was added. Curcumin was then incorporated into the mixture and stirred with a magnetic stirrer at 500 rpm until fully dissolved. Preheated distilled water (at 60°C) was then added dropwise to the solution while continuously stirring for 30 minutes. The mixture was left undisturbed for 24 hours and then homogenised at 15,000 rpm for 15 minutes at room temperature. The resulting liquid dispersion of cubosomes was stored at room temperature, protected from direct sunlight, for further study[17]. The formulation table for curcumin cubosomal dispersion is given in Table 1.

Characterization of curcumin cubosomal dispersion

Determination of particle size, zeta potential, and polydispersity index

In this study, the Panalytical ZetaSizer Malvern instrument was utilised to analyse the prepared samples. The samples were first diluted with distilled water to ensure proper measurement conditions. The ZetaSizer was then employed to determine the particle size, stability, and polydispersity index (PDI) of the samples. These are analysed for the quality and performance of the nanoparticle formulations, ensuring they meet the desired specifications for stability and uniformity[18].

Viscosity

The viscosity of the formulations was assessed using a Brookfield viscometer (DV-2PL), which was equipped with a small sample adapter and Spindle No. L4. The spindle was operated at a speed of 50

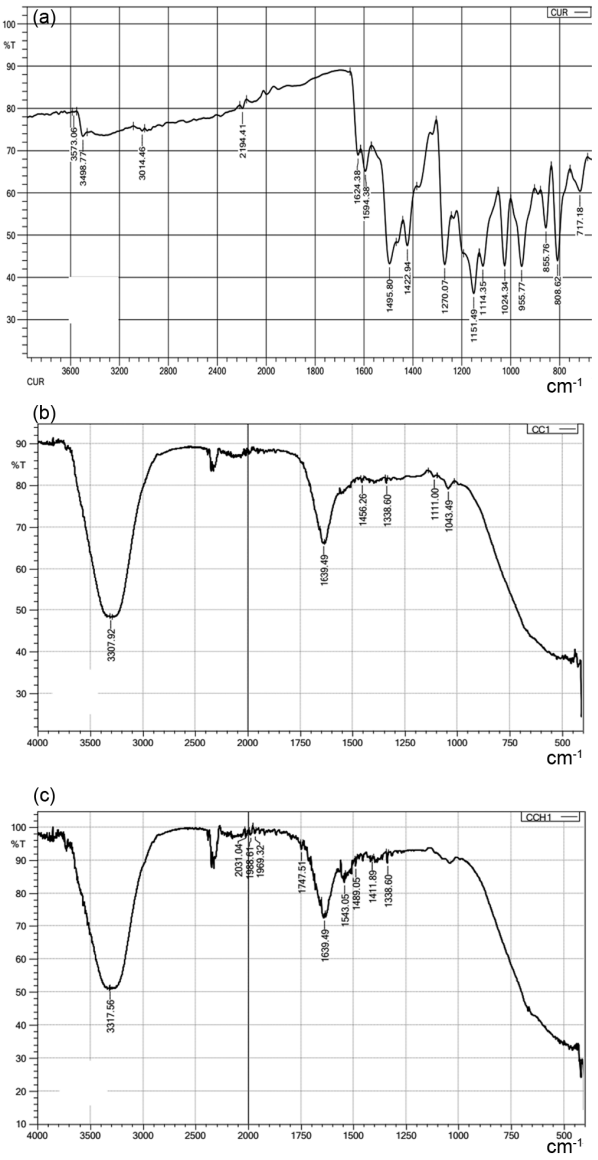

Fig. 2 — FTIR of (a) pure curcumin, (b) formulation with Carbopol 940, and (c) formulation with chitosan.

revolutions per minute (rpm). The viscosity measurements were recorded in centipoise (cps)[19].

Field Emission Scanning Electron Microscopy (FESEM)

The cubosome samples were prepared for surface morphology analysis by coating them with a thin layer of gold film. This preparation step was necessary to enhance the conductivity of the samples for examination using FESEM (analysis was conducted at ICON Labs in Mumbai, Quanta 200F), to capture digital images of the cubosomes. These images provide detailed insights into the surface morphology of the cubosomes, which is critical for understanding their structure[20].

Determination of percentage entrapment efficiency

The per cent encapsulation efficiency (EE) of the cubosome was assessed through a centrifugation process using a centrifuge (4100F). The cubosome dispersion was centrifuged at 8000 rpm for 30 min at room temperature. Following centrifugation, the supernatant, which contained the unentrapped drug, was carefully extracted. This supernatant was then diluted with methanol, and its absorbance was measured using UV spectrophotometry at 429 nm, with methanol serving as the reference[21]. The amount of drug encapsulated within the cubosome was calculated using the following formula:

% Drug entrapment = (Total amount of drug - unentrapped drug)/ (Total amount of drug) X 100

Formulation of curcumin-loaded cubosomal emulgel

The cubosomal emulgel was prepared using a cold method. The suitable concentration of polymer was soaked in distilled water and left to swell for 24 hours in refrigeration. It was then stirred for 10 minutes at 5000 rpm. Following this, the appropriate amount of the prepared cubosomal dispersion was added, and then further surfactant, preservative, and humectant were incorporated through stirring to achieve the cubosome incorporated emulgel. Formulation for cubosomal emulgel is given in Table 2.

Evaluation of cubosomal emulgel

Physical appearance

The prepared cubosomal emulgel was visually examined for colour, homogeneity, and consistency[22].

pH determination

The pH of the formulations was determined using a digital pH meter at room temperature. This involved immersing the electrode directly into the gel formulation to obtain an accurate reading. Monitoring the pH is crucial as it can impact the stability, efficacy, and compatibility of the formulation with the skin or intended application surface[22].

Viscosity

The viscosity of the formulations was assessed using a Brookfield Viscometer (DV-2PL) equipped with Spindle no-L4 operating at a speed of 30 revolutions per minute (rpm), and the viscosity measurements were recorded in centipoises (cps)[23].

