Original Article

Central Composite Design Assisted Formulation Development and Optimization of Gastroretentive Floating Tablets of Dextromethorphan Hydrobromide

Haranath Chinthaginjala[1,*], Hindustan Abdul Ahad[2], Sainath Kethandapatti Srinivasa[2], Srihith Roy Yaparla[1], Snehitha Buddadasari[1], Junaid Abul Hassan[1], Sai Sree Pullaganti[1]

[1]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Anantapur, Andhra Pradesh, INDIA.
[2]Department of Industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Anantapur, Andhra Pradesh, INDIA.

ABSTRACT

Objectives: The existing study is concerned with the formulation and optimization of dextromethorphan hydrobromide floating tablets via central composite design. **Materials and Methods:** Direct compression method was employed to prepare the tablets. Drug -excipient studies were executed through FT-IR and DSC analysis. The independent variables selected were the concentrations of Carbopol 934 (X_1) and HPMC K15M (X_2). The dependent variables designated were Floating Lag Time (FLT) and Drug Release (DR) at 12 hr. The model was found to be nonlinear and the curvature effect was significant. Hence, the system suggested to central composite design. **Results:** FT-IR studies demonstrated that there is no considerable interaction amid the drug and the excipients. DSC studies revealed that drug and excipient were compatible as there is no significant alteration in melting point of drug when blended with excipients. The precompression parameters of the formulations showed good flow properties. The evaluation of post compression parameters indicated that all the prepared formulations were within the specified limits. Floating lag time of formulations were marked to be less than 1 min and total floating time exceeding 12 hr. Percentage drug release of all formulations were in the range of 89.7% to 99.4%. The obtained design space/contour plots were used for selecting batches in desirable ranges. **Conclusion:** The results revealed that experimental design was successfully used to optimize polymer concentrations. It was determined that the central composite design would be used to formulate dextromethorphan gastroretentive floating tablets with fewer trials and higher quality features.

Keywords: Dextromethorphan Hydrobromide, Carbopol, HPMC, Central Composite design, Floating lag time.

INTRODUCTION

Gastroretentive Dosage Forms (GRDF) are one among the practical methods for attaining a longer and foreseeable drug delivery profile in the Gastrointestinal Tract (GIT) to manage the stomach Residence Time (RT). Floating Drug Delivery Systems (FDDS) have a lower bulk density than stomach fluids and hence keep on afloat in the stomach. The medicine is released slowly from the system at a predefined pace for a protracted length of spell deprived of impacting the gastric emptying rate.[1] Dextromethorphan Hydrobromide (DXMH) functions as a cough suppressant by inhibiting NMDA receptors. The oral bioavailability of DXMH is 11%. DXMH is a methylated dextrorotary analogue of levorphanol, a chemical linked to codeine and morphine's non-opioid derivate. DXMH exhibits poor absorption from the GI tract and has a 3-6 hr elimination half-life. DXMH has anti-tussive action but no analgesic or addictive properties.[2] This drug penetrates the BBB and triggers sigma opioid receptors in the CNS cough area, inhibiting the cough reflex.[3] DXMH acts quickly but is poorly absorbed and has a limited bioavailability in the stomach.[4] Due to the limited bioavailability and short biological half-life, controlled release floating formulations must be developed to lengthen the RT in the gastric vicinity and therefore progress bioavailability. The intention of this research is to upsurge the Gastric Residence Time (GRT) enabling the availability absorption site and to accomplish a protracted action for 12 hr. Quality by Design (QbD) has become a new concept for quality pharmaceutical products development. Central Composite Design (CCD) is a

statistical method availed in the optimization of formulations.[5] The application of CCD during the design and development process could simultaneously determine the interactive effect of different variables that influence the results/quality of products. CCD involves statistical techniques and mathematical methods for building an experimental design model based on fitted polynomial equations with experimental data. The primary purpose of this project is to employ CCD to build Gastroretentive Floating Tablets (GRFT) and evaluate the consequence of factors on the replies. The concentrations of Carbopol 934 (X1) and HPMC K15M were the independent variables (X2). The reliant replies were Floating Lag Time (FLT) and Drug Release (DR) at 12 hr.

MATERIALS AND METHODS

DXMH was presented as a complimentary from Waksman Selman Pharma Pvt. Ltd., in Anantapur, Andhra Pradesh. Kemphasol in Mumbai provided the HPMC K15M. Loba Chemicals, Mumbai, supplied carbopol 934, lactose talc, and magnesium stearate. All of the substances used were of analytical grade.

