Design and Optimization of *In*-Situ Floating Gel Containing Femotidine using Factorial Design

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Abstract

The present study was aimed at the development of stomach specific drug delivery systems using natural polymer. It concerns with the development and optimization of a formulation of *in-situ* gel of famotidine. The polymer used in the formulations is locust bean gum and sodium alginate. Nine different formulations were prepared by varying concentration of locust bean gum sols and calcium carbonate in demonized water where as the concentration of sodium alginate and tri-sodium citrate remain constant. The amount of drug is kept constant for all nine formulations. From the result we found that F6 formulation showed optimum drug release. The % drug release from the optimized formulation was found to be 98.9 % after 24 hr and viscosity 28.7 centipoises, thus batch F6 was selected as an optimized formulation because it shows more controlled release, which exhibited a drug content of 97.8 % and has a floating time of more than 24 hr. Stability study was done according to ICH guidelines. This study reports that the aqueous solutions of famotidine drug containing locust bean gum and sodium alginate forms *in-situ* gel in acidic environment as well layer formation occur on the mucous membrane of stomach.

Keywords: drug delivery; peptic ulcer; *in situ*; floating gel; locust bean gum

1. **Introduction** An innovative method of administering medication as a liquid dosage is in situ gel drug delivery. Nevertheless, obtains a prolonged drug release [1]. The sustained drug release, better patient compliance, convenience of administration, and lower frequency of administration are the benefits of in situ gel delivery systems [2]. Prior to being provided in the body, in situ gel delivery systems are in solution form; however, upon administration, they go through in situ gelation to create a gel [3]. When using a gastro-retentive in situ gelling method instead of a traditional liquid dosage form, the drug's bioavailability is increased. Because the gel created by

the in situ gelling technology is less dense than gastric fluids, it floats over the contents of the stomach, causing gastric retention of the dose form and enhancing gastric residency [4].

Famotidine is a white to pale yellow non-hygroscopic crystalline substance. It is very slightly soluble in water and practically insoluble in ethanol, acetone, ethylacetate, ethyl ether and acetone. It is freely soluble in glacial acetic acid [5]. Famotidine is a competitive histamine H-receptor antagonist (H2RA) that binds to the H-receptors located on the basolateral membrane of the parietal cell in the stomach, effectively blocking histamine actions [6]. Its pharmacologic activity results in the inhibition of gastric secretion by suppressing acid concentration and volume of gastric secretion. Famotidine inhibits both basal and nocturnal gastric acid secretion as well as reduces gastric volume, acidity, and secretion stimulated by food, caffeine, insulin, and pentagastrin.[7]

2. Material

Famotidine was obtained as gift sample from Cipla Ltd., Mumbai .Sodium alginate, Tri sodium citrate, Calcium Carbonate, Sodium bicarbonate, Locust bean gum (LBG) was procured from local shop of New Delhi.

3. Methods

Formulation

The weighed quantity of locust bean gum and sodium alginate solution heated at 60-70ºC then added sodium citrate in above solution this solution cooled below 40ºC. The calculated amount of drug, calcium carbonate or sodium bicarbonate to the above solution store the solution [8,9].

Optimization of formulation Factorial Design

Full Factorial Design was used to determine the effect of the independent variable (variable 1: concentration of cellulose and variable 2: concentration of acrylamide) over the drug loading (dependent variable) as shown in equation 8.1:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22} \text{……..Eq.-1}$$

Whereas: X_1 represents independent variable 1 (concentration of cellulose).

X_2 represents independent variable 2 (concentration of acrylamide).

Y represents the dependent variable (drug loading).

X_1Y represents the average result of changing the first variable at a time for low, medium, and high values.

X_2Y represents the average result of changing the second variable at a time for low, medium, and high values.

The interaction terms X_1X_2Y represent how the response changes when the two factors simultaneously change.

Polynomial terms (X_{11} and X_{22}) are included to investigate non-linearity.

