ORIGINAL ARTICLE

To Assess the Influence of Hydrophilic Polymers on the Performance of Effervescent Floating Tablets of Tinidazole using 3^2 Full Factorial Design

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Abstract

Aim: The current research was carried out to assess the influencing properties of hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) K4M and HPMC K15M on the performance parameters of effervescent floating tablets (EFT) of tinidazole such as floating lag time (FLT), total floating time (TFT), swelling index (SI) in HCl, and time taken to release 80% of the drug by applying 3^2full factorial design to improve the gastric residence time of the drug in the gastrointestinal tract. **Method:** The independent variables selected were the amount of HPMC K4M (X_1) and HPMC K15M (X_2) and the responses studied were FLT (Y_1), TFT (Y_2), Swelling Index (SI) in 0.1N HCl (Y_3), and time taken to release 80% of drug ($t_{80\%}$) (Y_4) by plotting response surface graphs and contour plots. **Results:** The FLT of prepared batches was in the range from 16 ± 0.02 to 45 ± 0.03 sec. and the minimum FLT was shown by OB-1 (16 sec.) batch. The TFT of all batches showed buoyancy and intactness for 12 h. The swelling in 0.1N HCl at 8 h ranged between 48.20 ± 0.02 and 54.33 ± 0.02. *In vitro*, drug release studies demonstrated that more than 95% of the drug was released in 12 h, whereas OB-2 took 10 h to release 80% of the drug. The response surface graphs and contour plots showed the effect of variables on responses such as FLT (Y_1) which was found to be positively influenced by X_2, and analysis of variance (ANOVA) for the response surface quadratic model for FLT was found to be significant ($P < 0.0004$). The TFT (Y_2) was found to be influenced by X_1 and ANOVA for the response surface quadratic model for TFT was found to be significant ($P < 0.0001$) whereas SI (Y_3) was found to be influenced by X_2 and ANOVA for response surface quadratic model for the SI was found to be significant ($P < 0.0001$) and time taken for 80% of drug release ($t_{80\%}$) (Y_4) was found to be influenced by X_2 and ANOVA for response surface quadratic model for the time taken to 80% drug release ($t_{80\%}$) was found to be significant ($P < 0.0006$). **Conclusion:** Both variables influenced the performance parameters, and HPMC K15M (X_2) was more predominant in the overall performance of EFT. From all the batches, the OB-2 batch possesses ideal performance parameters and hence can be further taken for conducting *in vivo* studies.

Key words: Analysis of variance, factorial design, floating lag time, response surface methodology, tinidazole, total floating time

INTRODUCTION

The effervescent floating tablets (EFT) having a density less than the gastric fluid can remain buoyant for a prolonged period of 3–4 h in the stomach without affecting the gastric emptying rate and can be used as an alternative dosage form to minimize some problems associated with conventional dosage forms.[1-8] The EFT also reduces fluctuations in drug concentration and can be used to increase the bioavailability of a drug.[9-11] Some common acids used to generate effervescence are citric, malic, tartaric, adipic, and fumaric acid, and bicarbonates used in the effervescent reaction are sodium and potassium bicarbonate.[12] Due to the generation of gas in EFT,

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the tablet's density is reduced and it floats in the stomach for an extended period, releasing the drug slowly and at the appropriate rate. Thus, it is feasible to enhance the gastric residence time (GRT) of the drug using EFT or a hydrodynamically balanced system. Hydrophilic or swellable polymers have great potential and are frequently utilized in floating systems for its characteristics that delay the release of drugs.[13] These include cationic, anionic, and non-ionic polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, and ethyl cellulose and are frequently used in sustained or delayed-release tablets because these polymers are unaffected by pH.[13] As a result, the pH of gastric fluid has minimal impact on drug release or EFT buoyancy. The non-toxicity, affordability, and safety of using non-ionic hydrophilic polymers as EFT are further qualities. However, parameters such as polymer quantity, viscosity grade, and molecular weight may influence drug release rate and tablet buoyancy, as well as other physicochemical properties such as tablet tensile strength, porosity, swelling and hydration rate, and gel strength.[14]