Spreadability

A predetermined quantity of prepared emulgel (1g) was placed in between two horizontal plates

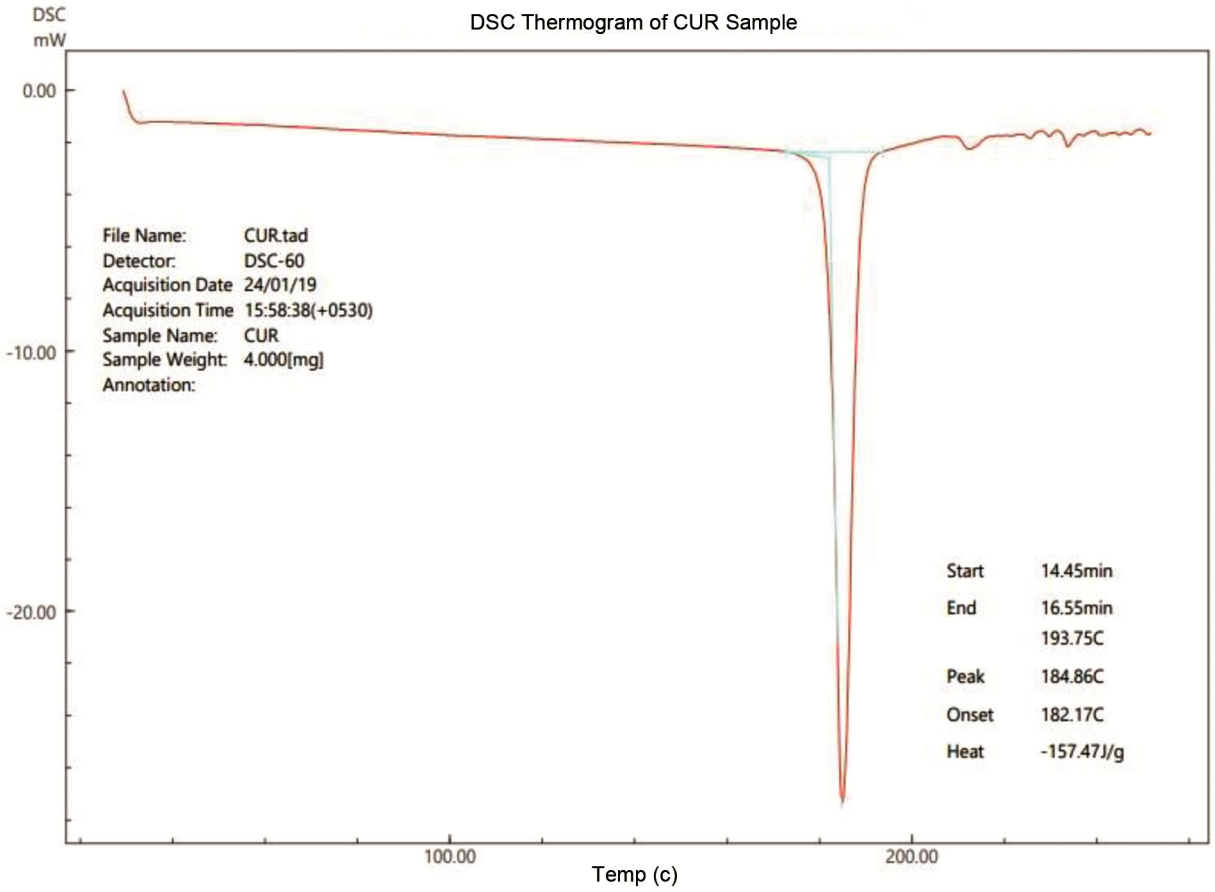

Fig. 3 — DSC of pure curcumin.

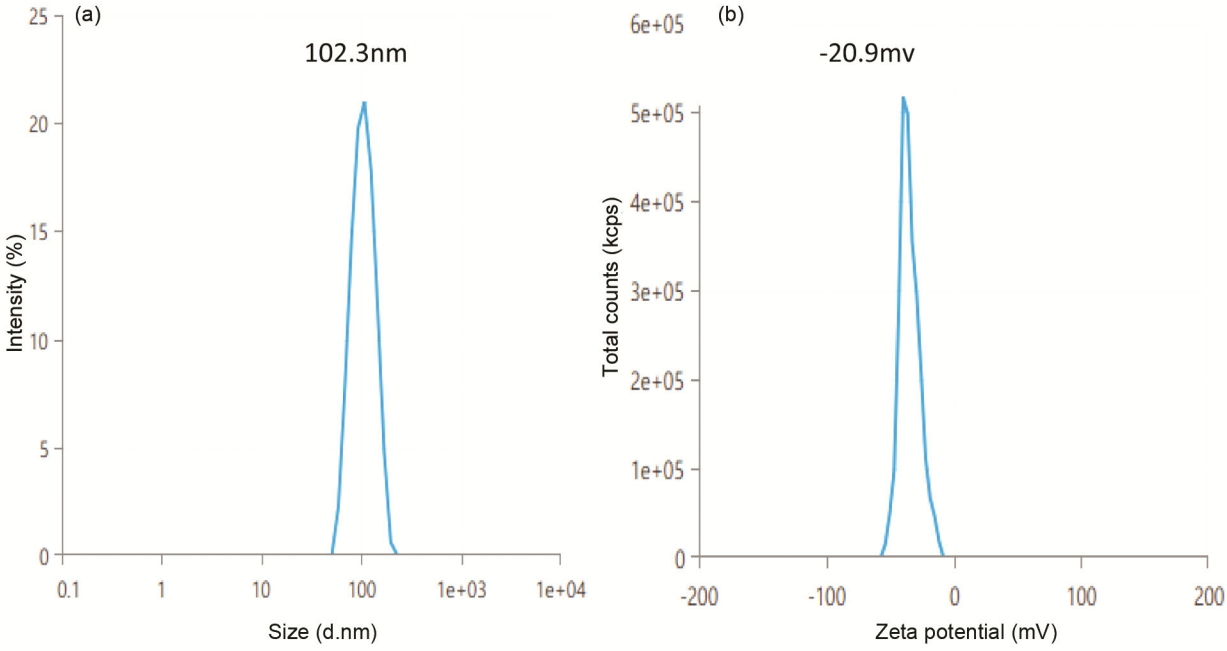

Fig. 4 — (a) particle size, and (b) zeta potential.

Table 1 — Formulation table for curcumin cubosomal dispersion (25 mL)

Formulation	GMO % W/V	Pluronic f 127 (g)	Drug %	Water
F1	3%	0.25	0.1	qs
F2	6%	0.25	0.1	qs
F3	9%	0.25	0.1	qs
F4	12%	0.25	0.1	qs

Table 2 — Formulation table for cubosomal emulgel (30 mL)

Ingredients	Formulation code			
	CF1	CF2	CHF3	CHF4
Cubosomal dispersion (mL)	3.3	3.3	3.3	3.3
Carbopol (g)	0.5	1	-	-
Chitosan (g)	-	-	1	1.5
Glycerol (mL)	0.25	0.25	0.25	0.25
Tween 80 (mL)	0.5	0.5	0.5	0.5
KOH (mL)	0.1	0.1	-	-
Triethanolamine (mL)	-	-	0.1	0.1
Sodium benzoate (g)	0.2	0.2	0.2	0.2
Water (mL)	qs.	qs.	qs.	qs.

measuring 20 cm x 20 cm. A standard weight of 500 g was placed on the upper plate. After a lapse of 20 minutes, the diameter of the resulting circle was measured in centimetres[24].

