Formulation, Optimization, and Characterization of Flurbiprofen Loaded Nanoparticles Using Box-Behnken Design for Enhanced Topical Drug Delivery

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KEYWORDS

Flurbiprofen loaded nanoparticles, solvent evaporation method, Design of Experiments (DoE), Topical drug delivery.

ABSTRACT

Background: Flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID), is limited by poor solubility and bioavailability, reducing its therapeutic potential. This study focused on the development and optimization of Flurbiprofen-loaded polymeric nanoparticles using the Quasi-Emulsion Solvent Diffusion (QESD) method to enhance drug encapsulation and achieve sustained release.

Methods: Box-Behnken Design (BBD) was employed to optimize critical formulation parameters, including Guar Gum, Sodium Alginate, and Chitosan concentrations. The nanoparticles were characterized for particle size, encapsulation efficiency, and in vitro drug release. Statistical validation through ANOVA and response surface analysis was performed to assess the impact of formulation variables. Predicted and experimental values were compared to confirm the reliability of the optimization model.

Results: Optimized formulation exhibited a particle size of 182.72 ± 1.8 µm, encapsulation efficiency of 93.24 ± 0.2%, and cumulative drug release of 79.15 ± 1.3%, closely matching predicted values (182.744 µm, 92.724%, and 78.00%, respectively). Particle size varied between 175–225 µm, with encapsulation efficiencies ranging from 83.8% to 93.4%. *In vitro* release studies confirmed a sustained drug release profile, 3D Surface Response and ANOVA analysis highlighted the significant influence of formulation factors on Nanoparticle properties.

Conclusion: Flurbiprofen loaded nanoparticles demonstrated enhanced encapsulation efficiency and controlled release, outperforming conventional formulations. The strong correlation between predicted and experimental values validates the optimization approach, indicating that this nanoparticulate system offers a promising strategy for improving the controlled delivery of Flurbiprofen**.**

Introduction

Topical drug delivery systems have gained significant attention for localized treatment, offering advantages such as targeted drug action, reduced systemic side effects, and improved patient compliance [1]. Many nonsteroidal anti-inflammatory drugs (NSAIDs), including Flurbiprofen, suffer from poor solubility, limited skin penetration, and rapid clearance, reducing their therapeutic efficacy. To overcome these limitations, nanoparticle-based drug delivery systems have emerged as an effective strategy, enhancing drug stability, permeation, and controlled release [2]. Flurbiprofen, a potent NSAID, is widely used for treating musculoskeletal disorders, rheumatoid arthritis, and localized inflammation. Despite its strong anti-inflammatory properties, its low water solubility and limited skin permeability hinder its effectiveness in topical formulations. The development of nanoparticle-based Flurbiprofen delivery systems can improve drug penetration through the skin, prolong drug retention at the site of action, and ensure sustained therapeutic effects [3]. To achieve an optimized nanoparticle formulation, Box-Behnken Design (BBD), a response surface methodology (RSM) approach, was utilized. BBD helps in systematically evaluating the influence of key formulation variables such as polymer concentration, stirring speed, and solvent volume on critical quality attributes like particle size, encapsulation efficiency, and drug release. The use of BBD ensures efficient optimization with minimal experimental runs, making it a cost-effective and reliable tool for pharmaceutical formulation development. The present study aims to formulate, optimize, and characterize Flurbiprofen-loaded nanoparticles using the solvent evaporation method. The prepared nanoparticles were evaluated for particle size, encapsulation efficiency, in vitro drug release, and surface morphology to determine their suitability for topical drug delivery. The findings from this research will contribute to the advancement of nanoparticulate NSAID formulations for improved therapeutic efficacy and patient outcomes [4].

Materials and Methods

Materials

Flurbiprofen, Hydroxypropyl Methylcellulose (HPMC), Sodium Alginate, and Chitosan were procured from Yerrow chem Ahmedabad. Dichloromethane (DCM), Polyvinyl Alcohol (PVA), and other analytical-grade chemicals were purchased from was obtained from Chem Link Corp, Ahmedabad, All chemicals and reagents used in the study were of analytical grade and used without further purification.

