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DEVELOPMENT AND CHARACTERIZATION OF CIPROFLOXACIN-LOADED MICROSPONGES FOR SUSTAINED DRUG DELIVERY

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Abstract

Ciprofloxacin loaded microsponges mainly belongs to category Biopharmaceutical Classification System class II which shown that it has low permeability and high solubility. Microsponges behaves as sustained and controlled release formulation in order to prolong the effect of ciprofloxacin for extended duration, the formulation phase of ciprofloxacin loaded microsponges was processed by emulsion solvent diffusion method, in which two phases are prepared i.e., the organic phase and the aqueous phase which were mixed at 1000 rpm to produce microsponges. Using BOX-BEHNKEN design of experiment, different quantity of drug- ciprofloxacin and excipients- Eudragit RS 100, and polyvinyl alcohol, are used. Total fifteen formulations were prepared, which were studied for the parameters like particle size determination, % drug release, % drug entrapment, % yield. The optimized formulation was subjected to SEM analysis and FT-IR study. The particle size of optimized formulation obtained as 387.1 nm, with 87.1% drug release, 91.2% drug entrapment, and 85.3% yield.

1. INTRODUCTION

In the current phase of drug delivery system, nano-technology has a crucial role in development of wide variety of formulation in targeted, controlled and sustained release dosage form(1). It lowers the quantity of drug required to produce effect, on the same side, it also reduces the toxic effect of the drug. Another great parameter is it enhances the bioavailability of the drug(2).

Nanotechnology involves design characterization, production and application of device system and methodology to control the size and shape to nano range(3) Role of nano-technology in drug delivery system has shown a valuable interest in the field of pharmaceutical technology to improve novel microsponge based drug delivery system(4). It has a great role to monitor the release of drug by incorporating the drug into a carrier system, that is helpful to make variation in therapeutic efficacy, duration of action, as well as reduction of side effects(5).

Microsponges are micro sized particles that belongs to the category of nano-technology that provides sustained and controlled release property to the drug, which lowers the rate of interval of drug administration and frequency of drug(6). Microsponges has targeted drug delivery property which makes it easier to release drug only at the desired site of action(7). The formulated microsponges can be used in formulating wide variety of dosage forms like tablets, capsules, creams, suppository, gels, etc(8)(9).

The mojor advantage in formulating ciprofloxacin(10) loaded microsponges is that ciprofloxacin has anti-bacterial property, which makes it different to treat severe GIT infections.(11)

The aim of this project was to formulate ciprofloxacin loaded microsponges for the treatment of GIT infections with controlled and sustained release property to reduce

the frequency of drug administration and also to lower the toxic effect of the drug by reducing the quantity of drug required to produce effect (12).

2. MATERIAL AND METHOD

2.1. Materials

Ciprofloxacin was obtained from Anant Pharmaceuticals pvt ltd, Maharashtra. Eudragit 100 RS, Dichloromethane and Polyvinyl alcohol was procured from CDH private limited.

2.2. Formulation Of Ciprofloxacin Loaded Microsponges

Formulation of ciprofloxacin loaded microsponges was done using emulsion solvent diffusion method. Two phases were prepared in this method i.e., the aqueous phase as well as the organic phase. Initially drug-ciprofloxacin and Eudragit 100 RS was mixed and diluted in dichloromethane of 10 ml as well as 10 ml of ethanol to produce organic phase. Into another beaker, 100ml of distilled water was taken to which, desired quantity of polyvinyl alcohol was added to produce aqueous phase. The aqueous phase was kept as magnetic stirrer at 1000 rpm for 1 hour with continuous mixing of organic phase for the formulation of microsponges. The formulated product was filtered grade-1 Whatmann filter paper. The obtained product was dried under hot air oven at 40°**C** and then stored (13)(14).

2.2.1 Optimization Of Ciprofloxacin Loaded Microsponges By Design Expert (Version 12)

A Box-Behnken design was employed to optimize the formulation parameters, including the quantities of ciprofloxacin and excipients. Fifteen formulations were prepared according to the design matrix and evaluated for various parameters. For the final optimization of ciprofloxacin loaded microsponges, a surface response approach, Box-Behnken design with three level, three factor, was implemented (16). The drug and polymer ratio, were taken as independent factors (17). Whereas, % entrapment efficiency, % release and % Yield and Particle Size were considered as dependent responses,

Table 1: Factors in Box Behnken Design with their used levels

Factor	Lower level (-1)	Upper level (+1)
A	200	500
B	100	500
C	50	100

A – Eudragit 100 RS

B – Ciprofloxacin

C- PVA

Table 2: Summary by Design Expert (Version 12.0.3.0)

Study type	Response surface
Design type	Box-Behnken
Sub Type	Randomized
Runs	15
Design Model	Quadratic

3. CHARACTERIZATION OF MICROSPONGES

The prepared microsponges were characterized for particle size determination, % drug entrapment, and % drug release and % yield. Scanning electron microscopy (SEM) and Fourier-transform infrared spectroscopy (FT-IR) were performed to assess the morphology and chemical composition of the optimized formulation.

