

Design and Fabrication of Flurbiprofen Nanosponges for the Treatment of Rheumatoid Arthritis

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Abstract:

➤ Introduction:

Nanosponges are tiny sponges that can circulate in the body to reach the specific site and binds on the surface to release the drug in a controlled and predictable manner. Nanosponges exhibit a porous structure in nature which has the unique ability to entrap the drug moieties and offers a merit of desire release. Flurbiprofen, a BCS class II medication with low solubility (8 mg/L) and high permeability (Log P = 3.80), is seen to be a good option for nanosponge formulation in order to address issues including short half-life, limited bioavailability, and stomach side effects.

➤ Objectives:

To Control/ modify release of drug at specific site and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy. To Show better in-vitro release/ diffusion performance than conventional dosage forms.

➤ Methods:

Flurbiprofen loaded Nanosponges were prepared using the Quasi Emulsion solvent diffusion method, and the main effect, interaction effects, and quadratic effects were evaluated using 3² FFD (Quality by Design) using Design Expert Software (VR 10.0.1). Drug:Polymer (X1) and Stirring Speed (X2) were chosen as independent variables with low, medium, and high values to maximize the Nanosponges. %Yield (Y1), % Drug Content (%) (Y2) and %CDR (Y3) were the dependent variables.

➤ Results:

Optimised Flurbiprofen Nanosponges (C1) were having 93.74±1.20 CDR in 12 hrs which clearly indicates better in vitro release/diffusion than conventional dosage form as well as shows better patient compliance. Also, it indicates controlled release pattern at specific site in reduced dose frequency.

Keywords: Flurbiprofen, Nanosponges, Rheumatoid Arthritis, Quality by Design Approach, 3² Factorial Design.

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I. INTRODUCTION

In order to achieve the desired result, it has long been a goal to target medication delivery mechanisms. In the twenty-first century, it is now possible to inject Nanosponges orally, topically, or intravenously. Initially, the

Nanosponge medication delivery method was only available for topical use. Nanosponge is a new type of material made of tiny particles with a hollow that is only a few nanometers wide. These little holes can be filled with a variety of materials. These small particles can improve the stability of pharmacological substances or compounds that are poorly

soluble in water due to their capacity to contain both hydrophilic and lipophilic therapeutic substances. The nanosponges are either a three-dimensional, spontaneously degradable polyester network (backbone). These polyesters are combined with a crosslinker in a solution to make nanosponges. Because polyester is typically biodegradable, it decomposes slowly in the body in this instance. When the nanosponge scaffold disintegrates, the loaded drug molecules are released in an unfavourable way.

Phenyl alkanoic acid, a structure-similar nonsteroidal anti-inflammatory drug (NSAID) to ibuprofen, is the source of flurbiprofen. The commercial dosage forms of flurbiprofen are tablets, sustained release capsules, and eye drops. Gout, rheumatoid arthritis, osteoarthritis, and other rheumatic diseases are all treated with it. Because it is non-invasive, convenient, and safe, skin administration of flurbiprofen may be preferable to oral administration for patients who are unable to use the oral route due to vomiting or unconsciousness. Additionally, the drug's GI side effects and first pass metabolism are eliminated through the topical route. Additionally, it may reduce administration frequency and improve patient compliance. Therefore, flurbiprofen, a BCS class II medication with low solubility (8 mg/L) and high permeability (Log P = 3.80), is seen to be a good option for nanosponge formulation in order to address issues including short half-life, limited bioavailability, and stomach side effects.

II. MATERIALS AND METHODS

➤ Formulation of API Loaded Nanosponges:

Nanosponges made with a method called quasi-emulsion solvent diffusion. Nanosponge is prepared by using different polymer ratio of Pluronic F68 and Eudragit RS100 (1:1, 1:2 and 1:3). First Polymer is dissolved in Dichloromethane. Drug was dissolved in methanol and this solution is added in above solution and mixed properly. PVA is dissolved in water in a different beaker. Under a magnetic stirrer at 1000-2000 RPM and room temperature for 60 minutes, add internal phase (organic solution) drop by drop to external phase (PVA solution). To solidify, this solution was kept for 24 hours. After centrifugation, the remaining solution was collected and kept for 20 minutes for cooling purposes. After that, this residue is frozen and dried, and nanosponges are taken. ^[1-2]

➤ Formulation and Development of Flurbiprofen Nanosponges by using QbD Approach

The Ether Injection method was used to prepare the Flurbiprofen-loaded Nanosponges. Design Expert (VR 10.0.1) used 32 FFD to evaluate the main effect, interaction effects, and quadratic effects. To get the most out of the Nanosponges, the Drug:Polymer Ratio (X1) and Stirring speed (X2) were chosen as independent variables with low,

medium, and high values, respectively. The dependent variables were the percentages of yield (Y1), drug content (Y2), and CDR (Y3). According to research, Drug: Polymer Ratio (X1) and Stirring speed (X2) were all shown to have a significant impact on the dependent variables, and were so chosen as independent variables. ^[3, 4]

➤ Characterization of Flurbiprofen Nanosponge [5, 6]:

- %Yield
- % Yield can be determined by calculating initial weight of raw materials and final weight of drug loaded nanosponges.

$$\text{Production Yield} = \frac{\text{Practical mass of Nanosponge}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

➤ Drug Content

Nanosponging suspension in sufficient quantities to dissolve the drug. Centrifuge the dispersion (e.g., 10,000 rpm for 10–15 min) or filter through a 0.45 µm filter to remove undissolved nanosponge matrix. Utilizing UV-Visible Spectrophotometry at 247 nm, measure the amount of drug in the clear supernatant. Utilize the pure drug's calibration curve to determine the drug content.