FT-IR studies

The drug's compatibility with the excipients was determined using FT-IR spectroscopy. Small quantities of the medication and polymers are combined with KBr and squeezed to produce tiny pellets.[6] These are analysed with FT-IR spectrophotometer and scanned in 4000 cm^{-1} to 400 cm^{-1} range.

DSC studies

The DSC equipment (Venchal Scientifics, 412105, USA) was engaged to conduct the DSC investigations to determine the drugs compatibility with the excipients. Precisely measured drug and excipient's mixture was shifted into the aluminium crucible and run in the range of 50°C to 300°C by a preset heat of 10°C/min.[7]

Optimization by the CCD

In the current study, 2^2 factorial design was used in the design of experimentation of the GRFT of DXMH using Sigma Tech software Version 3.1. (Swaroop tech, Hyderabad, India). It is the simplest factorial design having two variables with two levels. From the four experiments, three effects can be determined. These are two main effects (X_1 and X_2) and the interaction (X_1X_2). The considerable curvature result was obtained and the model was seen to be nonlinear, confirming the use of CCD. The nondependent factors recognized are CBP concentration (X_1) and HPMC K15M concentration (X_2). The outcomes elected were FLT and % DR projected in Table 1 and the developmental trials were signified in Table 2.

Preparation of GRFT

GRFT formulations containing DXMH 30 mg were formed by direct compression utilising varied ratios of HPMC K15M and Carbopol 934. Sodium bicarbonate as a gas producing agent. Entire constituents were precisely balanced and screened via sieve 40. Excluding magnesium stearate and talc, the ingredients were combined homogeneously in a glass mortar followed by the addition of magnesium stearate, talc and further mixed.[8] Table 3 shows the composition of several formulations. Rimek mini press - II MT, India was used to compress the resultant mass.

Pre compression constraints

BD

The BD was determined by placing a weighed sample in a 100 mL graduating cylinder. The preliminary volume and mass are recorded and calculated the BD.[9]

Tapped Density (TD)

It is valued by using TD apparatus (Electrolab ETD-1020, India) utilizing the total mass and tapped volume employing a graduated cylinder, subjected for 100 tappings.[10]

Angle of Repose (AR)

It is the highest feasible slant amid the powder pile surface and the horizontal plane,[11] and is valued by tan Θ = h/r

$$\Theta = \tan^{-1} h/r$$

h refers height

r refers radius

Carr's index (CI)

CI was estimated determined by considering TD and BD.[12]

$$CI = \frac{TD - BD}{TD} \times 100$$

HR

It states to the TD to BD ratio.[13]

$$HR = \frac{TD}{BD}$$

Post compression parameters

Uniformity of Weight (UW)

20 tablets were chosen, weighed and the AW was computed. The weight of no more than two tablets should depart from the AW and nothing ought to differ by further than double the percentage.[14]

Table 1: Coded variables with responses.

Factors	Actual values (mg)					Response
	-2	-1	0	+1	+2	
Carbopol 934	10	15	20	25	30	Y1= Floating lag time
HPMC K15M	10	17.5	25	32.5	40	Y2= %Drug release

Table 2: Investigational strategy layout.

	Formulation code	Combinations	Carbopol 934 (X1) in %	HPMC K15M (X2) in %
Factorial Design	F1	I	15	17.5
Mid-point	F2	X_1	25	17.5
Central Composite Design	F3	X_2	15	32.5
	F4	$X_1 X_2$	25	32.5
	F5	Mid-point	20	25
	F6	X_1 at -2L	10	25
	F7	X_1 at+2L	30	25
	F8	X_2 at -2L	20	10
	F9	X_2 at +2L	20	40

Table 3: Composition of DXMH floating tablets (F1 – F9).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
DXMH HBr	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Carbopol 934	45.0	75.0	45.0	75.0	60.0	30.0	90.0	60.0	60.0
HPMC K15M	52.5	52.5	97.5	97.5	75.0	75.0	75.0	30.0	120.0
Sodium bicarbonate	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Mg. Stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Lactose	136.5	106.5	91.5	61.5	99.0	129.0	69.0	144.0	54.0
Total weight(mg)	300	300	300	300	300	300	300	300	300

Hardness (HD)

Ten tablets from each formulation were utilized to perform the HD. It was measured using a Monsanto tester, which were selected randomly from the formulations.[15]

Friability (FR)

Tablets weighing 6.5 g were put in a friabilator (Electrolab EF-2, India) and spun at 25 rpm for 4 min.[16] The gathered tablets were cleaned and weighed once more. The formula was used to calculate the % friability.

$$\%FR = \frac{W1 - W2}{W1} \times 100$$

W1 and W2 are the primary and ultimate weights.

