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The Utilization of 3^2 Full Factorial Design (FFD) for Optimization of Lincomycin Hydrochloride (LNH) Loaded Nanogel Involving; Design of Experiments (DoE) an Advanced Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: The ongoing research aims to enhance the development of LNH-loaded nanogel by utilizing DoE as the computational method to statistically validate their formulation.
Methodology: In this research Chitosan used as a natural polymer and Poly (Ethylene glycol) [PEG] as a penetration or permeation enhancer. The different nanogel of LNH were synthesized using the Nanoprecipitation and Dispersion method, with variations in the drug-polymer ratio (1/0.03, 1/0.08, 1/0.12). The process parameters were carefully optimizing for enhance the efficiency of the synthesis. To achieve this, optimization studies were conducted using 3^2 FFD, employing the Design Expert Software Trial version 10.0.7. The total of 13 runs were generated to ensure comprehensive analysis and evaluation of the procedure. The selected independent variables included the concentration of Chitosan (R1) and Carbopol 934 (R2). The dependent variables, on the other hand, were particle size (P1), Polydispersity Index (P2), and % Drug release (P3), chosen in that order. By employing this optimization technique, one can acquire valuable information in a manner that is both efficient and cost-effective. This approach facilitates a deeper comprehension of the relationship between controllable independent variables and the performance and quality of the Nanogels being produced.
Conclusion: The nanogels containing drugs were tested for drug release, PDI, and particle size. The standardized formulation, ER12, was achieved successfully. Consequently, it was determined that LNH can be formulated as nanogels that can maintain drug release for 24 hours. This shows potential for improved drug delivery in topical treatments, surpassing the effectiveness of traditional therapy formulations.

Keywords: Design of experiments; optimization; formulations; nanogel; lincomycin; infection; antibiotics; lincosamide; response surface methodology; advance vehicles.

1. INTRODUCTION

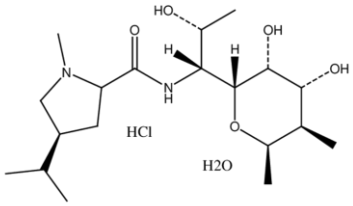
Lincomycin hydrochloride (LNH) is a broad-spectrum antibiotic with limited oral bioavailability and poor penetration into target tissues. Nanogels, due to their unique properties like sustained release, site-specific delivery, and enhanced bioavailability, offer a promising approach for improving the therapeutic efficacy of lincomycin hydrochloride. Streptococcal gangrene is a rare but serious condition caused by Group a Streptococcus (GAS) bacteria [1-2]. It is characterized by rapid tissue death and destruction, often accompanied by severe pain and fever. LNH is a member of the lincosamide class, functioning as an antibiotic. Its efficacy against GAS bacteria has been demonstrated, making it a valuable option for treating streptococcal gangrene. LNH belongs to the BCS Class III classification. This means it has high solubility in aqueous solutions but low permeability across biological membranes, including the intestinal wall. LNH is a salt with hygroscopic properties, which implies that it has the ability to absorb moisture from the surrounding air [3-5].

Consequently, it is crucial to store LNH in a container that is tightly sealed to prevent any moisture from entering. In addition, LNH exhibits solubility in aqueous solutions within a pH range of 4-8. The chemical structure of LNH can be observed in Fig. 1 as below followings.

The physicochemical properties of LNH discussed in the below Table 1 as followings:

Nanogels are three-dimensional, cross-linked polymeric networks with sizes ranging between 10-1000 nanometers. They are a specific class of

nanomaterials characterized by their high water content, swelling ability, and tunable properties [6]. Nanogels, as robust nanoparticles, offer a promising solution for controlled drug delivery applications. Their unique chemical composition and formulations make them suitable for delivering both hydrophilic and hydrophobic drugs, ensuring effectiveness and safety. By utilizing functionalized nanoparticles as drug carriers, nanogels enable the controlled release of drugs and other active materials at specific sites. This advanced drug delivery system demonstrates enhanced drug release and improved drug penetration, positioning it as a promising option for the topical administration of LNH in the management of streptococcal gangrene [7-9].