$$\text{Drug Content (\%)} = \left(\frac{\text{Amount of drug in sample}}{\text{Theoretical drug content}} \right) \times 100$$

➤ In Vitro Drug Release Study of Nanosponges

In a USP-I Type dissolving equipment, the dissolution test was performed in 900 mL Phosphate buffer (PH 7.4) at 37.5 °C, 150 RPM. Aliquots were removed and refilled with fresh solvent every hour for up to 12 hours. The sample's absorbance at maximum 247 nm was determined with a UV-visible spectrophotometer. Additionally, determine the percent CDR. ^[9]

III. RESULT AND DISCUSSION

For statistical evaluation, the design of Experiment 10.0.1 was used, and the first solicitation polynomial conditions were created. 32 full factorial designs were used from the major findings, with two factors being surveyed, freely at three levels, and possible nine mixes being sorted out. Two novel components were used to complete three-level factorial assessments. In the first factorial arrangement, the proportion of Drug:Polymer Ratio (X1) and the speed of stirring (X2) were chosen as independent factors, while the percentage yield (Y1), the percentage of drug content (%) (Y2), and the percentage of CDR (Y3) were chosen as dependent factors for both factorial plans.

➤ 32 Factorial Design Approach

Table 1 32 Factorial Batches

Independent variables of formulations			
Independent variables (X1)	Low (-1)	Medium (0)	High (+1)
Drug: Polymer (X1)	1:1	1:2	1:3
Stirring Speed (X2)	1000	1500	2000
Dependent variables			
Y1-Yield (%)			
Y2-%Drug Content			
Y3-%Cumulative Drug release			

➤ Compositions of Factorial Batches in Decoded Form

Table 2 Compositions of Factorial Batches in Decoded Form as per Design Expert

BATCH CODE	RUNS	Vol. of Cholesterol (mg) (X1)	Vol. of Span 60 (mg) (X2)	P.S. (nm) (Y1)	%E.E (%) (Y2)	
3 ² FFD		X-Variables Responses		Y-Variables Responses		
Batch code	Runs	Drug: Polymer (X1)	Stirring speed (X2)	Yield (%) (Y1) (n=3)	Drug Content (%) (Y2) (n=3)	%CDR in 12 Hr. (Y3) (n=3)
FLUNS1	1	1:1	1000	83.21±1.03	95.60±1.10	83.57±1.05
FLUNS2	2	1:2	1000	90.64±1.00	93.57±0.90	89.18±0.90
FLUNS3	3	1:3	1000	83.17±1.00	80.22±0.90	81.84±0.80
FLUNS4	4	1:1	1500	84.13±0.80	86.58±1.05	86.43±1.10
FLUNS5	5	1:2	1500	92.23±1.02	95.11±1.00	92.72±1.10
FLUNS6	6	1:3	1500	80.51±0.90	79.36±0.80	80.42±1.20
FLUNS7	7	1:1	2000	87.45±1.03	88.13±0.80	86.95±0.90
FLUNS8	8	1:2	2000	96.52±1.20	97.73±1.15	94.16±1.25
FLUNS9	9	1:3	2000	80.62±0.90	82.45±1.00	79.38±1.10

➤ Effect on %Yield (Y1):

Negative value of a indicates decrease in % Yield. The percentage yield will rise if the coefficient B has a positive value. Full modes were found to be significant for two independent variables, and detailed ANOVA, Response

surface counter plot, and 3D plots are as follows: It indicates linearity of surface response and contour plot as shown in figure.

$$\%Yield = +92.25 - 1.74*A + 1.26*B - 1.69*AB - 9.94*A^2 + 1.31*B^2$$

Table 3 Result of Analysis of Variance for Y1 (%Yield)

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	240.80	5	48.16	17.07	0.0206	Significant
A-drug:polymer ratio	18.34	1	18.34	6.50	0.0840	
B-stirring speed	9.55	1	9.55	3.39	0.1630	
AB	11.53	1	11.53	4.09	0.1365	
A ²	197.94	1	197.94	70.16	0.0036	
B ²	3.44	1	3.44	1.22	0.3500	
Residual	8.46	3	2.82			
Cor Total	249.26	8				