Thickness (TK)

The thickness of 10 tablets obtained from respective formulations was ascertained using Vernier callipers.[17]

Drug Content (DC)

Ten tablets were crushed and the sample matching to 30mg of drug was shifted to a 100 mL volumetric flask holding 0.1 N HCl and shaken for 30 min and filtered using Whatmann No. 42 filter paper. The filtered sample was analysed by UV spectrophotometer (Shimadzu UV-1800, Japan) at 278nm.[18]

Floating lag Time (FT)

The tablets were immersed in 900 mL of 0.1N HCl in a glass beaker. The period necessary for the tablet to climb from the bottom to the medium's superficial was calculated.[19]

Total Floating Time (TFT)

TFT is defined as the measurement of duration of total buoyancy for a tablet.[20]

Swelling Index (SI)

The SI of tablets was evaluated by inserting six tablets from each formulation on a petri plate with 0.1N HCl. The tablets were removed after 1, 2, 4, 6, and 8 hr and wiped with blotting paper to get rid of surplus water before being weighed.[21]

$$SI = \frac{W2 - W1}{W1} \times 100$$

In vitro DR

To assess the DR of DXMH floating tablets (basket type) was used. At 37.5°C and 50 rpm, 900 mL of 0.1N HCl was used as dissolving medium. Hourly for 12 hr, a sample (5 mL) of the aliquot was removed, filtered and substituted with media.[22] Shimadzu UV-1700 was availed to measure the absorbance of these solutions at 278 nm.

Statistical analysis and optimization

The Sigma Tech was used to evaluate the statistics from all formulations in order to develop the experimental design. A comparison of numerous statistical limits supplied software revealed that the best-fit model was selected. ANOVA was used to find noteworthy variable features on response regression co-efficient. Contour designs were utilised to investigate the relationship between dependent and non-reliant elements. A graphic optimization system with CP was utilised to develop exclusive trials with the anticipated outcomes. FLT and DR stood examined to correspond with the imaginary estimate. For respective response, the Relative Errors (RE) between the anticipated and explored outcomes were computed.

RESULTS

FT-IR and DSC studies

According to FT-IR and DSC investigations on drug excipients compatibility test, it was found that there are no noteworthy alterations in the spectra of the drug and excipients used. The results were represented in Figures 1 and 2 respectively.

Precompression Parameters

AR of the formulations was in amid 21°C to 25°C, suggesting that the Flow Properties (FP) of the formulations were excellent, The Prepared formulations have CI ranging from 5.91 to 13.1%, indicating that the FP of the formulations were good. The developed formulations HR were varied from 1.06 to 1.15, signifying that the formulations FP were good, as publicized in Table 4.

Floating lag time

The tablets from all the formulations were floated in between 4 sec to 41 sec and the TFT was more than 12 hr. The results were tabulated in Table 5. Statistical analysis of DOE experimental observations of FLT was represented in Table 6. The results of ANOVA for FLT were mentioned in Table 7.

SI studies

The SI of all the formulations (F1 – F9) were found to be in the range of 40.74% to 230%. Table 8 displays the SI results.

In vitro DR

All formulations had drug release values in the range 89.7% to 99.4%. Formulations F1 to F9 shows 99.4%, 95.8%, 92.6%, 90.0%, 92.93%, 89.7%, 91.75%, 96.1%, 98.89%. as depicted in Figure 3. Statistical analysis of DOE experimental observations of DR was represented in Table 9. The results of ANOVA for DR were mentioned in Table 10.

DISCUSSION

FT-IR and DSC studies

The pure drug exhibited C–N peak at 1291.51 cm^{-1}, C–O at 1068.67 cm^{-1}, and C–H at 2926.29 cm^{-1} and the same peaks were retained when combined with excipients as shown in Figure 1. DSC investigations revealed the melting peak of the pure drug at 125°C. DSC thermograms of drug combined with excipients showed the melting point at 126°C as shown in Figure 2. The melting point of drug does not change considerably, even though the drug was blended with excipients employed in the formulation which certifies the compatibility.