Drug content

One gram of curcumin-loaded cubosomal emulgel was transferred to a 50 mL volumetric flask and then diluted with methanol. Subsequently, 1 mL of this solution was further diluted to 25 mL with methanol. The absorbance was then measured at 429 nm using a UV-Visible spectrophotometer, and the drug content was calculated by using the formula[25].

Drug content (%) = [(Absorbance/Slope) × Dilution factor/ (1X1000)] X100

In-vitro diffusion studies

The *in-vitro* drug release was assessed using a Franz diffusion cell. (EDC-07). 1 g of curcumin-loaded cubosomal emulgel was applied to one side of a cellulose membrane within a vertical Franz diffusion cell, while the other side of the membrane was exposed to the dissolution medium, phosphate-buffered saline with a pH of 6.8. The study was conducted at a temperature of 37°C for a duration of 8 hours. The concentration of the drug in the dissolution medium was determined by UV spectrophotometry at 429 nm[26-27].

Optimization by DOE

In optimising a dosage form using a 2^2 factorial design, using Design Expert software 13. The concentration of polymers Carbopol 940 and chitosan, along with the homogenization process, were selected as independent factors, and the dependent variables were viscosity and the percentage of drug release at 8 hours. Each factor was tested at low and high levels to determine its effects on the dependent variables. This design allows for the identification of the optimal conditions for achieving the desired viscosity and drug release profile, ensuring an effective and reliable dosage form[28-29].

Photosensitivity and antifungal studies

The photo degradation and antifungal study of the optimised formulation, cubosomal emulgel, was assessed through agar disc diffusion method the strain *Aspergillus Niger* (ATCC no. 10581), Paper discs measuring 6 mm was saturated with 10 µL of optimized emulgel formulation, which had a concentration of 1000 µL/mL. The agar plates were incubated for 3 days at 27±2°C and the diameter of clear zones of inhibition was measured in mm. According to the literature, curcumin completely degrades when exposed to direct sunlight for 5-6 hours. The study was conducted to evaluate the photostability and antifungal efficacy of an optimised cubosomal emulgel formulation containing curcumin[30].

Stability studies

Stability studies were conducted for the emulgel formulations at 40°C±2°C for over a duration of three months. The formulation was assessed for changes in appearance, pH, homogeneity, consistency, and spreadability during this period[31].

Comparison of curcumin-loaded cubosomal emulgel with curcumin emulgel

The drug release of optimised curcumin-loaded cubosomal emulgel formulation was compared with that of the curcumin emulgel formulation to evaluate the release pattern[21].

Results

Preformulation studies

Determination of λ max of curcumin

The determination of the λ max of curcumin was carried out by preparing a sample with a concentration of 10 µg/mL, this sample was subjected

to UV-Vis spectrophotometric scanning in the wavelength range of 200 to 800 nm. The results indicated that curcumin exhibited maximum absorption at 429 nm.

Calibration curve of curcumin in Methanol

The standard calibration curve data is given in Fig. 1; the y-intercept and (R2) value were determined.

Antifungal studies-determination of Minimum inhibitory concentration (MIC study)

The Minimum Inhibitory Concentration (MIC) of curcumin was determined to be 500 µg/mL for both *Aspergillus niger* and *Candida albicans* indicating its antifungal efficacy against these strains. The MIC is a crucial parameter that defines the lowest concentration of an antimicrobial agent required to inhibit the visible growth of a microorganism. In this study, curcumin demonstrated significant inhibitory effects on the growth of both tested fungal strains at the specified concentration, showcasing its potential as a potent antifungal agent. These results are summarised in the accompanying Table 3, which shows the consistency of curcumin's antifungal activity across different fungal species.

Compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy analysis of curcumin in an emulgel formulation reveals significant insights into its chemical compatibility and stability. The FTIR spectra exhibit characteristic absorption bands corresponding to functional groups present in curcumin: the carbonyl group (C=O) around 1650 -1600cm^{-1}, the alkene group (C=C) and aromatic group in the range 1420 to 1500 cm^{-1} near 1450 to 1500 cm^{-1}, and the carbon-oxygen single bond (C-O) stretching vibration around 1270-1350 cm^{-1}. The consistency of these peaks in the emulgel formulation suggests that the curcumin retains its structural integrity and does not undergo significant chemical interaction or degradation within the emulgel matrix. This indicates good compatibility of curcumin with the emulgel components, ensuring its functional efficacy and stability in the final product. As shown in Fig. 2 a,b,c and Differential Scanning Calorimetry (DSC) analysis of curcumin has shown an endothermic peak at approximately 182°C. This peak represents the melting point of curcumin, indicating its thermal stability up to this temperature. As shown in Fig. 3.

Characterization of curcumin cubosomes dispersion

Determination of particle size, zeta potential and polydispersity index

The results revealed that the F4 formulation exhibited a particle size of 102.3 nm, a PDI of 0.301, and a zeta potential of -20.92 mV. The particle size indicates a nanoscale dimension, which is favourable for enhanced stability and bioavailability. A PDI of 0.301 suggests a moderate level of uniformity in particle distribution, indicating a relatively narrow size distribution. The zeta potential value of -20.92 mV reflects sufficient electrostatic repulsion between particles, contributing to the formulation's stability by preventing aggregation. These attributes collectively led to the optimisation of the F4 formulation, as illustrated in the accompanying Table 4 and Fig. 4a-b, highlighting its potential for effective application in drug delivery systems.

Viscosity

Table 4 illustrates a direct correlation between lipid concentration and the viscosity of the formulation. As the lipid concentration increases, the viscosity of the formulation correspondingly rises; this property is essential in applications where a specific viscosity is required to ensure proper consistency, stability, and

Table 3 — MIC studies of curcumin against *Aspergillus niger* and *Candida albicans* strains

Strain	1000 mcg	500 mcg	250 mcg	150 mcg	125 mcg	62.5 mcg	+ve	-ve	Drug control
Aspergillus niger	-	-	+	+	+	+	+	-	-
Candida albicans	-	-	+	+	+	+	+	-	-

Table 4 — Characterization of curcumin cubosomal dispersion for Particle size, PDI, Zeta potential and Viscosity (cPs)

Formulation code	Particle size (nm)	PDI (Mw/Mn)	Zeta potential (mv)	Viscosity (cps)
F1	89.86	0.312	-34.48	552
F2	98.3	0.337	-28.17	720
F3	102.3	0.301	-20.92	974
F4	119.4	0.331	-33.31	1193

performance of the product. The observed trend highlights the importance of optimising lipid concentration to achieve the desired rheological characteristics in formulations.

