Magna Scientia Advanced Biology and Pharmacy

eISSN: 2582-8363

Cross Ref DOI: 10.30574/msabp

Journal homepage: https://magnascientiapub.com/journals/msabp/

(RESEARCH ARTICLE)

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Design and optimization of ketoprofen floating tablets

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Magna Scientia Advanced Biology and Pharmacy, 2024, 11(01), 080–089

Publication history: Received on 03 March 2024; revised on 10 April 2024; accepted on 13 April 2024

Article DOI: https://doi.org/10.30574/msabp.2024.11.2.0026

Abstract

The objective of the present research work is design and optimize hydrodynamically balanced Ketoprofen (KF) floating tablets to enhance their gastric residence time because it has a narrow absorption window, poor bioavailability and short half-life. The Central Composite design is used to optimize the amount of Guar gum (X_1) and HPMC K100M (X_2) as two independent variables and study how they affect the two response such as *in vitro* Buoyancy lag time (Y1) and *in vitro* drug release (t_{50} Y_2). Eleven trials were developed through the Central Composite design (CCD) to study all the optimal interaction between variables and responses through a polynomial equation. The optimized formulation is then characterized using pre-compression, post-compression tests, *in vitro* drug release and kinetic drug release. The Buoyancy time (lag time) and t_{50} of optimized floating tablet are 2.5 min and 6.68 hr respectively. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix. The results show that the hydrodynamically balanced systems significantly prolonging the KF drug release also improving its gastric residence time in the stomach. This research contributes to the field of drug delivery systems by providing a novel approach for improving the therapeutic efficacy of KF and potentially other drugs with similar characteristics

Keywords: Ketoprofen; Central composite design; Floating tablets; HPMC K100M; Guar gum

1. Introduction

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT), and some drugs are absorbed only in a particular portion of GIT or absorbed to a different extent in various segments of the GIT[1]. Floating drug delivery systems are good promising options for drugs which show good absorption in the stomach and which are degraded, less efficient in the intestine. Gastro Retentive Drug Delivery System gets retained for longer period of time in stomach, thus helping in absorption of drug for the intended duration of time, which in turn improves bioavailability by reducing drug wastage, and improving solubility of drugs that are less soluble at high pH environment. It also helps in achieving local delivery of drug in the stomach and proximal small intestine[2]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach[3]. Rheumatoid arthritis (RA) is severe inflammatory state that can influence more than just your joints. In some instances, the condition can harm wide-body systems; including blood vessels, lungs, skin, eyes, and heart. KF is an essential non-steroidal anti-inflammatory drug (NSAID) and has been observed to be effective in relieving severe pain in patients with rheumatoid arthritis (RA)[4,5]. The main obstacle with the use of KF in RA is its short half -life necessitating frequent dosage. The present research was to design and optimize floating tablets of KF to give prolonged drug release resulting in reduced dosing frequency.

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2. Material and methods

2.1. Materials

Ketoprofen (KF) was obtained from Arrow Chemicals Mumbai, India. HPMC KM100 and Guar gum was obtained from SD Fine Chemicals, Bengaluru, India. All the chemicals and solvents were of analytical grade.

2.2. Methods

2.2.1. Fourier transform infrared spectroscopy (FTIR)

The drug polymer interactions were studied by FTIR. FTIR spectra of samples were obtained on a Perkin Elmer 2000 FTIR system (Perkin–Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450–4000 cm^{-1} and the resolution were 1 cm^{-1}.

2.2.2. Design of experiments

The QbD approach utilizes optimization by using response surface design viz., CCD. The CCD is an effective method of indicating the relative significance of a number of variables and their interactions. Design Expert® (Trial Version 13, Stat-Ease Inc., Minneapolis, U.S.A.) was used to generate CCD and the regression analysis was used to optimize the concentration of Guar gum (X_1) and HPMC K100M (X_2). In this design, 2 factors were evaluated each at 2 levels, 3 centre points and experimental trials were performed at all 11 possible combinations. Y_1 Buoyancy and Y_2 (t_{50}) were selected as dependent variables. Two independent factors were set at two levels viz., Low and High and were coded as - 1 and +1, respectively shown in table 1 and possible trial formula was given in table 2.

