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Formulation and Optimization of Sustained Release Floating Matrix Tablets of Baclofen

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Abstract

This investigation concerns the development of sustained released floating matrix tablets of Baclofen for improving its bioavailability by prolonging gastric residence time. Floating matrix tablets (FMT) of Baclofen were prepared using 3^2 optimization designs.Carbopol 934p, HPMC K4M and gas generating agents such as sodium bicarbonate and citric acid were used in formulation. The fabricated tablets were evaluated for their physical characteristics such as hardness, drug content, buoyancy, swelling properties and in vitro release studies in 0.1N HCl. The tablets without gas generating agents and HPMC K4M did not float at all. Tablets with gas generating agents and HPMC K4M and Carbopol 934p floated up to 12 h without complete erosion and showed slower drug release. HPMC K4M and Carbopol 934P maintain the integrity of the FMT and sustaining the drug release. The increase in the concentration of HPMC K4M and Carbopol 934p in FMT from 75 mg to 125 mg and 20 mg to 60mg respectively resulted in decrease in release rate of drug. The possibility of drug polymer interaction was determined by differential scanning calorimetric (DSC) and Fourier transform infrared (FTIR) spectrometer, and confirmed no interaction between drug and polymers. The mechanism of drug release is mainly described by diffusion and swelling mechanism of polymers.

Keywords: Tablet; Floating; Matrix; Gastric residence time

Introduction

Oral delivery of drugs is by far the most preferred route of drug delivery, due to ease of administration, patient compliance and flexibility in formulation. Conventional immediate oral dosage forms provides a specific drug concentration in the systemic circulation with limited control over drug delivery. Controlled-release drug delivery systems provide drug release at a predetermined, predictable rate and optimize the therapeutic effect of a drug by controlling its release in the body with lower and less frequent doses

A major constraint in oral controlled drug delivery is that most of the drug candidates are not absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed only in a particular region of the GIT or are absorbed to a different extent in various segments of the GIT and are said to have an 'absorption window' which identifies the primary region of absorption of the drug in the GIT because of physiological, physicochemical or biochemical factors. [1, 2, 3]

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems. Gastro retentive drug delivery system can improve controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring optimal bioavailability. [6]

Materials and methods

Materials

Baclofen was procured from Watson Pharma Goa; HPMC K4M was procured from Colorcon, Goa. All other chemicals used were of analytical grade.

Experimental design

To optimize the formulation the 3^2 design was implemented. The independent variables were amount of Carbopol 934 (mg) (X1) and amount of HPMC K4M (mg) (X2). The dependent variables (responses) were drug release in 4 hrs (%) (Y1), drug release in 8 hrs (%) (Y2) and drug release in 12 hrs (%) (Y3). The independent and dependent variables and the used levels are summarized in

Factors (independent variables)	Levels used			Responses (dependent variables)
	1	0	-1	
X1 = amount of Carbopol 934 (mg)	20	40	60	Y1 = drug release in 4 hrs (%)
X2 = amount of HPMC K4M (mg)	75	100	125	Y2 = drug release in 8 hrs (%)
				Y3 = drug release in 12 hrs (%)

Preparation of sustained released floating matrix tablets

The corresponding amount of drug, HPMC K4M, Carbopol 934, magnesium stearate,
sodium CMC, sodium bicarbonate, citric acid were accurately weighed. The powders
were screened through screen #60.The screened powders were transferred to mortar
and mixed for 20 minutes. After addition of lubricant and glidant (Mg Stearate)
compression was carried out using 10 mm flat-faced circular punches on rotary
compression machine (general machineries). Hardness was maintained between 3-6 Kg/cm^2.[5-10]

Floating properties

The time the tablets took to emerge on the water surface (floating lag time) and the time the tablets constantly float on the water surface (duration of floating) were evaluated in dissolution vessel (dissolution tester) filled with 500ml of artificial gastric fluid without pepsin, pH 1.2; T= 37 C ± 0.5, paddle rotation= 100 rpm. The measurement is carried out for each series of tablets (n=9) [11]

Drug release testing

The release rate of Baclofen from floating tablets was determined using USP DissolutionTesting Apparatus II (Paddle type). The dissolution test was performed using 900 ml of P^H 1.2 Buffer, at 37 ± 0.5 C with 50 rpm. Aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly for 12 hrs and were replaced with fresh dissolution medium. The aliquots were filtered through filter paper. Absorbance of these solutionswas measured at 264 nm. Cumulative percentage drug release was calculated. Analysis of data was done by using PCP Disso V-3 software and Microsoft excel. [12]

Result and discussion

The development of matrix floating tablet

On the basis of prior studies on the floating properties of matrix tablets, we conclude that the hydroxypropylmethyl cellulose K4M polymer is the best vehicle for the floating tablets design. (Baumgartner et al; 1998).[13] The floating properties of the tablet are, however, expected to be altered when a high dose of the active component is incorporated. Tablets with different ratios of the drugs versus polymer were prepared to optimize the drug content and floating properties. It was determine that besides the tablet composition, the tablet hardness has an essential role for floating properties.

