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Original Article

STATISTICAL DESIGN OF EXPERIMENT-BASED FORMULATION DEVELOPMENT AND OPTIMIZATION OF FLOATING MATRIX TABLET OF ANTI-EMETIC DRUG

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ABSTRACT

Objective: To employ Design of Experiment (DOE) for designing a floating matrix tablet of Domperidone Maleate (DM) using novel direct compression grade polymer METHOCEL K4M DC2 that offers advantages of extended or sustained release, providing for cost-effective manufacturing.

Methods: To prepare floating matrix tablets containing DM, the direct compression method was employed. The tablets were optimised using a 2^2 Central Composite Design (CCD). Concentration of the sustained release polymer METHOCEL DC2 K4M grade (X1= A) and Concentration of the floating agent potassium bicarbonate ($KHCO_3$) (X2= B) were the independent variables selected whereas floating lag time (Y1), drug release at 1 h (Y2), 4 h (Y3), 6 h (Y4) and 8 h (Y5) were the 5 dependent variables employed in the study design. Fourier Transform Infrared (FTIR) analysis was utilised to analyse drug-excipient compatibility, revealing no discernible interaction, and various mathematical models were employed to study the drug release mechanism.

Results: The prepared tablets were evaluated for weight, thickness, hardness, friability, and assay and the results were found to be satisfactory. The optimised formulation predicted by the software was found to have a desirability value of 0.982, containing 60 mg of METHOCEL DC2 K4M and 20 mg of $KHCO_3$, was prepared and evaluated. Predicted and experimental results were found to be comparable for all the responses. All formulations were shown to fit well into Zero-order release kinetics, but the optimised formulation (F4), with R^2= 0.9893 and n= 2.2797, exhibited the best fitting in both the Zero-order and Korsmeyers-Peppas model.

Conclusion: The study conducted revealed that floating tablets of DM could be developed using $KHCO_3$ as a gas-generating agent with sustained drug release till 14 h using polymer METHOCEL DC2 K4M.

Keywords: Floating drug delivery system (FDDS), Domperidone maleate (DM), Design of experiments (DOE), Central composite design (CCD), Sustained release

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INTRODUCTION

Oral drug delivery is favoured for its ease and patient compliance. Prolonging the time that drugs stay in the Gastrointestinal Tract (GIT) until they are released at the desired rate is a key challenge for oral controlled-release drug delivery systems. Various techniques address this, such as high-density formulations, swelling agents, mucoadhesive polymers, ion exchange mechanisms, raft formation, magnetic systems, and Floating Drug Delivery Systems (FDDS) [1]. Floating systems are identified as low-density systems that float over gastric contents, remaining buoyant in the stomach for an extended period without interfering with gastric emptying. This enhances drug retention at the absorption site, particularly in the stomach region. They're categorized based on formulation variables: effervescent (gas generating and osmotically controlled) and non-effervescent (hollow microspheres, alginate beads, microporous compartment systems, colloidal gel barrier systems, etc.) [2]. A straightforward and useful method for achieving more sustained drug release and a longer stomach residence time for the dosage form is the concept of buoyant preparation. In some situations, it is preferable to extend the stomach retention of a delivery system to maximise the therapeutic efficacy of the medication ingredient. Drugs that exhibit superior absorption in the proximal portion of the gastrointestinal system and those that are poorly soluble and break down at an alkaline pH, for instance, have been proven to be effective in extending gastric retention. Prolonging the gastric retention of the therapeutic moiety also helps to deliver drugs to the stomach and proximal small intestine for sustained treatment of certain ulcerative conditions. These benefits include enhanced bioavailability and therapeutic efficacy with fewer dosing intervals [3, 4].

DM is a synthetic benzimidazole molecule that functions as a dopamine D2 receptor antagonist to treat upper gastrointestinal motility problems prokinetically [5]. It is proposed that the main pharmacological mechanism of DM is the specific inhibition of peripheral dopaminergic D2 receptors. Increased acetylcholine release and decreased cholinesterase activity are two more hypothesised mechanisms [6]. As DM is a weak base with high solubility in acidic media, it is rapidly and effectively absorbed following oral administration via active transport from the stomach and upper GIT. It is, therefore, the most suitable option for developing a FDDS that is gastro-retentive. The drug's short (7 h) biological half-life encourages the development of FDDS tailored to the stomach. Since DM is administered in modest quantities of 10 mg 3-4 times a day, poor patient compliance results in repeated doses being needed. This can be avoided by creating a single-unit FDDS that delivers 30 mg of medication continuously for 12 h. By preventing variations in drug release this will maintain a steady state of plasma drug concentration [5].

The goal of the study was to create once-daily dosing of a controlled-release gastro-retentive floating formulation of DM with desirable characteristics such as extended or sustained release, maximal solubility in acidic environments, and fewer dose intervals using a 2^2CCD with the response and variable relation for formulation and statistical optimization.