Tinidazole is widely used in the treatment of *Helicobacter pylori* eradication and protozoal infections which is administered in 3-day dosages of 2.0 g/d (60 mg/kg) and gets absorbed entirely and rapidly through small and large intestines.[15-17] The typical side effects of tinidazole at high dosages affect the gastrointestinal tract (GIT) and the nervous system, thus, formulating a controlled oral dose form of tinidazole with minimum gastrointestinal fluctuations, frequency of dosage, and prolonging of the residence time becomes highly desirable.[18,19]

Statistical experimental design involves studying the influence of independent factors on dependent variables using the minimum number of trials possible, which decreases the time necessary for development work.[20] Full factorial design with response surface methodology (RSM) has lately acquired favor as a precise and accurate statistical approach for designing and optimizing process variables.[21-23]

The present study aims to assess the influencing properties of hydrophilic polymers such as HPMC K4M and K15M on the performance of EFT of tinidazole which includes buoyancy in the form of floating lag time (FLT) in second total floating time (TFT) in hour, swelling behavior in 0.1N HCl and delay in drug release at a specific site of GIT to improve its GRT, by keeping the amount of gas generating agent constant. For this, a full 3^2 Factorial design was adopted, and results were interpreted by plotting response surface graphs and contour plots with the help of Design Expert Software (Design Expert version 11.0.3 State Inc, Minneapolis, MN).

MATERIALS AND METHODS

Materials

Tinidazole was provided as a complimentary sample by J.B. Chemicals and Pharmaceuticals Ltd, Ankleshwar, India. HPMC K4M and HPMC K15 M (50cps in a 2% w/v aqueous solution at 20°C) were supplied by Colorcon Asia Pvt. Ltd, Goa, India. The gas-generating agent sodium bicarbonate, ethyl cellulose, polyvinylpyrrolidone (PVP), isopropyl alcohol (IPA), lactose, magnesium stearate, and talc were procured from Loba Chemie Pvt. Ltd, Mumbai, India. All additional chemicals and solvents were of analytical grade and purchased from Merck, Mumbai, India.

Methods

Preparation of EFT of tinidazole

A wet granulation technique was used to prepare EFT of tinidazole of varying compositions shown in Table 1.[24,25] According to the formula, all the ingredients needed for preparing a batch of 100 tablets were used. Tinidazole (equivalent to 300 mg) was accurately weighed and mixed with different HPMC K4M and K15M ratios. The other ingredients such as ethyl cellulose, sodium bicarbonate, and lactose were added in geometric proportion. The 5% w/v PVP: IPA solution used as a binder is prepared, and added drop by drop to the powder mixture until a cohesive mass is formed. The mass of the powder mixture was passed through #12 mesh to obtain granules. A hot air oven was used to dry the granules at 60°C for 10 min, passed through # 20 mesh, and collected on #40 mesh to get uniform particle size. Dried granules were combined with talc and magnesium stearate, and the resulting mixture was then compressed into tablets using a 16-station rotating tablet compression machine (Cadmach, Ahmedabad, India).

Evaluation of EFT of tinidazole

In vitro buoyancy studies[26,27]

In vitro, buoyancy lag time was calculated for FLT and TFT. The tablets were added to 200 mL of 0.1N HCl in a 250 mL beaker. The time the tablet was continually floating on the surface of the medium was calculated as TFT (h), and the time it needed for the tablet to rise to the surface and float was calculated as FLT (sec). The study was done in triplicate ($n = 3$).

Swelling index (SI) in 0.1N HCl (pH 1.2)[28]

The SI was calculated after weighing the tablets (Wt), which were then put in a flask of the USP-II dissolution equipment (Electrolab-08TDT) with 900 mL of 0.1N HCl (pH 1.2). After using blotting paper to remove extra fluid, the weight of the tablet (W_0) was then estimated at various time intervals of 2, 4, 6, and 8 h. Each experiment was performed in triplicate. The SI is measured in terms of % weight gain as given by the equation below,

$$SI = \frac{(Wt - Wo)}{Wo} \times 100$$

Where W_t and W_0 stand for the tablet's final weight at time "t" and its initial weight, respectively.