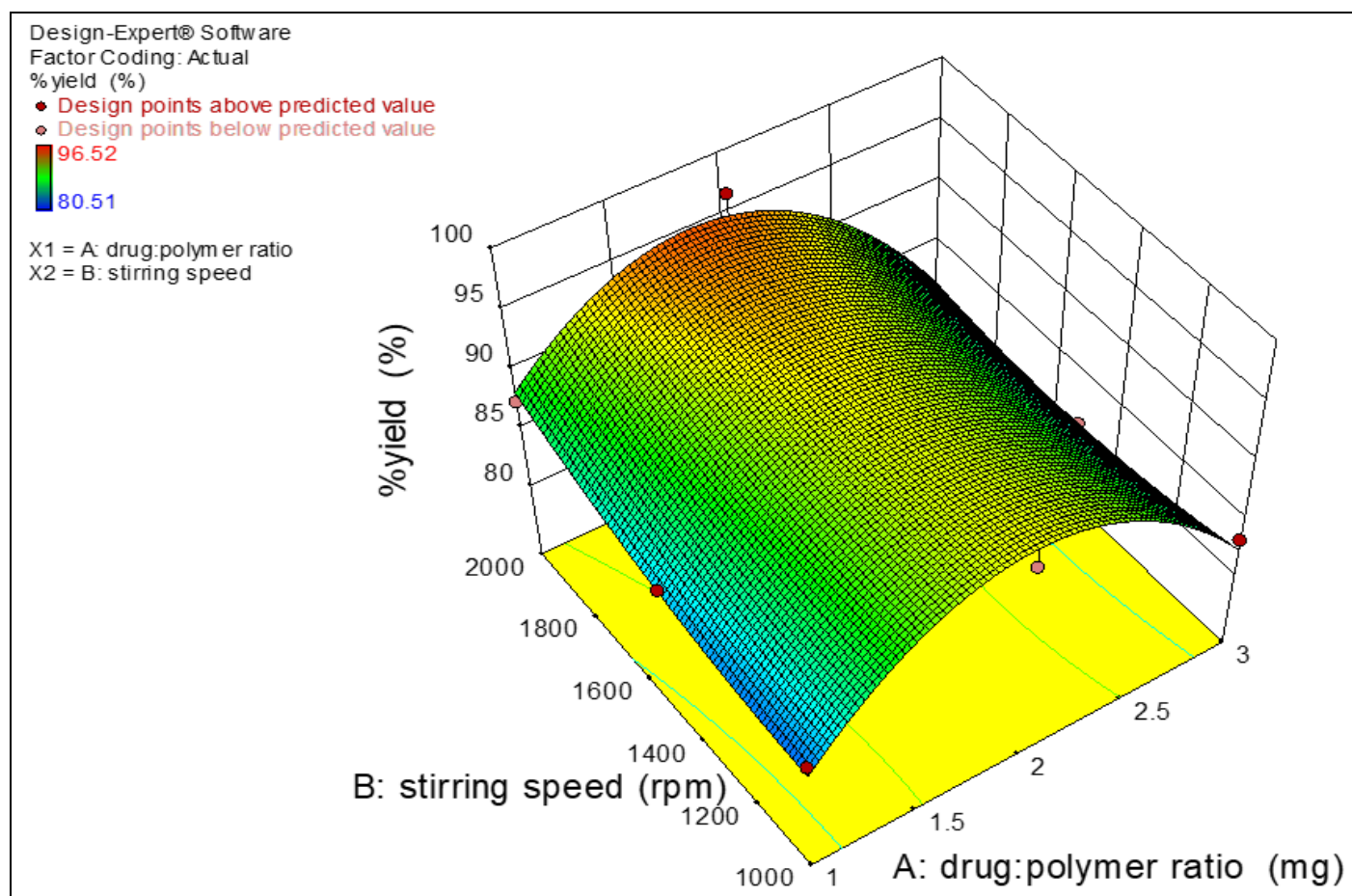


Fig 1 Response Surface Plot Illustrating the Influence of Drug: Polymer and Stirring Speed on the Effect of %Yield

