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Design And Characterization Of Chitosan Nanoparticles Of Felbinac Using Doe

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ABSTRACT

The design and characterization of chitosan nanoparticles loaded with felbinac have been optimized using a Design of Experiments (DOE) approach to improve the drug's therapeutic performance. Felbinac, a nonsteroidal anti-inflammatory drug (NSAID), suffers from poor bioavailability and limited therapeutic efficacy when administered conventionally. Chitosan nanoparticles offer an innovative solution for enhancing solubility, controlled release, and targeted delivery. In this study, various formulations of felbinac-loaded chitosan nanoparticles were prepared and characterized for key parameters, including percentage yield, entrapment efficiency, particle size, and drug release profile. Response surface plots and contour plots were employed to determine the optimal formulation parameters. The formulations exhibited significant variations in entrapment efficiency (63.25%–79.98%) and particle size (75.65–132.87 nm). The optimized formulation (F14) showed excellent drug entrapment efficiency (78.85%) and a small particle size (75.65 nm). The in vitro release studies demonstrated a controlled release profile, with 93.32% of the drug released after 24 hours. The drug release kinetics followed a diffusion-controlled mechanism, as indicated by the Korsmeyer-Peppas model (R^2 = 0.9836). The findings suggest that chitosan nanoparticles can effectively enhance the bioavailability of felbinac and provide a controlled-release system for sustained therapeutic effects.

Keywords: *Chitosan nanoparticles, Felbinac, Design of Experiments (DOE), Entrapment efficiency, Particle size, Drug release, In vitro release, Controlled release, Nanotechnology, NSAID delivery.*

1. INTRODUCTION

The design and characterization of chitosan nanoparticles for the delivery of active pharmaceutical ingredients, such as felbinac, is a promising area of research in drug delivery systems [1]. Felbinac is a nonsteroidal anti-inflammatory drug (NSAID) widely used for its analgesic and anti-inflammatory properties. However, the clinical application of felbinac is often limited by its poor solubility, low bioavailability, and gastrointestinal side effects associated with systemic administration [2]. Nanotechnology offers a solution to these challenges by enhancing drug solubility, controlled release, and targeted delivery, thus improving the therapeutic outcomes of felbinac[3].

Chitosan, a natural polysaccharide derived from chitin, is widely used in nanomedicine due to its biocompatibility, biodegradability, and ability to form nanoparticles with various drugs. Chitosan nanoparticles have been extensively studied for their use in drug delivery systems due to their favorable properties, including mucoadhesion, controlled release, and ability to encapsulate both hydrophilic and lipophilic drugs [4].

Additionally, chitosan nanoparticles can provide a platform for sustained or site-specific drug release, reducing the frequency of administration and minimizing side effects [5]. Design of experiments (DOE) is a systematic approach for optimizing and characterizing the formulation of drug delivery systems. By applying statistical methods, DOE can help identify the optimal formulation variables that impact the size, charge, drug encapsulation efficiency, and release profile of nanoparticles [6]. The use of DOE in nanoparticle formulation allows for the efficient exploration of the effects of formulation and process variables on the characteristics of chitosan nanoparticles and can significantly improve the reproducibility and scalability of nanoparticle production [7].

In the context of felbinac-loaded chitosan nanoparticles, the incorporation of DOE in the formulation process enables researchers to systematically optimize key parameters such as chitosan concentration, crosslinking agents, and drug loading to achieve an optimal formulation with desired drug release characteristics and stability. The controlled release of felbinac from the chitosan nanoparticles could potentially reduce the frequency of dosing, enhance patient compliance, and minimize side effects, thus providing an improved therapeutic solution for the treatment of inflammation and pain. This research aims to design and characterize felbinac-loaded chitosan nanoparticles using DOE, focusing on optimizing critical formulation variables and evaluating the physicochemical properties and in vitro release profiles of the nanoparticles. By employing a rational and systematic approach, this study seeks to develop an effective and efficient drug delivery system for felbinac.