3.1. Particle Size Determination

In each formulation the DLS method i.e., dynamic light scattering was used to determine the particle size in the formulation. Dynamic light scattering is a latest technology that is used for measuring the size of the particle and also used to describe the size distribution of particles(18). The basic principle of DLS involves the Brownian motion of motion of dispersed particles, when it comes in contact with the light. It measures the hydrodynamic diameter of the particle by measuring the speed of the particles.

3.2. Percentage Drug Entrapment-

In this method, microsponges required quantity was taken, equal to drug quantity. The microsponges were dissolved in 0.1N HCl and centrifuged for two hours. After completion, of centrifugation, 0.1ml of clear liquid was taken into volumetric flask of 10 ml, volume was made up with 0.1N HCl. By UV spectroscopy, absorbance was calculated at 277nm.

3.3. Percentage Drug Release:

Percentage drug release of all the formulations was calculated by determining the absorbance of sample**.**

3.4. Percentage Yield:

The percentage yield was measured by determining raw material initial weight and Microsponges final weight.

% yield= (Microsponges weighed practically / Theoretical mass) X 100

4. RESULT & DISCUSSION

The optimized formulation of ciprofloxacin-loaded microsponges exhibited a particle size of 387.1 nm, indicating suitable size distribution for pulmonary drug delivery. The drug release profile showed sustained release kinetics, with 87.1% of the drug released over the study period. High drug entrapment efficiency (91.2%) and yield (85.3%) were also achieved, indicating efficient drug loading and formulation process. SEM analysis revealed porous and spherical microsponge morphology, while FT-IR spectra confirmed the absence of chemical interactions between the drug and excipients.

Ciprofloxacin-loaded microsponges prepared using the emulsion solvent diffusion method demonstrated promising characteristics for sustained drug release applications. The optimized formulation exhibited suitable particle size, sustained drug release kinetics, high drug entrapment efficiency, and favourable morphology. Further studies are warranted to evaluate the in vivo performance and therapeutic efficacy of the developed microsponge formulation for prolonged drug delivery. The particle size, % Drug Entrapment, % Drug Release, and % Yield of each formulation was determined and the observed data for analysis in given in the table below:

Table 3: BOX-BEHNKEN DATA

RUN	Factor-1 A: Eudragit rs 100 (mg)	Factor-2 b: Ciprofloxacin hcl (mg)	Factor-3 C: Polyvinyl alcohol (mg)	Response 1 Particle size (nm)	Response2 % Drug Entrapment	Response 3 % Drug Release	Response 4 % Yield
1	400	75	50	321.1	63	70	67
2	400	75	100	329.3	66	71	69
3	400	50	75	333.5	66.5	73.2	70.2
4	400	100	75	339.5	69.3	76.5	72.1
5	500	50	50	345.7	70.2	77.3	74.1
6	500	50	100	350.2	73.1	79.5	74.23
7	500	75	75	356.4	76.1	79.5	76.1
8	500	100	50	363.2	77.3	82.1	79.5
9	500	75	75	366.5	78.2	84.2	79.5
10	500	75	75	379.2	80.1	86	80.1
11	500	100	100	380.1	83.3	86.1	83.2
12	600	75	50	385.4	85.2	87.2	84.2
13	**600**	**75**	**100**	**387.1**	**87.1**	**91.2**	**85.3**
14	600	100	75	389.5	89.2	94.1	91.2
15	600	50	75	393.2	91.5	97.2	93

The best formulation was reported as no.13.

4.1. Particle Size Determination:

The average particle size of all the formulation was measured and obtained between 321.1 nm to 393.2 nm. The particle size of final optimized formulation was obtained as 387.1 nm.

4.2. % Drug Entrapment:

The entrapment efficiency of all the formulation was found between 63% to 91.5%. The % drug entrapment of final optimized formulation was found to be 87.1%.

4.3. % Drug Release:

The percentage drug release was measured between 70% to 97.2%. % drug release of optimized formulation was obtained as 91.2%.

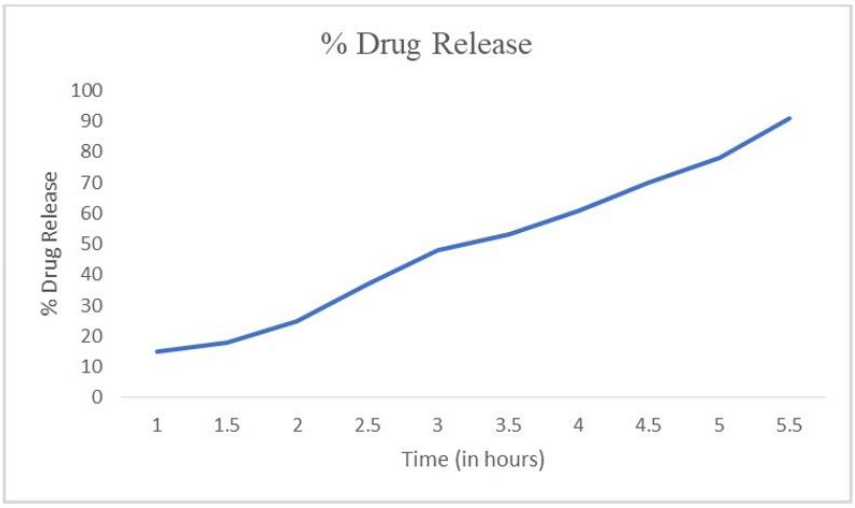


Figure 1: In-vitro Release of Optimized Formulation of Ofloxacin Loaded Microsponge

4.4. % Yield:

The percentage yield for all the formulation was obtained between 67% to 93%. The % yield of final optimized formulation was obtained as 85.3%.