Physicochemical characteristics of tablets

Swelling indices[16]
Drug release study
To study the release kinetics, the *in-vitro* dissolution drug release data of formulations applied to various kinetic models viz. zero order, first order, Higuchi and Korsmeyer-Peppas equation.
Results were shown in fig
The release constant was calculated from the slope of the appropriate plots and the regression coefficient (R^2) was determined.[14,15]
The corresponding plot for the Korsmeyer-Peppas equation indicated a good linearity (R^2). The mechanism of drug release is mainly described by diffusion and swelling mechanism of polymers.
Mathematical modeling and release kinetics of Baclofen from the prepared floating tablets.
Experimental design & factorial design [17, 18]
The mathematical model of the effects of independent variables upon the dependent variables was performed using stat-ease design expert (version 7.1.6) with a manual linear regression technique. Significant terms ($p < 0.05$) were chosen for final equations. Finally Response surface plots resulting from equations were drawn.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \quad \text{.....(1)}$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs and bi (b_1, b_2, b_{12}, b_{11} and b_{22}) is the estimated coefficient for the corresponding factor Xi (X_1, X_2, X_1X_2, X_{12} and X_{22}), which represents the average result of changing 1 factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. All 9 batches of design has shown wide variation in % drug release in 4 hours (23.06-55.78), 8 hours (47.62-89.09) 12 hours (88.1-111.77) The fitted equations relating the response Y_1 and Y_2 & Y_3 to the transformed factor are shown in equation-2 and equation -3 respectively.
i) Final Equation in Terms of Coded Factors: (for 1st approach)
Release in 4 hrs = +37.17 + 3.35* A - 12.06* B - 2.46*A* B..... (2)

ii) Final Equation in Terms of Actual Factors

Release in 4 hrs = + 58.99444 + 0.66067 *Carbopol 934 - 0.28527 * HPMC K4M -4.93 * Carbopol 934 * HPMC K4M…….. (3)

iii)Final Equation in Terms of Coded Factors

Drug release in 8 hrs = + 64.28 - 9.21* A - 8.72* B + 6.83 * A * B…….. (4)

d) Final Equation in Terms of Actual Factors

Release in 8 hrs = +172.27111 - 1.82767 * Carbopol 934 - 0.89560 * HPMC K4M+0.013670 * Carbopol 934 * HPMC K4M…….. (5)

iv) Final Equation in Terms of Coded Factors

Release in 12 hrs = +89.14 - 2.03 * A - 5.04* B+6.47 * A * B+3.58* A^2+6.33* B^2…….. (6)

v) Final Equation in Terms of Actual Factors

Release in 12 hrs = +280.68556 - 2.11175 * Carbopol 934 - 2.74387 * HPMC K4M+0.012940* Carbopol 934 * HPMC K4M+8.95417E-003 *Carbopol 934^2+0.010123* HPMC $K4M^2$ …….. (7)

Drug release of formulations at 4, 8 & 12 hrs[17, 18, 19]

Surface and contour plots for 4, 8, & 12hours respectively

ANOVA for Response Surface Model:

Response 1-Drug release in 4 hours

ANOVA for Response Surface 2FI Model:

Response 2-Drug release in 8 hours

ANOVA for Response Surface 2FI Model

Response 3-Drug release in 12 hours

ANOVA for Response Surface Quadratic Model

Table No – 1- Formulation quantities

	Quantities in milligram								
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	75	75	75	75	75	75	75	75	75
HPMC K4M	75	100	125	75	100	125	75	100	125
Carbopol 934	20	20	20	40	40	40	60	60	60
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Citric acid	25	25	25	25	25	25	25	25	25
Magnesium stearate	5	5	5	5	5	5	5	5	5
Sodium CMC	20	20	20	20	20	20	20	20	20
Total weight	270	295	320	290	315	340	310	335	360