MATERIALS AND METHODS

A gift sample of DM was obtained from Geno Pharmaceutical limited, Karaswada, Goa, India. The supplier of METHOCEL DC2 K4M grade was Colorcon Mumbai, India. Potassium bicarbonate was acquired from Molychem Mumbai, India. Dicalcium phosphate was obtained from Ozone International, Mumbai, India. Talc, magnesium stearate, sodium lauryl sulphate, and pre-gelatinized starch were procured from SD Fine-Chemicals limited. Mumbai, India. Solvents and all the other materials used were of analytical grade.

Initial trials

An initial screening investigation was conducted using a variety of effervescent agents and natural release-sustaining polymers; however, no beneficial conclusions emerged. METHOCEL DC2 K4M, a synthetic polymer, was utilised alongside $KHCO_3$ as an effervescent agent to achieve the intended drug release and appropriate floating capability. Dicalcium phosphate was used as a diluent and pre-gelatinized starch as a binder. Talc and magnesium stearate were utilised as glidant and lubricant respectively.

Methods

Development and optimization of floating tablets of DM using CCD

DM floating tablets were produced by the direct compression method [7, 8]. In addition to the pure drug, METHOCEL DC2 K4M, potassium bicarbonate, dicalcium phosphate, sodium lauryl sulphate, pre-gelatinized starch, magnesium stearate, and talc were also used as excipients. The powder mixture was passed through a sieve with a mesh size of 60 after the pure drug and other excipients were well combined. Using a Karnavati Rimek Mini Press II tablet compression machine, the resulting powder blend was compressed into biconvex tablets, each weighing 160 mg.

DOE was further employed to optimise floating tablets of DM using a 2^2CCD. The concentration of the sustained release polymer METHOCEL DC2 K4M grade (X1= A) and concentration of the floating agent $KHCO_3$ (X2= B) were the independent variables, wherein floating lag time (Y1), drug release at 1 h (Y2), drug release at 4 h (Y3), drug release at 6 h (Y4) and drug release at 8 h (Y5) were the 5 dependent variables employed in the study design. The table below (table 1) shows the Independent and Dependent variables selected for the CCD, whereas table 2 represents the formulation design of the floating tablets.

Table 1: Independent and dependent variables selected for CCD

Code	Coded values		Actual values		Dependent variables				
	X1	X2	X1	X2	Y1	Y2	Y3	Y4	Y5
F1	-1	-1	30	10	102	9.372	32.743	45.322	58.821
F2	+1	-1	60	10	53.83	7.105	25.072	37.181	48.477
F3	-1	+1	30	20	25.93	8.551	30.719	39.892	55.173
F4	+1	+1	60	20	19.51	6.521	23.127	33.883	45.004
F5	-α	0	23.79	15	55.41	8.647	30.942	42.111	54.775
F6	+α	0	66.21	15	18.35	7.150	24.815	37.266	46.682
F7	0	-α	45	7.93	90.67	6.666	25.307	38.596	53.772
F8	0	+α	45	22.07	22.82	7.343	25.360	35.568	46.956
F9	0	0	45	15	86.33	6.473	28.132	39.049	55.397

X1: Concentration of METHOCEL DC2 K4M (mg), X2: Concentration of KHCO3 (mg), Y1: Floating lag time (s), Y2: Drug release at end of 1 h, Y3: Drug release at end of 4 h, Y4: Drug release at end of 6 h, Y5: Drug release at end of 8 h.

Table 2: Formulation design for floating tablets from F1-F9

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
DM	30	30	30	30	30	30	30	30	30
METHOCEL DC2 K4M	30	60	30	60	23.79	66.21	45	45	45
$KHCO_3$	10	10	20	20	15	15	7.93	22.07	15
Pre-gelatinized Starch	40	40	30	30	35	35	40	40	40
Di calcium Phosphate	40	10	40	10	46.21	3.79	27.07	12.93	20
Sodium lauryl Sulphate	7	7	7	7	7	7	7	7	7
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Total Weight (mg)	160	160	160	160	160	160	160	160	160

Characterization of pre-compression parameters of tablets

Angle of Repose, Carr's index, and Hausner's ratio were used to measure the flow characteristics of pre-compressed powder of DM floating tablets [7].

Characterization of post-compression parameters of tablets

Thickness and diameter

Using a Vernier calliper, the tablets' diameter and thickness were measured. 10 tablets were chosen at random from each batch in order to measure the diameter and thickness. Both the thickness and diameter averages, as well as the standard deviation, were computed and noted [4].

Hardness test

A tablet's hardness indicates how well it can tolerate mechanical shocks during handling. To find out how hard the tablets were, the Monsanto hardness tester was used [4, 7].

Weight variation test

To observe for variations in weight, each batch of 20 tablets was weighed, and the average weight was determined. Next, the weight of each tablet was compared with the tablet's average weight [4, 7].