4.5. Analysis of Model

Analysis of model was done and following was reported:

4.5.1. Fit Statistics

Std. Dev.	10.5	**R^2**	0.9315
Mean	361.33	**Adjusted R^2**	0.8082
C.V. %	2.91	**Predicted R^2**	0.35
		Adeq Precision	8.8052

The R^2 value was reported as 0.9315, which is desirable.

4.5.1. ANOVA for Quadratic Model

The model was found as significant. It is mentioned in following Table:

Response 1: Particle Size

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	7491.44	9	832.38	7.55	0.0192	significant
A-EUDRAGIT RS100	6716.4	1	6716.4	60.94	0.0006	
B-CIPRCIPROFLOXACIN HCL	308.76	1	308.76	2.8	0.155	
C-PVA	122.46	1	122.46	1.11	0.3401	
AB	23.52	1	23.52	0.2134	0.6635	
AC	10.56	1	10.56	0.0958	0.7694	
BC	38.44	1	38.44	0.3488	0.5805	
A^2	52.15	1	52.15	0.4732	0.5221	
B^2	0.3703	1	0.3703	0.0034	0.956	
C^2	229.47	1	229.47	2.08	0.2086	
Residual	551.05	5	110.21			
Lack of Fit	290	3	96.67	0.7406	0.6182	not significant
Pure Error	261.05	2	130.52			
Cor Total	8042.49	14				

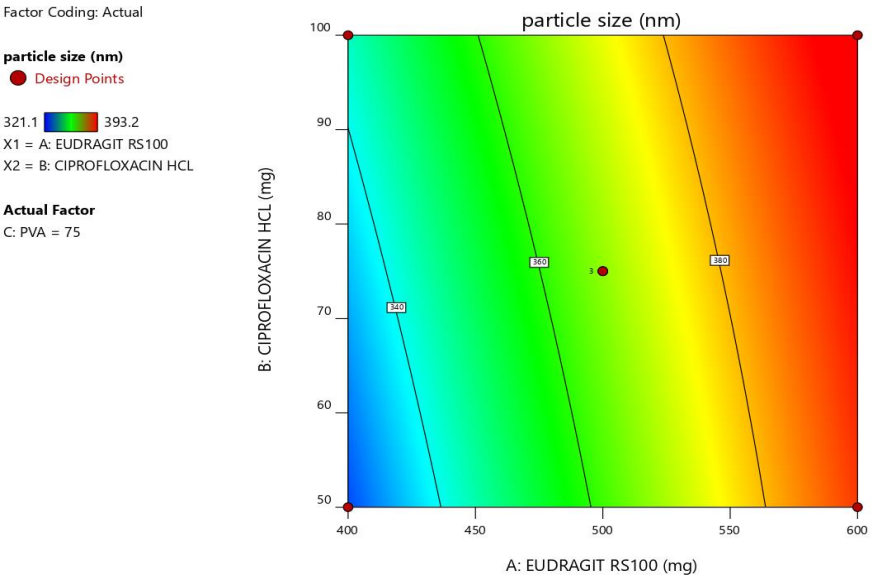
The **Model F-value** of 7.55 implies the model is significant. There is only a 1.92% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 0.74 implies the Lack of Fit is not significant relative to the pure error. There is a 61.82% chance that a Lack of Fit F-value this large could occur due to noise.

Equation was reported as

367.367 + 28.975 * A + 6.2125 * B + 3.9125 * C + -2.425 * AB + -1.625 * AC + 3.1 * BC + -3.75833 * A^2 + 0.316667 * B^2 + -7.88333 * C^2