Chemical Formula: C18H35ClN2O6S
IUPAC Name: N-(2-chloro-1-(3,4,5-trihydroxy-6-(methylthio)tetrahydro-2H-pyran-2-yl)propyl)-1-methyl-4-propylpyrrolidine-2-carboxamide

Fig. 1. The chemical (Molecular) structure representation of LNH with IUPAC

Table 1. The physicochemical properties of LNH

Sr. No.	Property	Value
01.	Molecular Weight	406.99 g/mol
02.	Melting Point	165-167 °C
03.	Boiling Point	Decomposes
04.	Log P	-0.5
05.	Water Solubility	1.0 mg/mL
06.	pKa	7.7

DoE provides a structured and efficient methodology for optimizing the formulation process. A 3^2 FFD is a type of DoE that investigates the impact of multiple factors and their interactions on the desired response. This approach can be advantageous for optimizing LNH-loaded nanogels due to its ability to:

- Analyze the main effects and interactions of various formulation factors on the nanogel properties.
- Decrease the quantity of experimental runs necessary when compared to traditional one-factor-at-a-time experiments.
- Develop a statistically robust model that can predict the nanogel properties based on the selected formulation factors [6-10].

The pharmaceutical industry places significant importance on the selection and optimization of formulation and process variables. DoE has become an invaluable tool for efficiently handling quality risks. It starts by setting clear objectives and concentrates on improving our comprehension of product and process parameters. The 3^2 FFD is a widely employed design style in DoE, enabling us to systematically estimate main effects and interactions [11]. Moreover, the application of optimization techniques further enhances the predictability of dosage forms. RSM is a widely recognized DoE tool that maximizes the extraction of valuable information from well-designed experiments [12-13].

The main goal or objective of this research work to used Factorial Design at 3^2 level in the optimization as well as the formulation of LNH-loaded nanogel and validate with statistical analysis data validation. The LNH nanogel formulate by the using two different techniques for the using of statistics as ANOVA for the current study.

2. MATERIALS AND METHODS

2.1 Chemicals and Agents

Mylan laboratory Ltd kindly provided a gift sample of Lincomycin Hydrochloride (LNH). SD Fine Chemicals Ltd supplied Chitosan, Polyvinyl alcohol (PVA), Dichloromethane, Triethanolamine, Di-sodium hydrogen orthophosphate, Glycerine Propylene glycol, and Potassium dihydrogen orthophosphate. Research Institute, Mumbai provided Carbopol and Methanol. Qualigens fine chemicals supplied Sodium hydroxide pellets, and Leo chem. R.D fine chemicals limited, Mumbai supplied Disodium Hydrogen Phosphate.

2.2 Preparation of Clindamycin Nanogel

LNH nanogels were prepared utilizing the Nanoprecipitation method [9-13], employing Chitosan and Tween 80 as stabilizing agents. To achieve maximum stability and avoid clumping or settling, the drug and polymer were combined in glycerol while being constantly stirred on a magnetic stirrer, ensuring optimal results. This resulted in complete dissolution of the drug and polymer, and the formation of nanoparticles

through the Nanoprecipitation method. For the preparation of the nanogel, the Dispersion method was employed using Carbopol 934, which was soaked in water for several hours to allow for swelling [14-16]. The Carbopol, which had become swollen, was subsequently positioned on a magnetic stirrer to continue the stirring process. In order to improve penetration, PEG was introduced into the Carbopol mixture, along with either the equivalent amount of the drug or the separate nanoparticulate system. Furthermore, triethanolamine was included in the nanogel mixture to ensure the pH of the formulation remained stable. Ultimately, the formation of the nanogels was achieved.

2.3 Utilization of Design Expert for Optimization

This procedure underwent optimization studies with utilization of 3^2 FFD (Design Expert Software Trial version 10.0.7), resulting in 9 runs. The independent variables chosen were the concentration of Chitosan (R1) and Carbopol 934 (R2). The dependent variables included PS (P1), PDI (P2), and % DR (P3). The formulations was labeled with ER1, ER2, and ER3 & ER9, with 4 control formulations provided by the model. For the optimization studies, three different concentrations of the polymer (5.5, 11, and 16 mg) were selected. These studies demonstrate how the responses change when both factors are altered simultaneously [15-18]. The experiment was carried out at three distinct levels: -1, 0, and +1, which corresponded to low, medium, and high concentrations, respectively. The optimization results are presented in Table. 2 and Table. 3 as follows:

The Table. 02 and Table. 03 display the values of the independent variables, both in coded and actual forms with briefly.