Table 1: 3^2 full factorial design for the preparation of EFT of tinidazole

Ingredients (mg)	Batch code								
	OB-1	OB-2	OB-3	OB-4	OB-5	OB-6	OB-7	OB-8	OB-9
Tinidazole	300	300	300	300	300	300	300	300	300
HPMC K4M	95 (−1)	95 (−1)	95 (−1)	100 (0)	100 (0)	100 (0)	105 (+1)	105 (+1)	105 (+1)
HPMC K15M	60 (−1)	65 (0)	70 (+1)	60 (−1)	65 (0)	70 (+1)	60 (−1)	65 (0)	70 (+1)
Ethylcellulose	50	50	50	50	50	50	50	50	50
Sodium bicarbonate	90	90	90	90	90	90	90	90	90
Lactose	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
PVP: IPA	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%

Independent variable level: Low (-1), Medium (0), High (+1), HPMC: Hydroxypropyl methylcellulose, qs: Quantity sufficient, PVP: Polyvinylpyrrolidone, IPA: Isopropyl alcohol

In vitro drug release study

The USP type-II (rotating paddle) dissolution test apparatus (Electrolab 08TDT) with 900 mL of 0.1N HCl (pH 1.2) and revolved at a speed of 100 rpm at a temperature of 37 ± 0.5°C was used for the drug release study. As per the pharmacopeial method, 5 mL of the sample was withdrawn at pre-defined time intervals of 12 h. After making the required aliquots, the samples were examined for drug release estimate by measuring the samples' absorbance at 318 nm using a Shimadzu UV1800 UV-visible spectrophotometer. The samples were taken in triplicate (n = 3). The dissolution profiles of all formulations were subjected to kinetic modeling utilizing zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to ascertain the drug release mechanism.[29] PCP Disso V3 software (Poona College of Pharmacy, IICP, Pune, India) was used to and analyze the data.

Optimization of EFT of tinidazole by RSM

Experimental design[30]

The Design Expert Software (Design Expert version 11.0.3 State Inc., Minneapolis, MN) was used to optimize the EFT of tinidazole. To optimize the values of the independent variables HPMC K4M (X_1) and HPMC K15M (X_2), which were tested at three levels each, a full 3^2 factorial design was created and implemented in action. All other aspects of formulation and processing were constant throughout the trial. Table 1 shows the nine experimental runs that were looked at, their factor combinations, and how the coded levels were converted to the experimental units that were employed in the study. The dependent variables selected for the study were FLT (Y_1), TFT (Y_2), SI in 0.1N HCl (Y_3), and time taken for 80% of drug release ($t_{80\%}$) (Y_4).

Data analysis and validation of optimization model for EFT

Design Expert software was used to perform several RSM computations for the current optimization investigation (Design Expert version 11.0.3 State-Ease Inc., Minneapolis, MN). Multiple linear regression analysis (MLRA) was used to create polynomial models with interaction and quadratic factors for all response variables. The following equation is the generic version of the MLRA model.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2$$

In this equation, X_1 and X_2 are the coded levels of the independent variable (s), and β_0 is the intercept, which is the arithmetic average of all quantitative findings from 9 runs. Coefficients 1–7 are derived from observed experimental response values of Y. The interaction and quadratic terms are represented by the expressions X_1X_2 and Xi2 (i = 1–2). The Design Expert Software's analysis of variance (ANOVA) feature was used to examine the polynomials' statistical validity. The composition of the most effective formulations was then determined through feasibility and grid searches.[31] Using Design Expert software, three-dimensional (3D) response surface plots and two-dimensional (2-D) contour plots were created based on the model polynomial functions. These charts are quite useful for observing how variables affect responses. Furthermore, the 3-D response surface graphs and 2-D contour plots were made in MS Excel utilizing the output files from the Design Expert Software.

RESULTS AND DISCUSSION

The results for the evaluation of the EFT of tinidazole are shown in Table 2.

The EFT of tinidazole was prepared and evaluated for their regular parameters such as weight variation, friability, hardness, and dug content as part of pre-formulation studies and were assessed further for performance criteria such as FLT. TFT, SI in 0.1N HCl, and drug release.

In-vitro buoyancy studies

The time delay with which a dosage form floats into the stomach fluid was determined to be FLT [Table 2 and Figure 1].