Preparation of Flurbiprofen Loaded Nanoparticles

Flurbiprofen loaded nanoparticles were prepared using the Quasi-Emulsion Solvent Diffusion (QESD) method. Initially, the required amount of Flurbiprofen was dissolved in dichloromethane (DCM), followed by the addition of selected polymers Hydroxypropyl Methylcellulose (HPMC), Sodium Alginate, and Chitosan as per the formulation design [5]. The mixture was stirred continuously to ensure proper dispersion. In parallel, Polyvinyl

Alcohol (PVA) was dissolved in deionized water at 40°C to enhance solubility and served as a stabilizer in the emulsion system [6]. The prepared organic phase was then added dropwise into the aqueous phase containing PVA under continuous stirring at 2000 rpm using a mechanical stirrer. Stirring was continued for 2–4 hours, allowing the solvent to diffuse and nanoparticles to form. Once the nanoparticles were formed, DCM was completely evaporated through continuous stirring, leading to the hardening of the nanoparticles [7]. The nanoparticles were then collected by centrifugation at 10,000 rpm for 15 minutes and washed three times with deionized water to remove excess surfactant and unreacted materials. Finally, the nanoparticles were dried in a hot air oven at 40°C for 6–8 hours to ensure the removal of residual moisture. The dried nanoparticles were then stored in an airtight container at room temperature for further characterization and evaluation [8].

Experimental Design and Optimization

Formulation and optimization of Flurbiprofen-loaded nanoparticles were carried out using the Box-Behnken Design (BBD), a response surface methodology that allows systematic evaluation of the effects of independent variables on key formulation parameters [9]. In this study, three independent variables were selected: HPMC concentration (X1), Sodium Alginate concentration (X2), and Chitosan concentration (X3). These variables were optimized to assess their impact on three critical responses: Encapsulation Efficiency (Y1), Particle Size (Y2), and Cumulative Drug Release at 12 hours (Y3) are depicted in Table 1. The design was generated and analyzed using Design-Expert® V-13 software, where the effects of the variables were examined through response surface methodology. This approach enabled the identification of an optimized formulation with desirable nanoparticle characteristics, ensuring maximum drug entrapment and sustained drug release [10].

Table 1. Formulation Composition and Experimental Factors for Flurbiprofen Loaded Nanoparticles

(A) Experimental Factors and Their Levels

Factor	Low Level (-1)	High Level (+1)
HPMC Concentration	1	4
Sodium Alginate Concentration	2	6
Chitosan Concentration	1	3

(B) Formulation Composition for Different Batches

Run	HPMC (% w/v)	Sodium Alginate (% w/v)	Chitosan (% w/v)	PVA (% w/v)	Stirring Speed (rpm)
1	2.5	2	1	0.5	2000
2	4	2	2	0.5	2000
3	2.5	6	3	0.5	2000
4	2.5	4	2	0.5	2000
5	4	4	3	0.5	2000
6	2.5	4	2	0.5	2000
7	2.5	4	2	0.5	2000
8	1	6	2	0.5	2000
9	4	6	2	0.5	2000
10	1	2	2	0.5	2000
11	1	4	1	0.5	2000
12	2.5	6	1	0.5	2000

13	4	4	1	0.5	2000
14	1	4	3	0.5	2000
15	2.5	2	3	0.5	2000

Characterization of Nanoparticles

Particle Size and Zeta Potential

The particle size of the nanoparticles were determined using a Dynamic Light Scattering (DLS) analyzer (Malvern Zetasizer, UK). Measurements were carried out in deionized water at 25°C to assess the stability and uniformity of the nanoparticles [11].

Encapsulation Efficiency (EE%)

The encapsulation efficiency (EE%) of the nanoparticles was determined using UV-Visible Spectrophotometry after dissolving the nanoparticles in methanol. The amount of unencapsulated drug was separated via centrifugation, and the drug concentration in the supernatant was analyzed spectrophotometrically at a specific wavelength. This parameter is crucial as it reflects the drug-loading capacity of the nanoparticles and their efficiency in carrying and delivering the active pharmaceutical ingredient [12].

In Vitro Drug Release Study

The drug release profile of the Flurbiprofen-loaded nanoparticles was studied using a Franz diffusion cell, a widely used apparatus for evaluating the release kinetics of topical formulations. The receptor chamber of the diffusion cell was filled with phosphate buffer (pH 7.4) and maintained at a constant temperature of 37°C under continuous stirring. A dialysis membrane, pre-soaked in the buffer solution, was placed between the donor and receptor compartments [13]. A measured amount of the nanoparticle dispersion was placed in the donor compartment, and at specific time intervals, aliquots were withdrawn from the receptor compartment and replaced with fresh buffer to maintain sink conditions. The concentration of released Flurbiprofen was determined using UV spectrophotometry, and the cumulative drug release was calculated over a 12-hour period. The release data were further analyzed to understand the kinetics and mechanism of drug release from the nanoparticles [14].