Factor Coding: Actual
particle size (nm)
Design Points
321.1
393.2
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
particle size (nm)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)
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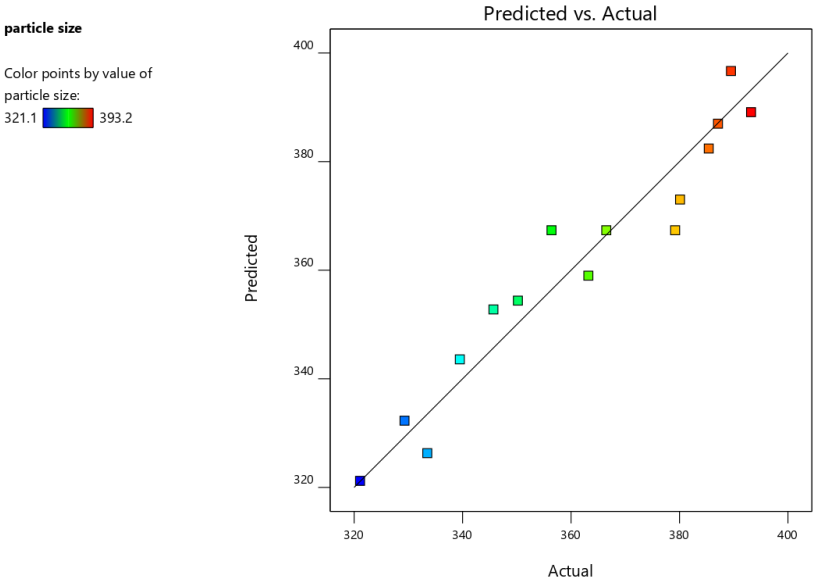
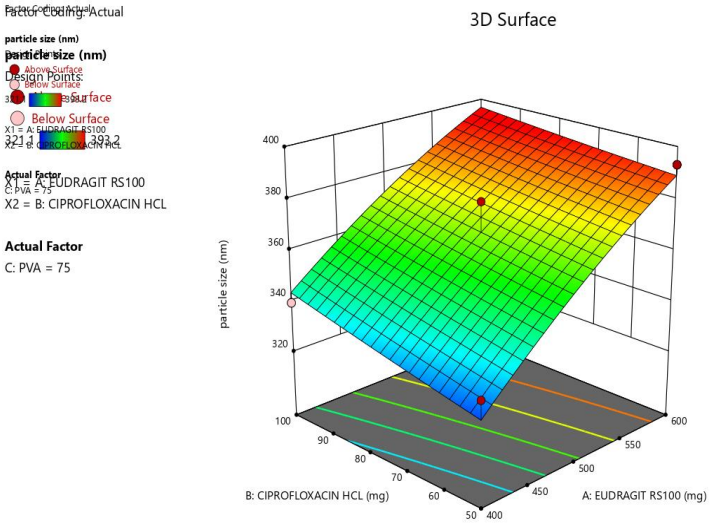
80
70
60
50
400
450
500
550
600
340
360
380


particle size
Color points by value of
particle size:
321.1
393.2
Predicted vs. Actual
Predicted
Actual
400
380
360
340
320


Factor Coding: Actual
particle size (nm)
Design Points
Above Surface
Below Surface
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
3D Surface
particle size (nm)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)

4.4.2. ANOVA for Quadratic model

Response 2: drug entrapment

It was found significant.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1082.28	9	120.25	13.18	0.0055	significant
A-EUDRAGIT RS100	972.4	1	972.4	106.61	0.0001	
B-CIPRCIPROFLOXACIN HCL	39.61	1	39.61	4.34	0.0916	
C-PVA	23.81	1	23.81	2.61	0.1671	
AB	6.5	1	6.5	0.7129	0.437	
AC	0.3025	1	0.3025	0.0332	0.8626	
BC	2.4	1	2.4	0.2634	0.6297	
A^2	0.1078	1	0.1078	0.0118	0.9177	
B^2	2.49	1	2.49	0.2727	0.6238	
C^2	32.77	1	32.77	3.59	0.1165	
Residual	45.61	5	9.12			
Lack of Fit	37.6	3	12.53	3.13	0.2514	not significant
Pure Error	8.01	2	4			
Cor Total	1127.89	14				

The **Model F-value** of 13.18 implies the model is significant. There is only a 0.55% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 3.13 implies the Lack of Fit is not significant relative to the pure error. There is a 25.14% chance that a Lack of Fit F-value this large could occur due to noise.

4.4.3. Fit Statistics

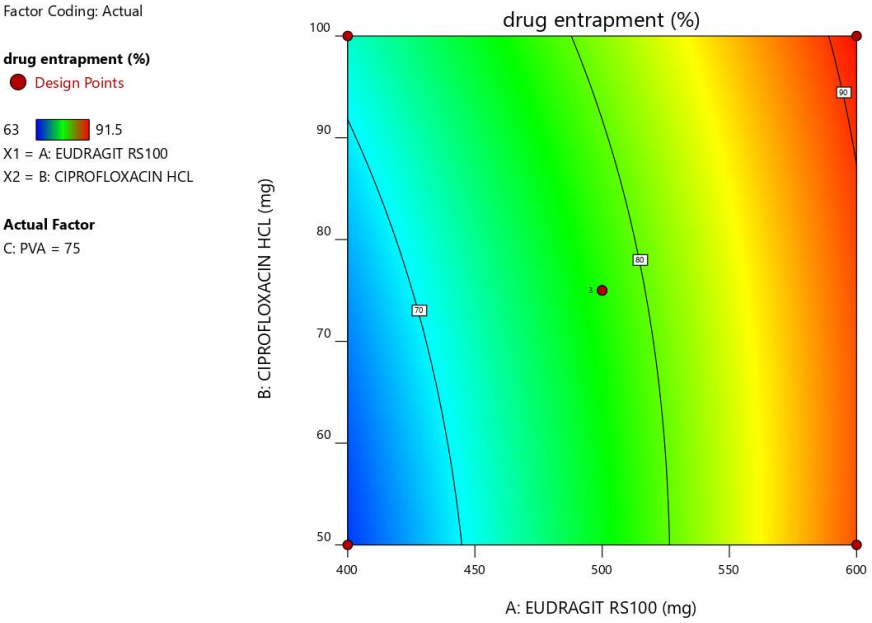
Std. Dev.	3.02	**R^2**	0.9596
Mean	77.07	**Adjusted R^2**	0.8868
C.V. %	3.92	**Predicted R^2**	0.4506
		Adeq Precision	11.679