Post compression parameters

FR was performed to the prepared tablets. All formulations FR was beneath 0.5% and was found to be of 0.13 to 0.31%, ensuring physically stable, having good compactness and showing enough resistance to mechanical shock and abrasion. The UW of all the formulations were found to be 296±0.03 to 307±0.08 mg. All formulations passed the UW test with a deviation of 5% as per IP specifications. The DC was determined to be between 95.15% and 99.52%. No tablet from ten tablets lies out of the range of 85–115% of the label claim. These results indicated that the tablets had uniform distribution and proper dose of drug. All the formulations seemed to have a hardness of 5.5 to 7.5 kg/cm^2, which ensured satisfactory handling properties. The results showed acceptable resistance of the tablet to shipping during storage and transport. The tablet thickness of all formulations was determined to be between 4.1 mm and 4.8 mm as addressed in the Table 5.

SI studies

SI studies were carried out for all formulations (F1 to F9). All the formulations were hydrated when placed in 0.1N HCl for 1 to 8 h. Swelling indices show that CBP 934 and HPMC K15M at high levels (+1) on code variable absorbed the most water, as the swelling index of formulation F4 rose to 230% after 8 h. When a significant proportion of Carbopol 934 and HPMC K15M were employed, the swelling index increases with time.[23]

Floating lag time (Y1)

FLT (Y1), as indicated in Table 7, was the most significant interaction of X1 and X2, with an SS ratio of 56.8816% and a co-efficient of 6.0.

Ultimate equation with coded elements

$$Y_1 = 10.1111 + 2.6667X_1 + 0.6667X_2 + 6.0X_1X_2 + 6.9792X_1^2 + 2.3542X_2$$

The ultimate equation in respect of factual elements:

$$Y_1 = 10.11 + 2.6667CBP + 0.6667HPMC + 6.0CBPHPMC + 6.979CBP^2 + 2.354HPMC^2$$

A polynomial equation predicts the quantifiable outcome of independent variables at unlike levels on response variables. Multinomial calculations were used to make a conclusion after analysing the amount of the co-efficient and the mathematical signs it possesses. As shown in Table 8, the obtained F value is further than the Critical F Value (CFV), and the outcome appeared to be noteworthy at ($p < 0.05$). The CFV is 4.26, and the attained F value (i.e., 6.54) is bigger than the CFV, meaning that the achieved F value is predicted to occur by chance with a $p < 0.05$. As a result, the connection between Y_1 and $X_1 X_2$ is non-linear, as indicated by software, and the CCD remains in place. Multiple Linear Regression (MLR) study revealed that lowering the quantity of both X_1 and X_2 causes the FLT to decrease. This quadratic models R^2 value was determined to be 0.8925, indicating that it is reliable. All formulations had a FLT of less than 1 min and a TFT of more than 12 hr, which is attributed to the collaboration between $NaHCO_3$ and 0.1N HCl, which

Table 4: Precompression parameters of F1-F9 formulations.

Formulation	Bulk Density± SD*	Tapped density± SD*	Angle of repose± SD*	Carr's index± SD*	Hausner's ratio± SD*
F1	0.166±0.03	0.178±0.02	22.3±0.05	6.74±0.07	1.07±0.01
F2	0.161±0.02	0.178±0.04	24.9±0.01	9.55±0.17	1.10±0.03
F3	0.165±0.01	0.190±0.01	25.4±0.14	13.1±0.10	1.15±0.08
F4	0.159±0.04	0.177±0.03	23.2±0.11	10.1±0.15	1.11±0.02
F5	0.175±0.03	0.186±0.01	21.4±0.07	5.91±0.05	1.06±0.05
F6	0.158±0.02	0.181±0.01	23.7±0.12	12.7±0.11	1.14±0.07
F7	0.162±0.01	0.179±0.02	25.1±0.08	9.49±0.13	1.10±0.06
F8	0.160±0.01	0.180±0.04	24.2±0.15	11.1±0.09	1.12±0.10
F9	0.158±0.04	0.179±0.03	23.8±0.16	11.7±0.02	1.13±0.04

*n=3 Entire values are stated as mean±SD.

Table 5: Post compression constraints of formulations F1 – F9 formulations.