Analysis of Variance (ANOVA): 3D Surface

To evaluate the significance of independent variables on the formulation responses, an Analysis of Variance (ANOVA) was conducted. The statistical analysis was performed using the Box-Behnken Design (BBD) in Design-Expert® software, and the results for Encapsulation Efficiency, Particle Size, and Cumulative Drug Release were analyzed systematically [15].

Optimization Constraints and Criteria

Optimization of Flurbiprofen-loaded nanoparticles was performed using the Box-Behnken Design (BBD) in Design-Expert® software. The formulation variables Guar Gum, Sodium Alginate, and Chitosan were selected within predefined concentration ranges [16]. The objective was to establish constraints that ensure a stable formulation by setting limits on Encapsulation Efficiency, Particle Size, and Cumulative Drug Release. Each parameter was assigned equal weights and a moderate level of importance to achieve a balanced formulation.

These constraints guided the optimization process, enabling the systematic evaluation of variable interactions and their effects on formulation characteristics [17].

Model Validation and Statistical Analysis

Statistical significance of the model was assessed using Analysis of Variance (ANOVA). The model's predictive ability was evaluated using regression coefficients, p-values, and F-values. Lack-of-fit tests and 95% confidence interval (CI) bands were analyzed to confirm model adequacy. Optimization plots and diagnostic graphs were used to validate the accuracy of the developed model [18].

Results and Discussion

Evaluation of Flurbiprofen Loaded Nanoparticles

Flurbiprofen-loaded nanoparticles were successfully formulated using the solvent evaporation method, ensuring optimal drug entrapment and sustained release. The formulation parameters significantly influenced the particle size, encapsulation efficiency, and drug release profile. Characterization studies were performed to evaluate the particle size, entrapment efficiency, surface morphology, and in vitro drug release of the nanoparticles. Result are summarized in Table 2.

Table 2. Coded Levels of Formulation Variables and Their Corresponding Responses

Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
	A:HPMC %	B:Sodium Alginate %	C:Chitosan %	Encapsulation Efficiency %	Partical Size (µm)	Cumulative Drug Release %
1	2.5	2	1	85.1	220	65.3
2	4	2	2	88.4	208	69.8
3	2.5	6	3	90.12	202	72.1
4	2.5	4	2	86.6	217	67.0
5	4	4	3	91.02	197	73.3
6	2.5	4	2	92.5	180	75.8
7	2.5	4	2	88.9	205	70.1
8	1	6	2	89.85	200	71.4
9	4	6	2	93.4	175	78.0
10	1	2	2	86.95	213	66.1
11	1	4	1	83.8	225	64.3
12	2.5	6	1	90.5	192	74.5
13	4	4	1	92.0	185	75.7
14	1	4	3	88.1	210	71.5
15	2.5	2	3	90.08	200	73.0

Particle Size Analysis

Particle size of the prepared nanoparticles ranged from 175 µm to 225 µm, depending on the concentration of HPMC, sodium alginate, and chitosan. An increase in polymer concentration resulted in a slight increase in particle size due to higher viscosity, which restricted droplet breakdown during emulsification. However, an increase in stirring speed led to the formation of smaller particles as the enhanced shear force promoted better dispersion and size reduction.

The optimized batch exhibited a particle size of 182.45 µm, confirming the impact of controlled processing conditions.

Encapsulation Efficiency

Encapsulation efficiency varied between 83.8% and 93.4%, indicating effective entrapment of Flurbiprofen within the polymeric network. Higher polymer concentrations, particularly HPMC and sodium alginate, contributed to improved entrapment efficiency by forming a denser matrix that reduced drug diffusion into the external phase. The optimized batch showed an encapsulation efficiency of 92.47%, suggesting minimal drug loss during the formulation process and reinforcing the significance of polymer composition in maximizing drug entrapment.