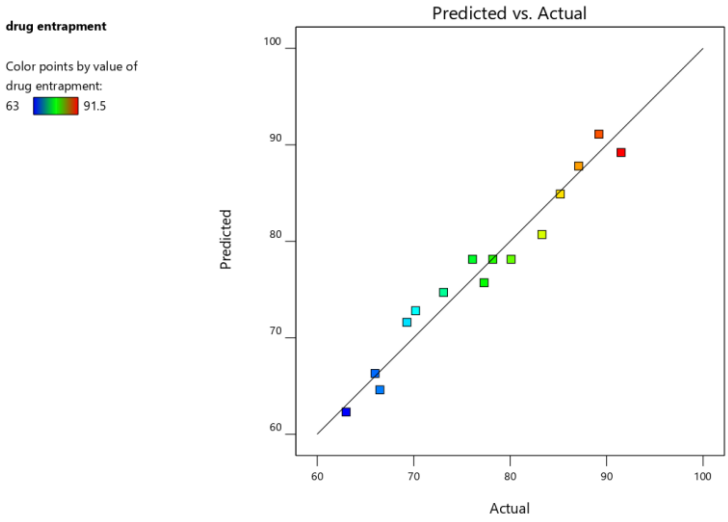
The **R^2 value was found as 0.9596**

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 11.679 indicates an adequate signal. This model can be used to navigate the design space.

Equation was found as:

78.1333 + 11.025 * A + 2.225 * B + 1.725 * C + -1.275 * AB + -0.275 * AC + 0.775 * BC + 0.170833 * A^2 + 0.820833 * B^2 + -2.97917 * C^2


Factor Coding: Actual
drug entrapment (%)
Design Points
63
91.5
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
drug entrapment (%)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)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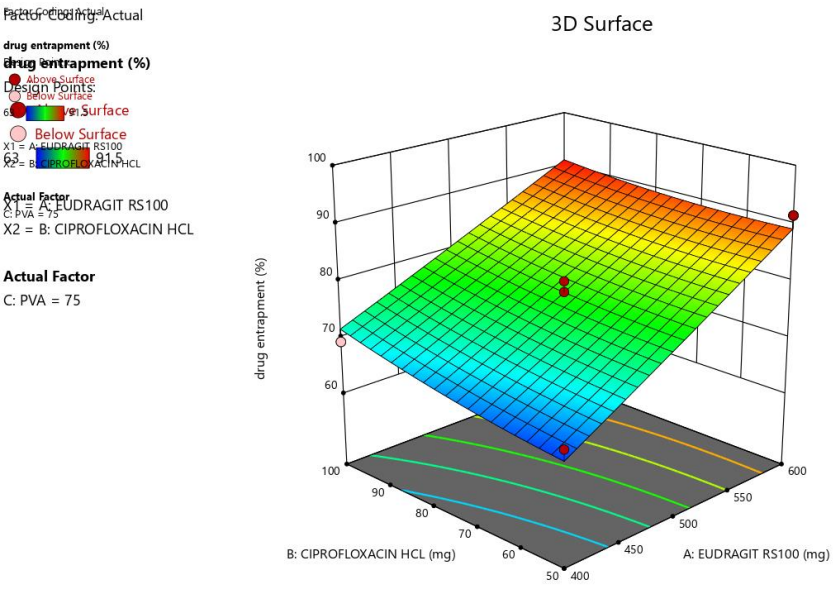
91.5
Predicted vs. Actual
Predicted
Actual


Factor Coding: Actual
drug entrapment (%)
Design Points
Above Surface
Below Surface
63
91.5
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
3D Surface
drug entrapment (%)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)

4.4.3 ANOVA for Quadratic Model

Response 3: Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	891.74	9	99.08	12.2	0.0066	significant
A-EUDRAGIT RS100	780.12	1	780.12	96.09	0.0002	
B-CIPRCIPROFLOXACIN HCL	16.82	1	16.82	2.07	0.2096	
C-PVA	15.68	1	15.68	1.93	0.2233	
AB	10.24	1	10.24	1.26	0.3124	
AC	2.25	1	2.25	0.2772	0.6211	
BC	0.81	1	0.81	0.0998	0.7649	
A^2	0.351	1	0.351	0.0432	0.8435	
B^2	10.78	1	10.78	1.33	0.3014	
C^2	50.32	1	50.32	6.2	0.0552	
Residual	40.59	5	8.12			
Lack of Fit	18.07	3	6.02	0.5346	0.7031	not significant
Pure Error	22.53	2	11.26			
Cor Total	932.34	14				