FESEM

The Fig. 5 depicts a detailed view of the surface morphology, revealing cuboidal-shaped particles with noticeable pores on their surfaces. Along with a minor population of hexagonal vesicles, it is also evident. The particles are in the nano-range and exhibit a fine, uniform size distribution and appear to be well-separated from each other, indicating no aggregation. This distinct and organised morphology, characterised by the presence of both cuboidal and hexagonal structures, suggests a well-formulated material with potential advantages in surface area and reactivity, which could be beneficial for various applications, including drug delivery.

Determination of percentage entrapment efficiency

The graph (Fig. 6) depicts the entrapment efficiency of the cubosome formulations. It was observed that with an increase in GMO concentration from 3% to 12% (w/v), the drug entrapment also increased. Consequently, formulations F3 and F4 exhibited high entrapment efficacy.

Evaluation of Cubosomal Emulgel

Physical appearance

The cubosomal emulgel was inspected visually and was found to be consistent, viscous, with a smooth and homogenous appearance. Emulgel appeared yellow in colour with gel consistency.

pH determination

The pH of the formulation is determined by using a digital pH meter. The pH was found to range from 5.8 to 6.9, which is close to skin pH as depicted in Table 5.

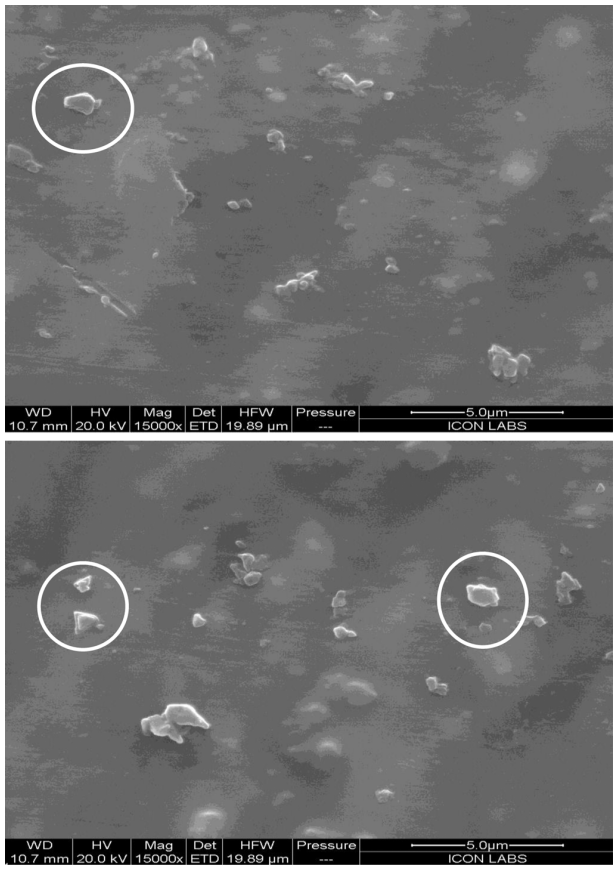

Fig. 5 — FESEM for surface morphology of curcumin cubosomal dispersion.

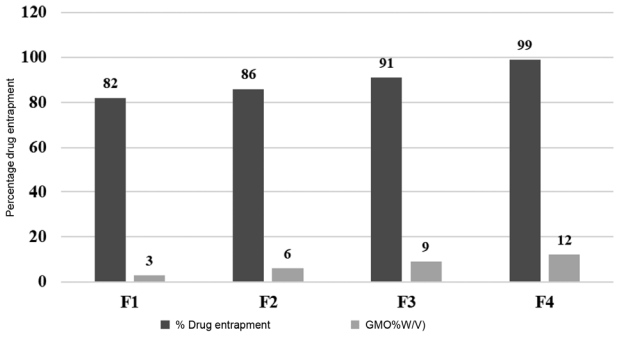

Fig. 6 — Percentage Drug entrapment of cubosome.

Table 5 — Evaluation of cubosomal emulgel for Spreadability (g.cm/s), pH, and Drug content % of formulation using carbopol and chitosan

Polymer	Formulation Code	Spreadability (g.cm/s)	pH	Drug content%
Carbopol 940	C1	6.2±0.4	5.9±0.15	79.2±0.57
	C2	5.8±0.17	6±0.09	86.05±1.15
	C3	6±0.23	6±0.11	78.5±1.0
	C4	5.9±0.09	5.9±0.5	88.3±1.15
Chitosan	Ch1	6.7±0.3	5.8±0.34	62.5±1.0
	Ch2	6.5±0.18	5.9±0.61	71.03±0.57
	Ch3	6.9±0.21	5.8±0.11	60.1±1.0
	Ch4	6.7±0.19	5.9±0.13	75.6±0.57