2.4 Data Optimization

The current optimization study: involved the utilization of Design Expert software to perform various response surface methodology (RSM) computations. Multiple linear regression analysis (MLRA) techniques were employed to generate polynomial models with interaction for all the response variables [19].

To assess the impact of the independent variables: on the responses, the researchers utilized the statistical technique known as Analysis of Variance (ANOVA) through the implementation of Design Expert software (version 10.0.7). In order to establish statistical significance, a significance level of $p < 0.05$ was adopted.

To visualize the variance in the response surface: Three-dimensional plots were created to visualize the measured responses. These plots prove to be highly valuable when examining the influence of two factors on the response concurrently, as they offer a graphical depiction of how independent variables affect the responses [20-21].

3. RESULTS AND DISCUSSION

3.1 The Production of Polynomial Equation

This interactive polynomial terms generate by the statistical model for each response can be represented by the following equations:

$$Y = \alpha 0 + \alpha 1R + \alpha 2P + \alpha 3RP + \alpha 4R2 + \alpha 5P2 \quad \text{Equation (1)}$$

In this equation, the variable Y is used to represent the independent variable. The coefficient β0 corresponds to the arithmetic mean response of the nine runs, while **α** 1 represents the estimated coefficient for factor R. The main effects of factors R and P provide insight into the average outcome when these factors are individually altered from their lower to higher values. On the other hand, the interaction terms (RP) illustrate how the response changes when both factors are simultaneously modified [22]. The data acquired from the Department of Energy (DoE) indicates a strong correlation between the chosen independent variables and particle size, PDI, and %DR. Analysing the polynomial equations allows for various conclusions to be drawn based on the mathematical signs they exhibit. Specifically, positive and negative signs indicate synergistic and antagonistic effects, respectively.

$$P1 – (PS) = 429.79 – 47.17\ R – 29.21\ P + 2.21\ RP + 48.19\ R2 + 14.18P2 \quad \text{Equation (02)}$$

$$P2– (PDI) = 0.54 – 0.017R – 0.066P – 0.19RP – 0.078\ R2 + 0.088P2 \quad \text{Equation (03)}$$

$$P3 – (\%DR) = 63.52 + 6.26R + 10.89P – 5.88RP + 6.29\ R2 + 4.76\ P2 \quad \text{Equation (04)}$$

Where, R= Chitosan Con. and P= Carbopol 934 conc. for the formulation.

The average result is mainly affected by the amount of R and P, showing how the variables

Table 2. The values of independent variables in the coded form

Independent Variables	ER1	ER2	ER3	ER4	ER5	ER6	ER7	ER8	ER9	ER10	ER11	ER12	ER13
R1	-1	-1	0	1	0	1	-1	1	-1	0	1	1	-1
R2	0	-1	0	1	-1	0	-1	-1	1	1	1	-1	1

Table 3. The values of coded and actual independent variable

Coded Value	Actual Value (mg)	
--	**R1**	**R2**
-1	**5.5**	**0.03**
0	**11**	**0.08**
1	**16**	**0.12**

change from lower to higher values. The interaction coefficients (RP) demonstrate how the response changes when both variables are modified at the same time. According to the polynomial equation, when the polymer concentration and gelling agent increase, the particle size of the formulation decreases and shows a PDI of less than 0.5 nm [23-25]. Additionally, the percentage of DR also increases.

3.2 Statistical Analysis of Data

ANOVA was utilized to identify insignificant factors. The data was analyzed using Design-Expert Software (version 11.0). It was evident from the obtained data that the p-value was less than 0.05 ($p<0.05$) for all the dependent variables. The Model F values for PS, PDI, and %DR were 14.01 (P1), 16.67 (P2), and 12.47 (P3) respectively, indicating the significance of the model. R-Squared serves as a measure of goodness-of-fit for linear regression models, representing the percentage of variance in the dependent variable explained collectively by the independent variables [26].