The **Model is found** significant. There is only a 0.66% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 0.53 implies the Lack of Fit is not significant relative to the pure error. There is a 70.31% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

4.4.3.1 Fit Statistics

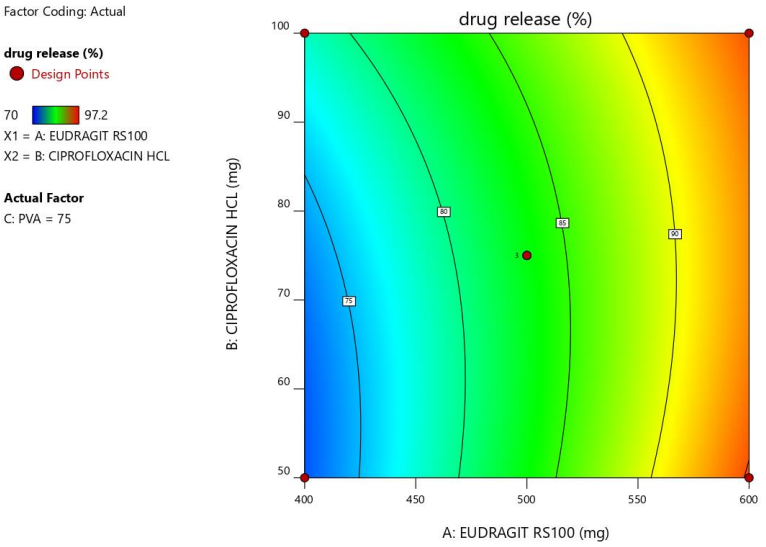
Std. Dev.	2.85	**R^2**	0.9565
Mean	82.34	**Adjusted R^2**	0.8781
C.V. %	3.46	**Predicted R^2**	0.6356
		Adeq Precision	11.1545

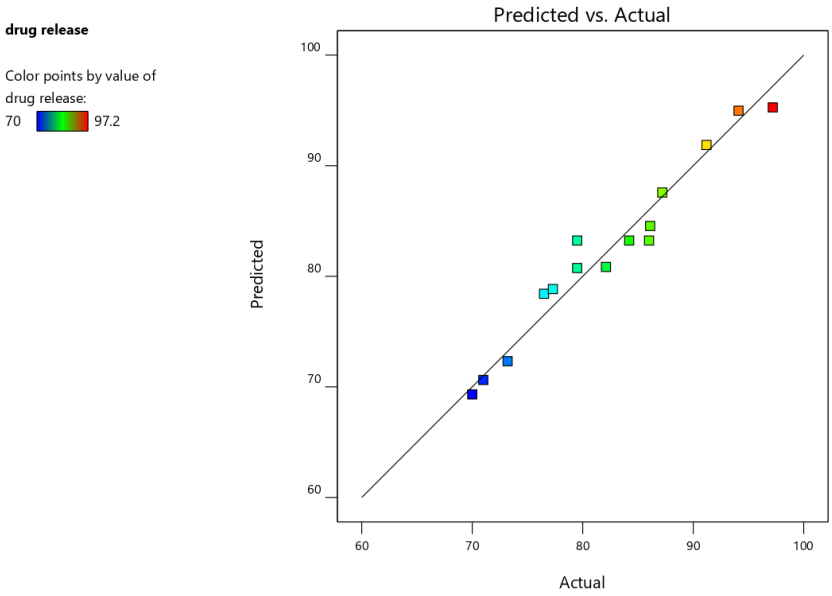
The **R^2 was found as 0.9565**

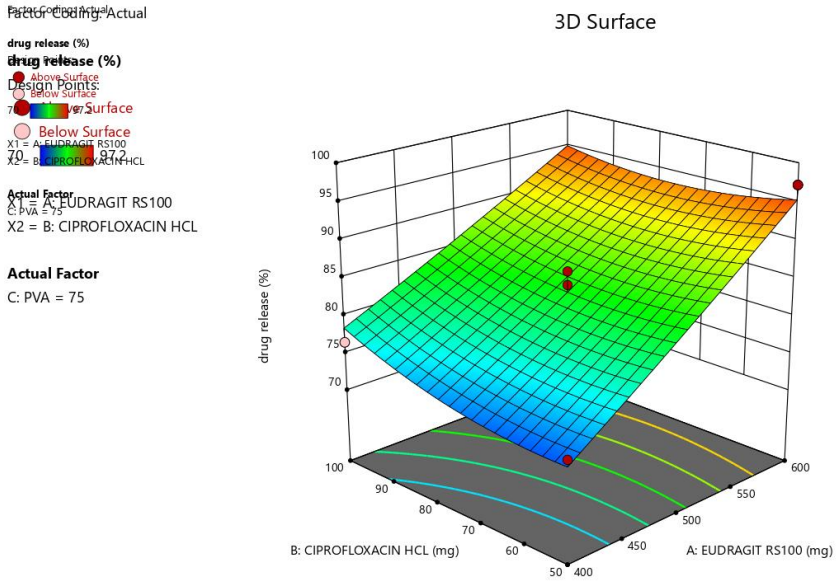
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 11.154 indicates an adequate signal. This model can be used to navigate the design space.