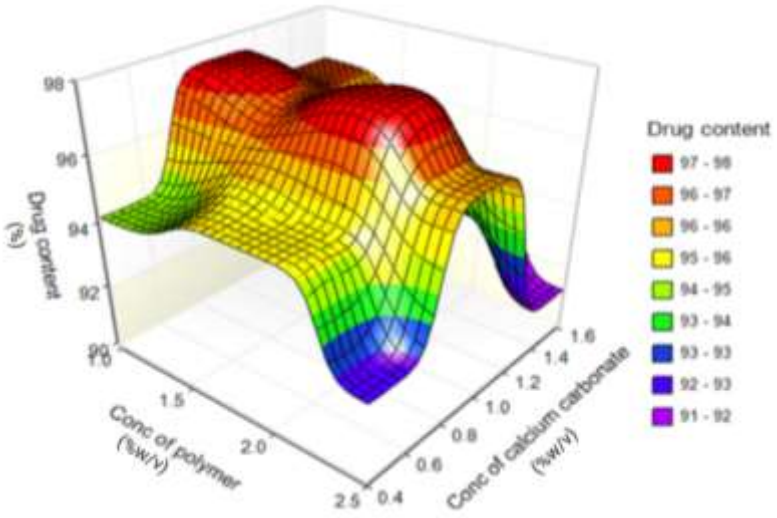


Figure 1: Surface response curve to show the effect of independent variables (Concentration of polymer and concentration of calcium carbonate) over dependent variable (drug content)

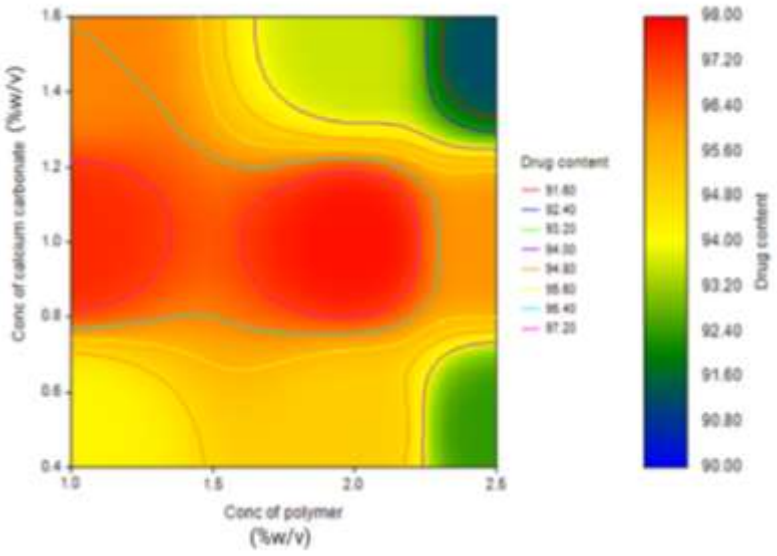


Figure 2 :Contour plot to show the effect of independent variables (Concentration of polymer and concentration. of calcium carbonate) over dependent variable (drug content)

Table 1: Correlation analysis using Pearson Correlation Test

Pearson Correlation Test					
Y-Axis Variable concentration of polymer					
X-Axis Variable concentration of calcium carbonate					
Run Summary Section					
Parameter	**Value**				
Y-Axis Variable	Concentration of polymer				
X-Axis Variable	Concentration of calcium carbonate				
Frequency Variable	None				
Sum of Frequencies	9				
Rows Processed	9				
Rows used in Estimation	9				
Rows with X missing	0				
Rows with Frequency Missing	0				
Column Summary Section					
Variable	**Count**	**Mean**	**Standard Deviation**	**Minimum**	**Maximum**
Conc. of polymer	9	1.83	0.66	1.00	2.50
Conc. of calcium carbonate	9	1.00	0.43	0.50	1.50
Pearson Correlation Confidence Interval Section (Two-Sided Confidence Interval of ρ)					
Pearson Correlation	**Count**	**R Distribution 95% Confidence limits**		**Normal Approximation 95% Confidence limits**	
		Lower	**Upper**	**Lower**	**Upper**
0.0000	9	-0.6319	0.6319	-0.6641	0.6641
Pearson Correlation Test Section (H0: ρ=0)					
Alternative Hypothesis	**Pearson Correlation**	**Count**	**Df**	**T-Value**	**P-Value**	**Reject H0 at α=0.05?**
ρ≠0	0.000	9	7	0.0000	1.0000	No