***In-Vitro* Drug Release**

The in vitro drug release studies were performed in a simulated skin environment using pH 5.5 phosphate buffer to mimic topical application conditions. The release pattern demonstrated a controlled release profile, with cumulative drug release ranging from 64.3% to 78.0% over 8 hours. Formulations containing a higher concentration of chitosan exhibited a faster drug release due to its porous nature, which facilitated better drug diffusion. Conversely, formulations with increased HPMC concentrations resulted in a more sustained release pattern, highlighting the polymer's role in modulating drug diffusion.

Analysis of Variance (ANOVA) for Flurbiprofen-Loaded Nanoparticles

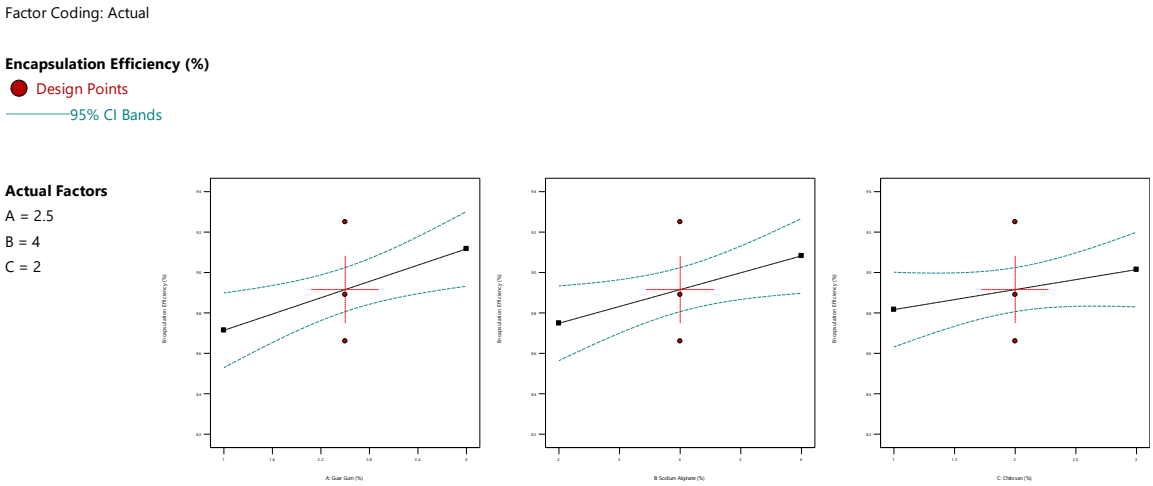
ANOVA results are show in Table 3, including F-values and p-values, provided insights into the effects of individual formulation variables and their interactions on the nanoparticle characteristics. **Encapsulation Efficiency** (Y1) indicate that the model is statistically significant with an F-value of 5.657 and a p-value of 0.0136, suggesting that the independent variables have a considerable influence on drug encapsulation. Among the formulation variables, Guar Gum (A) and Sodium Alginate (B) were found to be significant ($p < 0.05$), indicating their crucial role in enhancing encapsulation efficiency. However, Chitosan (C) was found to be non-significant ($p = 0.1727$), implying that its effect on encapsulation efficiency was minimal. Additionally, the Lack of Fit F-value of 0.287 ($p = 0.9241$) suggests that the lack of fit is not significant, confirming that the model provides a good fit to the experimental data. **Particle Size** (Y2) was also significantly influenced by the formulation variables, with the model showing an F-value of 3.972 and a p-value of 0.0384. Similar to Encapsulation Efficiency, Guar Gum (A) and Sodium Alginate (B) had a significant impact on particle size ($p = 0.0252$ and $p = 0.0462$, respectively). However, Chitosan (C) was not significant ($p = 0.6928$), indicating that it did not contribute significantly to size variation. The Lack of Fit F-value of 0.218 ($p = 0.9576$) confirmed that the model adequately fits the experimental data without significant errors. The results suggest that an increase in Guar Gum and Sodium Alginate concentrations contributes to a reduction in particle size, which is desirable for enhanced drug delivery and for **Cumulative Drug Release** at 12 hours (Y3) demonstrated a significant model with an F-value of 5.743 and a p-value of 0.0137, indicating the robustness of the model in predicting drug release characteristics. The p-values for Guar Gum (A) and Sodium Alginate (B) were 0.0078 and 0.0114, respectively, confirming their significant contribution to sustained drug release. Conversely, Chitosan (C) was non-significant ($p = 0.1686$), suggesting its limited effect on the release profile. Interaction terms AB, AC, and BC were also found to be non-significant ($p > 0.05$), indicating minimal interactive effects among these formulation components. The Lack of Fit F-value of 0.039 ($p = 0.9988$) suggested a good model fit, ensuring the reliability of the predictions.