Friability test

Tablet friability was assessed using the Roche Friability Tester. Twenty tablets were first added to the friability testing device and weighed (W). The device was programmed to operate at 25 rpm for 4 min, or until 100 revolutions have been made. The tablets were weighed again (Wo). The following formula was then used to get the friability as a percentage [7].

$$\% \text{ Friability} = (W - W_0/W) \times 100$$

Swelling index study

Three tablets of each batch were weighed and placed in a petri dish with 0.1N HCl buffer. Every hour, the tablet was removed, cleaned with tissue paper, and then weighed once again. After eight hours of this procedure, the swelling index was calculated using the below formula [4, 7].

$$SI = (\text{Wet weight of tablet} - \text{Dry weight of tablet}/\text{ Wet weight of tablet}) \times 100$$

Buoyancy/Floating lag Time (FLT)

The time a tablet needs to float or reach the liquid's surface is known as its floating lag. A tablet was put into a beaker containing 100 ml of 0.1N HCl buffer in order to measure the FLT. The tablet was left to float, and the amount of time it took to do so was noted [4, 8].

Total Floating Time (TFT)

A tablet was dropped and left to float in a beaker filled with 100 ml of 0.1N HCl buffer. The duration for which the tablet stayed suspended above the liquid layer was recorded [4, 7].

Assay

Each batch of 10 tablets was weighed and then crushed using a mortar and pestle. From the crushed powder blend, an amount equivalent to 30 mg of the drug was measured and transferred to a 100 ml volumetric flask. 100 ml of 0.1N HCl buffer was used to extract the powder. The solution was then filtered and appropriately diluted. Absorbance was then measured using a UV spectrophotometer (UV1800 Shimadzu) set to wavelength 283.9 nm for analysis [4, 7].

***In vitro* dissolution test**

The USP dissolution testing apparatus II (paddle type) was used to measure the amount of drug released from floating tablets. 900 ml of 0.1N HCl, kept at 37 °C±2 °C, served as the dissolution test medium. Every hour, a sample (5 ml) of the solution was taken from the dissolution apparatus and replaced with a fresh dissolution medium. Using a UV spectrophotometer set to 283.9 nm, the absorbance of these solutions was measured after the samples were passed through Whatman's filter paper [4, 7, 8].

Table 3: Interpretation of release mechanism

Release exponent (n)	Mechanism of drug transport
0.5	Fickian diffusion
0.45<n<0.89	Non – Fickian transport
0.89	Case II transport
n>0.89	Super case II transport

Release kinetics study

Model equations and release graphs were used to analyse each formulation for various kinetic models, including Zero-order, First order, Higuchi matrix model, Hixson Crowell Cube root, and Korsmeyer-Peppas model. The results were then utilised to identify the kind of diffusion process and release kinetics [5].

Compatibility testing

Drug: Excipient Compatibility was tested by using the FTIR spectrum obtained from Shimadzu FTIR equipment. The spectrum for different Drug: Excipient was determined by scanning in the range of 400–4000 cm^{-1} [7, 8].

Statistical analysis and optimization using DOE

DOE is a skilful experiment conducted in randomized order. The number of experiments required depends upon the selected design, which limits the number of trials. In order to optimize the formulations a 2-factor, 2-level CCD was used to explore and optimize the main effects, interaction effects, and quadratic effects of the formulation ingredients on the performance of the floating tablets. A 2-factor, 2-level CCD requires nine experimental runs to determine the experimental error and the precision of the design. The significant effect of independent factors on the response coefficient of dependent factors was studied by Analysis of Variance (ANOVA). Additionally, 3-dimensional Response surface plots were used to represent the relationship between independent and dependent factors [9].

Stability testing

The stability study of the formulation was carried out at room temperature for one month. After one month, the formulations were examined for drug content, floating behavior, and *in vitro* drug release [10].

RESULTS

Characterization of pre-compression parameters of tablets

The pre-compression properties of the powder, such as flow characteristics, were ascertained through the computation of Angle of repose, Carr's index, and Hausner's ratio. All formulations were found to have an Angle of repose of less than 40, indicating excellent particle flow properties. For every formulation, Carr's index was less than 15, suggesting good compressibility. The range of Hausner's ratio was 1.08-1.51. Table 4 reports all the data that has been mentioned.

Table 4: Results of pre-compression parameters

Formulations	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Angle of repose (θ)*	Carr's index*	Hausner's ratio*
F1	0.667 ± 0.005	0.769 ± 0.002	29.34± 0.11°	13.00± 1.289	1.15 ± 0.019
F2	0.689 ± 0.012	0.800 ± 0.014	27.38±0.01°	13.88 ± 0.167	1.16 ± 0.002
F3	0.714 ± 0.005	0.833 ± 0.007	26.50 ±0.012°	14.29 ± 0.285	1.16 ± 0.003
F4	0.689 ± 0.001	0.769± 0.003	25.17 ±0.04°	10.40 ±0.855	1.11 ± 0.010
F5	0.667 ± 0.001	0.769± 0.002	29.24 ± 0.012°	13.26 ± 0.307	1.15 ± 0.003
F6	0.769 ± 0.001	0.833± 0.001	24.70 ± 0.015°	7.68± 0.138	1.08 ± 0.002
F7	0.695 ± 0.002	0.801± 0.004	25.64 ± 0.025°	13.13 ± 0.548	1.51 ± 0.006
F8	0.716 ± 0.003	0.8 ± 0.002	26.57 ± 0.015°	10.75 ±0.281	1.12 ± 0.003
F9	0.681 ± 0.003	0.778 ± 0.005	28.28 ± 0.010°	13.54 ±0.158	1.20 ± 0.008