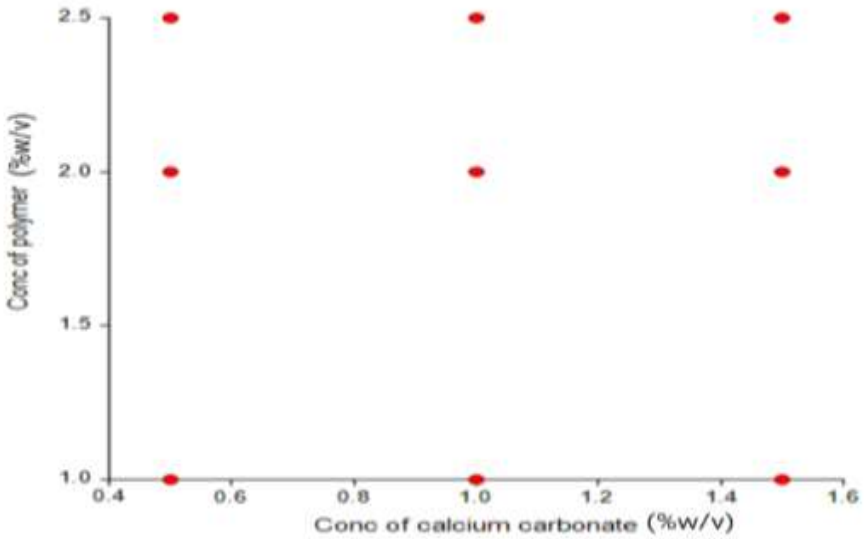


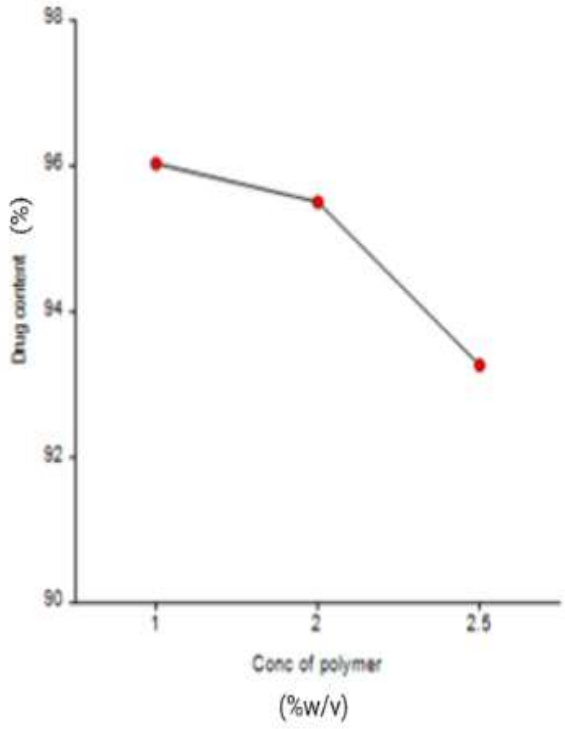
Figure 3: Correlation plot to show the effect of independent variables

As shown in table 9.2, the Pearson correlation test reflects the null hypothesis at a 0.05% significant level. Pearson correlation test easily elicits the fact that both the independent variable significantly affects the drug loading.