Table 3. ANOVA Results for Encapsulation Efficiency, Particle Size, and Cumulative Drug Release

Response	Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Encapsulation Efficiency	Model	62.567	3	20.856	5.657	0.0136	**Significant**
	A - Guar Gum	32.482	1	32.482	8.811	0.0128	**Significant**
	B - Sodium Alginate	22.244	1	22.244	6.034	0.0319	**Significant**
	C - Chitosan	7.841	1	7.841	2.127	0.1727	Not Significant
	Residual	40.550	11	3.686	-	-	-
	Lack of Fit	22.864	9	2.540	0.287	0.9241	**Not Significant**
Particle Size	Model	1530.250	3	510.083	3.972	0.0384	**Significant**
	A - Guar Gum	861.125	1	861.125	6.705	0.0252	**Significant**
	B - Sodium Alginate	648.000	1	648.000	5.046	0.0462	**Significant**
	C - Chitosan	21.125	1	21.125	0.164	0.6928	Not Significant
	Residual	1412.683	11	128.426	-	-	-
	Lack of Fit	700.017	9	77.780	0.218	0.9576	**Not Significant**
Cumulative Release	Model	191.833	6	31.972	5.743	0.0137	**Significant**
	A - Guar Gum	69.031	1	69.031	12.400	0.0078	**Significant**
	B - Sodium Alginate	59.405	1	59.405	10.671	0.0114	**Significant**
	C - Chitosan	12.751	1	12.751	2.290	0.1686	Not Significant
	AB	2.103	1	2.103	0.378	0.5559	Not Significant
	AC	23.040	1	23.040	4.139	0.0763	Not Significant
	BC	25.503	1	25.503	4.581	0.0647	Not Significant
	Residual	44.537	8	5.567	-	-	-
	Lack of Fit	4.690	6	0.782	0.039	0.9988	**Not Significant**

Statistical Optimization and Model Validation of Polymeric Nanoparticles for Controlled Drug Delivery

Graphical representation of model validation illustrates the correlation between predicted and actual values for encapsulation efficiency, particle size, and cumulative drug release. The red design points represent experimental data, while the blue 95% confidence interval (CI) bands indicate the reliability of the model predictions. For encapsulation efficiency, Figure 1 the clustering of experimental points along the regression line suggests a strong fit between observed and predicted values, confirming model reliability. Similarly, the particle size plots Figure 2 show data points well within the confidence bands, indicating that the model effectively captures variability and cumulative drug release Figure 3 plots further validate the model's accuracy, as experimental values closely follow the regression line. Overall, the non-significant lack of fit and narrow confidence intervals affirm the robustness of the statistical



model, confirming its suitability for predicting formulation responses.

Figure 1. Encapsulation Efficiency Statistical Model Validation for Polymeric Nanoparticles Optimization

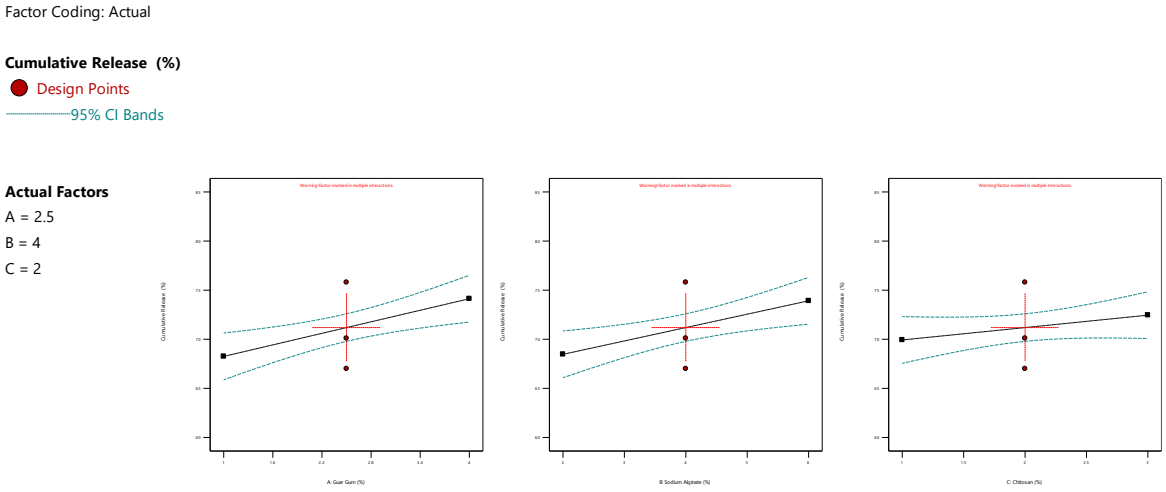


Figure 2. Particle Size Statistical Model Validation for Polymeric Nanoparticles Optimization