Table No- 2 - Physicochemical characteristics of tablets

Formulation code	Tablet thickness (mm)	Tablet weight (mg)	Drug content (%)	Tablet friability (%)	Floating lag time (s)	Total floating duration (h)
F1	4.92±0.05	262.48 ±2.74	95.5±0.92	0.24±0.10	70±1.23	> 12
F2	5.12±0.05	282.06 ±4.37	96.8±0.34	0.36±0.08	88±1.52	> 12
F3	4.95±0.05	313.31 ±5.70	96±0.55	0.45±0.12	55±1.09	> 12
F4	5.14±0.05	277.28 ±2.97	99±1.05	0.51±0.10	100±1.80	> 12
F5	4.96±0.05	315.00 ±5.11	97.5±0.88	0.48±0.04	80±1.20	> 12
F6	4.98±0.05	335.73±3.33	98.6±0.98	0.49±0.07	58±1.05	> 12
F7	5.05±0.05	311.27±3.53	97±0.70	0.46±0.05	80±1.09	> 12
F8	5.10±0.05	333.85±3.05	96±0.87	0.52±0.08	65±1.25	> 12
F9	4.94±0.05	357.74±2.12	97±1.08	0.55±0.15	120±2.1	> 12

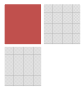

Table No- 3 – Release kinetics of baclofen

Formulacode	Zero-order plots Correlation coefficient (R2)	1st order plots Correlation coefficient (R2)	Higuchi's plots Correlation coefficient (R2)	Korsmeyer–Peppas plots Correlation coefficient (R2)	Diffusional exponent (n)	Order of release
F1	0.98	0.98	0.98	0.98	0.88	Non – fickian transport
F2	0.98	0.98	0.95	0.99	1.08	Super case 2 transport
F3	0.98	0.98	0.92	0.99	1.3	Super case 2 transport
F4	0.97	0.97	0.99	0.98	0.60	Non – fickian transport
F5	0.99	0.99	0.94	0.99	0.76	Non – fickian transport
F6	0.98	0.98	0.92	0.98	1.009	Super case 2 transport
F7	0.93	0.93	0.93	0.74	0.43	Non – fickian transport
F8	0.95	0.95	0.90	0.84	0.69	Non – fickian transport
F9	0.98	0.98	0.92	0.99	1.19	Super case 2 transport

Table No- 4- Drug release

Carbopol 934 (mg)	HPMC K4M (mg)	Drug release in (%) 4 hrs	Drug release in (%) 8 hrs	Drug release in (%)12 hrs
20	75	43.22	89.09	111.77
20	100	33.33	72.32	96.31
20	125	23.06	61.53	88.83
40	75	49.12	74.72	100.08
40	100	39.18	63.06	90.18
40	125	26.93	50.18	89.82
60	75	55.78	60.13	96.85
60	100	38.19	47.62	88.1
60	125	25.76	59.91	99.79

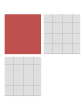

Table No. 5: Analysis of variance table for 4 hours [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	P value Prob > F	Significant or Non-significant
Model	964.6768	3	321.5589	107.0148	< 0.0001	Significant
A-Carbopol 934	67.46907	1	67.46907	22.4537	0.0052	Significant
B-HPMC K4M	872.9028	1	872.9028	290.502	< 0.0001	Significant
AB	24.3049	1	24.3049	8.08867	0.0361	Significant
Residual	15.02404	5	3.004808	-	-	-
Core Total	979.7008	8	-	-	-	-

Table No. 6:Analysis of variance table for 8 hours [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significant or Non-significant
Model	1152.412	3	384.1375	12.11831	0.0099	Significant
A-Carbopol 934	509.3131	1	509.3131	16.0672	0.0102	-
B-HPMC K4M	456.2304	1	456.2304	14.39261	0.0127	-
AB	186.8689	1	186.8689	5.895117	0.0595	-
Residual	158.4947	5	31.69893	-	-	-
Core Total	1310.907	8	-	-	-	-

Table No. 7: Analysis of variance table for 12 hours [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significant or Non-significant
Model	450.4498	5	90.08996	17.56895	450.4498	significant
A-Carbopol 934	24.68482	1	24.68482	4.813927	24.68482	-
B-HPMC K4M	152.6113	1	152.6113	29.76159	152.6113	-
AB	167.4436	1	167.4436	32.65413	167.4436	-
A^2	25.65667	1	25.65667	5.003454	25.65667	-
B^2	80.05342	1	80.05342	15.61167	80.05342	-

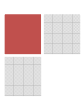

Table No -8-Software predicted value

No.	Carbopol 934	HPMC K4M	Drug release in 4 hrs	Drug release in 8 hrs	Drug release in 12 hrs	Desirability	Level selected
1	39.53	76.00	48.61	73.01	100.00	0.78	Selected
2	37.74	77.11	47.58	74.00	100.00	0.78	-
3	37.47	77.29	47.42	74.15	100.00	0.78	-

Table No. 9: Predicted & practical value for 1st Approach

	Carbopol 934	HPMC K4M	Drug release in 4 hrs	Drug release in 8 hrs	Drug release in 12 hrs
Software Predicted value	39.53974	76.00836	48.6180011	73.01571	100.0002
Practical value	40	75	49.12	74.72	100.08
value					

