RESEARCH PAPER

Quality by Design-Based Development of Clindamycin and Curcumin Drug-Loaded Lipospheres for Improved Topical Delivery and Antibacterial Efficacy

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ABSTRACT

Aim: The goal of this study was to formulate and statistically optimize lipospheres loaded with clindamycin and curcumin for improved topical antimicrobial therapy.

Materials and Methods: Stearic acid, cetyl alcohol, and paraffin wax were the lipid matrix components utilized to create the lipospheres, which were formed using the melt-emulsification congealing method. Particle size and entrapment efficiency were examined in relation to lipid content using a 3^2 complete factorial design (Quality by Design approach). The improved formulation's particle size, zeta potential, surface morphology (SEM), and drug entrapment % were assessed. Lipospheres were tested for pH, viscosity, homogeneity, spreadability, drug content, swelling index, and in vitro release kinetics after being added to a Carbopol 940 gel. According to the guidelines provided by the ICH, stability tests were conducted. The antibacterial activity of Staphylococcus aureus and Streptococcus pyogenes was assessed using the agar well diffusion method.

Results: Optimization of the Design of Experiments revealed a significant linear model for entrapment efficiency and particle size ($p < 0.0001$). The main factors influencing the particle size, which varied from 347.7 to 935.7 nm, were stearic acid (negative effect) and paraffin wax (positive effect). 89% encapsulation and 79% yield were achieved by the improved formulation, with entrapment efficiency ranging from 67 to 98%. A appropriate pH (7.15 ± 0.049), viscosity (2549 ± 0.054 cps), spreadability (28 ± 0.02 g•cm/sec), 86% drug content, and 81% swelling index were among the acceptable physicochemical parameters of the liposphere-loaded gel. Diffusion-based kinetics lead to regulated drug release, according to in vitro release studies. Long-term and accelerated stability tests revealed no appreciable variations in the formulation parameters.With mean zones of inhibition of 10.33 ± 1.527 mm against Staphylococcus aureus and 9 ± 1 mm against Streptococcus pyogenes, the antibacterial examination showed that the lipospheres were more active than the treatment gel, demonstrating better therapeutic potential.

Keyword: *Clindamycin, Curcumin, Liposheres, Antimicrobial, Quality by Design technique*

How to cite this article: Gupta P, Sonker S. Quality by Design-Based Development of Clindamycin and Curcumin Drug-Loaded Lipospheres for Improved Topical Delivery and Antibacterial Efficacy. Int J Drug Deliv Technol. 2026;16(58s): 529-540. DOI: 10.25258/ijddt.16.58s.55

Source of support: Nil.

Conflict of interest: None

Introduction

Clindamycin is a parenteral, topical, and oral broad-spectrum antibiotic used to treat sensitive organism-caused bacterial infections. Curcumin has a wide range of medically validated advantages, including the capacity to enhance heart health and defend against Alzheimer's and cancer. It works well as an antioxidant and antiinflammatory. Additionally, it might lessen arthritis and depression symptoms (Montenegro & Morales et al., 2017).

Bacterial diseases can be deadly. Every year, at least 700,000 people die around the world from superbug infections. Antibacterial drugs are very important for treating illnesses caused by germs. Despite this, bacteria have become more resistant to antibiotics because they are used too much in hospitals, farms, and animal farms (Darvishi et al., 2021; Dong et al., 2015). This is very dangerous to people's health and lives because it could cause many bacterial illnesses. Microbes can get around the way an antimicrobial drug works, which helps them stay alive. This is called antimicrobial resistance (Ahmed et al., 2017). The development of effective drug delivery systems is a critical aspect of modern pharmaceutical sciences. Lipospheres, first introduced in the early 1990s, represent a significant advancement in lipid based drug delivery technologies. The formulation of lipospheres involves the use of biocompatible and biodegradable lipids, such as triglycerides, fatty acids, and waxes, along with phospholipids as emulsifiers. The choice of lipids and emulsifiers plays a crucial role in determining the physicochemical properties of lipospheres, including particle size, zeta potential, and drug loading capacity (Liu et al., 2020). The biocompatibility, biodegradability, and capacity to encapsulate both hydrophilic and hydrophobic medications are among the benefits of lipospheres. They are easier to scale up for industrial manufacturing and provide better stability than liposomes. However, issues including restricted drug loading capacity, possible toxicity of specific lipids, and drug leakage during storage must be addressed (Natarajan & Laksmanan, 2013). We need more international cooperation and study that combines different fields in order to protect and improve public health measures against the global threat of antibiotic resistance. Because of this, pharmaceutical experts are becoming more and more interested in how medicines and