The degree of polymer wetting and effervescence both contribute to dosage form floating. The FLT of prepared batches ranged from 16 ± 0.02 to 45 ± 0.03 s, whereas the TFT of all batches demonstrated buoyancy for 12 ± 0.06 h. The minimum FLT was shown by OB-1 (16 ± 0.02 s), followed by OB-4 and OB-7 (20 ± 0.03 s), respectively. All the formulations produced effervescences required for floating and remained intact for 12 h as shown in Figure 1. In the presence of dissolving media (0.1N HCl), the amount of sodium bicarbonate (90 mg) produced CO_2 which is trapped and protected within the gel formed by polymer hydration, reducing the density of the tablet. Once the tablet's density goes below one, it becomes buoyant.[32]

SI in 0.1N HCl

The swelling results were expressed in terms of SI as shown in Table 2 and Figure 2.

The results show that as the polymer concentration increases, so does the water absorption. All tablets formulated with HPMCK4M and HPMCK15M demonstrated excellent swelling both radially and axially.[33] The swelling in 0.1N HCl (pH 1.2) at 8 h ranged between 48.20 ± 0.02 and 54.33 ± 0.02. The rank order for the SI was OB-9> OB-8> OB-5> OB-6 > OB-3 > OB-2 > OB-1 > OB7. In general, the curves in 0.1N HCl (pH 1.2) exhibited a quick increase in the first 30 min due to water entry through metastable pores and thereafter stayed fairly constant. This mechanism is known as swelling hysteresis.[32] With 0.1N HCl, the OB-9 formulation including HPMC K4M and a high concentration of HPMC K15M showed a slow rise and then persistent swelling. Swelling must be ideal to avoid the formation of an excessively hydrated form that loses its integrity before drug release at the target. The EFT's intact nature is necessary to sustain a delayed drug release throughout transit through the GIT.[32]

In-vitro drug release study

The drug release study was carried out using 0.1N HCl (pH 1.2) data, as shown in Table 2 and Figure 3. More than 85% of the drug was released after 12 h. The lowest drug release rate was observed with OB-8, OB-6, OB-3, and OB-7 because HPMC K4M forms an abnormally thick gel

Table 2: Evaluation results of EFT of tinidazole (OB-1 to OB-9)

Batch code	Floating lag time (s)	Total floating time (h)	Swelling index (%)	Drug release (12 h) (%)
OB-1	16±0.02	12±0.02	48.20±0.02	99.77±0.02
OB-2	29±0.01	12±0.02	49.00±0.01	99.89±0.01
OB-3	25±0.02	12±0.01	49.30±0.02	97.57±0.03
OB-4	20±0.03	12±0.03	47.80±0.02	98.29±0.03
OB-5	45±0.03	12±0.06	50.03±0.03	98.35±0.03
OB-6	42±0.02	12±0.04	50.30±0.02	97.07±0.01
OB-7	20±0.03	12±0.02	48.00±0.01	97.75±0.01
OB-8	30±0.02	12±0.05	52.00±0.02	96.95±0.05
OB-9	32±0.02	12±0.05	54.33±0.02	98.16±0.02

Mean±SD (*n*=3)

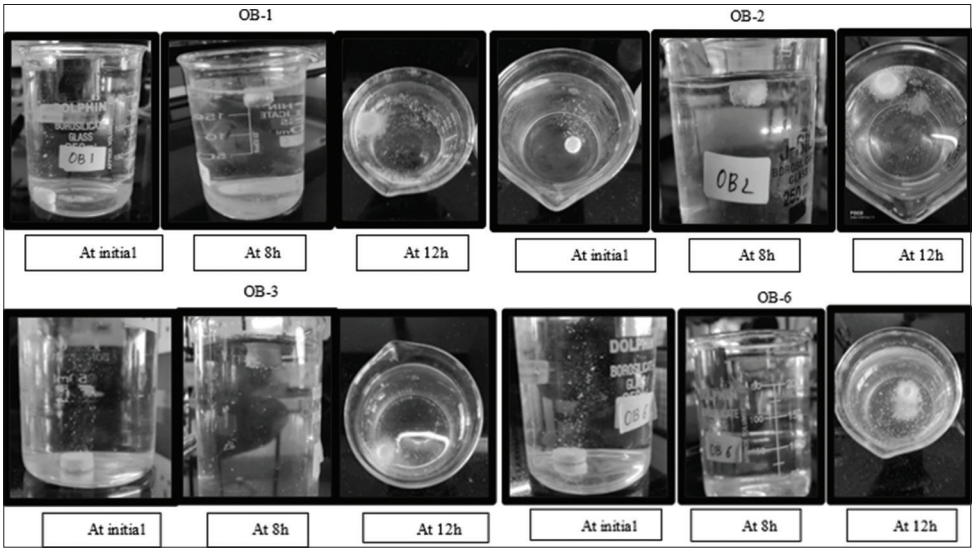

Figure 1: *In-vitro* buoyancy studies of effervescent floating tablets of tinidazole (OB-1, OB-2, OB-3,- and OB-6)