Table 3: MANOVA (Multivariate analysis of variance) analysis

Expected Mean Squares Section				
Source Term	**DF**	**Term Fixed**	**Denominator Term**	**Expected Square**
A: Conc. of polymer	2	Yes	S(AB)	S+bsA
B: Conc. of calcium carbonate	2	Yes	S(AB)	S+asB
AB	4	Yes	S(AB)	S+sAB
S(AB)	0	No		S

Analysis of Variance Table for Drug loading						
Source Term	**DF**	**Sum of Squares**	**Mean Square**	**F-Ratio**	**Prob Level**	**Power (α=0.05)**
A: Conc. of polymer	2	12.92667	6.463333			
B: Conc. of calcium carbonate	2	22.48667	11.24333			
AB	4	5.846667	1.461667			
S	0	0				
Total (Adjusted)	8	41.26				
Total	9					



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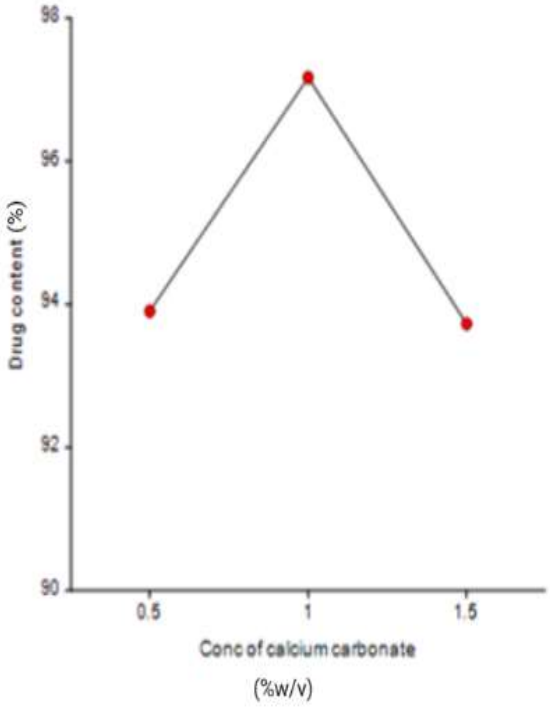
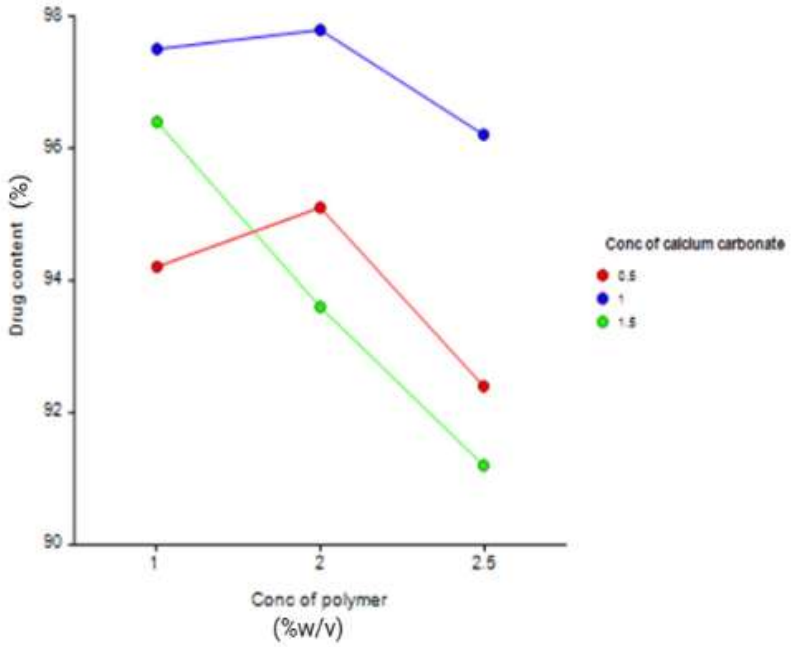


(b)



(c)

Figure 4: MANOVA plot to show the effect of (a) independent variables (concentration of polymer) over the dependent variable (drug content), (b) independent variable (concentration of calcium carbonate) over dependent variable (drug content), (c) independent variables (concentration of polymer and concentration of calcium carbonate) over the dependent variable (drug content)

The outcome of the MANOVA analysis figure 9.4 showed a non-linear correlation between the individual independent variable and drug loading

Table 4: Response surface regression analysis

Descriptive Statistics Section				
Variable	**Count**	**Mean**	**Minimum**	**Maximum**
Concentration of polymer	9	1.833333	1	2.5
Conc. of calcium carbonate	9	1	0.5	1.5
Drug content	9	94.93333	91.2	97.8