*n=3, data presented as mean±SD

Table 5: Results of post-compression parameters

Formulation	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm^2)*	Weight variation (mg)**	Friability (%)**	Swelling index (%)
F1	3.108 ± 0.115	9.716± 0.093	3.4± 0.547	160.1±1.252	0.625	68.62
F2	3.808 ±0.152	9.808±0.122	3.6±0.547	159.6± 1.500	0.689	76.81
F3	3.902 ±0.030	9.844±0.026	3.6±0.547	159.9±1.020	0.625	73.72
F4	3.788±0.374	9.828±0.023	4.2±0.447	160±1.213	0.584	76.11
F5	3.072 ±0.046	9.828±0.023	4.2±0.447	159.8± 1.105	0.617	74.27
F6	3.172 ±0.054	9.85±0.017	3.6±0.547	159.85±0.988	0.606	73.77
F7	3.912 ±0.041	9.764±0.022	3.6±0.547	159.85± 0.988	0.536	71.42
F8	3.868±0.039	9.84±0.024	3.6±0.547	160±0.648	0.709	72.88
F9	3.1 ±0.032	9.832 ±0.036	3.4 ±0.547	159.9±0.7181	0.671	70.90

*n= 10, data presented as mean ±SD.**n= 20, data presented as mean ±SD. Rest values are given as the mean of triplicate. The test results, the FLT ranged from 18.35 to 102 seconds. For formulation F6, the maximum TFT was 24 h. As the assay (%) was obtained between 95% and 105%, all formulations passed the test as recorded in table 6.

Characterization of post-compression parameters of tablets

The results of the various post-compression parameters that were applied to all of the formulations are stated in table 5. Indian Pharmacopoeia (IP) states that the weight variation limit for a 160 mg tablet is ±7.5%. The weight variation test was observed to be passed by every tablet formulation because every tablet fell within the permissible range (148-172 mg). All formulations pass the friability test since their percentages of friability lie between 0.536 and 0.709%, which is less than 1%. The range of the swelling index is 68.622-76.11%. Formulation F4 had the highest percentage of swelling index, whereas Formulation F1 had the lowest percentage.

Table 6: Results of FLT, TFT and assay

Formulations	FLT (s)*	TFT (h)*	Assay (%)*
F1	102±2	14	98.29±0.23
F2	53.83± 1.16	20	98.87±0.62
F3	25.93±1.74	12	97.09±0.72
F4	19.51±0.81	21	98.44±0.13
F5	55.41±1.78	15	97.63±0.27
F6	18.35±0.67	24	99.42±0.35
F7	90.67±2.51	17	99.06±0.36
F8	22.82±0.30	15	98.81±0.56
F9	86.33±3.78	19	98.90±0.60

*n= 3, data presented as mean±SD

***In vitro* dissolution test**

According to the results listed in table 7 and as depicted in fig. 1, the formulations F1, F7, and F8 demonstrated the highest drug release (up to 90%) after 12 h. The medication release from formulations F2 and F4 was at its best for 13 h. It was observed that formulation F6 showed maximum drug release until 14 h, while formulations F3, F5, and F9 released more than 85% of the drug by 11 h.

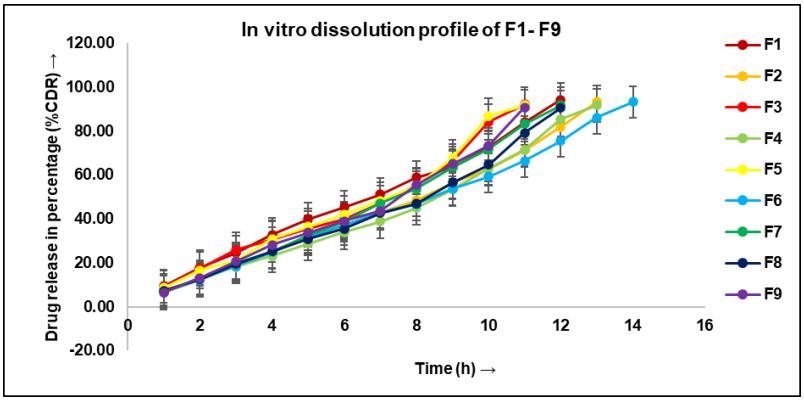

Fig. 1: Comparative *in vitro* drug release profile of DM floating tablets. Error bars indicated standard deviations of sample size of 3 determinations

Release kinetics study

All of the formulations fitted best into Zero-order release kinetics, according to table 7, based on their R^2 values. The optimised formulation, F4, demonstrated the best fitting in the Zero-order and Korsmeyer-Peppas model, with a Super case II transport mechanism depicted by R^2 = 0.9893 and n = 2.2797, both of which are>0.89.