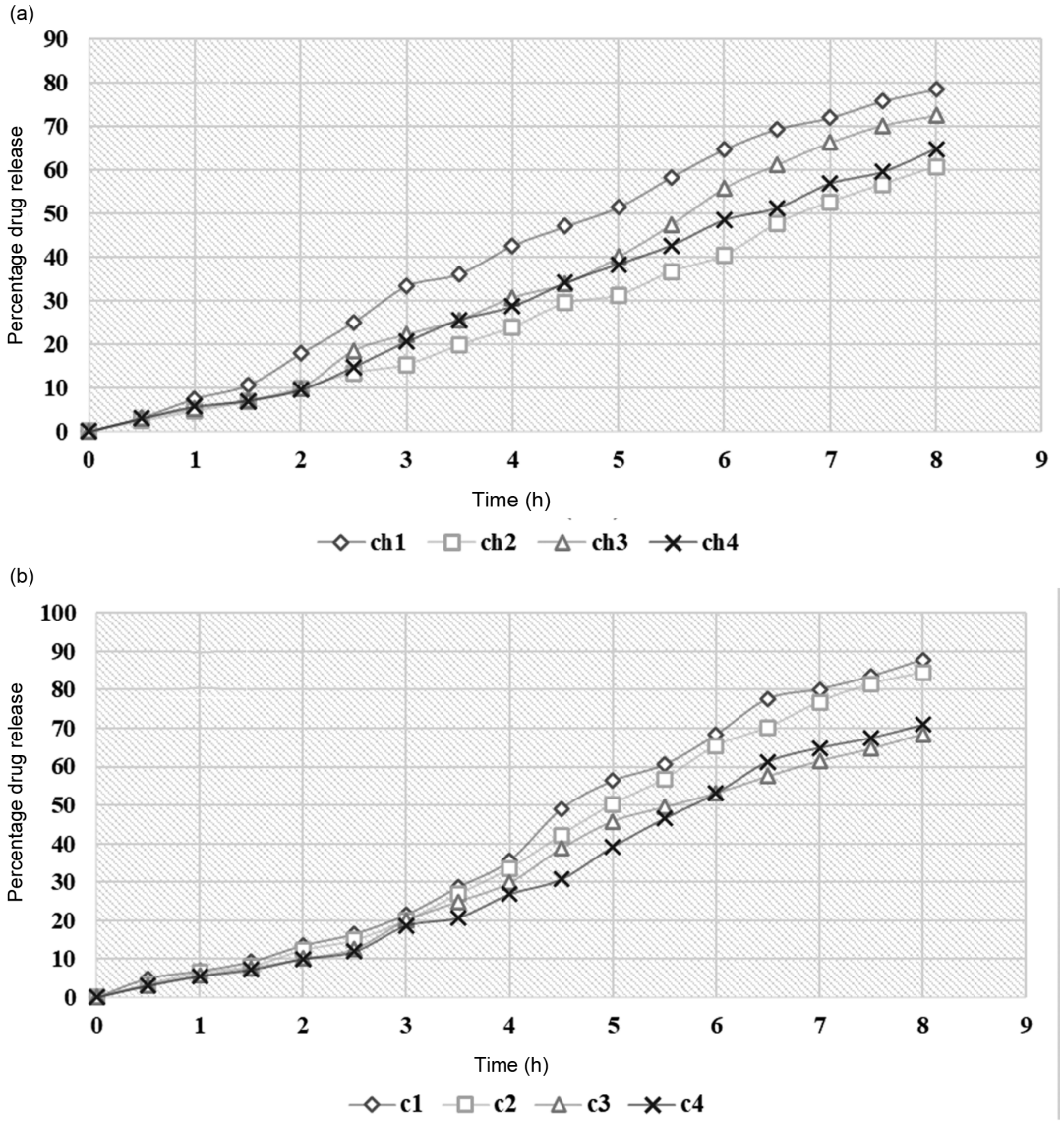

Fig. 7 — (a) Percentage drug release of formulation using chitosan, and (b) carbopol.

Viscosity

The viscosity of the cubosomal emulgel, as presented in Table 5, ranges between 12,000 and 22,000 centipoises (cps). Observations indicate a decrease in viscosity with an increase in rotational speed (rpm) and an increase in polymer concentration.

Spreadability

The spreadability of the cubosomal emulgel, as indicated in Table 5, falls within an acceptable range of 5.8 to 6.9 g.cm/s. Observations reveal that as the viscosity of the emulgel increases, its spreadability decreases.

Drug content

The percentage drug content of the cubosomal emulgel was found to range from 62.1% to 88.3%. The results indicate that increasing the polymer concentration enhances the drug loading capacity of the emulgel. Specifically, formulations with higher concentrations of Carbopol 940 exhibited better drug loading capacity compared to those with chitosan, as detailed in Table 5.

In-vitro diffusion study

The percentage drug release of the cubosomal emulgel was found to range from 60.89% to 87.8%. The results show (Fig. 7a and b) that increasing the polymer concentration leads to a decrease in drug release. Specifically, formulations containing lower concentrations of Carbopol 940 demonstrated enhanced drug release when compared to those

Table 6 — Optimization factors and responses of DOE for formulation using Carbopol 940

Run	Factor 1 A: concentration in Percentage	Factor 2 B: homogenization (rpm)	Response 1 Viscosity (cPs)	Response 2 Percentage drug release
C1	6000	0.5	14601	87.85
C2	12000	0.5	13604	84.47
C3	12000	1	17124	68.12
C4	6000	1	18120	70.91

Table 7 — ANOVA for the response parameters for formulation using carbopol 940

Source	Sum of squares	df	Mean square	F-value	p-value	
Viscosity	1.34E+07	2	6.69E+06	2.68E+07	0.0001	significant
A-homogenisation	9.93E+05	1	9.93E+05	3.97E+06	0.0003	significant
B-concentration of polymer	1.24E+07	1	1.24E+07	4.96E+07	< 0.0001	significant
% drug release	286.57	2	143.29	1646.5	0.0174	significant
A-homogenisation	9.52	1	9.52	109.36	0.0607	Non significant
B-concentration of polymer	277.06	1	277.06	3183.64	0.0113	significant

containing chitosan. The detailed graph reinforces these findings, highlighting the inverse relationship between polymer concentration and drug release.

Optimisation by DOE

The observed response values generated are shown in Table 6, and the summary of ANOVA for the response parameters formulation using chitosan is shown in Table 7. Quadratic equations were generated, and the best fit model was decided based on the p-values.

Full model equation and fit statistics for viscosity (Carbopol 940)

The quadratic equation for predicting viscosity is (Y1) =15862.25−498.25*A*+1759.

Both factors A (homogenization speed) and B (polymer concentration) are significant, as their p-values are less than 0.0500. Fit statistics show that the Predicted R^2 of 1.0000 aligns well with the Adjusted R^2 of 1.0000, indicating an excellent model fit with a difference of less than 0.2. An Adequate Precision ratio of 10429.255 demonstrates a robust signal-to-noise ratio, confirming the model's reliability for navigating the design space.

Full model equation and Fit Statistics for percentage drug release (Carbopol 940)

The quadratic equation for predicting the percentage drug release Y2=77.84-1.54A-8.32B

In this case, B (polymer concentration) is a significant model term, as its p-value is less than 0.0500, while A (homogenization speed) is not significant**.** Plots for viscosity and percentage % drug release of the formulation using Carbopol 940 are shown in Figs. 8 and 9. The overlay plot of Carbopol 940 is shown in Fig. 10.

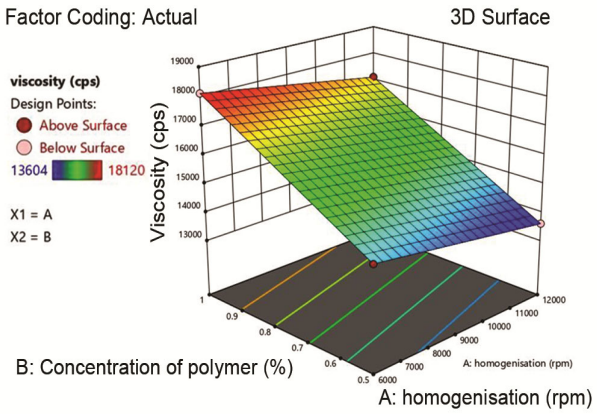

Fig. 8 — 3D Response Surface Plots for the effect of dependent variables on viscosity of the cubosomal emulgel comprising of Carbopol 940.