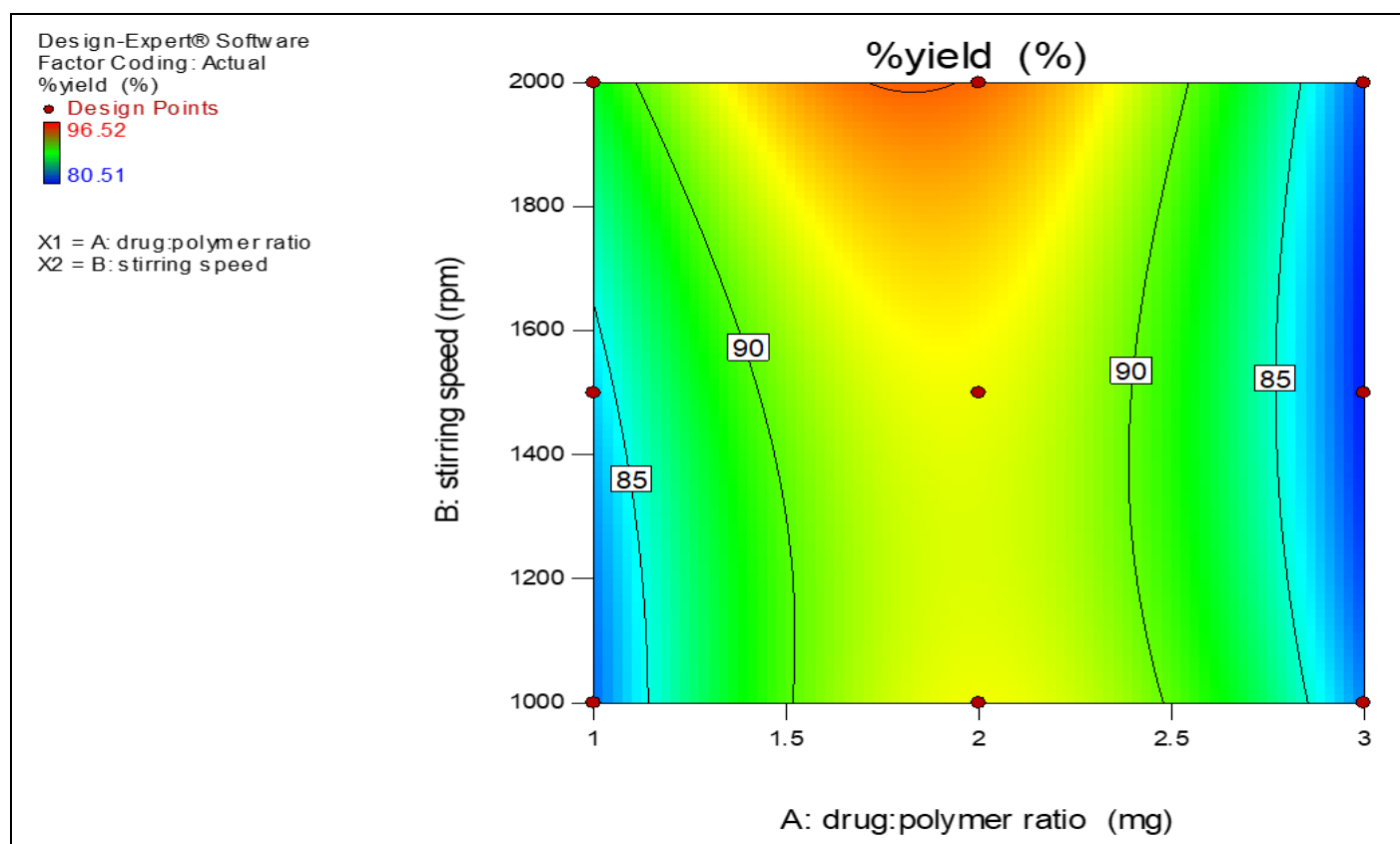


Fig 2 Contour Plot Illustrating the Influence of Drug: Polymer and Stirring Speed on the Effect of %Yield

➤ *Effect on %Drug Content (Y2) - Surface Response Study:*

Positive value for coefficient of B Stirring Speed in equation indicates increase in % Drug Content. Positive value of coefficient of A indicates in %Drug Content. It indicates linearity of surface response and counter plot.

$$\text{Drug content} = +93.74 - 4.71 \cdot A - 0.18 \cdot B + 2.42 \cdot AB - 10.08 \cdot A^2 + 2.60 \cdot B^2$$

Table 4 Result of Analysis of Variance for Y2 (%Drug Content)

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	373.74	5	74.75	9.66	0.0455	significant
A-drug:polymer ratio	133.29	1	133.29	17.22	0.0254	
B-stirring speed	0.19	1	0.19	0.025	0.8841	
AB	23.52	1	23.52	3.04	0.1796	
A ²	203.21	1	203.21	26.26	0.0144	
B ²	13.52	1	13.52	1.75	0.2780	
Residual	23.22	3	7.74			
Cor Total	396.96	8				

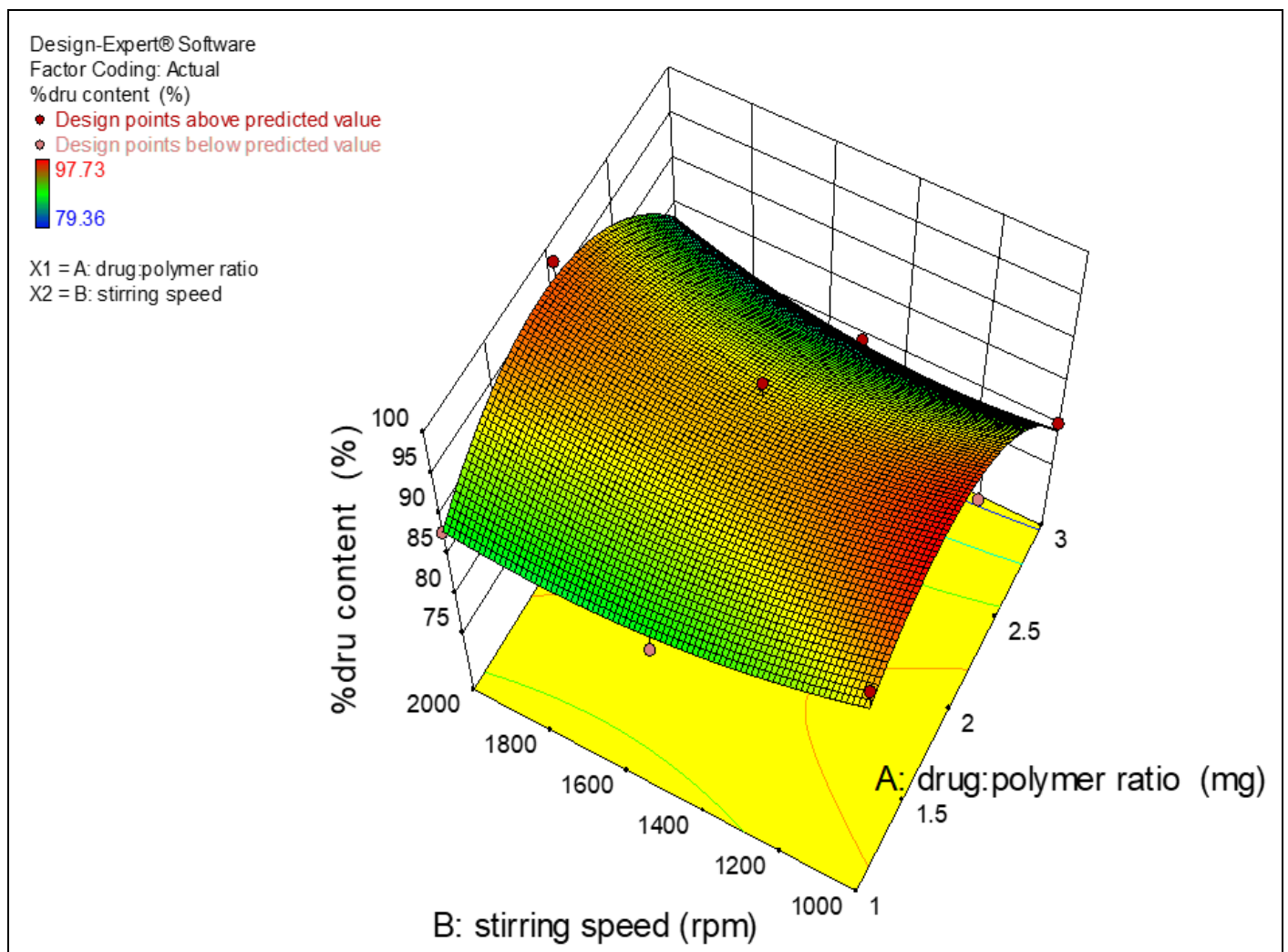


Fig 3 Response Surface Plot Illustrating the Influence of Drug: Polymer and Stirring Speed on the %Drug Content