Table 7: Correlation coefficients (R^2) values of different kinetic models

Formulation	Zero-order R^2	First order R^2	Higuchi model R^2	Korsmeyer–Peppas model	
				R^2	n
F1	0.9936	0.7136	0.9195	0.9968	2.1978
F2	0.9893	0.7705	0.8875	0.9946	2.3010
F3	0.9709	0.7411	0.866	0.9853	1.9557
F4	0.9789	0.7906	0.8614	0.9893	2.2797
F5	0.9749	0.7607	0.8642	0.9873	1.9671
F6	0.9925	0.7609	0.9011	0.9962	2.5071
F7	0.9918	0.7919	0.881	0.9959	2.1420
F8	0.976	0.7804	0.8605	0.9879	2.0707
F9	0.979	0.7898	0.8637	0.9894	1.9032

Compatibility testing

FTIR was used for obtaining the Infra-Red (IR) spectra of both pure drug DM and its mixture with excipients. The distinctive peak (table 8) that corresponded to a certain functional group found in the drug was identified (fig. 3). It was determined that there is no drug-excipient interaction that could influence the effectiveness of floating tablets containing DM because there was neither a significant change in peaks nor the formation of an extra peak.

Table 8: Distinctive peaks of pure drug and when in combination with excipients

S. No.	Functional group	DM frequency (cm^{-1})	DM+excipients frequency (cm^{-1})
1	O-H (carboxylic) stretching	3026.31	3028.24
2	C=O stretching	1701.22	1695.43
3	C-N stretching	1348.24	1361.74

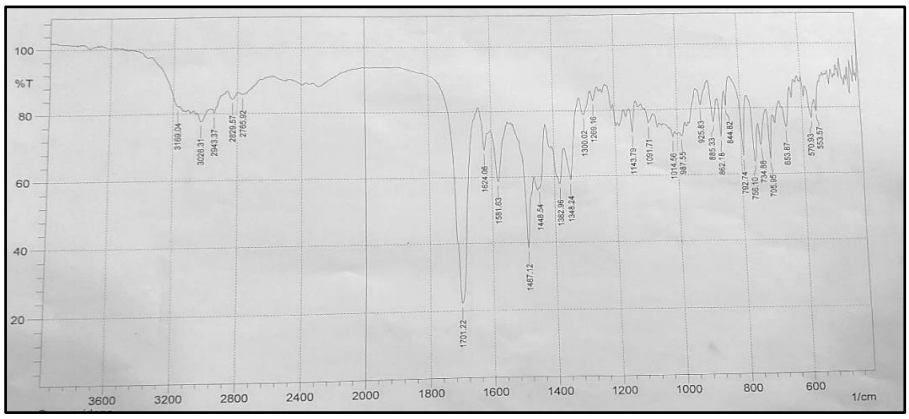

Fig. 2: IR spectrum of pure drug DM

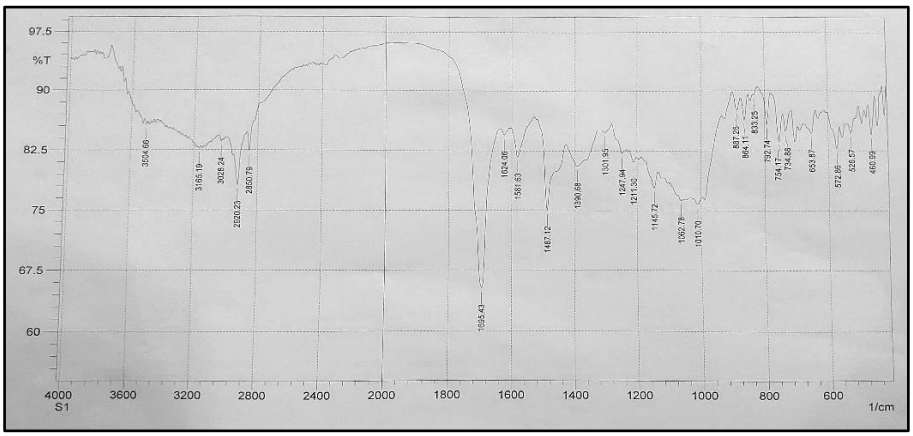

Fig. 3: IR spectrum of pure drug DM and excipients

Optimization of formulation by using DOE

Design expert software Stat Ease 360 trial version was used to optimise the formulation. Using software, the optimal model was identified to illustrate the association between the parameters that were chosen as independent and dependent variables. The model was considered significant when the p-value was less than 0.05 [11, 12].

Study of effect of independent variable on FLT

A quadratic model was found to be the best fit for the response Y1 in the 2^2CCD results. The model was significant as the p-value determined was less than 0.0001, which is<0.05. The value for predicted R^2 and adjusted R^2 value was 0.9655 and 0.9885, respectively and the difference between both was less than 0.2; hence it was found to be in reasonable agreement. The adequate precision measures signal to noise, was 34.0213, which was greater than 4, indicating adequate model discrimination.