Equation was as:

83.2333 + 9.875 * A + 1.45 * B + 1.4 * C + -1.6 * AB + 0.75 * AC + 0.45 * BC + 0.308333 * A^2 + 1.70833 * B^2 + -3.69167 * C^2


Factor Coding: Actual
drug release (%)
Design Points
70
97.2
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
drug release (%)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)


drug release
Color points by value of
drug release:
70
97.2
Predicted vs. Actual
Predicted
Actual


Factor Coding: Actual
drug release (%)
Design Points:
Above Surface
Below Surface
70
97.2
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
3D Surface
drug release (%)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)

4.4.4 ANOVA for Quadratic Model

Response 4: yield

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	808.87	9	89.87	10.3	0.0097	significant
A-EUDRAGIT RS100	710.64	1	710.64	81.41	0.0003	
B-CIPRCIPROFLOXACIN HCL	26.17	1	26.17	3	0.1439	
C-PVA	6	1	6	0.6877	0.4447	
AB	3.42	1	3.42	0.3921	0.5587	
AC	0.2025	1	0.2025	0.0232	0.8849	
BC	3.19	1	3.19	0.365	0.5721	
A^2	2.59	1	2.59	0.297	0.6092	
B^2	18.2	1	18.2	2.09	0.2083	
C^2	33.89	1	33.89	3.88	0.1059	
Residual	43.65	5	8.73			
Lack of Fit	34.34	3	11.45	2.46	0.3021	not significant
Pure Error	9.31	2	4.65			
Cor Total	852.52	14				

The **Model is found** significant. There is only a 0.97% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 2.46 implies the Lack of Fit is not significant relative to the pure error. There is a 30.21% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

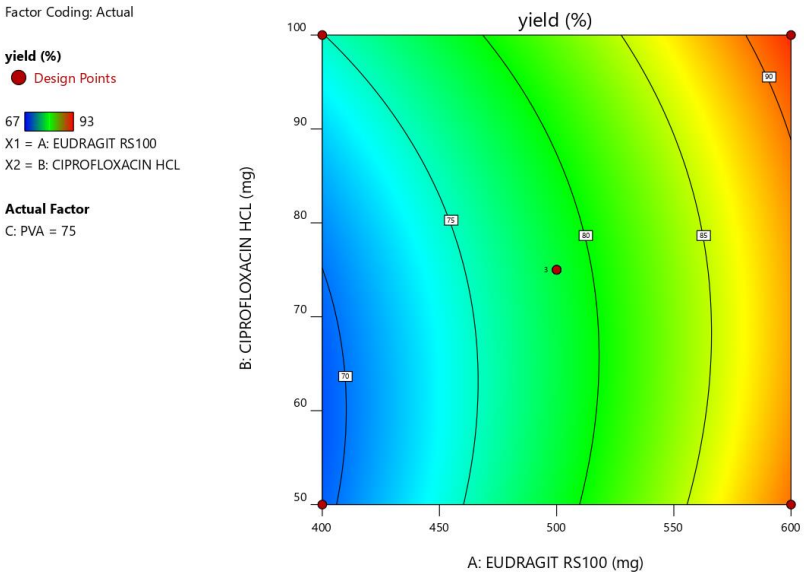
Std. Dev.	2.95	**R^2**	0.9488
Mean	78.58	**Adjusted R^2**	0.8566
C.V. %	3.76	**Predicted R^2**	0.3309
		Adeq Precision	10.8088