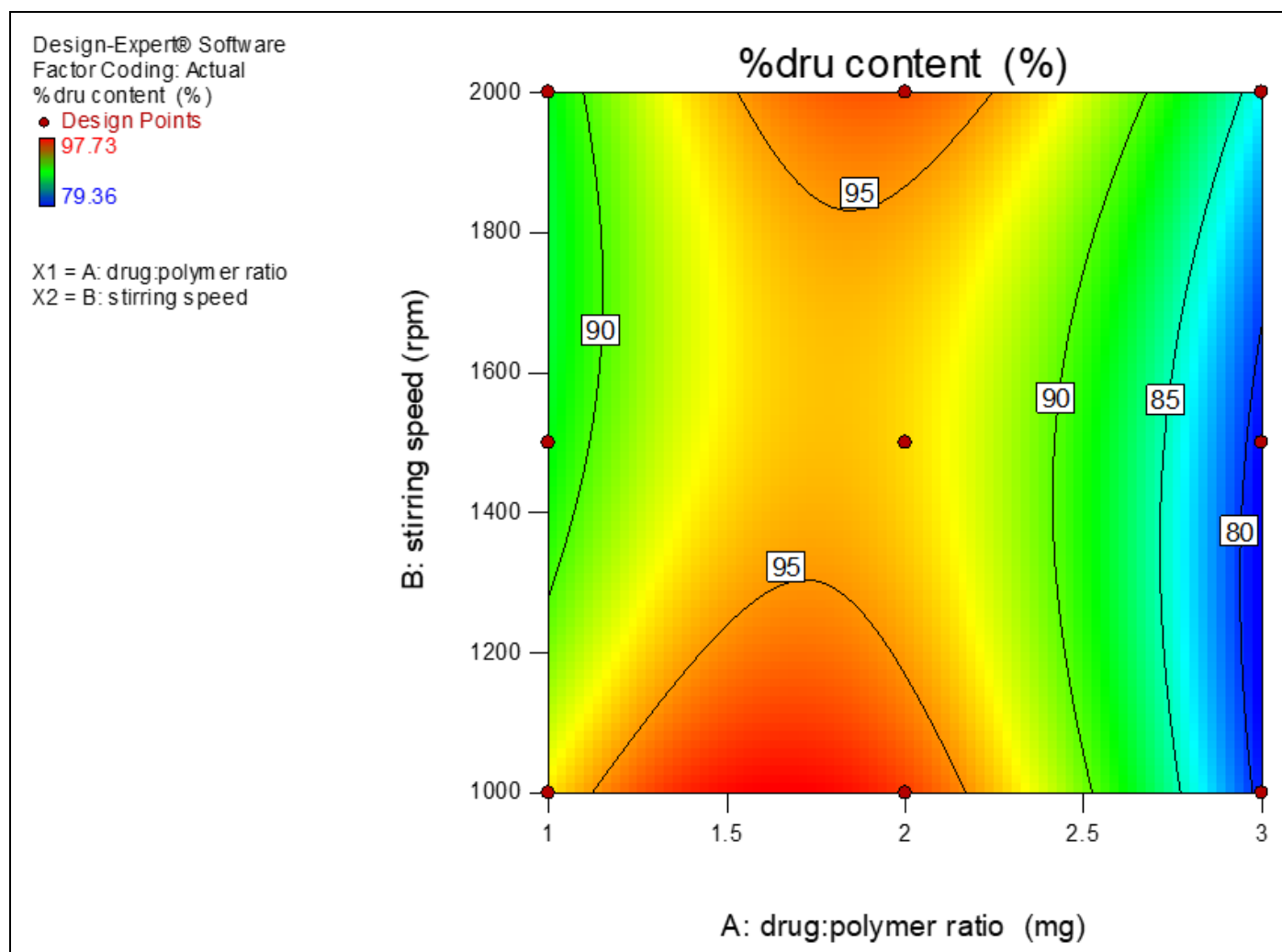


Fig 4 Contour Plot Illustrating the Influence of Drug: Polymer and Stirring Speed on the % Drug Content

➤ *Effect on % Cumulative Drug release (Y3) Surface Response Study:*

Positive value for coefficient of B Stirring Speed in equation indicates increase in %CDR. Positive value of coefficient of A indicates in %CDR. It indicates linearity of surface response and counter plot.

$$\text{Cumulative drug release} = +92.47 - 2.55 * A + 0.98 * B - 1.46 * AB - 8.92 * A^2 - 0.68 * B^2$$

Table 5 Effect on % Cumulative Drug release (Y3) Surface Response Study

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	213.50	5	42.70	16.93	0.0208	significant
A-drug:polymer ratio	39.07	1	39.07	15.49	0.0292	
B-stirring speed	5.80	1	5.80	2.30	0.2266	
AB	8.53	1	8.53	3.38	0.1633	
A ²	159.19	1	159.19	63.12	0.0042	
B ²	0.92	1	0.92	0.36	0.5893	
Residual	7.57	3	2.52			
Cor Total	221.07	8				