2. MATERIAL AND METHODS

Fabrication of chitosan nanoparticles using ionic gelation method

Chitosan nanoparticles of Felbinac were prepared using the ionotropic gelation method, which involves several steps to form the nanoparticles. First, a chitosan stock solution (1–2% w/v) was prepared by dissolving chitosan in acetic acid (1% v/v) at room temperature. In the next step, Felbinac (10 mg) was dissolved in the chitosan solution to create the drug-loaded formulation. Sodium tripolyphosphate (0.5–1% w/v) solution was then prepared in water, which serves as a crosslinking agent for the chitosan nanoparticles. This sodium tripolyphosphate solution was added dropwise to the chitosan-drug mixture using a syringe while stirring at speeds between 400 rpm to 1000 rpm. The solution was then magnetically stirred for 30 minutes to allow for proper crosslinking, after which it was filtered and rinsed with distilled water to remove any unreacted materials. The nanoparticles were then air-dried for 24 hours and further dried in an oven for 6 hours at 40°C to ensure complete removal of moisture. To optimize the preparation process, the formulation was designed using Design-Expert software with a Box-Behnken design (BBD), which included 17 experimental runs and 3 factors with 2 levels. This statistical design approach is ideal for investigating the quadratic response surface polynomial model, allowing for the efficient optimization of the chitosan nanoparticle formulation [8].

Table 1: Formulation variables and their levels in Box-Behnken experimental design

Sr. No.		**Formulation Variables**			
1	**Independent variables**		**Level**		
			Low (-)	**Medium (0)**	**High (+)**
	1	A: Chitosan (% w/v)	1	1.5	2
	2	B: Sodium tripolyphosphate (% w/v)	0.5	1.0	1.5
	3	C: Stirring speed (rpm)	5	7.5	10
2	**Response variables**				
	1	R1: Entrapment efficiency	Maximize		
	2	R2: Particle Size	Minimize		

Table 2: Variables with coded and actual values for box-behnken design

Std	**Run**	**Factor 1A: Chitosan (% w/v)**	**Factor 2B: Sodium tripolyphosphate (% w/v)**	**Factor 3C: Stirring speed**
11	1	1.5	0.5	1000
17	2	1.5	0.75	700
5	3	1	0.75	400
2	4	2	0.5	700
3	5	1	1	700
4	6	2	1	700

7	7	1	0.75	1000
16	8	1.5	0.75	700
10	9	1.5	1	400
12	10	1.5	1	1000
1	11	1	0.5	700
14	12	1.5	0.75	700
6	13	2	0.75	400
8	14	2	0.75	1000
15	15	1.5	0.75	1000
9	16	1.5	0.5	400
13	17	1.5	0.75	700

Evaluation of nanoparticles

Percentage Yield

The prepared nanoparticles F1-F17 were collected and weighed from each formulation [9]. The percentage yield (%) was calculated using formula given below:

$$\% \text{ Yield } = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Entrapment Efficiency

Amount of Felbinac in each formulation was calculated according to procedure given below:

10 mg of chitosan nanoparticles from each batch were accurately weighed. The powder of chitosan nanoparticles were dissolved in 10 ml 7.2 pH Phosphate Buffer and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 7.2 pH phosphate buffer. The supernant was analyzed for drug content by measuring the absorbance at 246nm [10].

Measurement of mean particle size

The mean particle size of the nanoparticle was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer **(**Malvern particle size analyser**)** at a scattering angle of 90°. A sample (0.5mg) of the nanoparticle suspended in 5 ml of distilled water was used for the measurement [11].

Determination of zeta potential

The zeta potential of the drug-loaded nanoparticless was measured on a zeta sizer (Malvern particle size analyser) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate [11].