Table 1 Variables and Levels as per CCD

Independent variables	**Levels**	
	Low (-1)	**High (+)**
Guar gum-X_1	100	150
HPMC K100M-X_2	75	100
Dependent variables; Buoyancy-Y_1; t_{50}-Y_2		

Table 2 Trials as per CCD

Trial runs	**KF mg**	**Guar gum (X_1) mg**	**HPMC K100M (X_2) mg**	**Sodium Bicarbonate mg**	**Total wt of the tablet mg**
F1	50	150	87.5	30	317.5
F2	50	150	75	30	305
F3	50	125	87.5	30	292.5
F4	50	125	87.5	30	292.5
F5	50	125	87.5	30	292.5
F6	50	100	100	30	280
F7	50	150	100	30	330
F8	50	100	75	30	255
F9	50	125	75	30	280
F10	50	125	100	30	305
F11	50	100	87.5	30	267.5

2.2.3. Preparation of tablets

All the ingredients according to the formulae shown in table 2 were mixed geometrically with specified excipients in order to get a uniform blend, the produced blend was lubricated with magnesium stearate and compressed into tablets on a 10 station rotary tablet punching machine (M/s. Cadmach Minipress Machinery Co. Pvt. Ltd, India) using 10 mm round, flat, plain punches.

2.3. Evaluation of tablets

- ***In vitro* floating characteristics:** All trial batch tablets of KF were studied for Buoyancy time (Lag time) and Floating period. Buoyancy time and Floating period were determined for 3 tablets of each batch in glass beaker containing 900 ml of 0.1 N HCl[6].
- **Swelling index:** The drug release from any tablet depends upon the % of uptake of medium, here, the medium used was 0.1 N HCl. The medium temperature was maintained at 37 ± 0.5 °C throughout the study. The swelling study of all trial tablet batches were conducted, during the study the preweighed tablets were placed in the test medium viz., 0.1 N HCl. At regular intervals viz., tablets were removed from the medium, lightly blotted with tissue paper to remove excess medium and weighed[7]. The percentage water uptake in terms of % SI was estimated using the following formula.

$$\text{Swelling Index (SI)} = \frac{\text{Swollen tablet weight (W0)} - \text{Initial tablet weight (W)}}{\text{Initial tablet weight (W)}} \times 100$$

- **Uniformity of weight test:** As per official pharmacopeia, 20 tablets were taken in random, studied for difference in weight both individually and in group. The mean and percent deviations were determined8.
- **Hardness test:** The strength of each tablet was measured using tablet hardness tester (Monsanto type, MHT-20). The mean hardness was determined and expressed in kg/cm2. Five tablets were taken to perform the above phenomenon9.
- **Friability test:** The friability test was carried out in Roche Friabilator. 20 tablets were selected randomly and initial weight (wo) was noted down after de-dusting and placed in a rotating drum. They were subjected to 100 falls of 6 in height (25 rpm for 4 min)10. The percent loss in weight (or friability) was calculated by the formula given below.

$$\%\ \text{Friability (F)} = \left(1 - \frac{\text{Weight (W)}}{\text{Weight (W0)}}\right) \times 100$$

- **Drug content:** 5 tablets were taken and crushed into fine powder. Powder equivalent to 50 mg of KF was taken in to the volumetric flask. The drug was extracted into 25 ml of 0.1 N HCl with vigorous shaking for 1 hr and sonicate for 10 min, further the volume was made up to the mark with 0.1 N HCl. The solution was filtered through 0.45 µm Millipore nylon filter disc and appropriate dilutions were further made with 0.1 N HCl. The dilutions were measured for the absorbance by UV spectrophotometer (UV-1800, Shimadzu, Japan) at 257 nm against blank (0.1N HCl). Content of each trial batch tablets were determined.
- ***In vitro* drug release studies:** The drug release from the all trial batch floating tablets were studied using USP XXIV type-II dissolution rate test apparatus. Then, 900 ml of 0.1 N HCl was used as dissolution medium maintained at a temperature of 37 ± 0.5 °C and the paddle was rotated at 50 rpm. At different intervals of time samples were withdrawn, diluted with 0.1 N HCl and absorbance was measured by UV spectrophotometer (UV-1800, Shimadzu, Japan) at 257 nm.

2.4. Data analysis

Design expert software was used for analyzing the data. It selects and suggests the highest order polynomial equation as a suitable model based on coefficient of determination (R^2). Analysis of variance (ANOVA) was performed on the suggested model for the responses Y_1 and Y_2 to identify significant effect. Multiple regression analysis was performed on the dependent variables to know the significance of the regression coefficients on the model. The models generated were used to construct contour (2D) and response surface (3D) plots for Buoyancy time and t_{50} to understand the main and interaction effects of factors under the study[11-13].