Polynomial equation for Y1 response: FLT is given as

$$Y1 = +86.33 - 13.48A - 25.69B + 10.23AB - 23.80A^2 - 13.87B^2$$

The software-generated polynomial equation for the Y1 response indicates that A and B, ie: METHOCEL DC2 K4M and $KHCO_3$, are important variables that affect the FLT. It can be observed that while A and B alone have an antagonistic influence on floating lag time, their relationship has an agonistic effect as well. This can also be noticed from the response surface plot in fig. 4.

Study of effect of independent variable on drug release at 1 h

A quadratic model was determined to be the best fit for response Y2 i. e., drug release at 1 hour based on the findings of 2^2CCD. The model was significant as the p-value was less than 0.0003. The adjusted R^2 value was 0.9046 and the predicted R^2 value was 0.7051, respectively, and the difference between the two was less than 0.2, with adequate precision of 14.3148, which was higher than 4; hence there was sufficient model discrimination.

Polynomial equation for Y2 response: drug release at 1 h

$$Y2 = +6.40 - 1.00A - 0.0386B + 0.0245AB + 1.18A^2 + 0.3180B^2$$

The polynomial equation produced by the software for the Y2 response indicates that A and B, ie METHOCEL DC2 K4M and $KHCO_3$, are important variables influencing the release of the drug after 1 hour. It is seen that, at 1 hour, A and B both have antagonistic effects on drug release, but that, at the same time, there is a slight agonistic effect on drug release from their interaction (fig. 5).