The using of 3^2 factorial design tom identifies the independent variables have a significance effect on the dependent variables. They also used for the determination of increasing the polymer and drug con. When might increasing size in PS, PDI as well as LNH con. for the more accuracy. The design also identifies the interaction between the independent variables, that's meaning the effect of one variable depends on the level of the other.

Table 4. The ANOVA values for the models model-F value of PS (P1) [25-26]

Ingredients	Sum of squares	df	Mean Square	value	p-value Probability >F
Models	23020.04	4.9	4909.03	13.12	0.0361
R-CHITOSAN	12489.19	0.08	12489.19	39.91	0.0089
P- CARBOPOL934	5460.17	1	5460.17	15.93	0.0282
RP	20.25	1	20.25	0.059	0.8236
R2	4834.72	1	4834.72	14.11	0.0330
P2	346.72	1	346.72	1.01	0.3886
Remaining Value	1031.22	3.4	334.71	--	--
Final Values	26037.35	7.8	--	--	--

Table 5. The ANOVA for models indicating-Squared value Model-F value of PS [27]

Standard Deviation	19.53	R^2 Value	0.9479
Total Mean	472.44	**Adjustable R^2**	0.9804
CV%	3.92	**Predictable R^2**	0.5368
--	11869.57	**Precision**	11.415

3.3 Generation of 3D Response Surface Plots

The 3D plots were utilized to analyze the measured responses and identify any changes in the response surface. This plots proved to a valuable in examining the impact of two factors on the response simultaneously. The surface plots generated aligned with the polynomial term, providing insights into the influence of

Chitosan concentration (R1) and carbopol 934 concentration (R2) on the responses [26-29].

The impact of independent variables on the dependent variables is illustrated through the 3D plots displayed in Fig. 02 to 06. The Fig. 03 focuses on presenting the 3D response plots for particle size (P1), revealing a decrease in particle size as the concentration of Chitosan increases and the concentration of carbopol 934 decreases. Likewise, the counter plots in Fig. 02 also exhibit a decrease in particle size with an increase in the concentration of the polymer and gelling agent [30].

Table 6. The ANOVA for quadratic models of PDI (P2) [26-28]

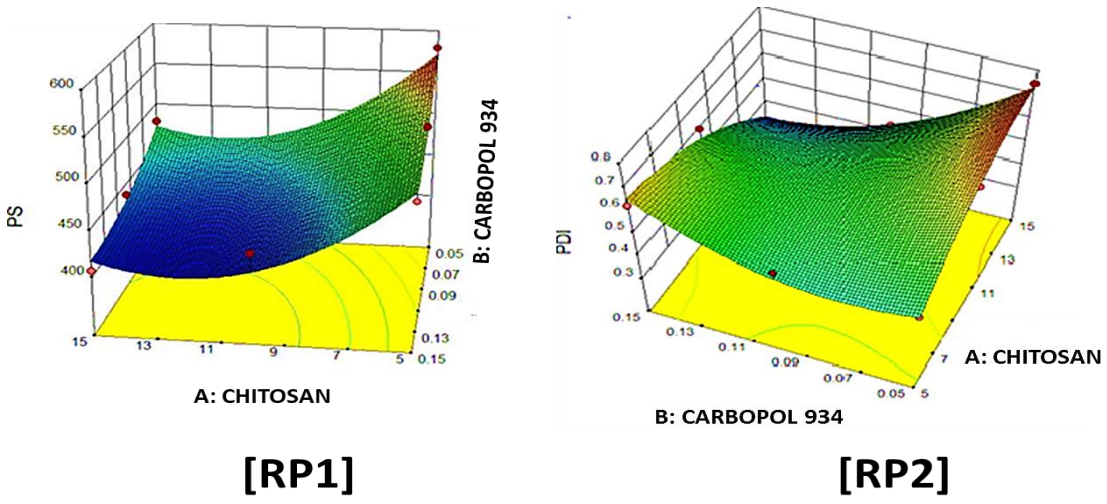
Ingredients	Sum of Square	df	Mean Square	F Value	p-value Probability >F
Models	0.12	4.8	0.036	17.61	0.0216
R-CHITOSAN	3.054E-004	1	2.054E-003	1.35	0.3416
P-CARBOPOL 934	0.019	1	0.019	12.10	0.0401
RP	0.084	1	0.083	53.79	0.0066
R2	8.778E-004	1	8.778E-004	6.78	0.0882
P2	0.018	1	0.018	11.42	0.0431
Remaining Value	4.611E-003	3	1.537E-003		
Final Values	2703.32	8.3	--	--	--