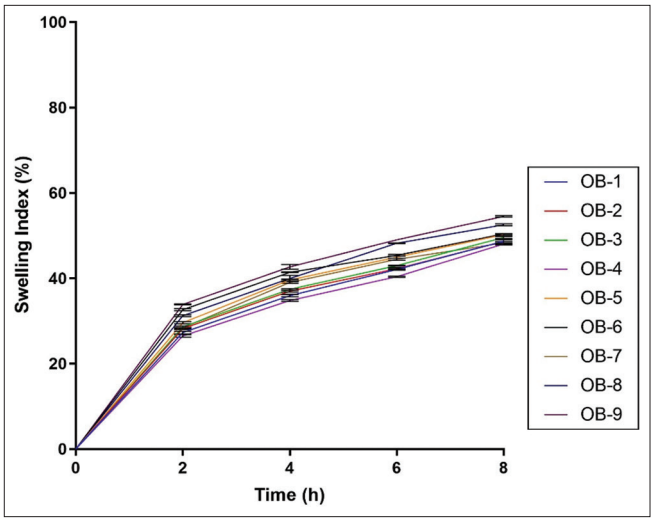

Figure 2: Swelling index at 8 h in 0.1N HCl (pH 1.2) of EFT of OB-1–OB-9

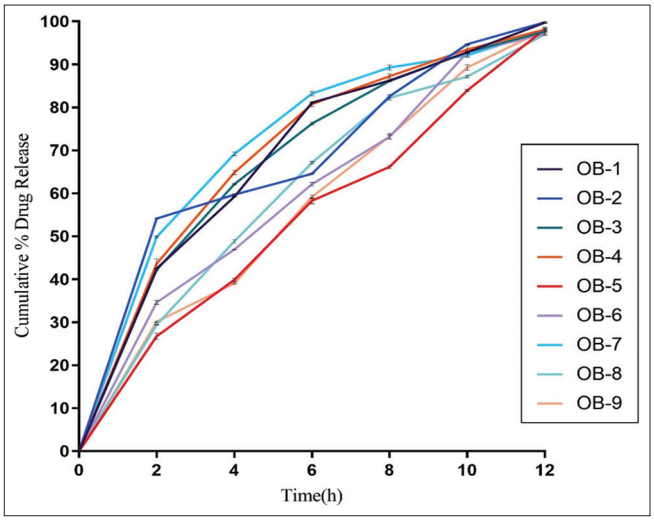

Figure 3: *In-vitro* dissolution profile of effervescent floating tablets of tinidazole (OB-1–OB-9)

surrounding the tablets following disintegration. This is less susceptible to water penetration and erosion. The release of the drug is caused by the diffusion of the dissolved drug through the thick gel. Because the rate of erosion of the swollen gel is slow in comparison to the pace of advancement of the swelling front, the drug's diffusion duration may increase with time, causing the release rate to decrease.[34] To discover the precise mechanism of drug release from floating tablets, drug release data was analyzed using the zero order, first order, Korsmeyer–Peppas equation, Hixson–Crowell, and matrix models.[29] The goodness of fit test was used to determine which model was most suited. As indicated in Table 3, the best-fit model for OB-1, OB-3, OB-7, OB-8, and OB-9 was the matrix, whereas the best-fit model for OB-2, OB-4, OB-5, and OB-6 was Korsmeyer–Peppas.