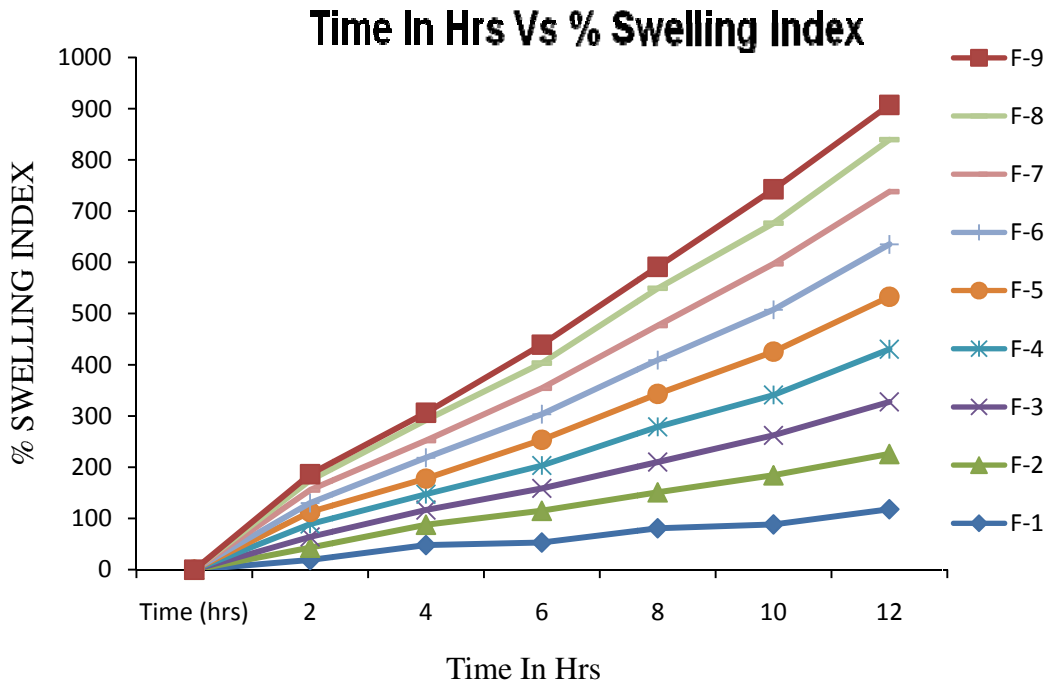

Fig No- 1 – Graph for swelling indices

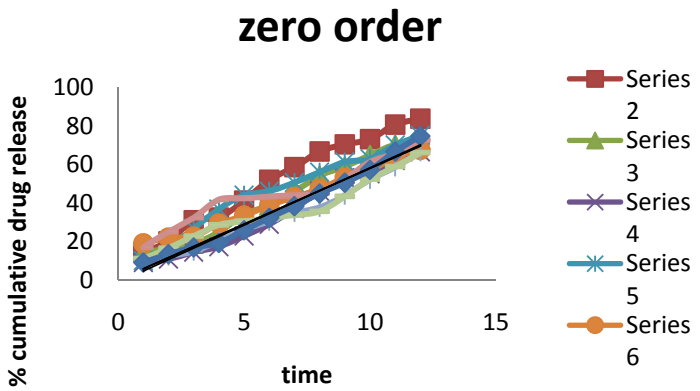

Fig. No. 2: Zero order drug release graph

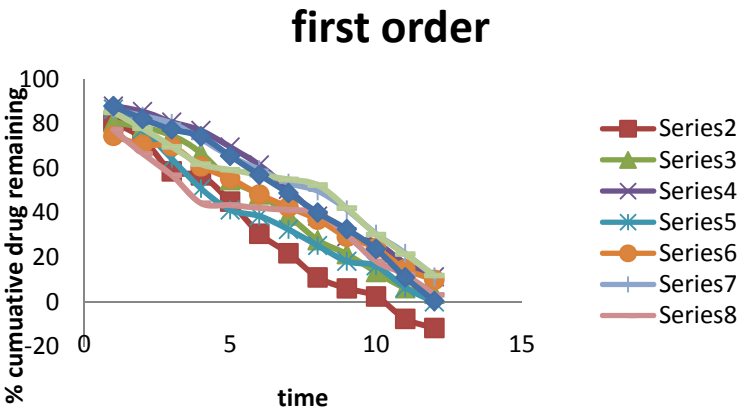

Fig. No. 3: First order drug release graph

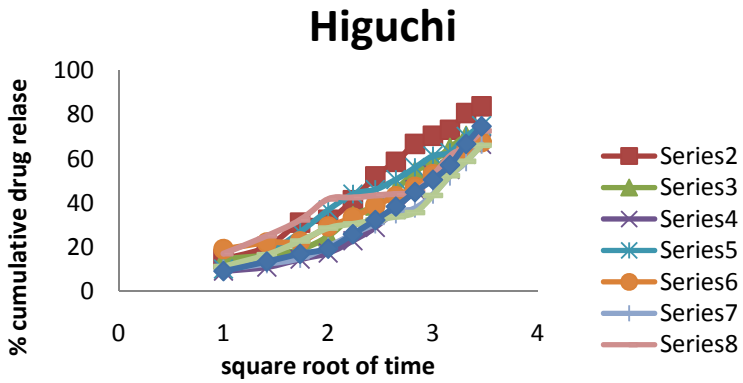

Fig. No. 4: Higuchi model drug release graph

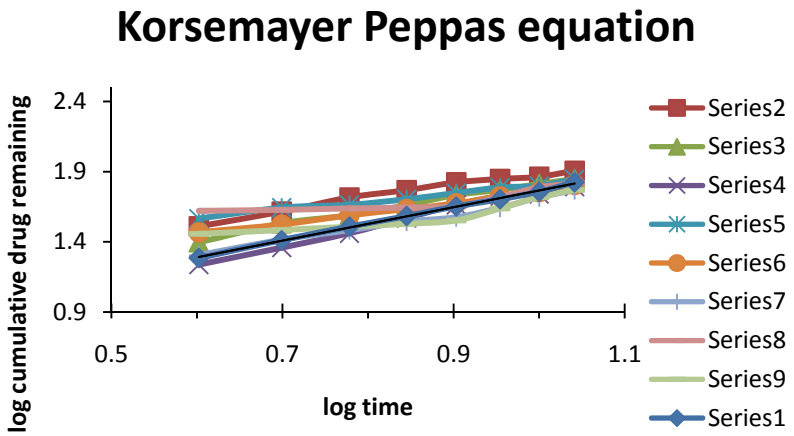

Fig. No. 5: Korsmeyer Peppas model drug release graph