Table 7. The ANOVA for models indicating R^2 Value Model-F value of PDI [29]

Standard Deviation	0.039	R^2 Value	0.9652
Total Mean	0.54	**Adjustable R^2 Value**	**0.9073**
CV%	7.25	**Predictable R^2 Value**	**0.6317**
--	0.049	**Precision**	12.381

Table 8. The ANOVA for quadratic models model-F value of % DR (P3) [28-29]

Ingredients	Sum of squares	df	Mean Square	F-Value	p-value Probability >F
Models	1291.12	5.1	259.23	13.42	0.0421
R-CHITOSAN	234.03	1	232.02	12.17	0.0341
P-CARBOPOL934	836.15	1	836.15	40.39	0.0079
RP	96.33	1	96.33	4.65	0.1199
R2	80.35	1	80.35	3.88	0.1434
P2	48.29	1	47.28	2.38	0.2269
Remaining Value	64.12	2.9	21.72	--	--
Final Values	1254.23	7.9	--	--	--



[RP1] **[RP2]**

Fig. 2. The schematic representation of counter plot: RP1: The Counter plot for PS; RP2: The counter plot for the PDI

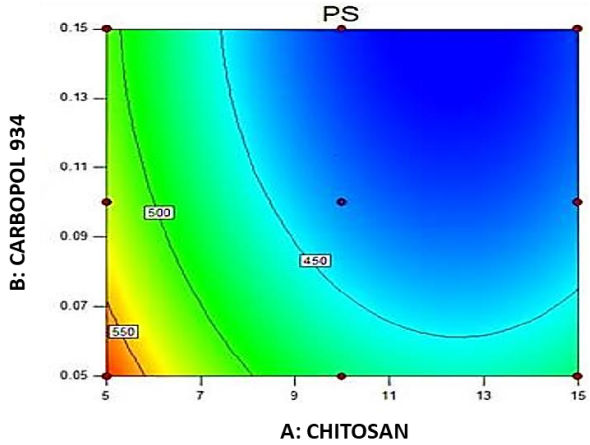


Fig. 3. The schematic representation of 3D response surface of PS (Particle Size)

Table 9. The ANOVA for models indicating R^2 Value Model-F value of % DR [27]

Standard Deviation	**4.66**	**R^2 Value**	**0.9531**
Total Mean	62.66	**Adjustable R^2 Value**	0.9665
CV%	8.19	**Predictable R^2 Value**	0.4671
	833.43	**Precision**	12.54

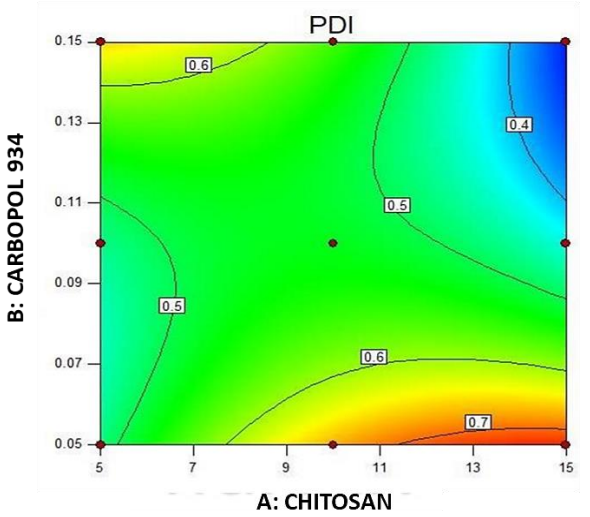


Fig. 4. The PDI is shown on the Surface plot, which demonstrates the impact of Chitosan and Carbopol 934 Concentration

The response plots in 3D for PDI (P2) depicted in Fig. 05 demonstrate a decrease in PDI with a notable increase in the concentration of polymer and gelling agent.