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nanotechnology can work together. As an example of how important nanodrugs are, this study will look at recent progress in new drug delivery methods for treating microbial infections

1.Materials and methods

1.1 Formulation of the lipospheres by emulsion method

The trial formulation of the liposphere was made using the emulsion method, which involved varying the proportions of the lipid phase and aqueous phase components. In a beaker, the lipid phase was first melted at 700–800 degrees Celsius. Then the drug was added and mixed into it. The aqueous phase was then heated in a separate beaker to 700–800 degrees Celsius. At the same temperature and with stirring, the lipid and aqueous phases were mixed to form an emulsion. After that, stirring continued for an additional hour while keeping the temperature constant using a mechanical stirrer set to 2000 rpm. The resulting emulsion was then swirled continuously for up to two hours before being dropped into a beaker filled with 1000 milliliters of ice-cold water and allowed to sit at room temperature overnight. It was then filtered using Wattman filter paper, collected, and dried from the filter paper. This comprises the lipid phase (stearic acid, cetyl alcohol, and paraffin wax) and aqueous phase (water, butanol, and tween 80). (Rasul et al., 2021).

1.2 Optimization of the liposphere

The software 32 full factorial design was used for optimization of clindamycin and curcumin loaded lipospheres. Design Expert software (Version 1.0.2.1, Stat-Ease Inc., USA) was used for factorial design. Factorial design consists of two variables, independent variables such as lipid concentration and surfactant concentration and dependent variables were entrapment efficiency and particle size. Analysis of variance (ANOVA) was applied to estimate the significance of the model. 3D response surface plots were plotted by using models generated by regression (Bhosale et al., 2016).

Table 1: Trial formulation

Formulation code	Drug (total 30mg) (1:1ratio)	Stearic acid (gm)	Cetyl alcohol (gm)	Paraffin wax (gm)	Tween 80 (ml)	Butanol (ml)	Water (ml)	Stirring rate (rpm)
LpCC1	30mg	1.5	3	2	1.5	4	Up to 100	2000
LpCC2	30mg	2	3.5	1.5	1.5	4	Up to 100	2000
LpCC3	30mg	2.5	2	1	1.5	4	Up to 100	2000
LpCC4	30mg	3	2.5	2	1.5	4	Up to 100	2000
LpCC5	30mg	3.5	1	1.5	1.5	4	Up to 100	2000
LpCC6	30mg	1	1.5	1	1.5	4	Up to 100	2000
LpCC7	30mg	1.5	1	2	1.5	4	Up to 100	2000
LpCC8	30mg	2	1.5	1.5	1.5	4	Up to 100	2000
LpCC9	30mg	2.5	3	1	1.5	4	Up to 100	2000
LpCC10	30mg	3	2	2	1.5	4	Up to 100	2000
LpCC11	30mg	3.5	2.5	1.5	1.5	4	Up to 100	2000
LpCC12	30mg	1	2	1	1.5	4	Up to 100	2000
LpCC13	30mg	1.5	3	2	1.5	4	Up to 100	2000

1.3 Evaluation parameter

1.3.1 Particle size

The mean size of the lipospheres was determined by Malvern zetasizer a submicron particle size analyzer at a scattering angle of 90°(Sangolkar et al., 2012)..

1.3.2 Entrapment efficiency

A 10 ml of curcumin and clindamycin, dispersion was centrifuged for 45 min. Settled lipospheres were diluted in mixture of 1 ml chloroform and 9 ml methanol and sonicated for 5 min to obtain a clear solution. Entrapment efficiency was checked by using UV visible spectrophotometer (Shimadzu, model UV-1800) at wavelength of 262 nm (isobestic point) after appropriate dilution and calculated through the following formula:

% Entrapment efficiency = [Amount of drug in lipospheres/ Initial amount of drug incorporated in formulation] × 100

1.4 Optimized lipospheres gel formulation containing clindamycin and curcumin

For the preparation appropriate quantity of carbopol940P was soaked in water for a period of 2 h. Carbopol was then neutralized with triethanolamine (TEA) with stirring. Then

specified amount of liposphere, glycerin and permeation enhancer (Propylene glycol) was mixed. Solvent blend was transferred to carbopol container and agitated for additional 20 min. The dispersion was then allowed to hydrate and swell for 60 min, finally adjusted the pH with 98 % TEA until the desired pH value was approximately reached (6.8-7). During pH adjustment, the mixture was stirred gently with a spatula until homogeneous gel was formed (Müller et al., 2000).

1.5 Characterization of lipospheres gel

1.5.1 Physical characterization

The physical characterization was performed by visual inspection and later by the finger rubbing such as grittiness etc (Pardeike et al., 2009).