The Korsmeyer–Peppas model was used to calculate the value of exponent n. OB-1 and OB-2 had $n = 0.40$ and 0.29, respectively. This indicates that Fickian diffusion appears to be the primary drug delivery mechanism ($n < 0.45$). The results of formulations OB-3 to OB-9 varied from 0.45 to 0.53, showing that abnormal transport (n value 0.45–0.89) is the drug transfer mode. This might be due to HPMC, which creates a hydrogel when exposed to an acidic solution, allowing the tablets to expand and float. HPMC K4M and K15M are high viscosity grades of HPMC that make a superior matrix than many other polymers in which CO_2 is emitted from gas-generating agents.[35]

Statistical analysis

The influence of independent variables on dependent variables or responses is assessed using statistical design. Data from several batches were subjected to multiple regression analysis for Y_1, Y_2, Y_3, and Y_4. The term's positive or negative sign indicates the influence of the factor on the response, with the former indicating a positive (additive) influence and the latter indicating a negative (antagonistic) influence. Since it provides sufficient degrees of freedom, this design was chosen to address both the principal effects and the factor interactions. Several RSM computations were performed using Design Expert software for the current optimization study. Polynomial models with interactive and polynomial components were developed for all response variables using the MLRA approach.

FLT (Y_1)

The FLT equation is shown according to the MLRA model as below.

$$Y_1 = 43.93 + 2.00\,X_1 + 7.17X_2 + 0.7500X_1X_2 - 11.76X_1^2 - 10.26X_2^2 \quad (SD = 3.63;\ r^2 = 0.938)$$

The equation measures the influence of HPMC K4 M (X_1) and HPMC K15 M (X_2) on the FLT. In the EFT, sodium bicarbonate was utilized as a gas-generating agent, and a swelling matrix composed of HPMC K4M and HPMC K15M was used. As the fluid comes in touch with the acidic medium (0.1N HCl), it penetrates the matrix and starts the effervescence process. The polymeric network traps the released CO_2. As a result, the matrix of polymer expands quickly, and the expanded tablet attains the needed density, allowing it to float, reach the top, and remain buoyant for an extended amount of time as long as it maintains the desired buoyancy. Figure 4a shows response surface graphs and 2-D contour plots of the effects of independent factors on FLT (Y_1). FLT was discovered to be inversely linked, rather than proportionate to HPMC concentration. Nevertheless, contour plots show that HPMC K15 M has a substantial influence on FLT when the dose exceeds 70 mg per tablet; 90 mg generated the lowest value of FLT. This value may be regarded as a minimal effervescence requirement to balance the gravitational pull with the buoyancy force imposed on

the tablet during floating.[36,37] The summary of the ANOVA response is given in Table 4.

TFT (Y_2)

The TFT equation is shown according to the MLRA model as below

$$Y_2 = 12.06 + 0.0117X_1 + 0.0050X_2 + 0.0100X_1X_2 - 0.0178X_1^2 - 0.0178\,X_2^2 \text{ (SD} = 0.0053; r^2 = 0.9569)$$

According to the above equation, both the quantity of HPMC K4 M and HPMC K15M had a positive influence on the TFT of the produced EFT of tinidazole. Yet, it was discovered that X_1 had a considerable influence on TFT. This means that the formulations undergo increased floating time as the concentration of HPMC K4M increases. Figure 4b shows the 3D response surface graphs for TFT. Table 4 displays the ANOVA findings for the applied model on TFT. A $P < 0.005$ proved the model's significance. This provides details on the primary and interaction impacts of the individual components.

SI in 0.1N HCl (Y_3)

The SI in 0.1N HCl equation is shown according to the MLRA model as below.

$$Y_3 = 49.97 + 1.30\,X_1 + 1.65X_2 + 1.31X_1X_2 + 0.6812X_1^2 - 0.7688X_2^2 \text{ (SD} = 0.3247; r^2 = 0.9797)$$

According to the above equation, both the quantity of HPMC K4M and the amount of HPMC K15M had a positive influence on the SI of the EFT of tinidazole. However, it was discovered that X2 significantly impacted the SI in HCl. This suggests that when the concentration of HPMC K15M in the formulations increases, so does the SI. Figure 4c shows three-dimensional response surface graphs for the SI in 0.1N HCl. Table 4 displays the ANOVA findings for the applied

Table 3: Model fitting of *in vitro* release data using correlation coefficient (r^2) and *n* value