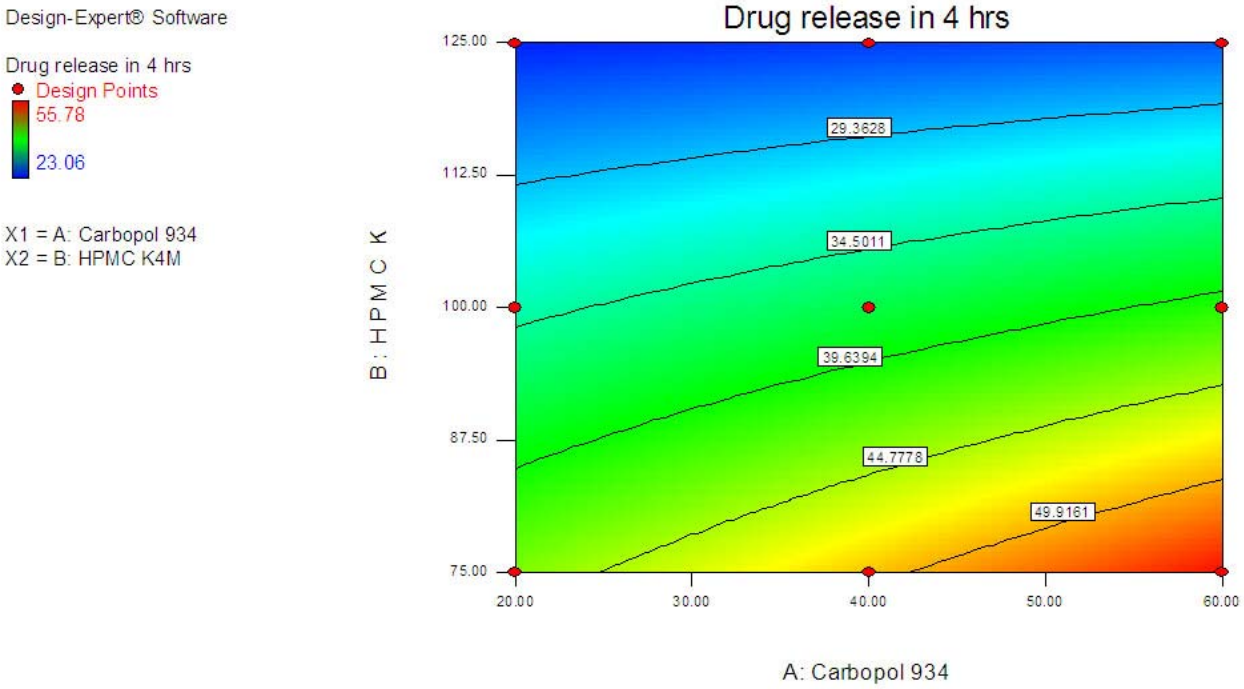

Fig. No. 6: Contour plot for 4 hours drug release

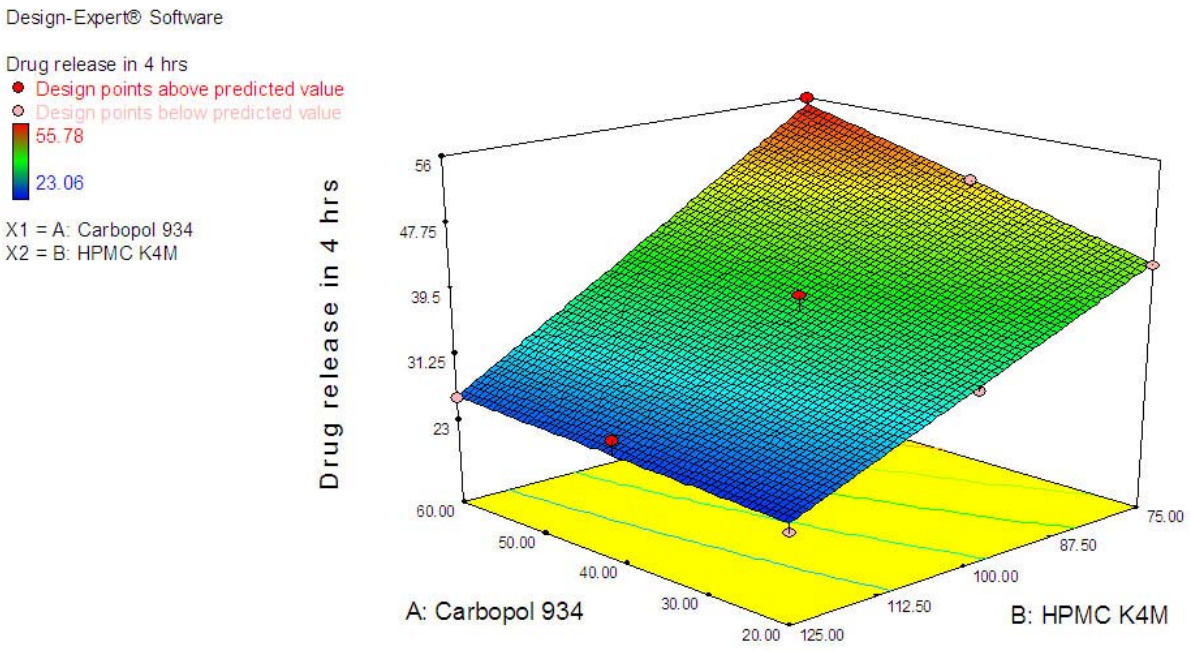

Fig. No. 7: Surface response plot for 4 hours drug release

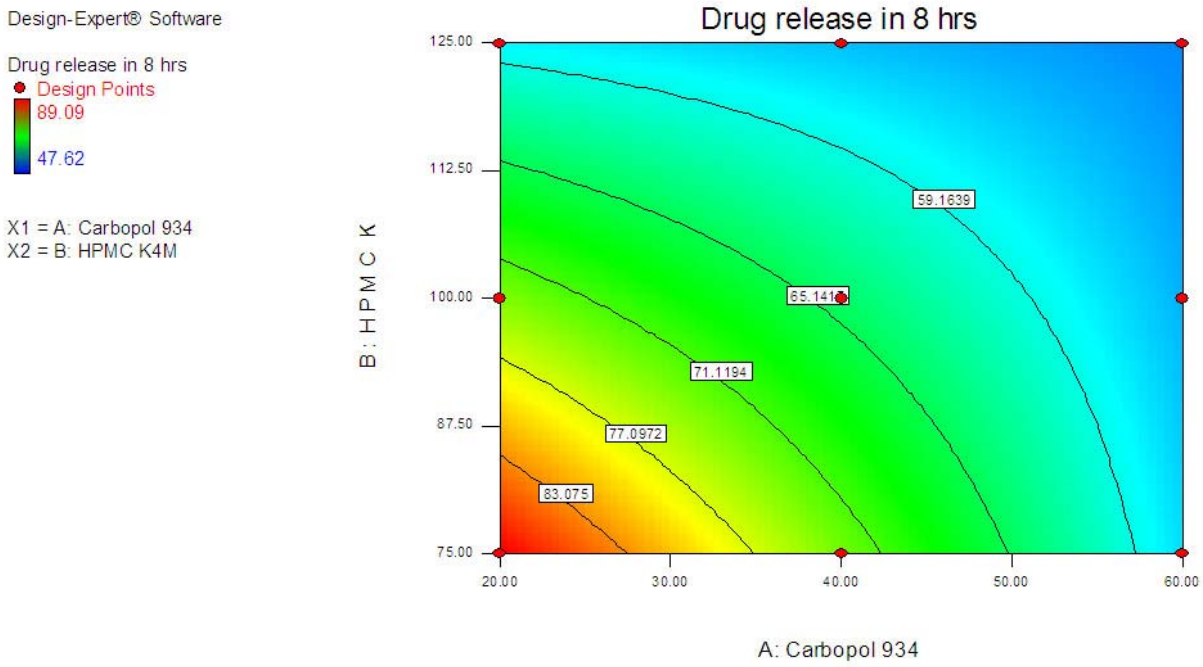

Fig. No. 8: Contour plot for 8 hours drug release

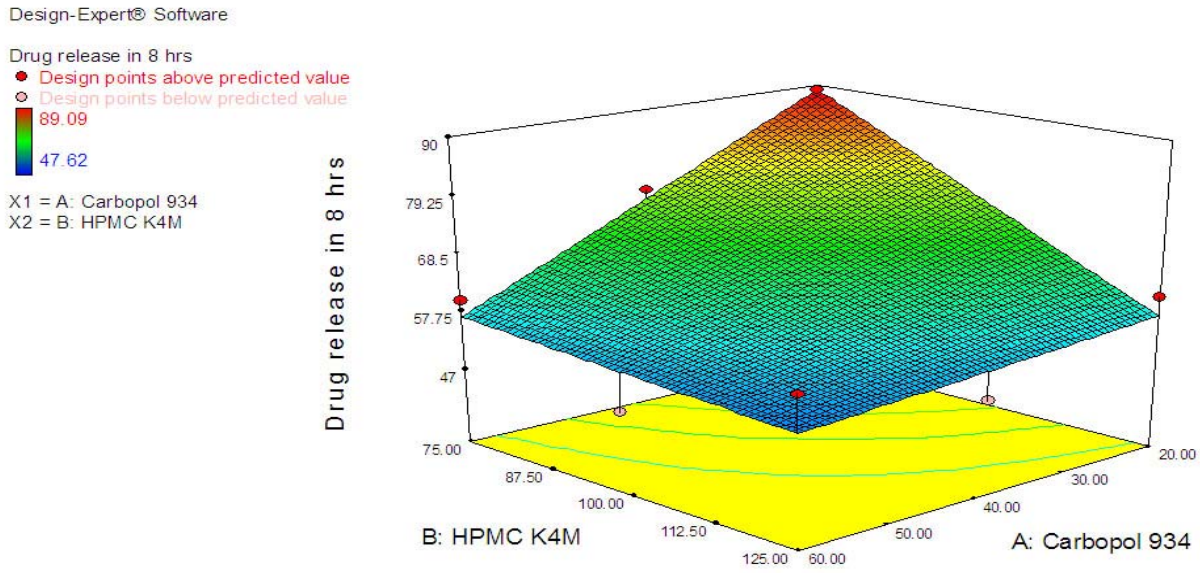

Fig. No. 9: Surface response plot for 8 hours drug release

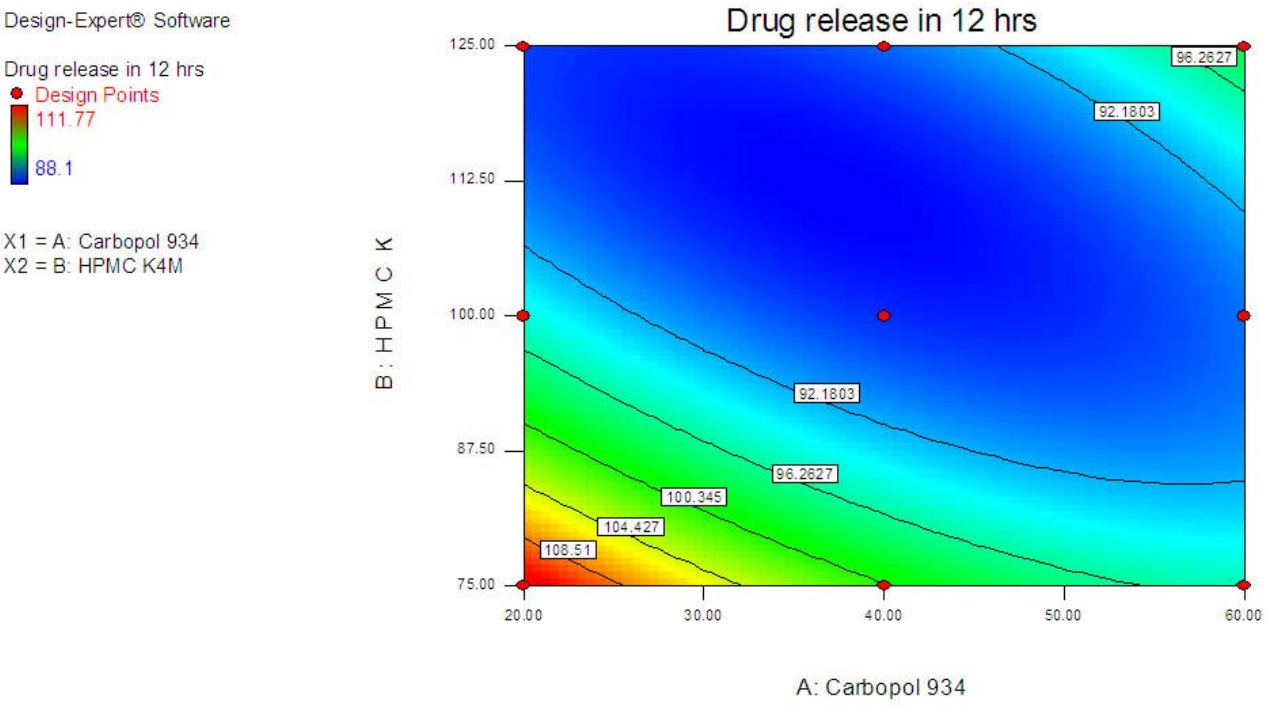