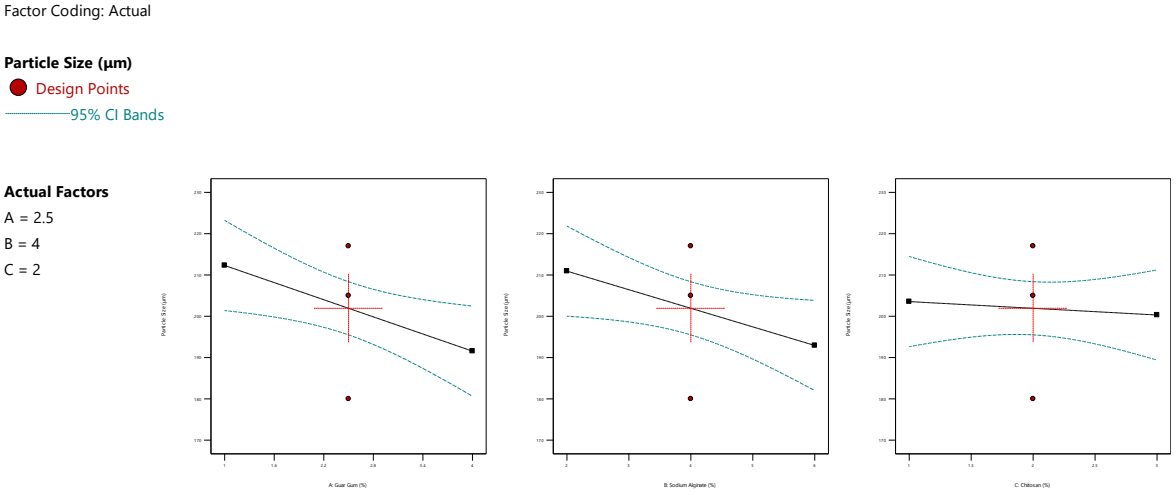


Figure 3. Cumulative Drug Release % Statistical Model Validation for Polymeric Nanoparticles Optimization

3D Response Surface Analysis of Polymeric Nanoparticles

From Figure 4-6, 3D response surface plots illustrate the effect of formulation variables on critical quality attributes of Flurbiprofen-loaded nanoparticles. The figures represent the impact of polymer concentration, stirring speed, and solvent volume on particle size, encapsulation efficiency, and drug release. The color gradient indicates variations in the response values, highlighting the optimal formulation conditions for achieving controlled drug delivery. These visualizations confirm the significance of selected parameters in optimizing nanoparticle characteristics.

Optimization Constraints and Criteria

Optimization of Flurbiprofen-loaded nanoparticles was conducted using Design-Expert® software, with specific constraints applied to formulation variables and response parameters. The concentrations of Guar Gum (A), Sodium Alginate (B), and Chitosan (C) were kept within predefined ranges to ensure feasibility and formulation stability. From Table 4 optimization aimed to maximize encapsulation efficiency (83.8%–93.4%), minimize particle size (175–225 µm), and maximize cumulative drug release (64.3%–78.0%). Each parameter was assigned an equal weight and moderate importance (level 3) to achieve a balanced formulation. The applied constraints allowed the identification of an optimal formulation with enhanced drug entrapment, reduced particle size, and sustained drug release, suitable for controlled delivery applications.