2.5. Optimization

Desirability and graphical optimization technique (overlay plots) were employed to optimize the formulations with the desired responses (responses from theoretical profile values). Numerical optimization was performed with fixed

constraints of Y_1 Buoyancy time and Y_2 t_{50}, which were obtained from the theoretical profile. For finalizing the optimum formulation, targets were set for these constraints for getting respective desirability function response and overlay plots.

2.6. Cross-validation of model

Optimized floating tablet was prepared experimentally and evaluated for uniformity of weight, hardness, friability, uniformity of content, *in vitro* floating, and *in vitro* dissolution. To ratify the CCD, compare the theoretical and experimental response values and determine the percentage relative error.

3. Result and discussion

3.1. Characterization of KF floating tablets

The FTIR spectra of the KF and optimized formulation shown in figure 1. The KF peaks at 2978.49 cm-1 and 2932.58 cm-1 (CH-CH stretching absorption band of CH, CH_3),1692.33 cm-1 and 1650.28 (symmetric carbonyl due to dimeric carboxyl and ketonic group stretching vibration C= O). The characteristic absorption bands of KF were observed in the optimized formulation assures no chemical interaction between drug and polymer. The bulk density was found to be in the range of 0.389 ± 0.0023 to 0.476± 0.0346 g/cm^3; tapped density 0.464 ± 0.0330 to 0.590 ± 0.0264 g/cm^3; Carr's index value 10.80 ± 1.935 to 26.56 ± 2.11 and Hauser's value 1.118 ± 0.0202 to 1.360 ± 0.040 for F-1 to F-11 floating tablet formulations indicates good compressibility and flowability and can be used for direct compression. The angle of repose was found to be in the range of 22.97 ± 17.21 to 38.31 ± 2.640 for F-1 to F-11 formulations showing that the blends of powder were free flowing. The hardness of the F1 to F11 tablets was found to be in the range of 3.080±0.078 to 4.460±0.226 kg/cm^2 which were below 1% indicating the sufficient mechanical integrity and strength of the floating tablets. The swelling index was found to be within 145.3±36.7 to 188.0±42.1. All other parameters were found to be within specified limits and are complying with pharmacopeial standards. The % drug content of floating tablets and were found between the range 95.85±0.5781 to 99.64±0.1706, low SD values indicate uniformity in drug distribution and method adapted was reproducible. The time taken for dosage form to float on surface medium called floating lag time and duration of time by which it constantly floats on surface of medium is called floating time. For extended gastric residence, rapid floating and long floating duration are desired. The floating lag time and floating time was noted visually. Buoyancy time of F1 to F11 tablets were in the range of 1.7 min to 4.6 min. All batches of tablets shown good floating ability (100 %) and remained buoyant for more than 12 hr. These results are in accordance with the viscosity of polymer which has a major role on swelling process, matrix integrity as well as floating capability. The *in vitro* drug release from all batches of floating tablets was slow and spread over extended period of time with excellent floating properties by maintaining good integrity as shown in figure 2. It was observed that the type of polymer and polymer combinations at different ratios influenced the drug release pattern. The cumulative percentage of drug release after 12 hr from floating matrix tablets of F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 and F11 was 90.22%, 89.50%, 90.13%, 90.31%, 90.13%, 95.41%, 89.98%, 94.44%, 91.25%, 89.79% and 95.53% respectively.