Batch code	Zero order	First order	Matrix (Higuchi)	Hix. Crow.	Korsmeyer–Peppas	
					r^2	*n*
OB-1	0.825	0.820	0.987	0.818	0.984	0.400
OB-2	0.597	0.617	0.936	0.610	0.967	0.296
OB-3	0.850	0.856	0.996	0.854	0.995	0.475
OB-4	0.798	0.806	0.991	0.804	0.993	0.458
OB-5	0.967	0.969	0.974	0.969	0.978	0.524
OB-6	0.932	0.936	0.987	0.935	0.989	0.501
OB-7	0.855	0.861	0.993	0.859	0.991	0.533
OB-8	0.931	0.934	0.991	0.933	0.986	0.503
OB-9	0.949	0.952	0.977	0.951	0.969	0.477

Hix. Crow.: Hixson Crowell

Table 4: ANOVA for response surface quadratic model for Y_1: FLT, Y_2: TFT, Y_3: Swelling index in 0.1N HCl, and Y_4: Time taken for 80% of drug release ($t_{80\%}$). Analysis of variance table (Partial sum of square-Type III)

Response	Source	Sum of squares	df	Mean square	F-value	P-value	Remarks
Y_1	Model	1418.05	5	283.61	21.52	0.0004	Significant
	A	24	1	24	1.82	0.2192	
	B	308.17	1	308.17	23.38	0.0019	
Y_2	Model	0.0042	5	0.0008	31.05	0.0001	Significant
	A	0.0008	1	0.0008	30.33	0.0009	
	B	0.0001	1	0.0001	5.57	0.0503	
Y_3	Model	35.61	5	7.12	67.54	<0.0001	Significant
	A	10.22	1	10.22	96.90	<0.0001	
	B	16.43	1	16.43	155.85	<0.0001	
Y_4	Model	30.86	5	6.17	19.47	0.0006	Significant
	A	0.6667	1	0.6667	2.10	0.1902	
	B	8.17	1	8.17	25.77	0.0014	