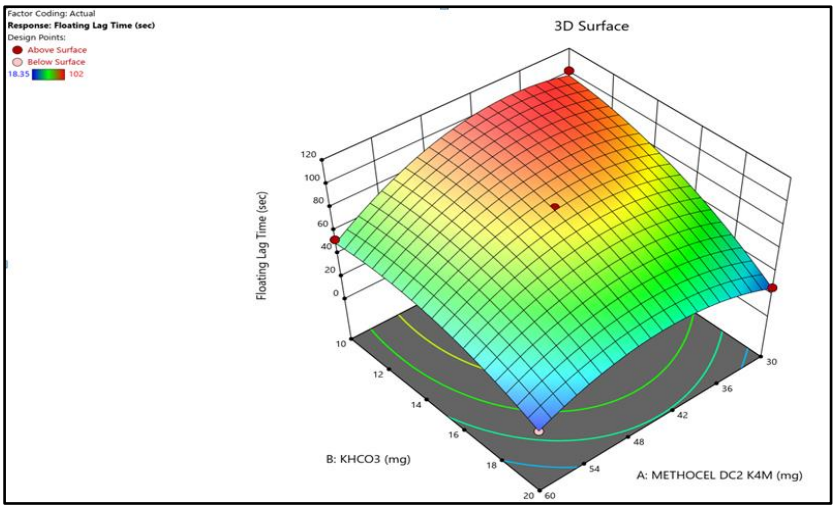

Fig. 4: Response surface plot of FLT

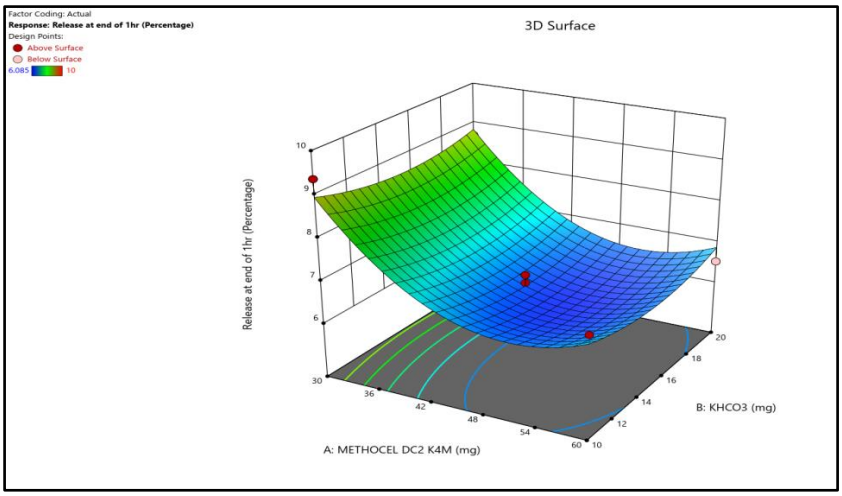

Fig. 5: Response surface plot of drug release at 1 h

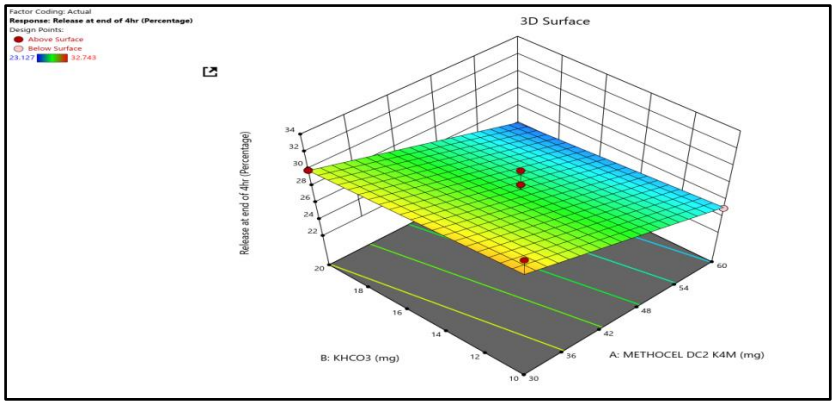

Fig. 6: Response surface plot of drug release at 4 h

Study of effect of an independent variable on drug release at 4 h

A linear model was suggested as the best fit for the response Y3 by the ANOVA results. The model's p-value was determined to be 0.0012. It was determined that the adjusted R^2 value predicted R^2 value the difference between the two was less than 0.2. A sufficient model discrimination was suggested by the adequate precision that measures signal to noise, of 10.868, which was greater than 4.

Polynomial equation for Y3 response: drug release at 4 h

$$Y3 = +27.58 - 2.82A - 0.6483B$$

The software-generated polynomial equation for the Y3 response indicates that A and B, ie METHOCEL DC2 K4M and $KHCO_3$, had a greater influence on drug release at 4 h. At four h, it is evident that A and B both have antagonistic effects on drug release. As A has a

higher coefficient value (2.82) than B, it was shown that A has a bigger effect on drug release at 4 h. This is also depicted in fig. 6 where an increase in concentration of the novel polymer resulted in sustained release of the drug. The concentration of floating agent did not show much effect on drug release.

Study of effect of independent variable on drug release at 6 h

The results of ANOVA analysis indicated that a linear model (drug release at 6 h) was the best fit for the response Y4. The model's p-value was determined to be less than 0.0005 with an adequate precision of 11.9240.

Polynomial equation for Y4 response: drug release at 6 h

$$Y4 = +38.87 - 2.76A - 1.50B$$

The software-generated polynomial equation for the Y4 response indicates that A and B, novel polymer METHOCEL DC2 K4M and floating agent $KHCO_3$, are important variables influencing drug release at 6 h. At the 6^{th} hour, it is evident that both A and B have an antagonistic impact on drug release. It can be seen from fig. 7 that polymer (A) has a bigger effect on drug release at 6 h and this is also depicted with a higher coefficient value of 2.76 in the equation than floating agent (B).

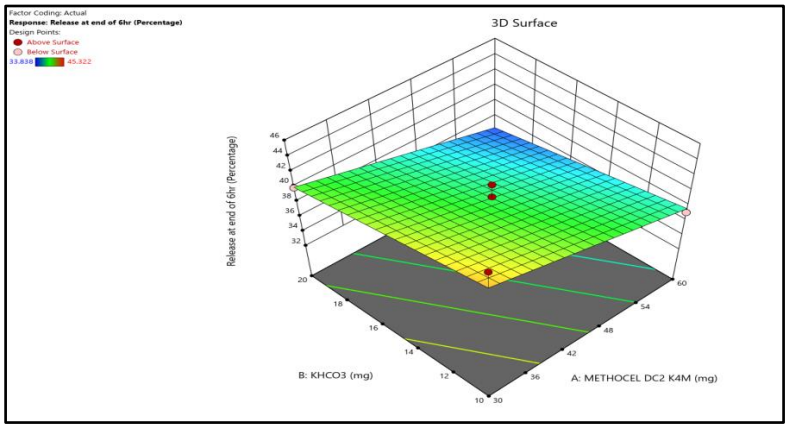

Fig. 7: Response surface plot of drug release at 6 h

Study of effect of an independent variable on drug release at 8 h

The ANOVA analysis depicted the quadratic model as the best fit for the response Y5 drug release at 8 h. The p-value was found to be less than 0.0002; hence the model was found to be significant. The value for predicted R^2 and adjusted R^2 value was 0.923 and 0.9137, respectively and the difference between both was less than 0.2 hence it was found to be in reasonable argument. The adequate precision measures signal to noise was 16.4521 which was greater than 4, indicating adequate model discrimination.

Polynomial equation for Y5 response: drug release at 8 h

$$Y5 = +55.60 - 0.8933A - 2.50B + 5.12AB - 2.90A^2 - 2.29B^2$$

The Polynomial equation generated by the software for Y5 response represents that A and B i. e. METHOCEL DC2 K4M and KHCO3 are significant factors that have an effect on drug release at 8 h. It is seen that A and B both have antagonistic effects on drug release at 8 h where an increase in the concentration of polymer decreases the release of the drug and an increase in the concentration of potassium bicarbonate decreases the drug release and this can also be seen through the response surface plot in fig. 8.