1.5.2 Homogeneity

Physical appearance and homogeneity of the prepared gels were evaluated by visual perception.

1.5.3 pH

pH of gel was determined using digital pH meter. About 1 g of gel was stirred in distilled water till a uniform suspension effected.

1.5.4 Viscosity

Viscosity of the gel was determined by using Brookfield viscometer (Dial type). As the system is non-Newtonian spindle no. 62 was used. Viscosity is measured for the fixed time 2 min for 30 rpm (Ullah et al., 2024).

1.5.5 Spreadability

The spreadability of the gel was determined using the following technique: 0.5 g gel was placed within a circle of 1 cm diameter premarked on a glass plate over which a second glass plate was placed. A weight of 500g was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to spreading of the gels was noted (Sangolkar et al., 2012). It was calculated using formula

S = M. L / T

1.5.6 Drug content of gel

The 0.5 gm of gel was dispersed and drug extracted in Chloroform: ethanol (1:1) media by keeping on sonicate (lab instruments) for 20 min. Residue was filtered. The absorbances of drugs were taken at 262 nm to find out the concentration of clindamycin and curcumin in gel(Islam et al., 2022).

1.5.7 Swelling index

The swelling index of lipospheres in gel form is a measure of their ability to absorb a liquid and increase in size. It's calculated by comparing the weight of the lipospheres gel before and after swelling.

The swelling index was typically calculated using the following formula:

*Swelling Index = [(Weight of swollen lipospheres gel , Weight of dry lipospheres gel) / Weight of dry lipospheres gel, and 100%.

1.5.8 In vitro permeation of liposphere based gel

One batch of formulations, one prepared with the permeation enhancer LF8 and the other without, was tested across a cellophane membrane using a dissolving testing instrument that was commercially manufactured. Dissolving media were created from freshly prepared PBS buffer (pH 7.4). One end of a specially constructed glass cylinder with a diameter of 5 cm and an open side was fitted with a cellophane membrane that had been soaked in the dissolution media the night before. 5 ml of the formulation was carefully pipetted into this assembly. 50 milliliters of dissolving medium, maintained at 37 degrees Celsius, were used to suspend the cylinder so that the membrane just brushed the receptor media surface. The dissolving liquid was stirred at 50 rpm using a magnetic stirrer (Chime et al., 2013).

1.5.9 Stability

The procedure begins with the preparation of the lipospheres using an established formulation method, followed by filling the samples into suitable containers, such as airtight glass vials or plastic bottles. These samples are then stored under accelerated conditions typically set at 4–8 °C With 75% RH for first 2 months, 25 ± 2 °C with 60 ± 5% relative humidity and 40 ± 2 °C and 75 ± 5% relative humidity, in accordance with ICH (International Council for Harmonisation) guidelines. The samples are withdrawn at predefined time intervals—commonly at 0, 1, 3, and 6 months—for evaluation (Paarakh et al., 2018).

1.6 Antimicrobial activity

The agar well diffusion method was used to perform the antimicrobial assay of a number of plant extracts in Nutrient Agar Media (NAM) plates. 28 g of Nutrient Media were dissolved in 1 liter of distilled water, the pH was checked, and the mixture was autoclaved for 15 minutes at 121°C and 15 pounds of pressure to create NAM Media. The NAM media was then placed into plates and allowed to harden in a laminar air flow. The test organisms were inoculated in nutrient broth and cultivated for a full night at 37°C to get the turbidity down to 0.5 McFarland standards, resulting in a final inoculum of 1.5 × 108 CFU/ml. On the NAM agar plate, a well with a diameter of 5–6 mm was created using a cork borer. After that, 100µl of the inoculum was transferred to a fresh, sterile, solidified Agar Media Plate. After inoculating the agar plate using a sterile spreader, two 6 mm wells were bored into the infected medium. Each well was then filled with various materials, including formulation and treatment gel. The plates were incubated for 24 hours at 27°C after being allowed to diffuse for 30 minutes at room temperature (Manandhar et al., 2019).