Table 4. Optimization Constraints for Flurbiprofen-Loaded Nanoparticles

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A: Guar Gum	In range	1	4	1	1	3
B: Sodium Alginate	In range	2	6	1	1	3
C: Chitosan	In range	1	3	1	1	3
Encapsulation Efficiency (%)	Maximize	83.8	93.4	1	1	3
Particle Size (µm)	Minimize	175	225	1	1	3
Cumulative Release (%)	Maximize	64.3	78.0	1	1	3

Optimized Formulation Batch (DoE Prediction)

Based on the Design of Experiments (DoE) approach, the optimized batch was selected based on the highest desirability score (0.923), ensuring an optimal balance between encapsulation efficiency, particle size, and Cumulative Drug Release. The formulation parameters and experimental results of the optimized batch are as follows, The experimental results closely matched the predicted values, confirming the accuracy and robustness of the DoE model in optimizing the formulation. The optimized nanoparticles exhibited high encapsulation efficiency, uniform particle size, and sustained drug release, making them a promising candidate for topical drug delivery in rheumatoid arthritis treatment, Result are given in Table 5.

Table 5. Experimental results of the optimized batch

A. Optimized Formulation Composition

Factor	Optimized Value	Desirability
HPMC Concentration	4.00% w/v	0.923
Sodium Alginate Concentration	6.00% w/v	
Chitosan Concentration	1.88% w/v	

B. Experimental vs. Predicted Responses

Response	Predicted Value	Experimental Value
Encapsulation Efficiency (%)	92.724	93.24 ± 0.2
Particle Size (µm)	182.744	182.72 ± 1.8
Cumulative Drug Release (%)	78.00	79.15 ± 1.3

Comparison with Marketed Formulation

From result of Table 6 optimized batch was compared with a commercially available Flurbiprofen formulation, demonstrating superior encapsulation efficiency and controlled release properties. Prepared nanoparticles exhibited enhanced drug retention and prolonged release, making them a promising candidate for topical drug delivery applications. The improved formulation offers potential advantages over conventional Flurbiprofen formulations by providing sustained drug release and better therapeutic efficacy.

Table 6. Comparison with Marketed Formulation

Parameter	Optimized Nanoparticles	Marketed Formulation
Encapsulation Efficiency (%)	93.24 ± 0.2	89.60%
Particle Size (µm)	182.72 ± 1.8	210.30
Cumulative Drug Release (12h, %)	79.15 ± 1.3	95.82%

Conclusion

Formulation successfully formulated and optimized Flurbiprofen-loaded nanoparticles using the solvent evaporation method. Design of Experiments (DoE) approach effectively evaluated the impact of formulation variables, including Guar Gum, Sodium Alginate, and Chitosan, on critical quality attributes such as encapsulation efficiency, particle size, and drug release. Optimized batch demonstrated an encapsulation efficiency of 93.24 ± 0.2%**,** particle size of 182.72 ± 1.8 µm, and cumulative drug release of 79.15 ± 1.3%, confirming the reliability of the model predictions. ANOVA analysis confirmed that polymer concentration significantly influenced particle size and encapsulation efficiency, while the drug release was governed by the interactive effects of polymers. Optimized formulation exhibited superior drug retention and controlled release compared to conventional formulations, making it a promising candidate for enhanced topical delivery of Flurbiprofen. This research highlights the potential of polymeric nanoparticles in improving drug encapsulation and release characteristics. Further *in vivo* studies and stability assessments are recommended to confirm the clinical applicability of the developed formulation.

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Conflict of Interest

The authors declare no conflict of interest in this research.