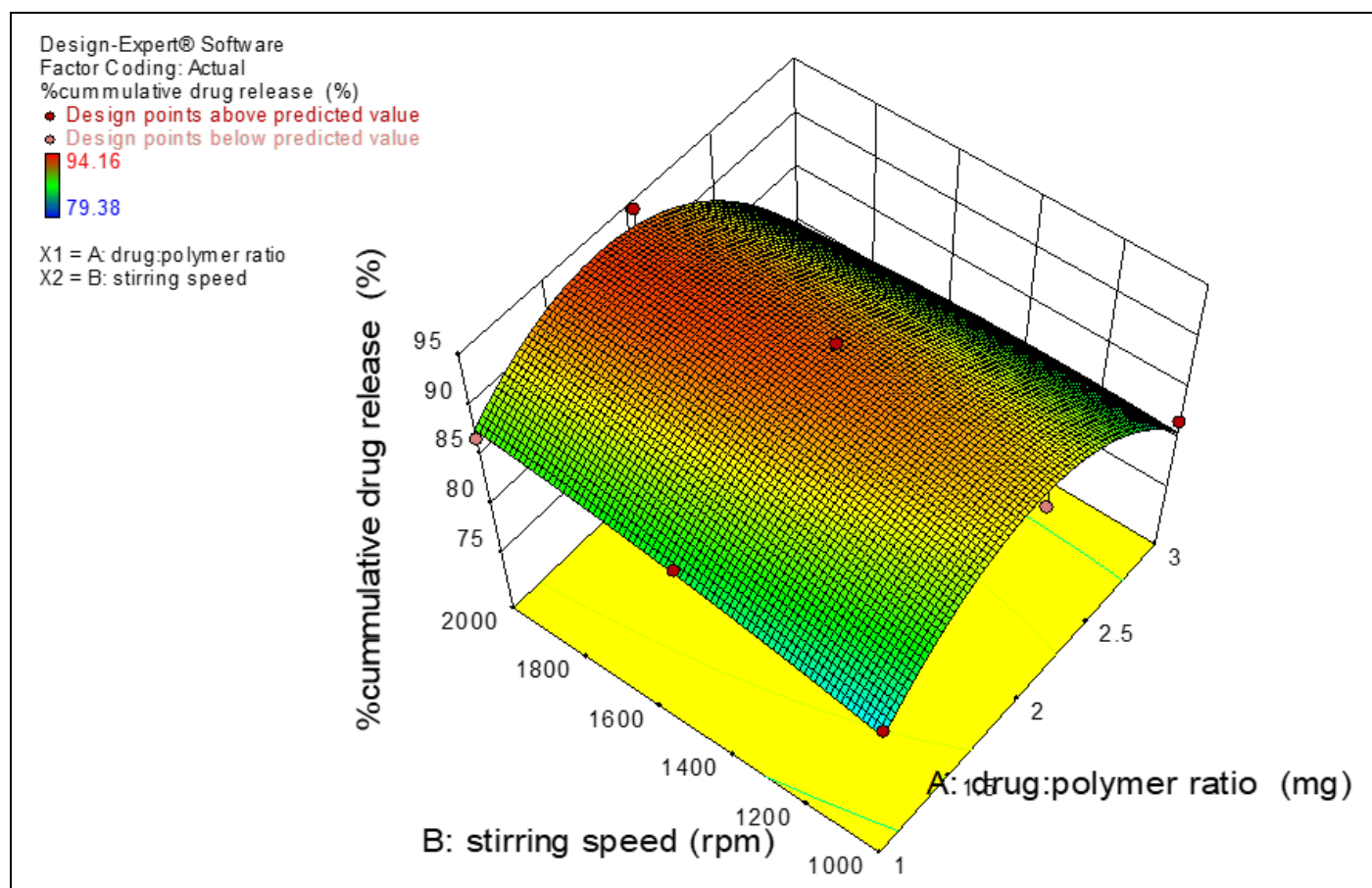


Fig 5 Response Surface Plot Illustrating the Influence of % Cumulative Drug Release (Y3) Surface Response Study