2. Results

1.1 Optimisation Of The Liposphere

Table 2: Trial formulation run from the DOE mm

Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2

	A:Stearic acid	B:Cetyl alcohol	C:Paraffin wax	particle size	entrapment efficiency
	(gm)	(gm)	(gm)	nm	%
1	2.5	1	2	753.1	67
2	4	2	2	890.9	69
3	1	1	1.5	677	87
4	4	2	1	410	98
5	1	3	1.5	678.6	88
6	2.5	3	1	347.7	97
7	2.5	2	1.5	671.1	86
8	2.5	3	2	802.9	72
9	4	3	1.5	671.1	82
10	4	1	1.5	635.4	85
11	1	2	2	935.7	78
12	2.5	1	1	429.6	95
13	1	2	1	491.1	96

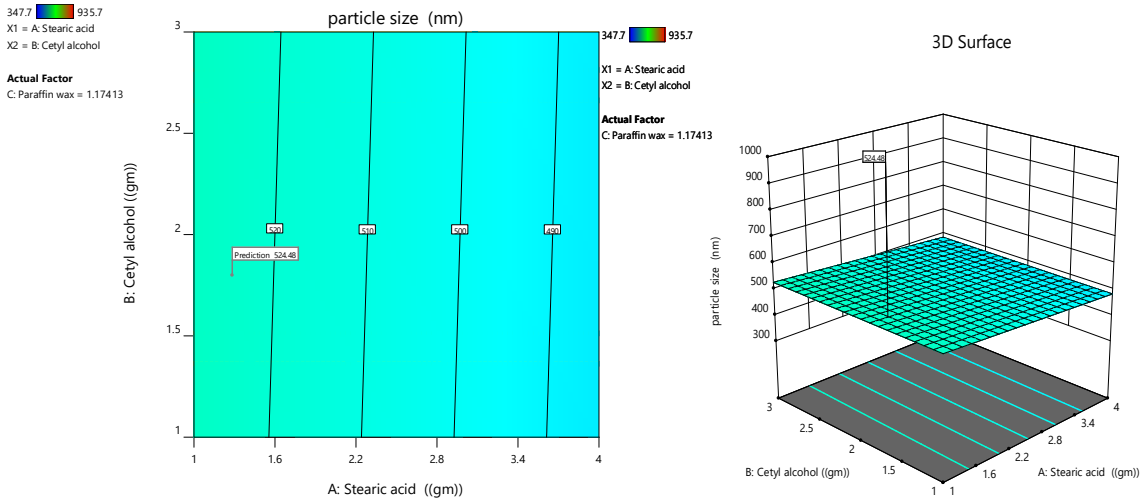
Table 3: Regression of the trial formulation run

Source	Sequential p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001	0.8930	0.8245	Suggested
2FI	0.7803	0.8643	0.6281	
Quadratic	0.0932	0.9596		

Final Equation in Terms of Coded Factors

Particle size=+645.71-21.88A+0.6500B+213.03C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.



(A) (B)

Figure 1: (A) Contour plot of the particle size against independent variable (B) Response surface plot of the particle size

Table 4: Response 2: entrapment efficiency

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001		0.9292	0.8843	Suggested
2FI	0.2062		0.9478	0.8604	
Quadratic	0.3955		0.9564		

Final Equation in Terms of Coded Factors

Entrapment efficiency=+84.62-1.88 A+0.6250 B-12.50 C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors

Entrapment efficiency=+123.99038-1.25000 Stearic acid+0.625000 Cetyl alcohol-25.00000 Paraffin wax

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the centre of the design space.

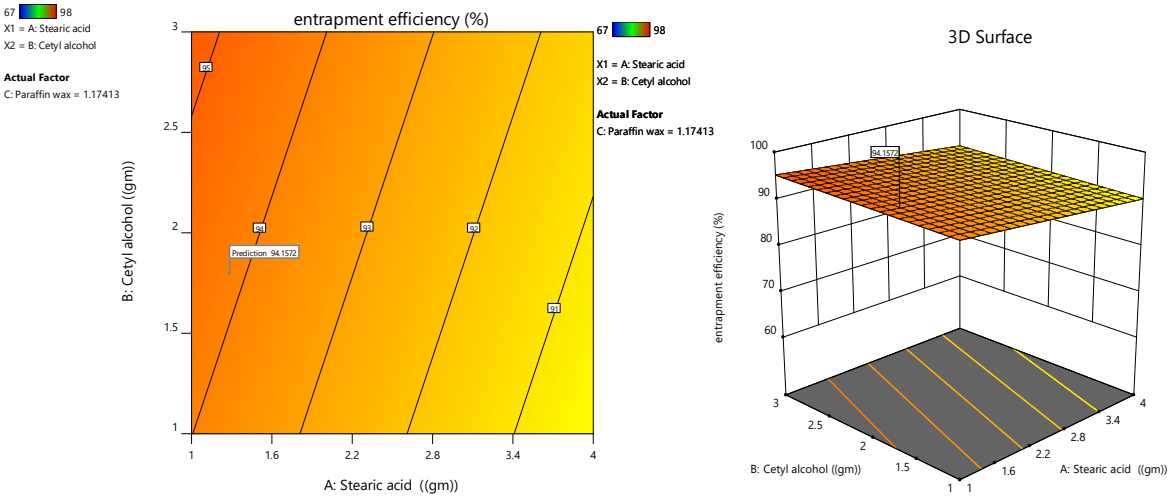


Figure 2: (A) Contour plot of the entrapment efficiency against independent variable (B) Response surface plot of the entrapment efficiency