Fig. No. 10: Contour plot for 12 hours drug release

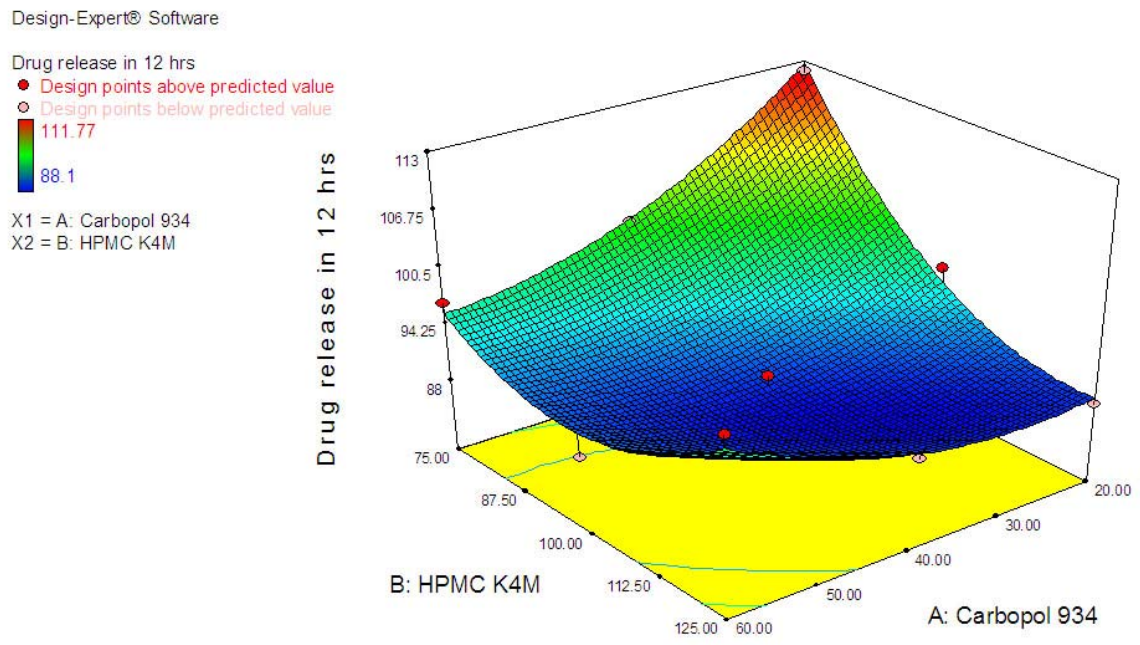

Fig. No. 11: Surface response plot for 12 hours drug release

Conclusion

An oral sustained released dosage form offer many advantages for drugs having absorption from the upper gastrointestinal tract and improves the bioavailability of medications that are characterized by the narrow absorption window. A Gastro retentive sustained released floating matrix tablets was developed with polymers like HPMC (K4 M), Carbopol (934P) & effervescent mixture (sodium bicarbonate & citric acid) with floating and swellable properties. Where the polymers act as a release retarding agent and the effervescent mixture aid for floatation.

As the concentration of the polymers increases the swelling properties goes on increasing as well as the release rate decreased. The optimized formulation followed Korsmeyer-Peppas kinetics, while the drug release mechanism was found to be of non-fickian type (diffusion & swelling type of drug release).

Hence the formulated systems F_4 have better bioavailability of drug due to increase gastric residence time. Because floating tablets remains float in stomach reason due to this absorption of window increases and hence the bioavailability of formulation code F_4 increased

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