Formulation	Hardness (kg/cm²) ±SD*	Friability ±SD*	Average Weight ±SD*	Drug Content ±SD*	Thickness ±SD*	Floating lag time (sec)	Total floating time(h)
F1	5.7±0.12	0.21±0.02	297±0.05	99.24±0.18	4.5±0.07	4	>12
F2	5.5±0.10	0.15±0.03	296±0.03	96.8±0.22	4.3±0.04	7	>12
F3	6.3±0.15	0.24±0.01	307±0.08	98.64±0.31	4.1±0.01	14	>12
F4	6.0±0.11	0.27±0.03	302±0.01	97.8±0.25	4.6±0.05	41	>12
F5	6.5±0.21	0.18±0.01	298±0.02	99.52±0.19	4.8±0.02	16	>12
F6	5.7±0.22	0.31±0.02	296±0.04	95.15±0.32	4.5±0.03	39	>12
F7	6.0±0.13	0.23±0.01	301±0.05	97.53±0.21	4.3±0.06	40	>12
F8	7.5±0.20	0.13±0.03	298±0.07	98.29±0.26	4.5±0.03	30	>12
F9	7.0±0.15	0.25±0.02	297±0.02	96.43±0.14	4.7±0.07	12	>12

*Entire values are stated as mean±SD.

Table 6: Statistical analysis of DOE experimental observations of Y1 (Floating lag time).

Sl. No.	Combination	Name of variable	Coefficient values	SS % (% of sum of squares)
1	b_0	-	16.5	-
2	b_1	Carbopol 934	7.5	26.3775%
3	b_2	HPMC K15M	11.0	16.7409%
4	b_1b_2	Carbopol+ HPMC	6.0	56.8816%

SS is Sum of squares.

Table 7: Results of ANOVA for response Y_1 (floating lag time).

Sl. No.	Source of variable	SS	DF	MS	F-value	F std at 0.1p	F std at 0.05p	F std at 0.01p
1	Model	11.0562	4	7.6425	6.5429	3.01	4.26	8.02
2	Error	0.0	3	0.0				
3	Total	11.0562	7					

95% confident level of curvature effect Non-linear

Standard Deviation (SD): 0.05; F Standard Value (SV) at 0.05 p: 10.2; Curvature Effect (CE): -5.6239; F Standard Value (SV) at 0.01 *p*: 40.7; 95% Confident Level of Curvature Effect (CLCE); FROM: -7.5843; TO: -6.5322 (Non-Linear).DF is Degrees of freedom, MS is mean squares, P is probability.

Table 8: Swelling index of formulations (F1 – F9).

Time (h)	Swelling index (SI %) ± SD*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	40.74±0.13	52±0.10	62.96±0.18	60±0.17	53.33±0.06	59.25±0.10	48±0.12	44.4±0.15	56.6±0.21
2	51.8±0.11	76±0.09	85.1±0.13	96±0.03	70±0.02	81.4±0.21	88±0.20	62.96±0.22	83.3±0.22
3	62.96±0.12	84±0.16	114.8±0.12	124±0.07	83.3±0.10	92.5±0.15	96±0.21	77.7±0.20	110±0.10
4	66.6±0.02	108±0.10	140.7±0.17	148±0.15	110±0.09	114.8±0.19	116±0.11	100±0.17	123.3±0.19
5	77.7±0.01	124±0.06	148±0.09	180±0.20	130±0.12	129±0.22	132±0.19	111.1±0.21	130±0.13
6	84±0.07	132±0.05	154±0.02	194±0.18	144±0.11	136±0.20	143.3±0.12	127±0.19	149±0.11
7	99±0.15	141±0.17	177.3±0.10	210±0.05	156±0.14	144±0.17	161±0.26	134±0.11	168±0.23
8	116±0.05	152±0.02	183±0.07	230±0.21	180±0.20	158±0.11	177.7±0.22	148±0.14	191±0.24

Table 9: Statistical analysis of DOE experimental observations with two variables of Y2 (% drug release).

Sl. No.	Combination	Name of variable	Coefficient values	SS % (% of sum of squares)
1	b_0	-	94.45	-
2	b_1	Carbopol 934	1.55	19.3946%
3	b_2	HPMC K15M	3.15	46.3745%
4	b_1b_2	Carbopol+ HPMC	0.25	80.1739%

Table 10: Results of ANOVA for response Y2 (% drug release).

Sl. No.	Source of variable	SS	DF	MS	F-value	F std at 0.1p	F std at 0.05p	F std at 0.01p
1	Model	9.6284	5	5.9438	6.6826	3.01	4.26	8.02
2	Error	0.0	4	0.0				
3	Total	11.0562	9					

95% confident level of curvature effect Non-linear

SD: 0.0541; F SV at 0.05 p: 10.8; CE: -7.6593; F SV at 0.01 p: 43.6; 95% CLCE; FROM: -8.9546; TO: -7.8265 (NL).

Table 11: Comparison of experimental results with predicted response of DXMH floating tablet formulations.