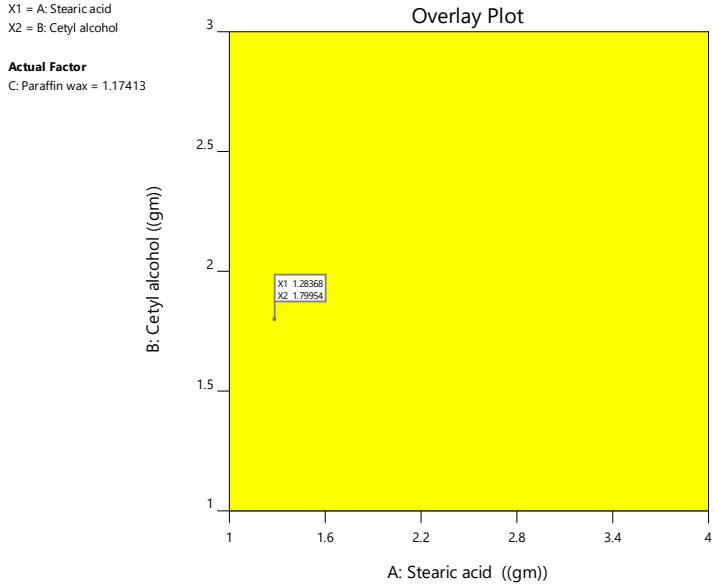


Figure 3: Overlay plot of the independent variable

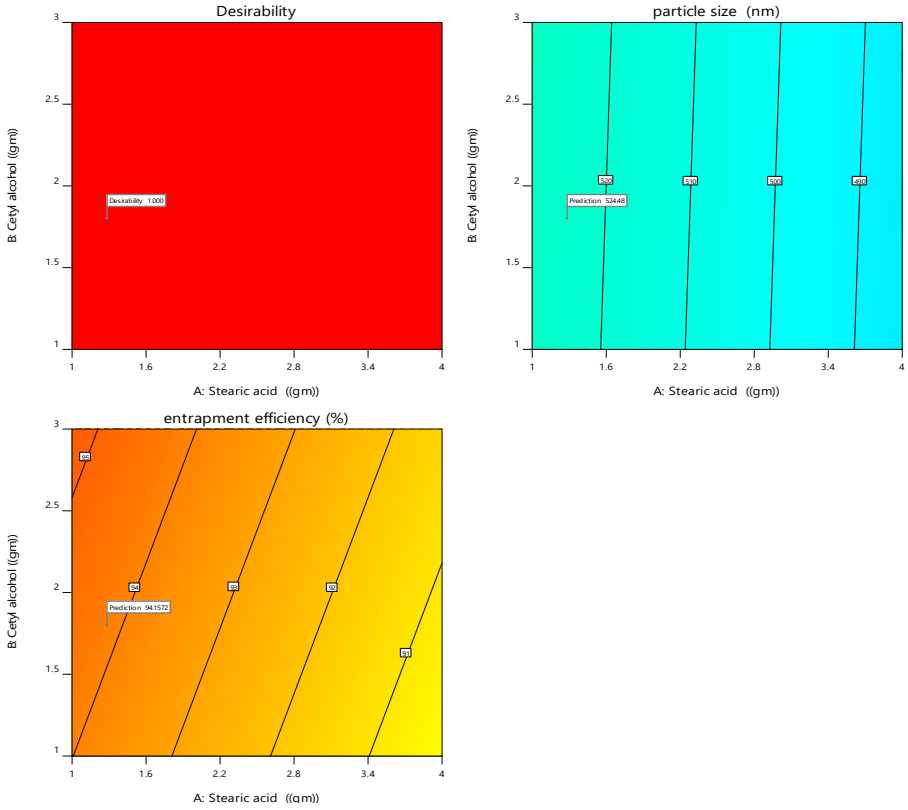


Figure 4: Desirability plot of the dependent variables and the independent variables

2.2 Characterisation of the lipospheres loaded with clindamycin and curcumin

2.2.1 Percentage Yield of Lipospheres

Table 5: Represent the % Yield of the optimized lipospheres loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCC	% Yield	79%