Sequential ANOVA Section						
Source	**Sequential df**	**Sum Square**	**Mean Square**	**F-Ratio**	**Prob Level**	**Incremental R-Squared**
Regression	5	39.57631	7.915262	14.10	0.026968	0.959193
Linear	2	27.29309	13.64655	24.32	0.014006	0.661490
Quadratic	2	8.120238	4.060119	7.23	0.071169	0.196807
Lin x Lin	1	4.162976	4.162976	7.42	0.072334	0.100896
Total Error	3	1.68369	0.5612302			0.040807

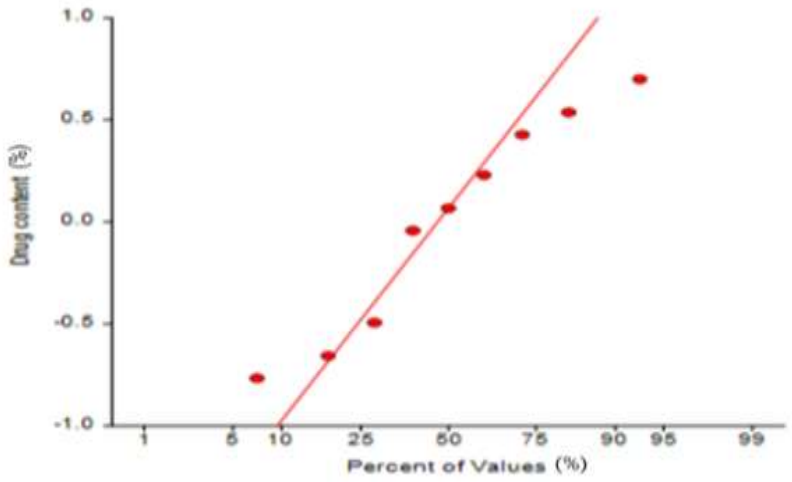
ANOVA Section						
Factor	**Df**	**Last Sum-Squares**	**Mean Square**	**F-Ratio**	**Prob Level**	**Term R-Squared**
Conc. of polymer	3	17.08964	5.696548	10.15	0.044349	0.414194
Conc. of calcium carbonate	3	26.64964	8.883214	15.83	0.024149	0.645895
Total Error	3	1.68369	0.5612302			0.040807

Estimation Section						
Parameter	**Last df**	**Regression Coefficient**	**Standard Error**	**T-Ratio**	**Prob Level**	**R-Squared**
Intercept	1	95.0246				
Conc. of polymer	1	10.00476	3.847829	2.60	0.080368	0.091959
Conc. of calcium carbonate	1	-10.93571	4.644058	-2.35	0.099872	0.075424
Conc. of polymer^2	1	-2.622222	1.078904	-2.43	0.093292	0.080350
Conc. of calcium carbonate^2	1	6.2	2.118925	2.93	0.061198	0.116457
Conc. of polymer* conc. of calcium carbonate	1	-2.671429	0.9808715	-2.72	0.072334	0.100896