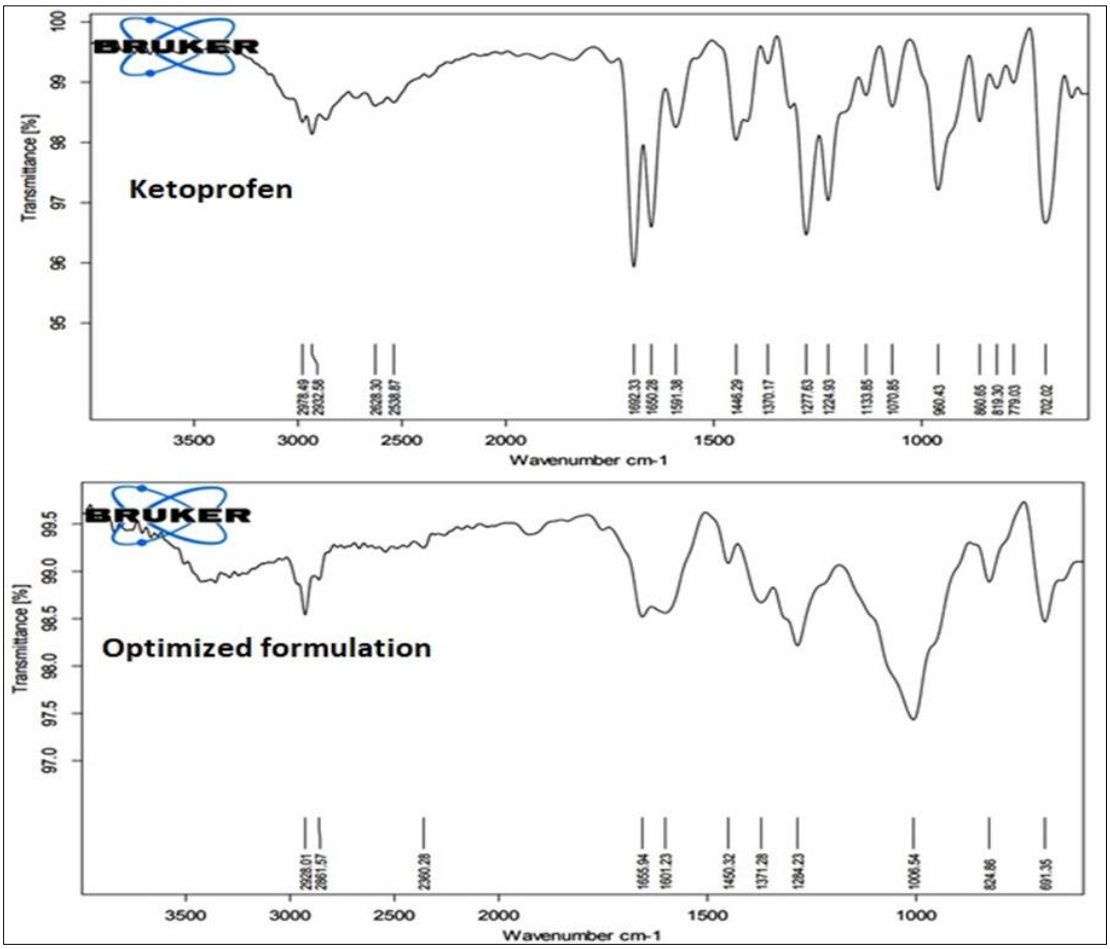

Figure 1 Comparative FTIR spectra of KF and optimized floating tablet

3.2. Statistical analysis of experimental data by Design-Expert software

The results of the optimized batch were analyzed using Design-Expert software. The selected independent variables include the amount of guar gum and HPMC K100M influencing the response of the Buoyancy lag time and t_{50} study. The results of the statistical analysis of the design batches are depicted in Table 3. The polynomial equations of the statistical model were established by ANOVA, R^2 value, p-value, F-value, and correlation coefficient generated in Design Expert software and data was given in table 4. The interaction effects of two independent variables on responses, were graphically represented through response surface plots. The contour plot, 3-D response surface plot and relative plots of various responses of Buoyancy lag time and t_{50} study were depicted in figures 3,4. This parameter helps to observe the qualitative effect of each factor on the responses.

3.2.1. Response 1 (Y_1) Buoyancy time (min)

The *in vitro* Buoyancy time (min) ranged from 1.7 min (Trial 6) to 4.6 min (Trial 8) for various formulations. The regression analysis proved the significant effect of independent variables on the quantity of guar gum and HPMC K100M on the Buoyancy time. The effect can be explained through the following polynomial equation:

$$Y1= 2.78 – 0.1167\ A – 1.27\ B + 0.1750\ AB – 0.0605\ A^2 + 0.2895\ B^2$$

The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. The equation indicates that the responses increase with a lower amount of Guar gum and a lower amount of HPMC K100M, and the R^2 value of the above equation is 0.9995, which indicates a good fit for the model.

3.2.2. Response 2 (Y_2) t_{50} (hr)

The t_{50} ranged from 4.8 hr (Trial 6 and 11) to 6.8 hr (Trial 1 and 7) for various formulations. The regression analysis proved the significant effect of independent variables on the quantity of guar gum and HPMC K100M on the t_{50}. The effect can be explained through the following polynomial equation,

$$Y2= 5.48 + 0.9000\ A + 0.0667\ B + 0.1500\ AB + 0.2895\ A^2 - 0.0105\ B^2$$

The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. The equation indicates that the responses increase with a higher amount of Guar gum and a higher amount of HPMC K100M, and the R^2 value of the above equation is 0.9995, which indicates a good fit for the model.