Particle size and zeta potential

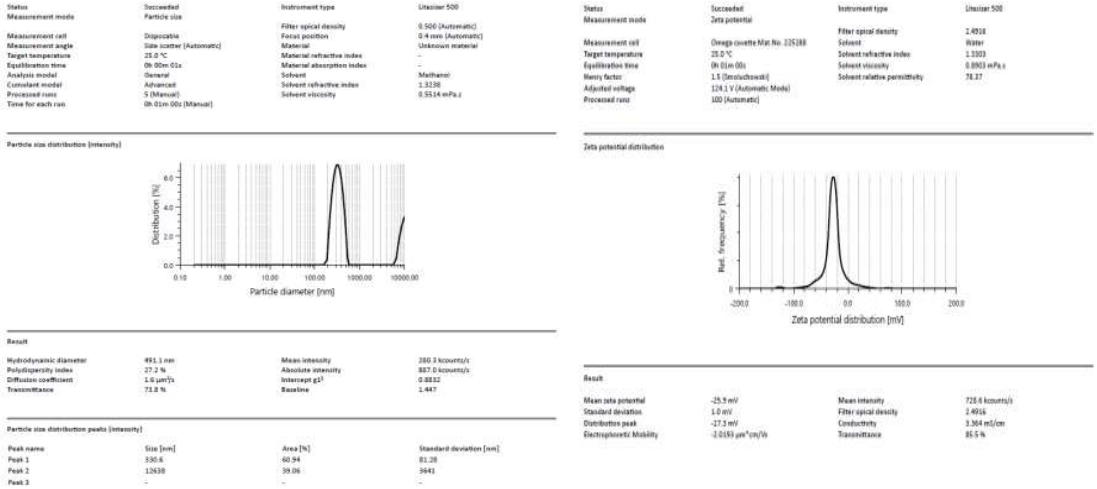


Figure 5: Particle size and Zeta potential of the optimised formulation

2.2.2 Entrapment efficiency

Table 6: Represent the % Entrapment efficiency of the optimised lipospheres loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCC	% Entrapment efficiency	89%

2.2.3 Surface morphology by SEM

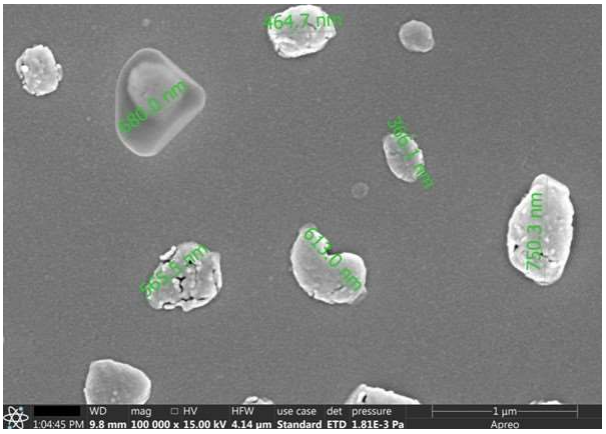


Figure 6: SEM of the optimised formulation

The spheres were vacuum dried, coated with a thin gold-palladium layer with a sputter coater unit and observed microscopically at an accelerating voltage of 10 kV.

2.3 Optimized lipospheres gel formulation containing clindamycin and curcumin

Table 7: Optimized liposomal gel formulation

Formulation code	Composition	Quantity
LpCCG	Lipospheres	1gm
	CARBOPOL GEL	10 gm

2.4 Characterization of lipospheres gel

2.4.1 Physical characterization

Table 8: Represent the physical properties of the lipospheres gel loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCCG	Color	yellowish in color
		Texture	Smooth
		Appearance	Pleasant
		Odour	Odourless
		Gritty	Non gritty

2.4.2 Homogeneity

Table 9: Represent the homogeneity of the lipospheres gel loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCCG	Homogeneity	Homogenous mixture

2.4.3 pH

Table 10: Represent the pH of the lipospheres gel loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCCG	pH.	7.15±0.049

2.4.4 Viscosity

Table 11: Represent the Viscosity of the lipospheres gel loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCCG	Viscosity (Viscosity (cps) at Room Temperature ±SD.)	2549±0.054

2.4.5 Spreadability

Table 12: Represent the spreadability of the lipospheres gel loaded with drug

S.N.	Formulation code	Parameters	Result
1	LpCCG	Spreadability (gm.cm/ sec)	28 ±0.02