Final equation in terms of coded factors

Entrapment Efficiency = +65.96+0.5388 A-1.32 B+5.85C-2.57 AB+0.8100 AC-2.52 BC+1.10 A^2+2.76 B^2+3.18 C^2

Statistical Analysis

Final Equation in Terms of Actual Factors

Entrapment Efficiency = +71.67575-0.494500 Chitosan-17.24567 Sodium tripolyphosphate-0.012943 Stirring speed-20.54000 Chitosan * Sodium tripolyphosphate+0.005400 Chitosan * Stirring speed-0.033533 Sodium tripolyphosphate * Stirring speed+4.39900 Chitosan^2 +44.15600 Sodium tripolyphosphate ^{2}+0.000035 Stirring speed ^{2}

Final equation in terms of coded factors

Particle Size = +109.89-5.00 A-1.75 B-20.93 C+12.94 AB-2.85 AC-1.35 BC-3.76 A^2+2.08 B^2-2.52 C^2

Final equation in terms of actual factors

Particle Size=+237.22331-29.20400 Chitosan-199.72967 Sodium tripolyphosphate+0.011481 Stirring speed+103.56000

Chitosan * Sodium tripolyphosphate-0.019000 Chitosan * Stirring speed-0.018033 Sodium tripolyphosphate * Stirring speed-15.05700 Chitosan ^{2}+33.33200 Sodium tripolyphosphate^2-0.000028 Stirring speed ^{2}

***In vitro* drug release**

The *in-vitro* drug release studies were performed using following method. Drug loaded chitosan nanoparticles were suspended in PBS at pH 7.4 and free drug centrifuged to collect nanoparticles and resuspended in PBS. The nanoparticle was poured in dialysis tube and tied at both end (HiMedia, Mumbai) with cut-off of 12 kDa and kept in 50 ml PBS at pH 7.4 and placed in bath shaker at 37°C for 24 h. An aliquot of release medium withdrawn using syringe at different time interval including 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 h and replaced with equal amount of fresh release medium. The concentration of drug was quantified using UV/VIS spectrophotometer at 246 nm[12].

Stability studies

Optimized formulations was subjected to accelerated stability testing as per ICH guidelines at a temperature 40 ± 2°C and RH 25 ± 5% for a period of 3 Months. Nanoparticles were filled in sealed glass vials and kept in stability chamber and were analyzed for particles size, zeta potential, and entrapment efficiency [13].

3. RESULTS AND DISCUSSION

The development of chitosan nanoparticles loaded with felbinac using a Design of Experiments (DOE) approach has been successfully carried out, focusing on optimizing key formulation parameters such as entrapment efficiency, particle size, and percentage yield. The results provide valuable insights into the formulation characteristics and performance of the nanoparticles, which are essential for enhancing the drug's therapeutic efficacy and stability.

From the experimental data in **Table 3**, the entrapment efficiency and particle size of the different formulations were analyzed. The entrapment efficiency ranged from 63.25% to 79.98%, with formulation F1 exhibiting the highest entrapment efficiency of 79.98%, while F3 had the lowest at 63.25%. These variations are likely due to differences in the chitosan concentration, which plays a significant role in encapsulating the drug within the nanoparticles. Chitosan's ability to form a stable nanoparticle matrix is influenced by its molecular weight and concentration, which directly affects the encapsulation of felbinac.

The particle size of the formulations varied from 75.65 nm (F14) to 132.87 nm (F16), with formulation F14 having the smallest size and highest entrapment efficiency. Smaller particle sizes are beneficial for improving the bioavailability and controlled release of the drug. The increase in particle size in some formulations could be due to an excess of chitosan or an inefficient drug encapsulation process, which affects the nanoparticle morphology.

Figures 1 and 2 show the response surface plots for entrapment efficiency and particle size, respectively. The response surface plots were generated to better understand the effect of formulation variables on the responses. For entrapment efficiency, the plot indicates a significant relationship between chitosan concentration and the resulting drug encapsulation, confirming the findings from the experimental data. For particle size, the plots reveal that increasing chitosan concentration tends to increase the particle size, which is consistent with previous studies that show a correlation between higher polymer concentrations and larger nanoparticles.