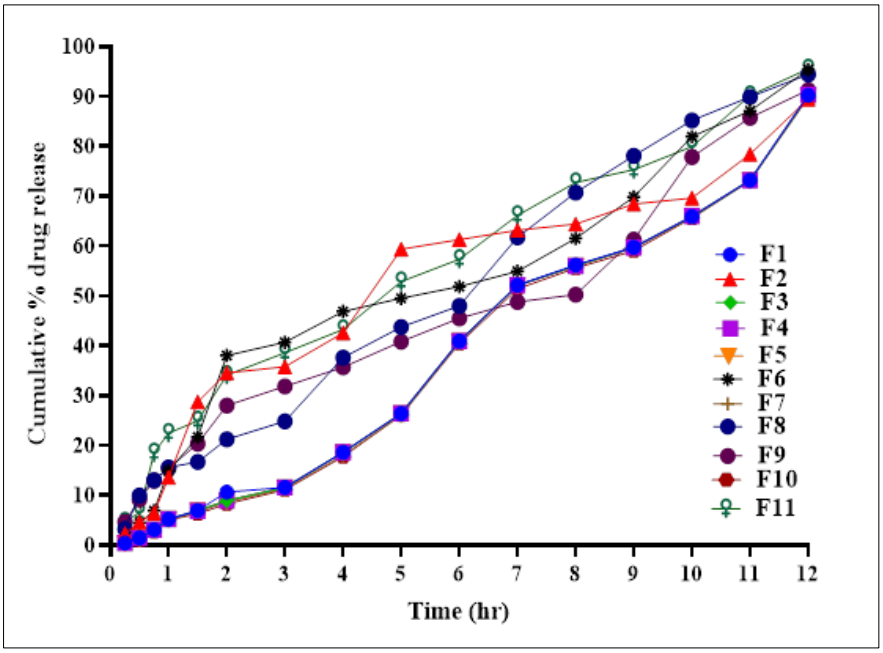

Figure 2 *In vitro* dissolution profile of F1 to F11 KF floating tablets

Table 3 Results of response data and statistical experimental data by CCD

Trial runs	Buoyancy time (lag time) -Y_1	t_{50}
1	2.6	6.8
2	4	6.4
3	2.8	5.5
4	2.8	5.4
5	2.8	5.5
6	1.7	4.8
7	1.8	6.8
8	4.6	5
9	4.3	5.4
10	1.8	5.6
11	2.8	4.8

Table 4 Statistical analysis of experimental data by CCD method

Parameters	Buoyancy time (lag time) Y_1		t_{50} Y_2	
	F-Values	**p-value**	**F-Values**	**p-value**
Model- Significant	1924.37	< 0.0001	117.18	< 0.0001
A-Guar Gum	78.24	0.0003	547.47	< 0.0001
B-HPMC K100M	9222.18	< 0.0001	3.00	0.1436
AB	117.35	0.0001	10.14	0.0244
A^2	8.89	0.0307	23.91	0.0045
B^2	203.36	< 0.0001	0.0316	0.8658
Suggested Model	Quadratic		Quadratic	
R^2	0.9995		0.9915	
Adjusted R^2	0.9990		0.9831	
Predicted R^2	0.9959		0.9246	