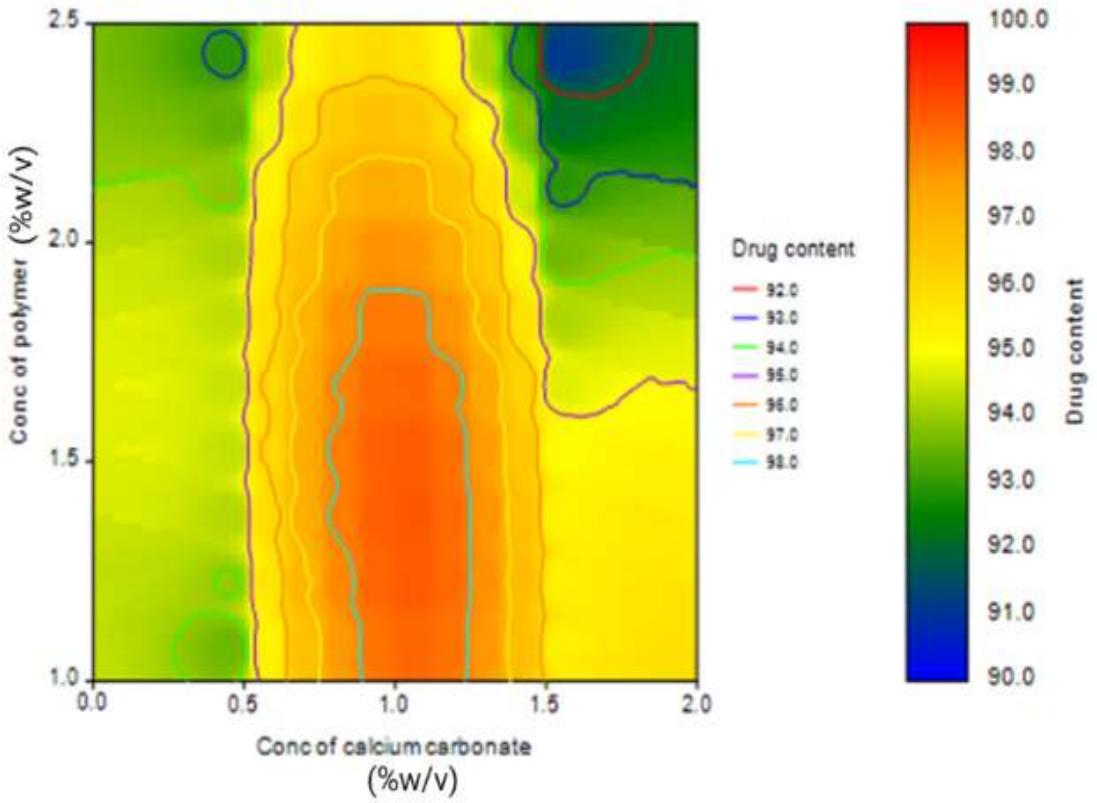
Optimum Solution Section		
Parameter	**Maximum Exponent**	**Optimum Value**
Conc. of polymer	2	18336.83
Conc. of calcium carbonate	2	3951

Optimization Details	
Function at Optimum	-9.783116E+08
Number of Function Evaluations	501
Maximum Functions Evaluations	500

Residual Section			
Formulation	**Experimental Drug loading**	**Predicted Drug loading**	**Residual drug loading**
F1	91.2	91.17619	0.02380952
F2	92.4	92.23333	0.1666667
F3	96.2	96.39047	-0.1904762
F4	93.6	94.07738	-0.477381
F5	95.1	94.46667	0.6333333
F6	97.8	97.95596	-0.1559524
F7	96.4	95.94643	0.4535714
F8	94.2	95	-0.8
F9	97.5	97.15357	0.3464286



(a)



(b)

Figure 5:(a) Probability plot, (b) contour plot to show the effect of independent variables (conc. of polymer, conc. of calcium carbonate) over the dependent variable (drug content)

To identify the difference between experimental drug content and the prediction value of drug content, response surface regression analysis was carried out. The finding of the study showed significantly very less difference between these values. The outcome of the MANOVA analysis is also supported by the result of the response surface regression analysis [10,11,12, 13,14].

4. Results

Drug Release:

The amount of drug release is an important parameter for controlled release formulation. The drug release of formulations F1- F9 was found to be 98.3, 94.51, 97.82, 98.34, 96.78, 98.94, 98.92, 98.88 and 92.73 % respectively; the drug release of formulation F6 was maximum while F2 was minimum .The drug release data of all the formulations is depicted in Table 9.5 shows that varying concentration of polymer (LBG) was responsible drug release of famotidine from *in-situ* gel [15,16,17].