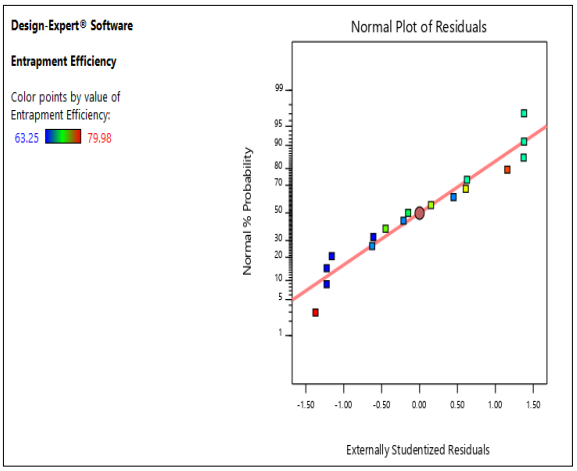
The **contour plots** and **3D surface plots** (Figures 1 and 2) further reinforce these relationships, highlighting the importance of optimizing both chitosan concentration and other formulation variables to achieve the desired nanoparticle characteristics.

The comparison between actual and predicted values (Table 4) for formulation F14 demonstrates the reliability of the DOE approach in predicting formulation outcomes. The slight variation between actual (78.85% for entrapment efficiency and 75.65 nm for particle size) and predicted values (77.44% and 74.82 nm, respectively) indicates the robustness and accuracy of the experimental design. The small discrepancies between predicted and observed values may be attributed to minor experimental errors or factors not fully accounted for in the modeling process, but they do not significantly impact the overall validity of the model.

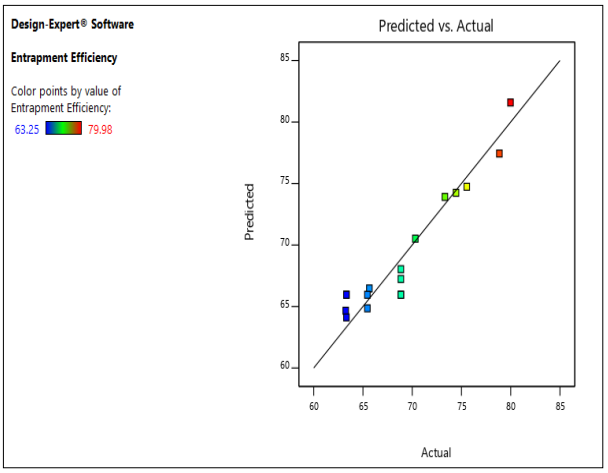
The cumulative drug release data (Table 5) for the plain drug and invasomal formulation F15 indicate that the invasomal formulation significantly improves the sustained release of felbinac. The percentage drug release after 24 hours for the invasomal formulation was 93.32%, compared to a much lower release profile for the plain drug. This sustained release profile is highly advantageous, as it minimizes the frequency of administration and maintains therapeutic drug concentrations over an extended period.

In **Table 6,** the in vitro drug release data for the optimized formulation (F14) were evaluated. The release follows a typical pattern, with an initial rapid release phase followed by a slower, more sustained release over time. This behavior is indicative of a controlled release system, which is desirable for achieving therapeutic levels of felbinac over an extended period, thereby reducing the risk of side effects associated with high peak drug concentrations. The data were further analyzed using the **regression analysis** (Table 7), where the formulation demonstrated a good fit for Korsmeyer-Peppas equation ($R^2 = 0.9836$), indicating a diffusion-controlled release mechanism. This suggests that the drug release from the chitosan nanoparticles is

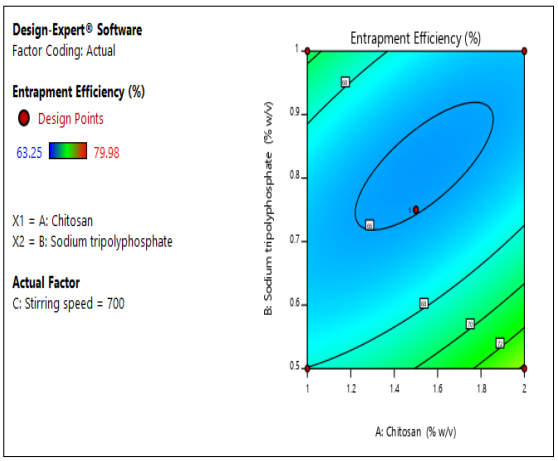
primarily governed by diffusion rather than dissolution.