2.4.6 Drug content of gel

Table 13: Represent the Drug content (%) of the lipospheres gel

S.N.	Formulation code	Parameters	Result
1	LpCCG	Drug content (%)	86 %

2.4.7 Swelling index

Table 14: Represent the Swelling index (%) of the lipospheres gel

S.N.	Formulation code	Parameters	Result
1	LpCCG	Swelling index (%)	81%

2.4.8 Drug release kinetics investigation

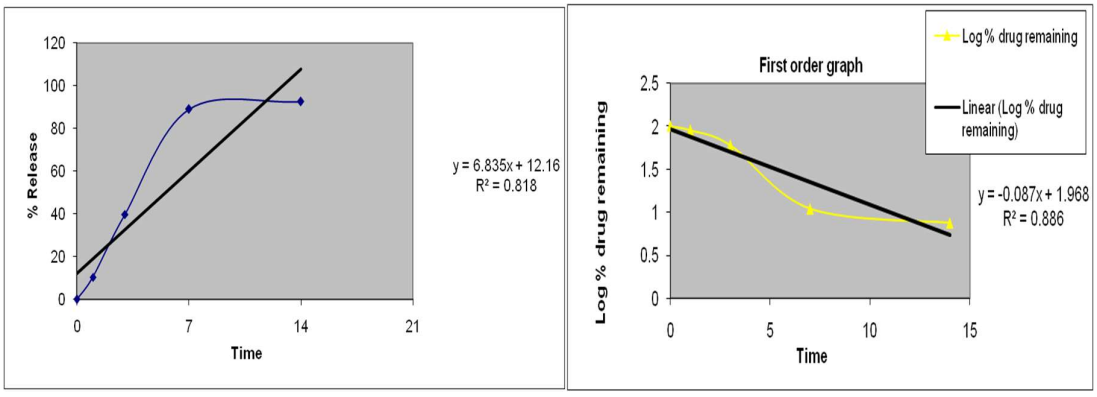


Figure 7: Zero order and First order kinetic release model

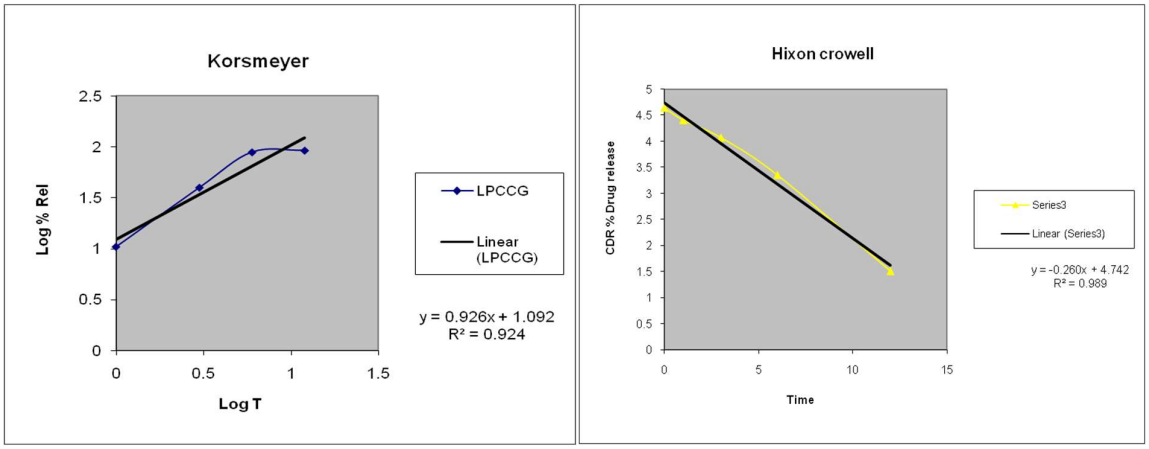


Figure 8: Korsmeyer and Hixon crowell kinetic release model

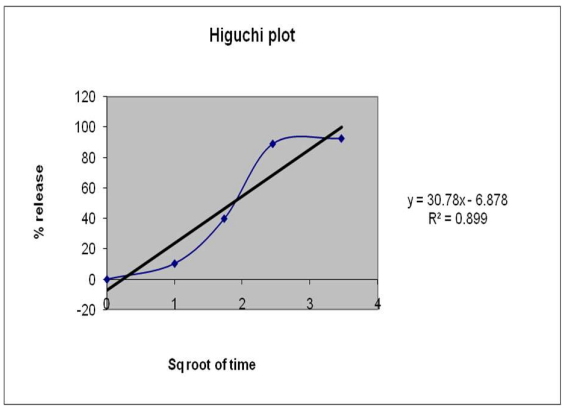


Figure 9: Higuchi kinetic release model

2.5 Stability

Table 15:Stability studies

S.N	Formulation code	Stability parameter	Month	Parameters	Result
1	LpCCG	4–8 °C With 75% RH	0-2	Appearance pH viscosity spread ability drug content swelling index	No change 7.17±0.012 2571±0.026 28 ±0.02 86 % 81%
		25 ± 2 °C with 60 ± 5% relative humidity	2-4	Appearance pH viscosity spread ability drug content swelling index	No change 7.17±0.012 2598±0.045 27.9 ±0.01 86 % 82%
		40 ± 2 °C with 75 ± 5% relative humidity	4-6	Appearance pH viscosity spread ability drug content swelling index	No change 7.25±0.012 2612±0.052 27 ±0.015 85 % 82.7%