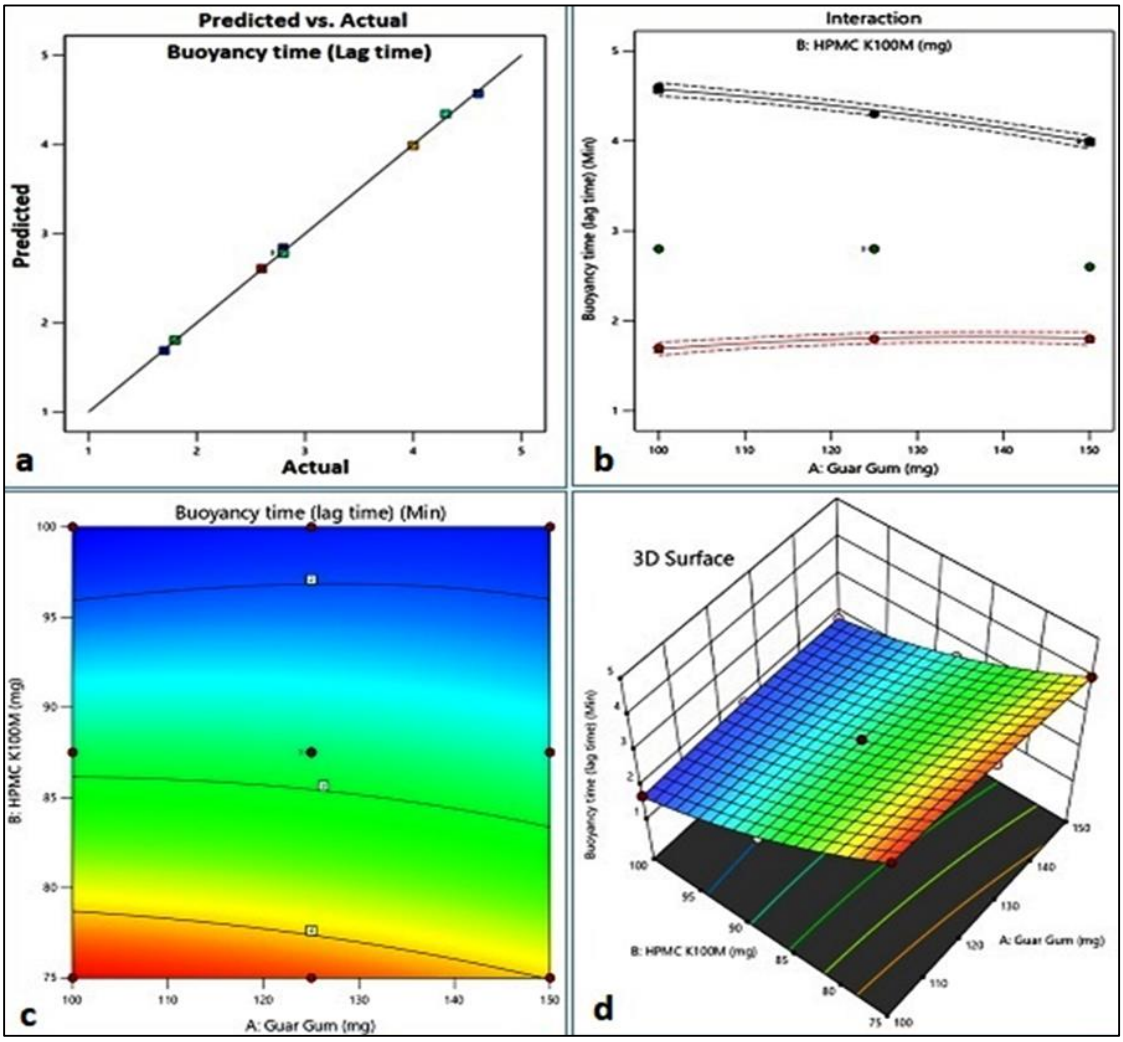

Figure 3 Predicted vs Actual plot (a), Interaction plot (b), Contour plot (c) and 3D surface plot (d) depicting the effect of Guar gum and HPMC K100M on Buoyancy time (min)