ANOVA: Analysis of variance, FLT: Floating lag time, TFT: Total floating time

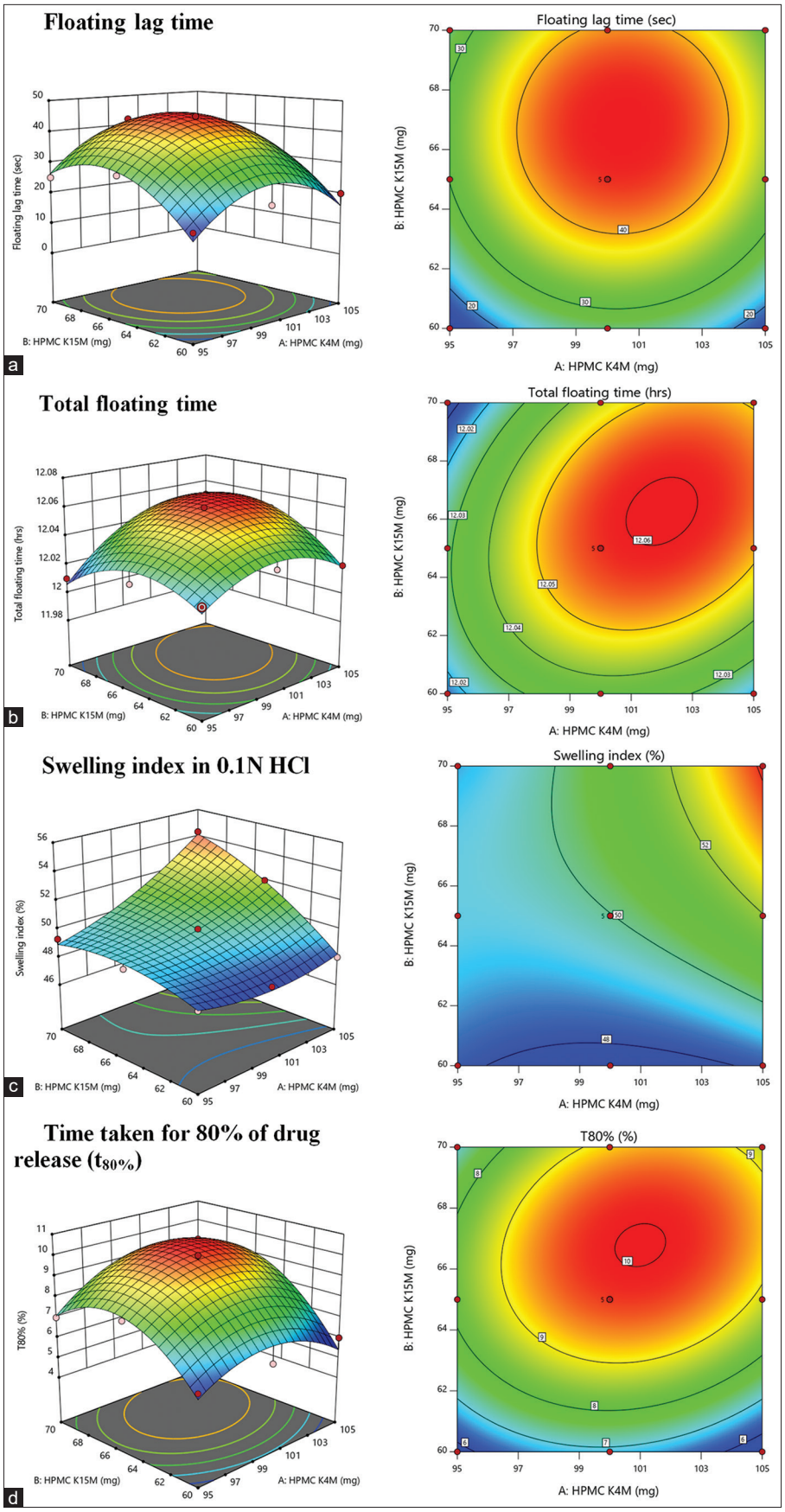

Figure 4: Response surface graph, and contour plots for (a) floating lag time (b) total floating time (c) swelling index in 0.1N HCl (d) time taken for 80% of drug release ($t_{80\%}$)

Table 5: Predicted and actual values of the responses for validation run

Responses	OB-1		OB-2	
	Predicted values	Actual values	Predicted values	Actual values
Y_1: Floating lag time (S)	13.49	16.00	30.17	29.00
Y_2: Total floating time (h)	12.01	12.02	12.02	12.02
Y_3: Swelling index in 0.1N HCl (%)	48.22	48.2	49.34	49.00
Y_4: Time taken to 80% drug release ($t_{80\%}$)	5.74	6.00	8.18	8.00

model on SI. A $P < 0.005$ proved the model's significance. This provides details on the primary and interaction impacts of the individual components.

Time taken for 80% of drug release ($t_{80\%}$) (Y_4)

The time taken for 80% of drug release ($t_{80\%}$) equation is shown according to the MLRA model as below.

$$Y_4 = 9.79 + 0.3333X_1 + 1.17X_2 + 0.5000X_1X_2 - 1.28X_1^2 - 1.78\ X_2^2\ (SD = 0.5630;\ r^2 = 0.9329)$$

The equation demonstrates that both parameters had a positive effect on the time required for 80% of drug release ($t_{80\%}$). Nonetheless, X_2 was found to have a significant influence on the time required for 80% of drug release ($t_{80\%}$). This indicates that the formulations suffer a longer time for 80% drug release as the concentration of HPMC K15M increases. Figure 4d shows 3D response surface graphs $t_{80\%.}$ Table 4 shows the ANOVA findings for the applied model on $t_{80\%.}$ A $P < 0.005$ proved the model's significance. This provides details on the primary and interaction impacts of the individual components.

Validation of model

An additional two formulations advised by design experts were built to test and evaluate the reliability of the mathematical simulations produced here with 3^2 factorial designs. The prepared formulation was evaluated, and the experimental results were compared to the model's predictions as shown in Table 5.

CONCLUSION

The EFT of tinidazole could be prepared by wet granulation method using sodium bicarbonate (90 mg) and varying compositions of HPMC K4M (95–105 mg) and K15M (60–70 mg). The formulations showed FLT of 16–45 s and TFT of 12 h. The drug release was about 98% for all formulations and followed the matrix and Korsmeyer–Peppas model. The contour plots show that HPMC K15 M (X_2) had a substantial influence on FLT when the dose exceeds 70 mg per tablet and it was discovered that HPMC K4M (X_1) had a considerable influence on TFT. The SI in HCl and the time required for 80% of drug release ($t_{80\%}$) were influenced by HPMC K15M (X_2). Overall, HPMC K15M was found to be more predominant in the performance of EFT. From all the formulations OB-2 possesses all required performance parameters and hence can be selected for *in-vivo* studies.

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