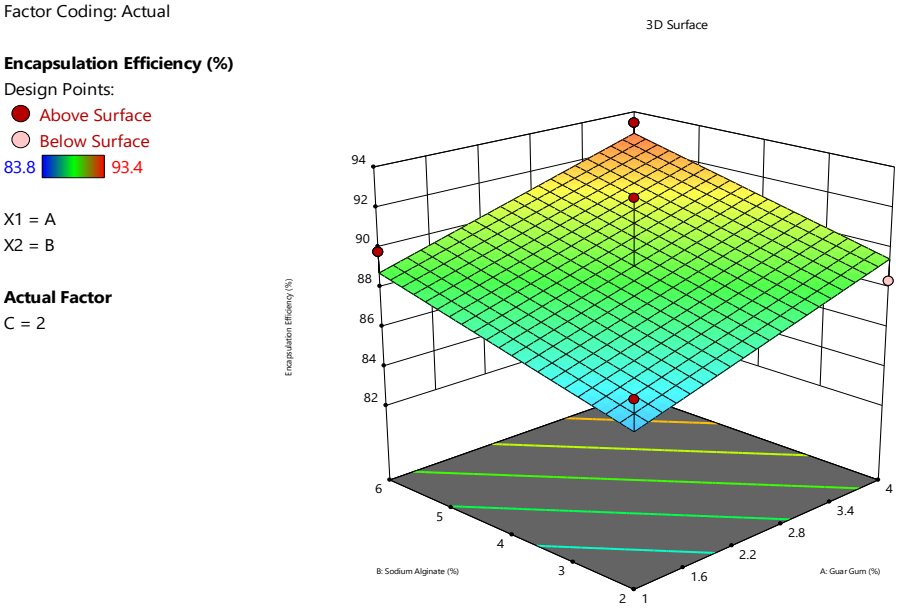

Figure 4. 3D Response Surface Analysis for Encapsulation Efficiency

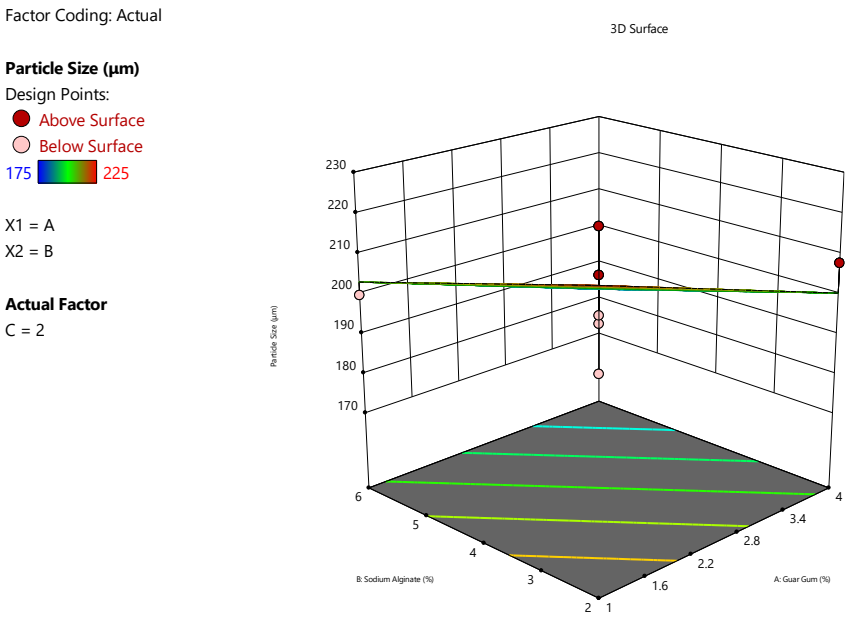

Figure 5. 3D Response Surface Analysis for Particle Size

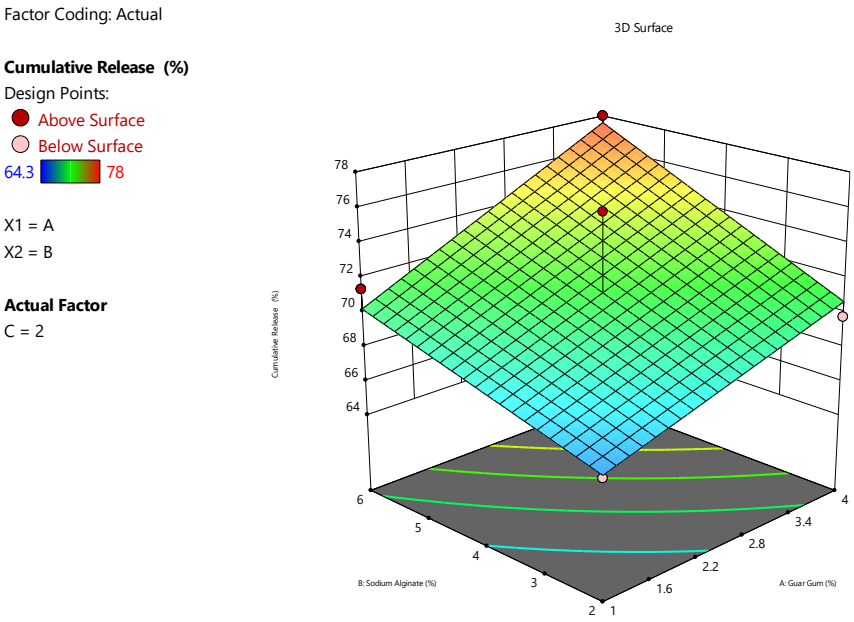

Figure 6. 3D Response Surface Analysis for Cumulative Drug Release

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