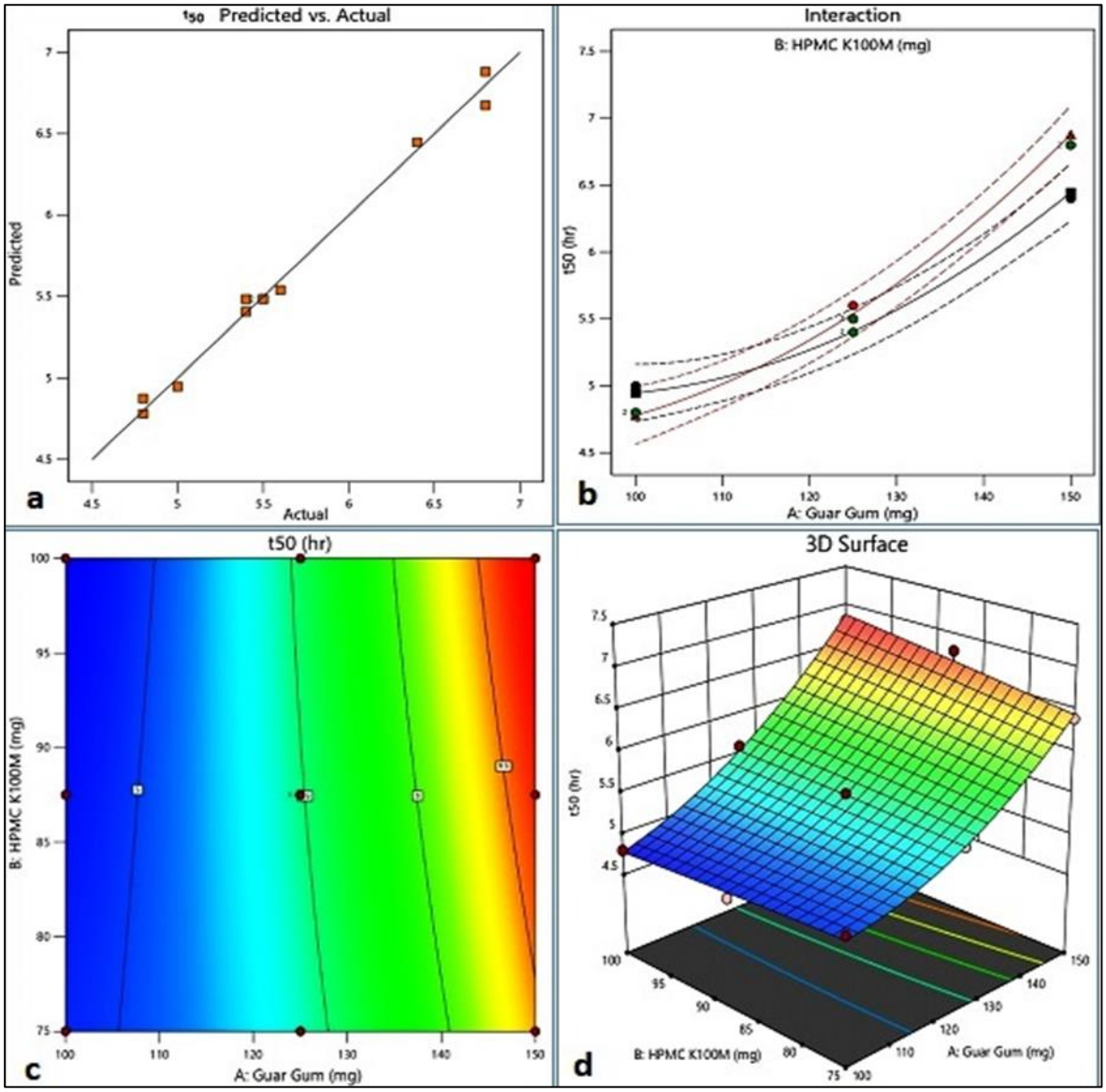

Figure 4 Predicted vs Actual plot (a), Interaction plot (b), Contour plot (c) and 3D surface plot (d) depicting the effect of Guar gum and HPMC K100M on t_{50} (hr)

3.3. Optimization characterization and validation of optimized KF floating tablets

The optimized floating tablets of KF as per CCD were identified by numerical optimization and desirability function by "trading off" of various response variables for attaining the desired goals, minimization of response variables. The optimum formulation was based on the set target of 2.5 min for Buoyancy time and maximize hr for t_{50} from drug release study. Therefore, the predicted levels of responses with a new formulation of optimized KF floating tablet were prepared to confirm the validity of the optimization procedure. The composition of the optimized formulation was 150 mg of guar gum and 88.76 mg of HPMC K100M, which satisfy the requirements. The responses of the optimized batch have 2.5 min for Buoyancy time and 6.68 hr for t_{50} which is almost similar to the Trial 1 batch and predicted value. The desirability plot and overlay plot are depicted in Figure 5.