2.6 Antimicrobial activity

Table 16 Anti bacterial activity of samples against S. aureus

Sample	Zone of inhibition in mm			
	Plate 1	Plate 2	Plate 3	Mean±SD
Treatment gel	6	7	6	6.333±0.577
Liposphere	9	12	10	10.333±1.527

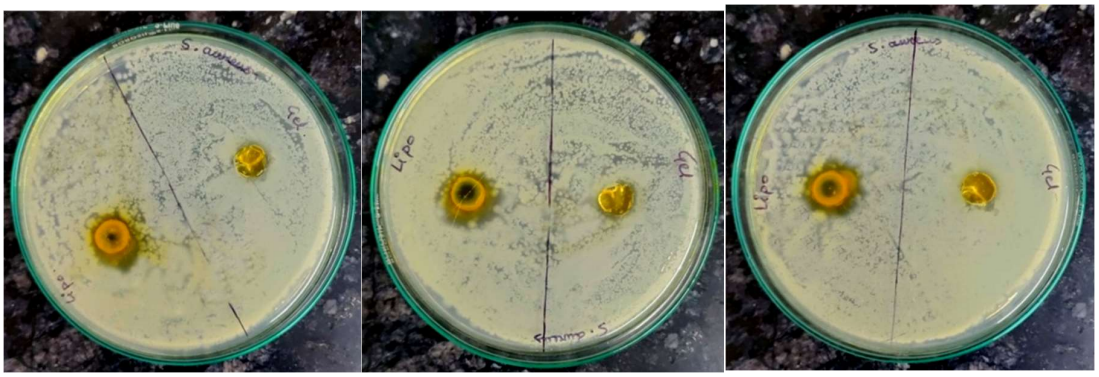


Figure 10: Anti bacterial activity of samples against S. aureus

Table 17 Anti bacterial activity of samples against S. pyogens

Sample	Zone of inhibition in mm			
	Plate 1	Plate 2	Plate 3	Mean±SD
Treatment gel	7	7	6	6.666±0.577
Liposphere	9	8	10	9±1

Figure 11: Anti bacterial activity of samples against *S. pyogens*

4. Discussion

This work used a three-factorial Quality by Design strategy to successfully design and optimizes clindamycin–curcumin loaded lipospheres for topical antimicrobial treatment. A thorough evaluation of the effects of paraffin wax, cetyl alcohol, and stearic acid on particle size and entrapment efficiency was conducted. The linear model's predictive power and significance were validated by statistical analysis ($p < 0.0001$). It was discovered that lipid content was a crucial factor in determining formulation effectiveness; at larger concentrations, paraffin wax increased particle size and decreased entrapment efficiency. Effective encapsulation of both medications within the solid lipid matrix was demonstrated by the improved formulation's submicron particle size and excellent entrapment efficiency (89%). Zeta potential measurements showed sufficient colloidal stability, and morphological analysis verified spherical and uniformly distributed particles. Lipospheres were added to a Carbopol 940 gel, resulting in a homogenous, non-gritty formulation with a pH that was close to physiological, an appropriate viscosity, and high spreadability—all of which supported the gel's cutaneous application. Drug release in vitro was shown to be sustained and diffusion-controlled, in accordance with Higuchi and Korsmeyer-Peppas kinetics. Minimal change in physicochemical properties over a six-month period was confirmed by

stability studies conducted under ICH conditions. In comparison to conventional gel, the liposphere-based gel demonstrated higher antibacterial activity against Streptococcus pyogenes and Staphylococcus aureus, suggesting increased therapeutic potential. Overall, the study shows that liposphere technology is a reliable and efficient way to enhance the delivery of topical antibiotics.

5 .Conclusion

Clindamycin–curcumin loaded lipospheres were successfully created and optimized in this work by employing a statistically validated three-factorial Quality by Design approach. Submicron particle size, good entrapment efficiency, regulated diffusion-mediated drug release, and adequate physicochemical stability under ICH storage conditions were all displayed by the improved formulation. A topical formulation that was stable, uniform, and dermally compatible was created by incorporating it into a Carbopol 940 gel foundation.

The improved therapeutic potential of the liposphere-based system is confirmed by increased antibacterial activity against Streptococcus pyogenes and Staphylococcus aureus. All things considered, the results show that lipospheres are a viable and efficient nanocarrier platform for cutting-edge topical antibiotic treatment.

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