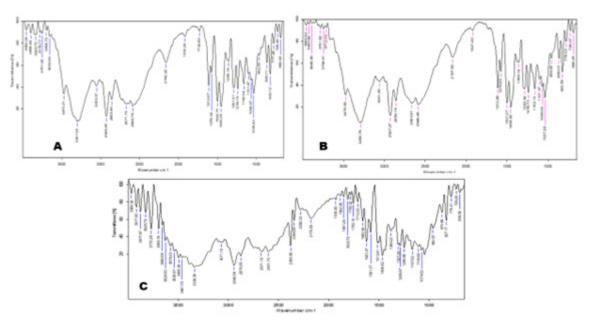| Ingredients	Composition (%/tab)	Response	Predicted value	Experimental value	Standard error
CBP934	20	Y1(FLT) (sec)	11	12	0.38%
HPMC K15M	10	Y2(% DR) (h)	93	93.3	0.17%

Figure 1: FT-IR spectra of A) DXMH B) DXMH with Carbopol C) DXMH with HPMC K15M.
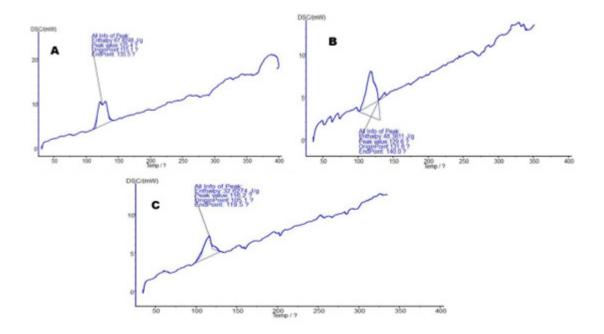
Figure 2: DSC thermograms A) DXMH B) DXMH with Carbopol C) DXMH with HPMC K15M.
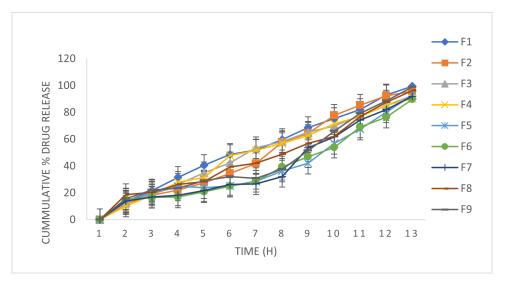
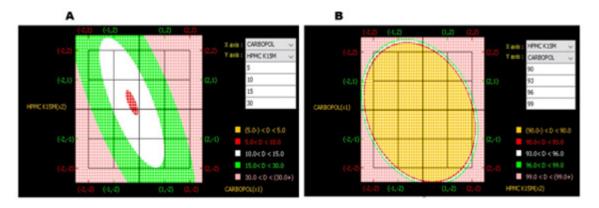**Figure 3:** *In vitro* DR outline of F1 – F9.

Figure 4: Contour plots A) Floating lag time B) Drug release.

induces release of carbon dioxide and aids in floating for a long time. Incorporation of CBP in the formulation reduces floating lag time because it has a higher hydration rate than HPMC, resulting in early carbon dioxide entrapment and a reduced floating lag time.[24]

In vitro **DR (Y_2)**

In terms of encrypted components, the ultimate equation:

$$DR\ Y_2 = 24.4678 + 2.8417X_1 + 4.1317X_2 + 6.0X_1X_2 + 12.2854X_1^2 + 13.9779X_2^2$$

Ultimate equation in respect of factual elements:

$$Y_2 = 24.4678 + 2.8417CBP + 4.1317HPMC + 6.0CBPHPMC + 12.2854^2 + CBP13.9779HPMC^2$$

In vitro **DR**

Table 9 shows that the collaboration of X_1 and X_2 was the utmost substantial, with an SS ratio of 80.1739% and a positive growth of the co-efficient (0.25). MLR analysis naked that lowering the amount of X_1 (Carbopol) and X_2 (HPMC) leads to an increase in percentage drug release. This quadratic model's R^2 value was determined to be 0.8618, indicating that it is a reliable model for establishing predictions and contour plot/design space. The outcomes were represented in Table 10. The system with (HPMC K15M) and CBP 934 leads to controlled release drug delivery due to their hydrophilicity and speedy hydration.[25] All formulations had drug release values in the range 89.7% to 99.4%. Formulations F1 to F9 shows 99.4%, 95.8%, 92.6%, 90.0%, 92.93%, 89.7%, 91.75%, 96.1%, 98.89%. as depicted in Figure 3.