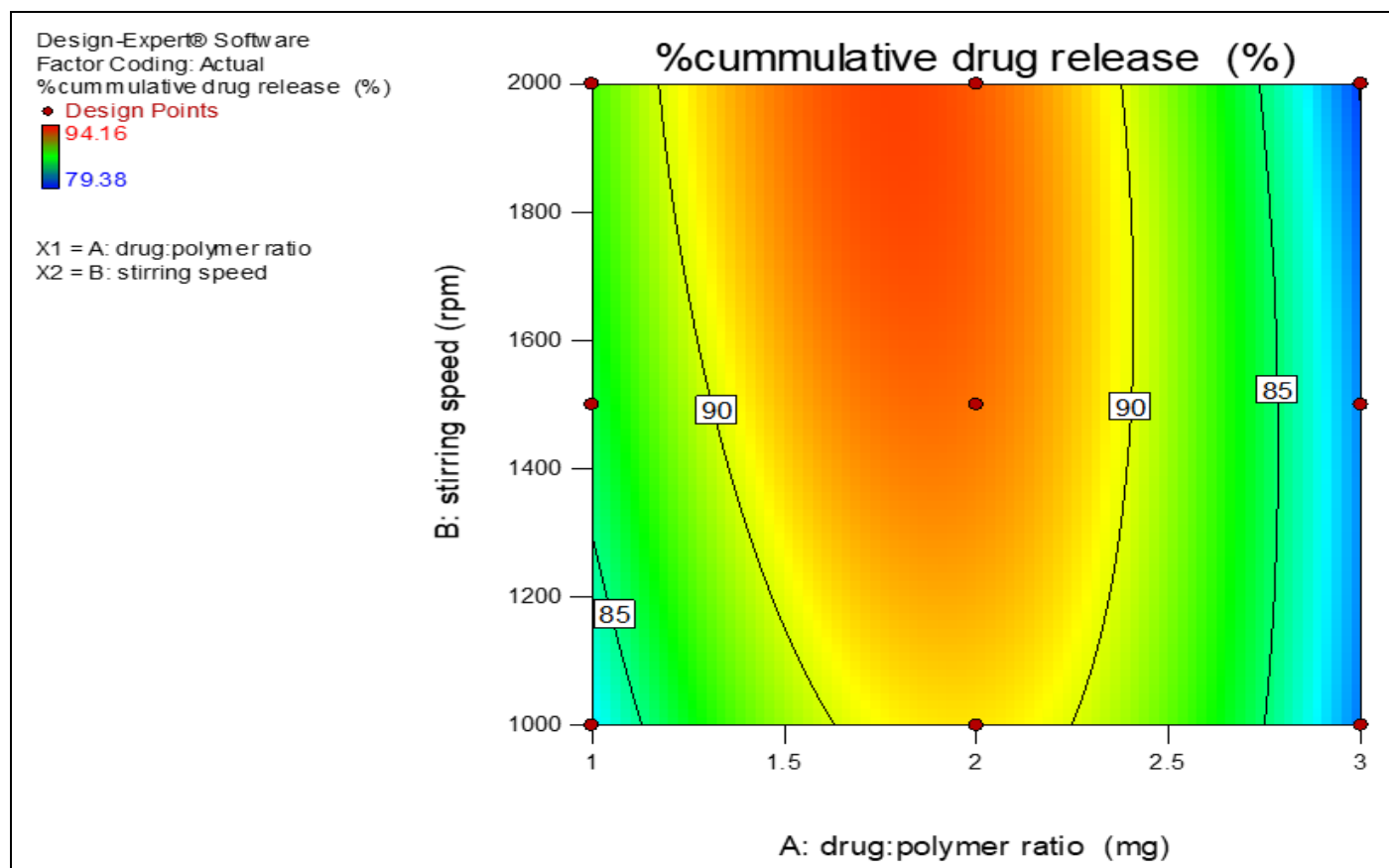


Fig 6 Contour Plot Illustrating the Influence of % Cumulative Drug Release (Y3) Surface Response Study

➤ *Validation of Model:*

Formulation and characterization of predicted batches from overlay plots suggested by Design Expert software

were used for validation or check point analysis. The predicted and observed batches results were compared.

Table 6 Validation of Model

Check point batches	Independent Variables		Response variables	Predicted value	Observed value
	Drug: polymer(X1)	Stirring speed(X2)			
FLUNS 10	1:2	2000	Y1 (%): Yield	94.82	95.03
			Y2 (%): Drug Content	96.15	97.15
			Y3 (%):CDR	92.77	93.74
FLUNS 11	1:2	1500	Y1 (%): Yield	92.25	92.78
			Y2 (%): Drug Content	93.73	94.38
			Y3 (%):CDR	92.47	92.69