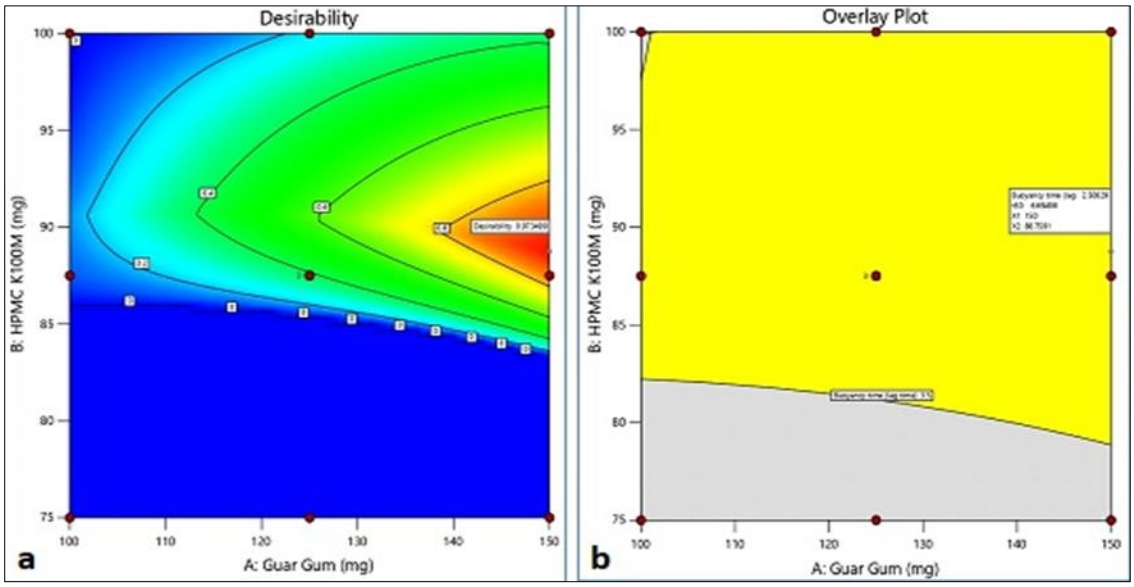

Figure 5 Desirability plot (a) and Over lay plot (b) for obtained results

Validation of the predicted values of responses was performed experimentally and comparing the data, which indicated high degree closeness between the predicted and observed values of the responses and confirmed excellent prognostic ability of the employed mathematical model. The experimental optimized formulation was evaluated for precompression, post compression parameters and *in vitro* drug release studies. The results of bulk density, tapped density, compressibility index value and Hausner's value indicates good compressibility and flowability and can be used for direct compression. The angle of repose was found to be within the range indicate the blends of compression coated powder were free flowing. The thickness and diameter were within the permissible range. The post compression parameter results suggest that the optimized KF floating tablet have desired mechanical strength and weight distribution within the tablets. The optimized formulae comprising Guar gum and HPMC K100M studied as per CCD. The optimized KF floating tablets were subjected for *in vitro* drug release studied under the standard conditions. the drug release profile was shown in figure 6, the drug release at 12 hr was found to be 95.14±0.16. The drug release was controlled because of swelling property of Guar gum and floating property of HPMC K100M. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix.

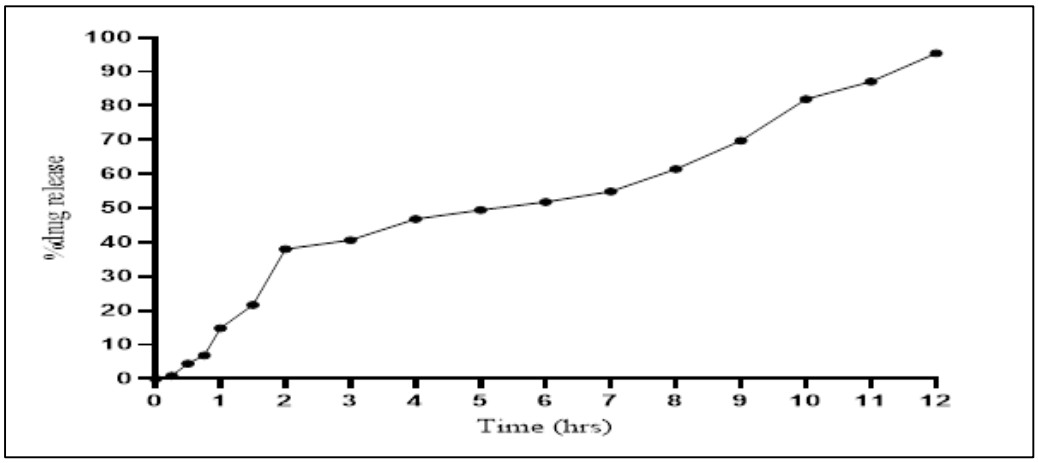

Figure 6 *In vitro* dissolution profile of optimized KF floating tablet

4. Conclusion

The Hydrodynamically balanced KF floating tablets were optimized by CCD. Two variables and two responses were selected to meet the requirement of floating tablets to achieve desired properties. The optimal tablet comprising 150

mg of Guar gum and 88.68 mg of HPMC K100M has excellent buoyancy lag time and shows greater than 12 hr floating time. Eleven batches were developed with two different variables, and their interaction between response were analyzed through the polynomial equation, interaction, contour and 3D plot. The results demonstrate that the hydrodynamically balanced Guar gum and HPMC K 100M based KF floating tablets significantly enhances the absorption by enhancing gastric retention time and prolonging the drug release in the stomach.

Compliance with ethical standards

Acknowledgments

We wish to thank Arrow Chemicals Mumbai, India for supplying the Ketoprofen and thanks to the principal and management of V.L. College of pharmacy for providing the facilities to carry out the work.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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