Using contour plots, a suitable design space for FLT and DR amid the implied values was determined, as shown in Figure 4. The research produced a design space from a multidimensional

combination of FLT and DR, which resulted in tolerable operational series for articulating floating tablets. The expected values were used to construct and test the response to the formulation. Contour plots enabled the creation of a wide range of designs. CBP was set to 20% (0) and HPMCK15M was set to 10% (-2) for an ideal formulation, with all other ingredients remaining constant. The RE for respective outcome was calculated by means of the expected and experimental values, and the findings were determined to be 0.38%, 0.17%, as shown in Table 11. The investigated data were consistent with the expected values, showing the models expectedness and quality.

CONCLUSION

DXMH floating tablets were successfully fabricated utilizing the direct compression process, with Carbopol 934 and HPMC K15M serving as independent variables. The concentration of variables has a dramatic and interactive influence on FLT and DR, as per the model created through central composite design. Experimental design was effectively employed to optimize polymer concentrations, according to the outcomes. Finally, it was determined that the central composite design would be availed to formulate DXMH GRFT with fewer trials and higher quality features.

ACKNOWLEDGEMENT

The authors are grateful for RIPER (Autonomous).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DOE: Design of Experiments; **CCD:** Central Composite Design; **FDDS:** Floating drug delivery systems; **CBP:** Carbopol; **HPMC:** Hydroxypropyl Methylcellulose; **FT-IR:** Fourier-transform infrared spectroscopy; **DSC:** Differential scanning calorimetry; **IP:** Indian Pharmacopoeia; **UV:** Ultraviolet; **HCl:** Hydrochloric acid; **RPM:** Revolutions per minute; **ANOVA:** Analysis of variance; **SS:** Sum of squares. **F value:** Fisher's value; **NMDA:** N-methyl-D-aspartate.

SUMMARY

- The study describes the DXMH floating tablets with polymers like Carbopol 934, and HPMC K15M and sodium bicarbonate as a gas generator.

- Carbopol 934, and HPMC K15M were chosen as independent factors, with FLT and percentage drug release as reliant variables.

- DXMH floating tablets were developed.

- The quantitative impact of independent variables at diverse levels on response variables forecast by a polynomial equation.

- The rapport amongst independent variables and dependent variables was further explicated via contour plots.

REFERENCES

1. Prinderre P, Sauzet C, Fuxen C. Advances in gastro retentive drug-delivery systems. Expert Opin Drug Deliv. 2011;8(9):1189-203. doi: 10.1517/17425247.2011.592828, PMID 21671821.

2. Silva AR, Dinis-Oliveira RJ. Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspects. Drug Metab Rev. 2020;52(2):258-82. doi: 10.1080/03602532.2020.1758712, PMID 32393072.

3. Taylor CP, Traynelis SF, Siffert J, Pope LE, Matsumoto RR. Pharmacology of dextromethorphan: relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. Pharmacol Ther. 2016;164:170-82. doi: 10.1016/j.pharmthera.2016.04.010, PMID 27139517.

4. Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int J Pharm. 2016;510(1):144-58. doi: 10.1016/j.ijpharm.2016.05.016, PMID 27173823.

5. Chinthaginjala H, Telkar MB, Hindustan AA, Bhupalam P. Formulation development and optimization of famotidine mucoadhesive tablets by central composite design. Ind J Pharm Educ Res. 2022;56(4):1044-51. doi: 10.5530/ijper.56.4.185.

6. Salatin S, Jelvehgari M. Expert Design and Optimization of Ethyl Cellulose-poly (ε-caprolactone) Blend Microparticles for Gastro-Retentive Floating Delivery of metformin hydrochloride. Curr Drug Deliv. 2021;18(8):1125-35. doi: 10.2174/1567201818666210204164145, PMID 33563167.

7. Pathak S, Pandey H, Shah SK. Formulation and evaluation of floating matrix tablets of sacubitril and valsartan. J Drug Deliv Ther. 2019;9(4-s):298-309. doi: 10.22270/jddt.v9i4-s.3322.

8. Raza A, Hayat U, Wang HJ, Wang JY. Preparation and evaluation of captopril loaded gastro-retentive zein based porous floating tablets. Int J Pharm. 2020;579:119185. doi: 10.1016/j.ijpharm.2020.119185, PMID 32112929.

9. Alhamdany AT, Abbas AK. Formulation and *in vitro* evaluation of amlodipine gastroretentive floating tablets using a combination of hydrophilic and hydrophobic polymers. Int J Appl Pharm. 2018;10(6):126-34.