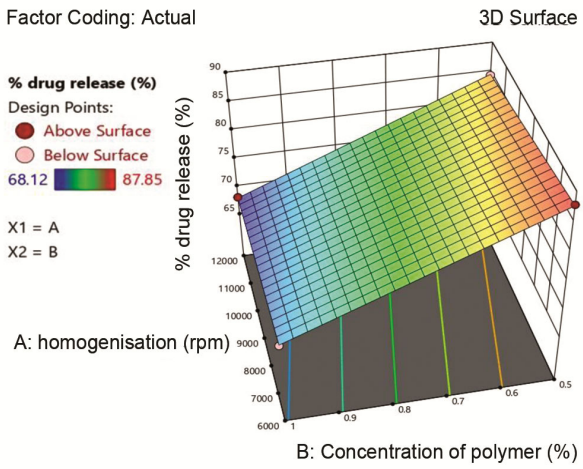

Fig. 9 — 3D Response Surface Plots for the effect of dependent variables on the percentage drug release of cubosomal emulgel comprising of Carbopol 940.

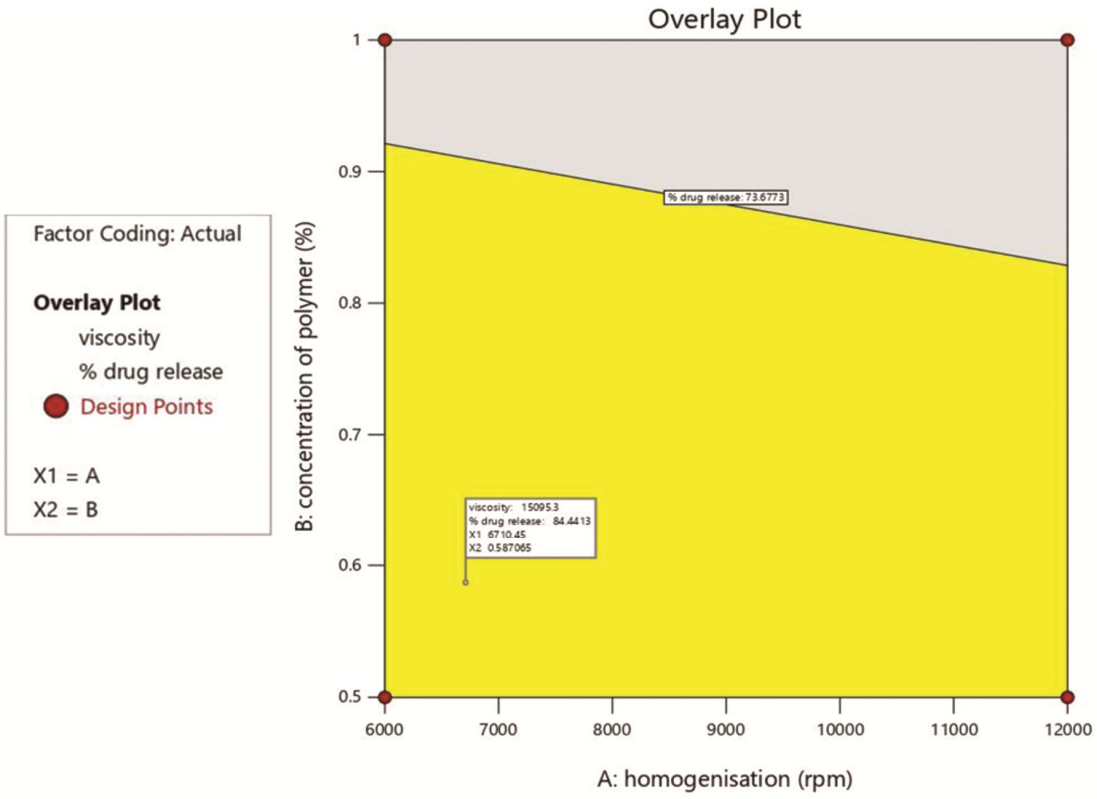

Fig. 10 — Design space of optimization for concentration of Carbopol 940 in cubosomal emulgel.

Table 8 — Optimization factors and responses of DOE for formulation using chitosan

Run	Factor 1	Factor 2	Response 1	Response 2
	A: concentration in Percentage	B: homogenization (rpm)	Viscosity (cPs)	Percentage drug release
Ch1	1.5	12000	15113	57.89
Ch2	1	12000	11530	74.7
Ch3	1	6000	12490	77.03
Ch4	1.5	6000	16210	60.41

Table 9 — ANOVA for the response parameters formulation using chitosan

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Viscosity	1.44E+07	2	7.20E+06	1533.51	0.0181	significant
A-concentration	1.33E+07	1	1.33E+07	2841.59	0.0119	significant
B-homogenization	1.06E+06	1	1.06E+06	225.44	0.0423	significant
% drug release	285.27	2	142.64	15804.53	0.0056	Non significant
A-concentration	279.39	1	279.39	30957.48	0.0036	significant
B-homogenization	5.88	1	5.88	651.59	0.0249	significant

Formulation using chitosan as polymer

Observed response values are shown in Table 8, respectively, and a summary of ANOVA for the response parameters formulation using chitosan as shown in Table 9.

Full model equation and Fit Statistics for viscosity (Chitosan)

The quadratic equation for viscosity is X1=13835.75+1825.75A-514.25B

P-values less than 0.0500 indicate significant model terms; in this case, both A and B are significant. Plots for viscosity and percentage drug release of the formulation using chitosan are shown in Figs. 11 and 12.

Optimization of formulation

Selection of optimum formulation was done on the basis of the criteria of minimum and maximum values

of dependent variables, optimized batch, which has desirability one. Result of the evaluation parameters of the optimised batch. Comparisons between observed and predicted responses for optimised batch are shown in Tables 10 and 11. The actual response of optimised batch was measured and compared with the predicted response. The percentage error was discovered to be less than 5%, demonstrating good agreement between the observed and predicted values. Consequently, it was determined that this design was valid.

The optimised formula Ch1 showed viscosity of 11320 cPs, and drug release of 66.5 at homogenisation at 11035.4 and concentration of polymer at 1.18 as shown in the Table 11. The optimised formula C1 showed viscosity of 14700, and drug release of 82.5 at homogenisation at 11035.4 and concentration of polymer at 0.609771 as shown in Tables 10 and 11. The overlay plot of chitosan is shown in Fig. 13.

Photosensitivity and antifungal studies

The antifungal activity of curcumin, without sunlight exposure, showed a zone of inhibition 14 mm, whereas after 6 hours of sunlight exposure, the inhibition zone decreased significantly to 6 mm, indicating substantial photodegradation in Table 12. The formulation, without sunlight exposure, maintained an inhibition zone of 14 mm, identical to the pure drug without exposure. The optimised cubosomal emulgel formulation, when exposed to sunlight for the same duration, showed a minor reduction in antifungal activity with a zone of inhibition of 13.5 mm. The results demonstrated in Fig. 14 show that while pure curcumin significantly degrades after sunlight exposure, the formulation effectively protects curcumin from photo degradation. The key novelty of the present finding is the photoprotective effect of the cubosomal emulgel, which substantially preserved the antifungal activity of curcumin following sunlight exposure, while simultaneously maintaining a nanosized topical delivery system.