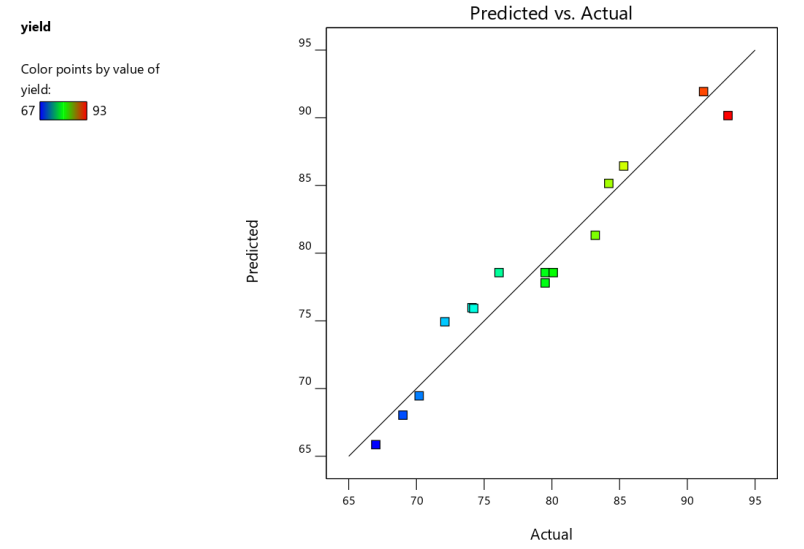
The **R^2 value of 0.9488**

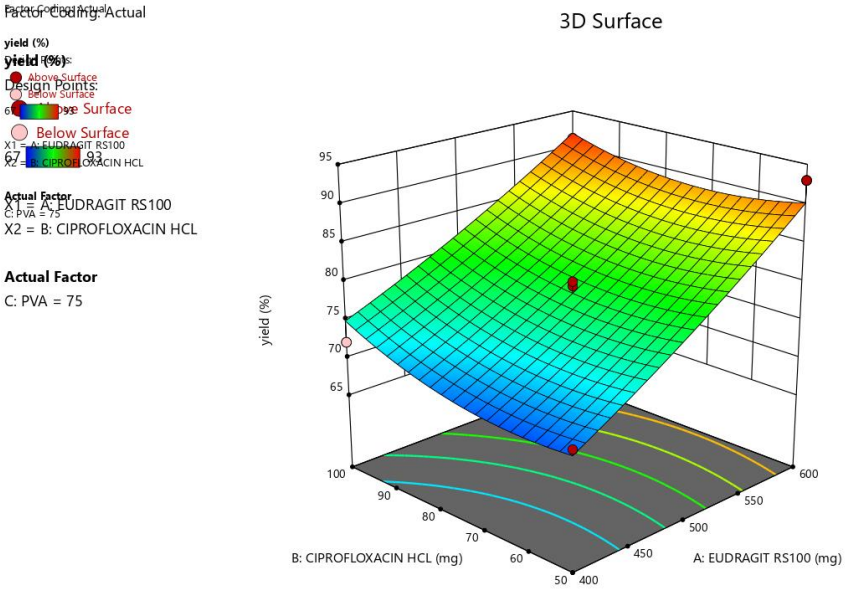
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.809 indicates an adequate signal. This model can be used to navigate the design space.

Equation

78.5667 + 9.425 * A + 1.80875 * B + 0.86625 * C + -0.925 * AB + -0.225 * AC + 0.8925 * BC + 0.837917 * A^2 + 2.22042 * B^2 + -3.02958 * C^2


Factor Coding: Actual
yield (%)
Design Points
67
93
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
yield (%)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)


yield
Color points by value of yield:
67
93
Predicted vs. Actual
Predicted
Actual


Factor Coding: Actual
yield (%)
Design Points:
Above Surface
Below Surface
67
93
X1 = A: EUDRAGIT RS100
X2 = B: CIPROFLOXACIN HCL
Actual Factor
C: PVA = 75
3D Surface
yield (%)
B: CIPROFLOXACIN HCL (mg)
A: EUDRAGIT RS100 (mg)

SEM Study

The morphological properties of ciprofloxacin loaded microsponges were studied by SEM analysis and evaluated. The shape of microsponges were examined as spherical shaped. The droplet size observed between the range of 20µm to 100µm and distributed evenly in nanometre range. The observed image was shown in the figure-

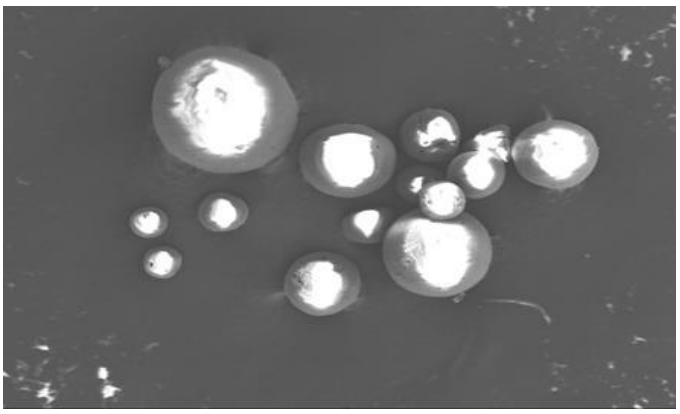


Figure : Figure showing SEM evaluation of microsponges

5. CONCLUSION

Successfully formulated microsponges loaded with ciprofloxacin, so as to improve the controlled and sustained release property of the formulation. Use of experimental design in formulating ciprofloxacin loaded microsponges has a significant role. The formulation of microsponges loaded with ciprofloxacin was done by the method of emulsion solvent diffusion method. In this method, Eudragit RS 100 was dissolved in organic solvent and polyvinyl alcohol was dissolved in aqueous solvent. Using different compositions, varieties of formulations were prepared which were subjected to study parameters such as determination of particle size, % drug release, % drug entrapment, and % yield. Box- Behnken design was implemented to get optimized formulation. The SEM analysis was done to study the morphological properties of the optimized formulation. The particle size of the optimized formulation was obtained as 387.1 nm, with 87.1% drug release, 91.2% drug entrapment, and 85.3% yield.

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