10. Dolas RT, Sharma S, Sharma M. Formulation and evaluation of gastroretentive floating tablets of lafutidine. J Drug Deliv Ther. 2018;8(5):393-9. doi: 10.22270/jddt.v8i5.1898.

11. Chinthaginjala H, Ahad HA, Pradeepkumar B, Gandhi KS, Kalpana K, Pushpalatha G, et al. Formulation and *in vitro* evaluation of Gastroretentive ofloxacin floating tablets using natural polymers. Res J Pharm Technol. 2021;14(2):851-6. doi: 10.5958/0974-360X.2021.00151.7.

12. Rashmitha V, Madhusudan Rao Y, Pavani S. Formulation and evaluation of fenoverine floating tablets. Asian J Pharm Clin Res. 2021;14(4):175-80.

13. Sahoo BK, Pattajoshi SP, Pattajoshi S. Formulation and evaluation of Bimolar release of ciprofloxacin HCl from bilayer gastro-retentive floating system. Asian Jour Pharmac Rese. 2018;8(2):61-70. doi: 10.5958/2231-5691.2018.00011.4.

14. Rahamathulla M, Saisivam S, Gangadharappa HV. Development of valsartan floating matrix tablets using low density polypropylene foam powder: *in vitro* and *in vivo* evaluation. AAPS PharmSciTech. 2019;20(1):35. doi: 10.1208/s12249-018-1265-z, PMID 30604045.

15. Thulluru A, Basha SS, Rao CB, Kumar CSP, Mahammed N, Kumar KS. Optimization of HPMC K100M and sodium alginate ratio in metronidazole Floating Tablets for the Effective Eradication of Helicobacter pylori. Asian J Pharm Technol. 2019;9(3):195-203. doi: 10.5958/2231-5713.2019.00033.3.

16. Mali AD, Bathe RS. Development and evaluation of gastroretentive floating tablets of a quinapril HCl by direct compression technique. Int J Pharm Pharm Sci. 2017;9(8):35-46. doi: 10.22159/ijpps.2017v9i8.12463.

17. Devi CM, Nath L, Laldinchana LL, Goswami A, Barakoti H. Formulation and evaluation of gastroretentive floating tablets of diclofenac sodium based on effervescent technology. Int J Pharm Biol Sci. 2019;9:249-55.

18. Elmosallamy MA, Amin AS. New potentiometric and spectrophotometric methods for the determination of dextromethorphan in pharmaceutical preparations. Anal Sci. 2014;30(3):419-25. doi: 10.2116/analsci.30.419, PMID 24614739.

19. Haranath C, Reddy JR, Devanna N. Formulation and evaluation of noneffervescent floating tablets of cimetidine employing ozokerite wax. Int J Res Pharm Chem. 2017;7(2):171-80.

20. Kousar S, Abdul Ahad HA, Chinthaginjala H, Babafakruddin P, Lakunde J, Tarun K. Gas generating floating tablets: A quick literature review for the scholars. Asian J Res Chem. 2022;15(2):171-5. doi: 10.52711/0974-4150.2022.00029.

21. Kim S, Hwang KM, Park YS, Nguyen TT, Park ES. Preparation and evaluation of non-effervescent gastroretentive tablets containing pregabalin for once-daily administration and dose proportional pharmacokinetics. Int J Pharm. 2018;550(1-2):160-9. doi: 10.1016/j.ijpharm.2018.08.038, PMID 30138708.

22. Meruva S, Rezaei L, Thool P, Donovan MD. Use of drug release testing to evaluate the retention of abuse-deterrent properties of polyethylene oxide matrix tablets. AAPS PharmSciTech. 2020;21(7):270. doi: 10.1208/s12249-020-01804-y, PMID 33025237.

23. Gangane PS, Pachpute T, Mahapatra DK, Mahajan NM. HPMC polymers and xanthan gum assisted development and characterization of stavudine extended-release floating tablets. Indian J Pharm Educ Res. 2021;55:S681-92.

24. Raza A, Bukhari NI, Karim S, Hafiz MA, Hayat U. Floating tablets of minocycline hydrochloride: formulation, *in vitro* evaluation and optimization. Future J Pharm Sci. 2017;3(2):131-9. doi: 10.1016/j.fjps.2017.05.001.

25. Butreddy A, Nyavanandi D, Narala S, Austin F, Bandari S. Application of hot melt extrusion technology in the development of abuse-deterrent formulations: an overview. Curr Drug Deliv. 2021;18(1):4-18. doi: 10.2174/1567201817999200817151601, PMID 32811398.