Stability

Upon evaluation, the pH and viscosity of the cubosomal emulgel formulations remained similar after two months, indicating good stability over time.

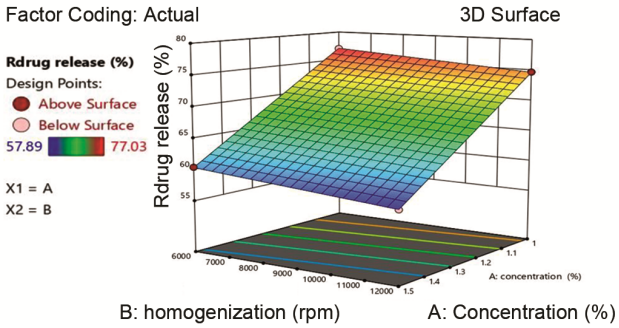

Fig. 11 — 3D Response Surface Plots for the effect of dependent variables on viscosity of the cubosomal emulgel comprising of chitosan.

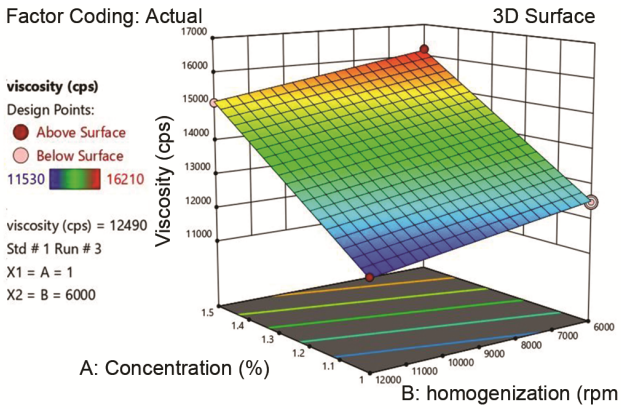

Fig. 12 — 3D Response Surface Plots for the effect of dependent variables on the percentage Drug release of cubosomal emulgel comprising of chitosan.

Table 10 — Conformation table for statistical analysis of formulation using carbopol 940

Analysis	Predicted Mean	Predicted Median	Observed	Std Dev	n	SE Pred	95% PI low	Data Mean	95% PI high
Viscosity 9 (cPs)	14537.1	14537.1	14700	0.5	2	0.485729	14531	14625	14543.3
Percentage drug release	81.4592	81.4592	82.5	0.295	2	0.28658	77.8179	83	85.1005

Table 11 — Conformation table for statistical analysis for formulation using chitosan

Analysis	Predicted Mean	Predicted Median	Observed	Std Dev	n	SE Pred	95% PI low	Data Mean	95% PI high
Viscosity	13780.6	13780.6	11320	0.46	1	0.40	12731	11320	14830.3
Percentage drug release	70.8334	70.8334	66.5	0.095	1	0.11457	69.3778	66.5	72.2891

Table 12 — Photosensitivity and antifungal studies

Fungal strain	Formulation	Inhibition (mm)
Aspergillusniger	Not exposed to pure drug	14
(ATCC no. 10581)	Exposed drug to sunlight (6 hours)	6
	Exposed formulation to sunlight (6 hours)	13.5
	Formulation not exposed to sunlight	14

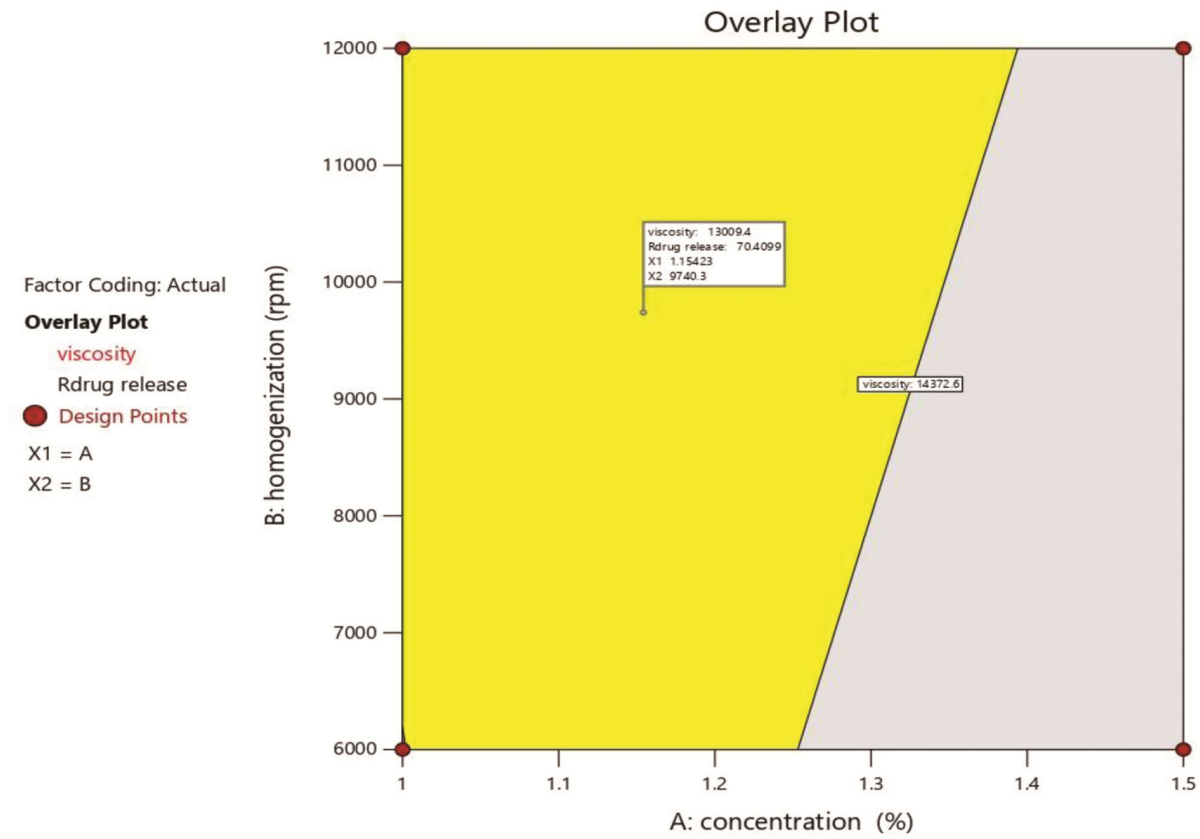

Fig. 13 — Design space of optimization for concentration of chitosan in cubosomal emulgel.