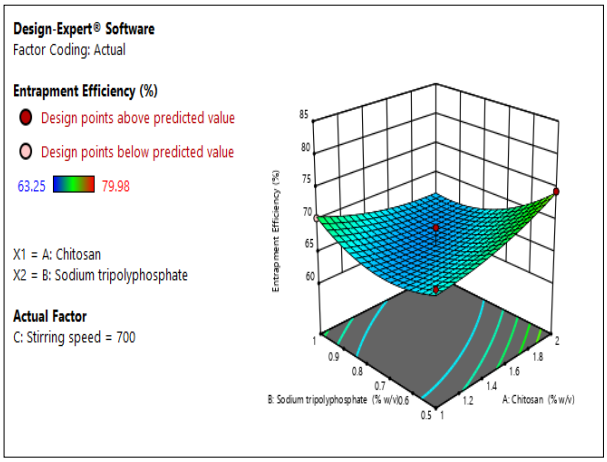
Normal plots of Residuals



Predicted vs Actual

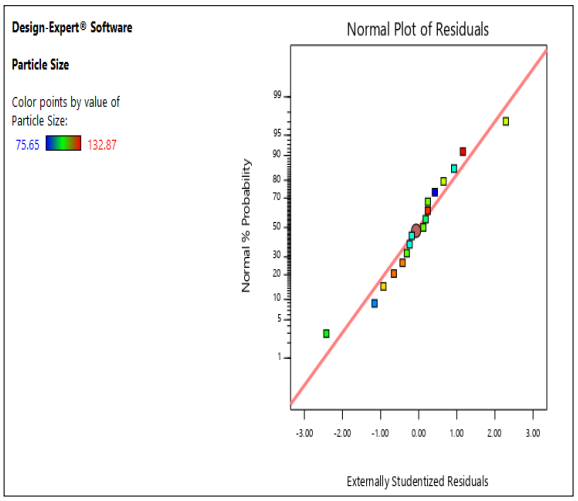


Contour plots

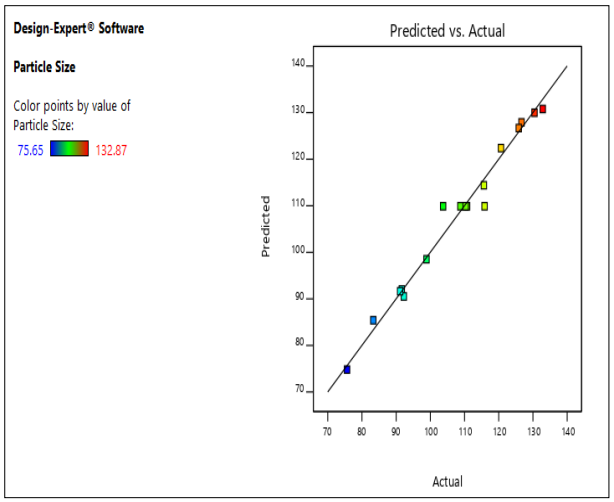


3D surface plot

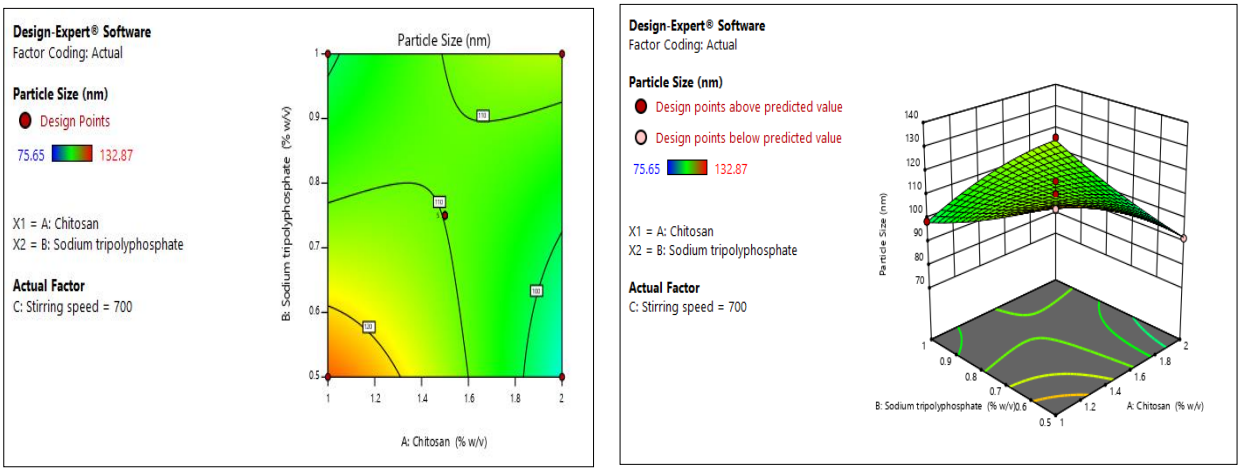
Figure 1: Response surface plot for entrapment efficiency