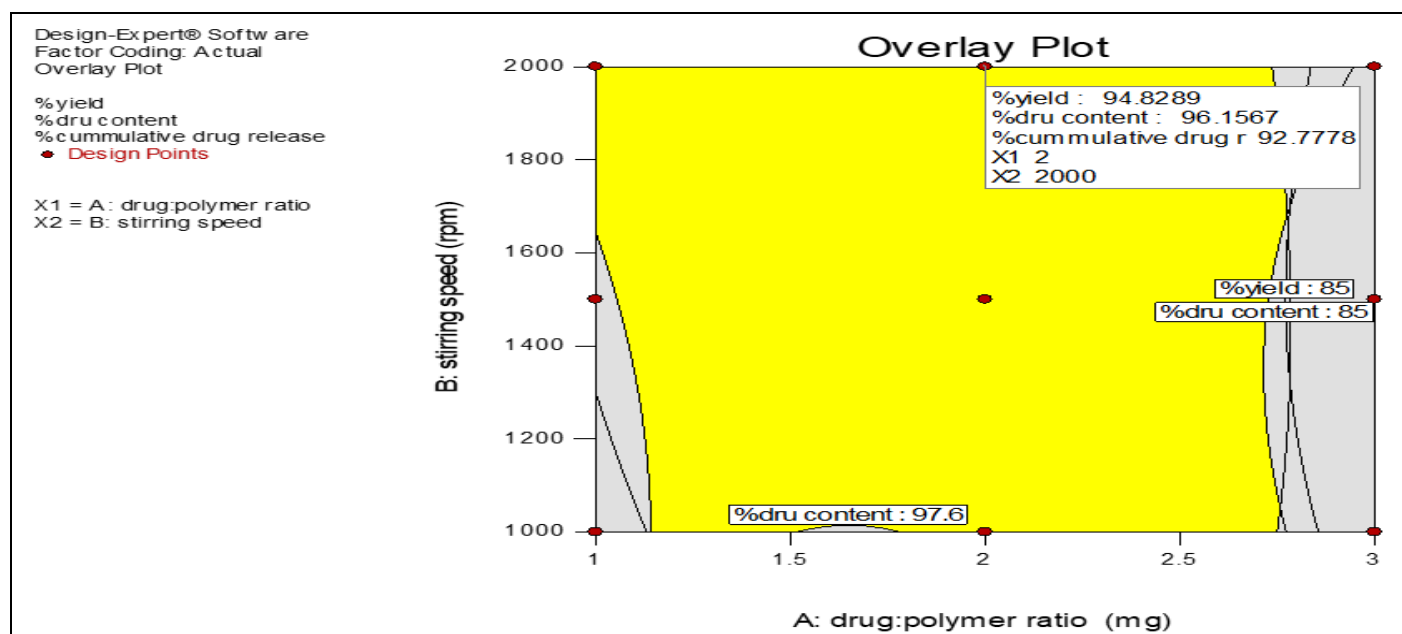


Fig 7 Overlay Plot 1

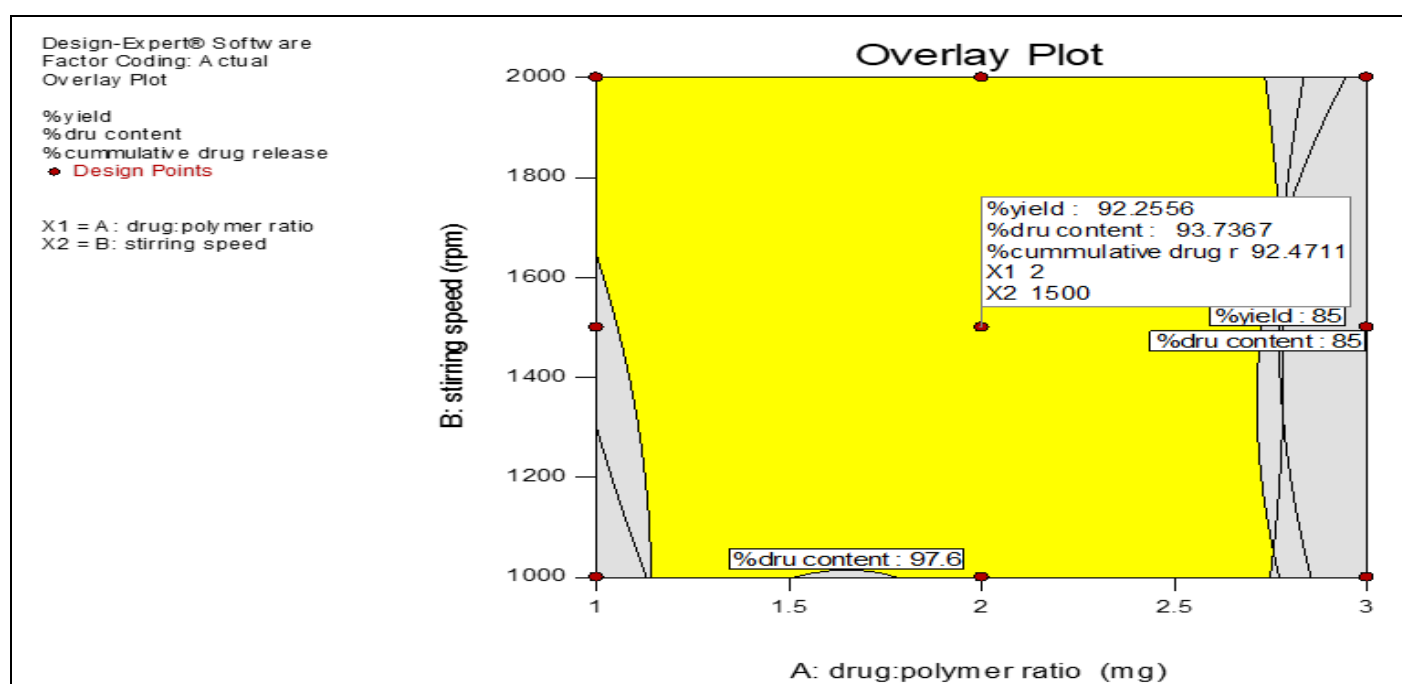


Fig 8 Overlay Plot 2

➤ % Cumulative Drug Release Profile

Table 7 % CDR Profile

Time (hr)	C1	C2
0	0	0
1	24.30±1.15	22.52±1.05
2	36.72±1.08	30.10±1.1
3	41.26±1.27	39.92±1.02
4	52.30±1.04	47.58±0.9
5	58.68±1.34	54.18±1.03
6	64.25±1.07	60.39±1.10
7	72.63±1.10	69.75±1.04
8	81.43±1.05	74.26±0.8
9	83.21±1.28	79.52±0.9
10	86.54±1.25	85.41±1.02
11	90.38±1.06	89.76±0.9
12	93.74±1.20	92.69±1.10

IV. CONCLUSION

Nanosponges have been identified as a drug delivery mechanism that can encapsulate or aggregate both lipophilic and hydrophilic drugs by establishing a complex. They can transport the medication safely and effectively to the intended location. Topical preparations like lotions, creams, ointments, etc., can contain nanosponges in liquid or powder form. The ability of this technology to target the medication to a specific area reduces side effects, increases formulation flexibility, and boosts patient compliance.

• *Conflict of Interest:*

The authors affirm that there were no financial or business ties at the time of the research that could have been interpreted as a conflict of interest.

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- Ethics approval and consent to participate: None.

LIST OF ABBREVIATIONS

- BCS: Biological System of Classification
- FFD: Factorial Design
- CDR: Cumulative drug release
- NSAID: Non-Steroidal anti-inflammatory drugs
- GI: Gastro Intestinal tract
- PVA: Polyvinyl Alcohol
- RPM: Revolution per Minute
- QbD: Quality By Design

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