Fig. 14 — The antifungal activity of curcumin, before and after exposure to sunlight.

Comparison of curcumin-loaded cubosomal emulgel with curcumin emulgel

The obtained results in Fig. 15 show that the optimised curcumin-loaded cubosomal emulgel achieved an 82.5% drug release at 8 h, whereas the curcumin emulgel showed 70.1% drug release at 8 h. This indicates that the cubosomal curcumin emulgel formulation shows a faster and more complete release of curcumin compared to the curcumin emulgel formulation. The fast diffusion along the biological membrane due to high penetration of the glyceryl monooleate and drug class itself, and the decrease in particle size of the drug show good results. Therefore, the present finding confirmed the potential of cubosomal incorporation in improving the release of curcumin from a topical emulgel compared with the

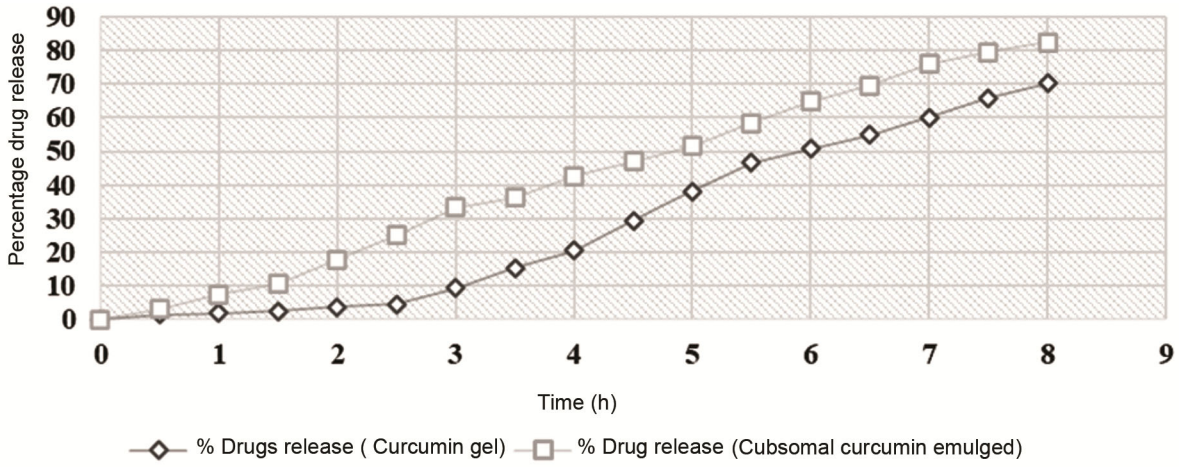

Fig. 15 — Percentage drug release comparison of curcumin-loaded cubosomal emulgel with curcumin gel.

conventional formulation, thereby supporting the utility of the cubosomal approach for enhanced topical delivery[21].

Discussion

The determination of λ max of curcumin at 429 nm confirms its characteristic absorption peak, crucial for quantification and subsequent formulation development. The establishment of a calibration curve in methanol provides a reliable method for quantifying curcumin concentrations in formulations. The MIC study reveals curcumin's potent antifungal efficacy against *Aspergillus niger* and *Candida albicans*, with a MIC of 500 µg/mL, indicating its potential therapeutic use against fungal infections[8]. The optimised F4 formulation exhibits desirable attributes with a nanoscale particle size, moderate polydispersity, and sufficient negative zeta potential, indicating stability and potential for enhanced bioavailability[21]. The cubosomal dispersion shows organised morphology with cuboidal-shaped particles and hexagonal vesicles, indicating a well-formulated material with potential advantages for drug delivery applications[18]. The cubosomal emulgel demonstrates consistency, viscosity, and homogeneity, essential for topical application. The pH falls within the range close to skin pH, ensuring compatibility and minimising irritation upon application. The viscosity and spreadability of the emulgel formulations meet acceptable criteria, crucial for ease of application and patient compliance[32]. It can be seen that as the concentration of polymer increased, viscosity increased and spreadability decreased. Drug content and concentration of the polymer are directly proportional. From this literature, it was evident that the formulations exhibit satisfactory drug content and controlled drug release, highlighting the potential for effective and sustained therapeutic outcomes[18,33-34].

The DOE analysis reveals significant factors affecting viscosity and drug release, facilitating the optimisation process for achieving desired formulation characteristics. Viscosity is significantly affected by both homogenization speed and polymer concentration, with polymer concentration having a stronger impact, and Percentage Drug Release is significantly affected by polymer concentration but not by homogenization speed[35].

Photosensitivity and antifungal study demonstrate the protective effect of the cubosomal emulgel formulation against curcumin photodegradation, enhancing its stability and efficacy upon exposure to sunlight. The ability of the formulation to retain antifungal activity following sunlight exposure represents an important finding, as it addresses one of the major limitations associated with the topical application of curcumin. Thus, the novelty of this finding lies in the demonstrated photoprotective capability of the cubosomal emulgel, which enabled the preservation of curcumin's antifungal activity under photostress conditions.

The stability evaluation confirms the robustness of the cubosomal emulgel formulations over two months, ensuring consistent performance and efficacy[8].

Comparison with conventional emulgel formulations reveals superior drug release characteristics of the cubosomal formulation, highlighting its potential for enhanced therapeutic

outcomes in antifungal treatment. The novelty of this finding underscored the specific contribution of the cubosomal architecture toward improving curcumin release from the topical emulgel system, thereby supporting its potential for enhanced topical antifungal delivery.

Conclusion

The present study successfully developed and optimised a curcumin-loaded cubosomal emulgel as a topical antifungal delivery system. The optimised cubosomes (F3) exhibited a particle size of 102.3 nm, PDI of 0.301, and zeta potential of −20.92 mV, with FESEM confirming their characteristic cuboidal morphology. Glyceryl monooleate concentration enhanced curcumin entrapment, while incorporation into a Carbopol 940–chitosan emulgel provided desirable physicochemical properties and controlled drug release. The optimised emulgel released 70.1% curcumin over 8 h compared with 82.3% from the cubosomal dispersion, demonstrating effective modulation of drug release by the emulgel matrix. DoE-based optimisation achieved an appropriate balance between viscosity and drug release. The formulation remained stable for three months at 40 °C and retained antifungal activity. Overall, the developed cubosomal emulgel represents a stable and controlled-release topical platform for curcumin, warranting further ex vivo skin permeation/retention and in vivo antifungal efficacy studies.

Conflict of interest

The authors declare that they have no conflicts of interest related to this work.

AI use disclosure

The authors declare that no artificial intelligence (AI) tools were used for data generation, analysis, interpretation, or preparation of scientific conclusions in this manuscript. AI-assisted tools were used only for language improvement and grammatical editing purposes.

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