Normal plots of Residuals



Predicted vs Actual



Contour plots **3D surface plot**

Figure 2: Response surface plot for particle size

Table 3: Results of Percentage Yield (%), Entrapment Efficiency (%) and Particle Size (nm)

Formulation Code	Percentage Yield (%)	Entrapment Efficiency (%)	Particle Size (nm)
F1	81.25	79.98	91.15
F2	72.74	68.85	110.32
F3	68.78	63.25	125.85
F4	76.65	74.45	91.65
F5	73.32	70.32	98.87
F6	69.98	65.65	115.65
F7	78.85	75.54	92.25
F8	68.85	63.32	108.78
F9	72.25	68.85	130.45
F10	75.85	73.32	83.32
F11	73.32	68.85	126.65
F12	70.41	65.45	103.74
F13	68.85	63.32	120.65
F14	**83.25**	**78.85**	**75.65**
F15	72.25	68.85	110.74
F16	67.85	65.45	132.87
F17	65.85	63.32	115.85

Table 4: Experimental data with predicted response

Formulation Code	Parameters	Actual Value	Predicted Value
F14	**Entrapment Efficiency (%)**	78.85	77.44
	Particle Size (nm)	75.65	74.82

Table 5: Cumulative % drug release of from plain drug and invasomes formulation F15

S. No.	Dissolution medium	Time (h)	% Cumulative Drug Release
1	Phosphate buffer saline pH 7.4	0.5	8.95
2		1.0	14.45
3		2.0	23.32
4		4.0	36.65
5		6.0	48.85
6		8.0	59.98
7		10.0	66.62
8		12.0	88.85
9		24.0	93.32

Table 6: *In vitro* drug release data for optimized formulation F14

S. No.	Time (H)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	0.707	-0.301	8.95	0.952	91.05	1.959
2	1	1.000	0.000	14.45	1.160	85.55	1.932
3	2	1.414	0.301	23.32	1.368	76.68	1.885
4	4	2.000	0.602	36.65	1.564	63.35	1.802
5	6	2.449	0.778	48.85	1.689	51.15	1.709
6	8	2.828	0.903	59.98	1.778	40.02	1.602
7	10	3.162	1.000	66.62	1.824	33.38	1.523
8	12	3.464	1.079	88.85	1.949	11.15	1.047
9	24	4.899	1.380	93.32	1.970	6.68	0.825

Table 7: Regression analysis data of optimized invasomal gel formulation

F. Code	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
	R^2	R^2	R^2	R^2
F14	0.824	0.9128	0.9435	0.9836

4. CONCLUSION

The formulation and optimization of felbinac-loaded chitosan nanoparticles using DOE have resulted in an efficient drug delivery system with desirable characteristics, including high entrapment efficiency, small particle size, and sustained drug release. The in vitro drug release studies further confirm that the nanoparticles offer a controlled release profile, which could improve the therapeutic efficacy and minimize side effects of felbinac. The use of DOE not only allowed for the efficient optimization of formulation parameters but also provided predictive models that align well with experimental outcomes. This study highlights the potential of chitosan-based nanoparticles for effective drug delivery, and the findings can be utilized to further develop felbinac-loaded formulations with improved pharmacokinetic profiles.

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