Table 5: Drug release study

Time (min)	Cumulative drug release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
15	23.88 ± 0.62	23.71 ± 0.53	28.11 ± 0.57	28.47 ± 0.29	27.58 ± 0.28	30.65 ± 0.54	31.56 ± 0.56	31.41 ± 0.43	23.71 ± 0.47
30	28.99 ± 0.99	27.23 ± 0.86	32.52 ± 0.82	33.04 ± 0.64	32.69 ± 0.78	44.33 ± 0.76	44.18 ± 0.85	44.64 ± 0.80	26.88 ± 0.82
45	33.74 ± 1.16	28.82 ± 1.24	36.74 ± 1.10	38.33 ± 1.32	36.57 ± 1.30	47.68 ± 1.06	46.92 ± 1.04	53.61 ± 1.03	31.11 ± 1.28
60	37.72 ± 1.61	34.10 ± 1.78	40.97 ± 1.45	40.09 ± 1.69	42.20 ± 1.58	56.80 ± 1.45	56.04 ± 1.54	55.74 ± 1.52	36.22 ± 1.59
90	38.15 ± 1.72	37.09 ± 2.11	53.48 ± 1.88	53.13 ± 1.81	52.24 ± 1.84	60.29 ± 1.99	59.23 ± 1.88	60.75 ± 1.89	37.27 ± 1.89
120	39.56 ± 2.04	39.74 ± 2.57	59.11 ± 2.02	58.76 ± 2.00	59.11 ± 2.02	66.84 ± 2.01	67.14 ± 2.10	67.29 ± 2.07	39.21 ± 2.09
135	43.61 ± 2.15	60.42 ± 2.64	86.48 ± 2.43	85.71 ± 2.38	85.78 ± 2.43	89.95 ± 2.34	90.55 ± 2.35	90.09 ± 2.28	61.58 ± 2.35
150	61.83 ± 2.56	61.58 ± 3.01	86.59 ± 2.64	85.78 ± 2.52	86.59 ± 2.67	90.92 ± 2.63	91.68 ± 2.64	91.53 ± 2.43	61.83 ± 2.64
165	61.93 ± 2.79	62.63 ± 3.48	88.53 ± 2.82	87.65 ± 2.85	87.47 ± 3.36	92.38 ± 2.86	93.75 ± 2.99	93.89 ± 2.83	63.16 ± 2.98
180	63.52 ± 3.05	63.87 ± 3.76	88.88 ± 3.28	88.18 ± 3.54	88.71 ± 3.36	94.35 ± 3.16	95.11 ± 3.48	94.96 ± 3.42	63.34 ± 3.36
210	64.04 ± 3.78	64.05 ± 3.91	89.59 ± 3.64	89.41 ± 3.89	88.88 ± 3.53	95.26 ± 3.65	95.42 ± 3.84	95.42 ± 3.83	63.87 ± 3.89
240	64.93 ± 4.13	64.22 ± 4.23	90.12 ± 4.43	90.12 ± 4.38	89.23 ± 3.99	96.94 ± 3.87	96.18 ± 4.30	97.69 ± 4.30	64.22 ± 4.31
300	65.10 ± 4.89	64.39 ± 4.58	91.17 ± 4.74	90.47 ± 4.61	89.41 ± 4.43	97.24 ± 4.23	96.64 ± 4.72	98.31 ± 4.76	64.57 ± 4.76
360	65.45 ± 5.34	65.10 ± 5.12	91.87 ± 5.52	90.82 ± 5.16	89.59 ± 5.10	97.92 ± 4.95	96.94 ± 5.12	98.46 ± 5.11	64.75 ± 5.32
1440	98.30 ± 6.24	94.15 ± 6.43	97.82 ± 6.13	98.34 ± 6.06	96.78 ± 6.35	98.94 ± 5.64	98.92 ± 5.93	98.88 ± 5.88	92.75 ± 5.87

5. Conclusion

To identify the difference between experimental drug release and prediction value of drug release, response surface regression analysis was carried out. Finding of the study showed significantly very less difference between these values. Outcome of the MANOVA analysis is also supported the result of response surface regression analysis. Whole study is done to get an optimized formulation which shows more controlled release of drug from locust bean gum *in-situ* floating gel. The % drug release from the optimized formulation was found to be 98.94 after 24 hrs. Thus batch F6 was selected for further study.

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