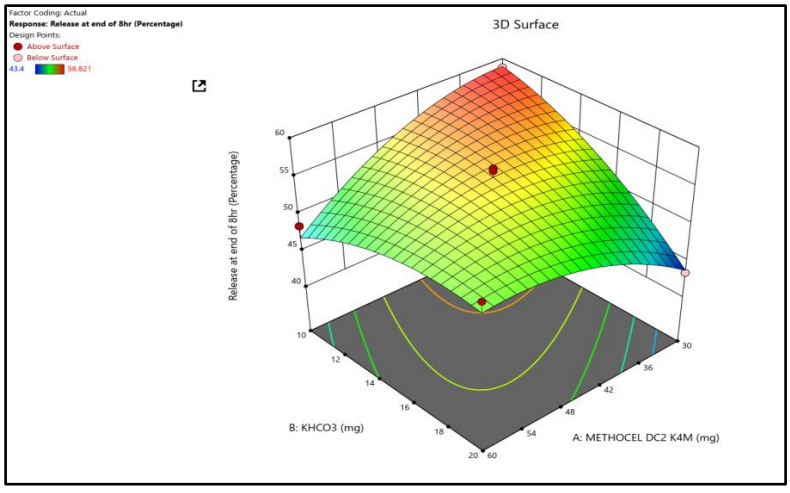

Fig. 8: Response surface plot of drug release at 8 h

Statistical optimization

The intended goals for optimisation, which included a minimum FLT and a targeted drug release at time points of 6 and 8 h, were determined using the design expert software Stat Ease 360 trial edition. Out of the 11 solutions the software offered, one of the solutions the software showed was formulation F4 having the highest desirability score of 0.982. Therefore, F4 was selected as an optimal formulation since it provided the intended drug release at 6 and 8 h with the least amount of FLT.

Stability testing

For 30 days, the optimal formulation F4 of DM floating tablets underwent a stability investigation at room temperature and ambient humidity for various parameters, as mentioned in table 9. There was not much difference in the hardness and assay of tablets after 1 mo, but the FLT increased by 0.09 s and the TFT reduced by 1h.

Table 9: Stability study results of optimised formulation (F4)

Duration	Hardness (kg/cm²)*	Assay (%)*	FLT (s)*	TFT (h)
1 month	4.2±0.44	98.24±0.80	19.60±0.67	20 h
Duration	Drug release at 1 h*	Drug release at 4 h*	Drug release at 6 h*	Drug release at 8 h*
1 month	6.81±1.02	24.0955±0.27	39.9955±1.33	44.6995±0.82

*n= 3, data presented as mean±SD

DISCUSSION

The present study aimed to develop floating matrix tablets of DM using METHOCEL K4M DC2 polymer for sustained release, employing DOE. CCD with 4 centre points was used with concentrations of METHOCEL DC2 K4M and potassium bicarbonate as independent variables, and floating lag time and drug release at various intervals as dependent variables. A key aspect of this research was the utilization of METHOCEL K4M DC2, a direct compression grade polymer, along with potassium bicarbonate as a floating agent in the direct compression method for floating matrix tablets, offering advantages in terms of cost-effectiveness and ease of manufacturing. Previous studies have investigated this drug using various polymers such as guar gum [13], xanthan gum [14], HPMC K4M, carbopol, and sodium alginate [15, 16], either alone or in combination mostly through wet granulation or solvent evaporation methods. These methods are laborious and time-consuming compared to direct compression. The use of METHOCEL K4M DC2 in this research ensures improved flow and tabletting performance, as well as reliable release performance, by simplifying manufacturing steps and reducing costs. The previous studies utilised sodium bicarbonate as a floating agent while the present study explores the use of potassium bicarbonate as a floating agent and its effect on floating lag time and drug release. Advanced release kinetic modelling, including Zero-order and Korsmeyers-Peppas models, was employed to characterize the release kinetics of the optimized formulation. The optimized formulation from this study offers a well-balanced release profile that meets the desired duration of action while minimizing the risk of drug overexposure or underexposure.

CONCLUSION

The goal of the current study was to use METHOCEL DC2 K4M grade polymer using a direct compression method to create and assess a gastro-retentive FDDS for DM. The novel polymer METHOCEL K4M DC2 grade was found to have good compression characteristics and at the same time was found to effectively sustain the release of the drug up to 14 h. The $KHCO_3$ was found to produce buoyant tablets with a minimum floating time of 14 h for formulation F1 and a maximum floating time of 24 h for formulation F6. The Design Expert software 360 trial version from State Ease was found to be a useful tool in predicting the influence of independent formulation variables on FLT, and drug release at various time intervals. Good formulation integrity was indicated by the results of post-compression testing, which included measurements for thickness, diameter, hardness, weight variation, friability, swelling index, FLT, TFT, and assay, all of which were achieved within acceptable limits. With the aid of Design Expert software, the optimised formulation (F4) which followed Zero-order as well as the Korsmeyers-Peppas model obtained with a desirability of 0.982 from the given 11 solutions. METHOCEL K4M DC grade was found to be a promising polymer that can be used to sustain the release of the drug to prepare a once-a-day formulation.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

All the authors declare no conflict of interest.

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