The 3D response plots for the percentage of drug release %DR of (P3) are shown in Fig. 05 and Fig. 06. The graphs demonstrate that increasing the concentration of Chitosan and carbopol 934 initially leads to a notable increase in %DR. This can be attributed to the combination of the same concentration of polymer and gelling agent, resulting in a higher overall polymer concentration [29-31].

Chitosan had different impacts on the drug release percentage (% DR). Initially, when the concentration of Chitosan in the formulation decreased, there was a decrease in % DR. However, when the concentration remained unchanged, there was an increase in the percentage of drug release [31]. This can be

attributed to the combined effect of the polymer and gelling agent concentration, which had a stronger influence on the drug release percentage.

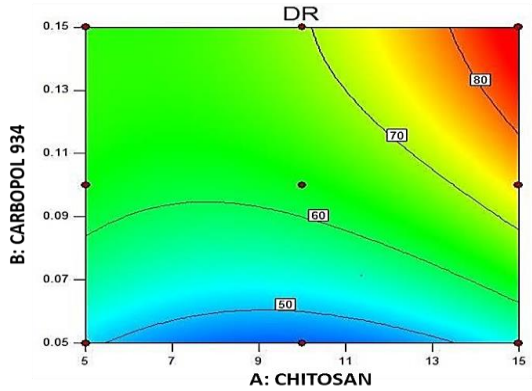


Fig. 5. The Response Surface Plots of Chitosan and Carbopol 934 for % DR are presented in a 3D format

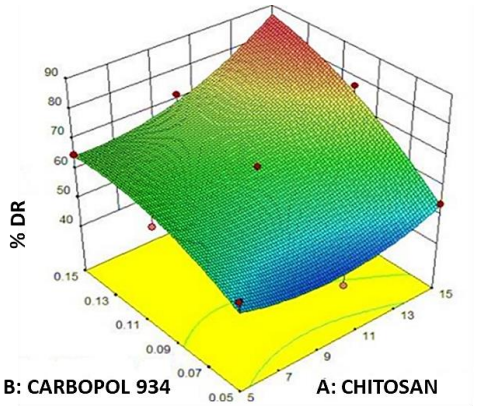


Fig. 6. The Contour Plots for % DR provide a visual representation of the impact of two factors on the response

The formulation 12 (ER12), which exhibited a favorable PDI range, was chosen as the optimized formulation for evaluation studies based on the highest drug release achieved from a 3^2 FFD with 2 factors and 3 levels [32].

4. CONCLUSION

The Design Expert software was utilized to analyze the response surface of a 3-level FD with 13 runs in a quadratic model. The formulations were developed using a 3^2 full factorial design, allowing for the concurrent evaluation of two formulation variables and their interaction. The utilization of 3^2 FFD combined with advanced approaches can significantly improve the development and optimization of LNH-loaded nanogels. This can lead to the production of nanogels with superior properties and enhanced therapeutic efficacy for various clinical applications.

The comparison of these variables took place across three levels: high, medium, and low. An examination of the impact of these factors on the dependent variables, specifically PS (P1), PDI (P2), and % DR (P3), was conducted through the utilization of a polynomial equation. The significant findings derived from the 3^2 FFD yielded valuable insights that greatly contributed to the successful advancement of LNH Nanogel for topical administration. Through a comparison of the observed and projected outcomes, it became apparent that the RSM effectively optimized the formulation of LNH Nanogel, resulting in the desired PS and DR characteristics. Optimization, a sophisticated experimental process commonly employed in nanoparticle development, enables the creation of robust preparation techniques that consistently yield the desired product characteristics. Factorial designs, widely utilized for optimization purposes, help identify the key factors influencing the output and determine the optimal levels of these variables for achieving an improved and desired dosage form.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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