RESEARCH ARTICLE

Development and Optimization of Orodispersible Tablets of Fexofenadine Hydrochloride (FFH) by Box-Behnken Statistical Design (BBD)

P. V. Kamala Kumari*, M. Sai Sri Vastav, Y. Srinivasa Rao

Vignan Institute of Pharmaceutical Technology, Beside VSEZ, Duvvada, Visakhapatnam, Andhra Pradesh, India

Received: 24th June, 2022; Revised: 29th August, 2022; Accepted: 03rd September, 2022; Available Online: 25th September, 2022

ABSTRACT

The aim of the present study was to formulate orodispersible tablets (ODT) of fexofenadine Hydrochloride (FFH) by studying the effect of the variable for response with the help of Box-Behnken design (BBD). A total of 17 formulations were prepared by altering the proportion of crospovidone, sodium starch glycolate and mannitol by direct compression technique. BBD was employed to study the relations among the variables and to statistically optimize the formulation parameter for ODT tablets of fexofenadine Hydrochloride. Response surface and contour plots were plotted based on BBD and relationship between the variables and responses were established. Further evaluation of responses with respect to variables was made with 3D surface plot that allows evaluating a blend selected variables at a time and assessing the effect of variation and interaction on responses. In conclusion, an optimized model was obtained based on predicted and observed response for the three dependent variables.

Keywords: Box-Behnken design, Contour plots, Direct compression, Optimization, Perturbation.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.3.71

How to cite this article: Kumari PVK, Vastav MSS, Rao YS. Development and Optimization of Orodispersible Tablets of Fexofenadine Hydrochloride (FFH) by Box-Behnken Statistical Design (BBD). International Journal of Drug Delivery Technology. 2022;12(3):1357-1366.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Design of experiments helps in establishing cause and effect relationships among the factors and responses by applying the science and statistics principles. For optimizing the end results in the form of output managing the input control is required. In other words, an experimental design aims at predicting the outcome on the basis of actual model built with the help of planned set of experiments by introducing a change of existing conditions, representing more than one independent variables referred to as "input variables". By changing independent variables, dependent variables also known as output variables or response variables also change.[1] The experimental design may also identify variables that must be held constant to prevent external factors affecting the results. Planning the experiments, selecting independent, dependent and control variables under statistically optimal conditions is the main aim of experimental designs.

An independent quadratic design which doesn't contain factorial of full factorial design is Box Behnken design (BBD). These designs are rotatable and require one factor and three levels and also have limited capability for orthogonal blocking compared with the Central Composite Design (CCD).[2] BBD is good as (i) parameters are estimated of the quadratic model; (ii) sequential designs can be built; (iii) lack of fit of the model can be detected; and (iv) use of blocks. When BBD is compared with other response surface designs such as central composite (CCD), Doehlert matrix and three-level full factorial design) it has demonstrated that the BBD and Doehlert matrix are more efficient than CCD and much more than the three-level full factorial designs.[3] Responses and the factors are the two types of variables during the multivariate optimization procedure. The responses are the dependent variables which depend on the values based upon the levels of the factors.[4]

Orally Disintegrating Tablets are designed to disintegrate and/or dissolve in the patient's mouth in a very small volume of saliva. Weak mechanical strength is attributed to high porosity formulation by moulding at low pressure, an undesirable quality of orodispersible tablets.[5] Granulation and compression methods have been adapted to formulate ODTs with higher mechanical strength but these methods show longer disintegration time. In this study, superdisintegrants such as crospovidone and sodium starch glycolate (SSG) were used as they both have porous structure facilitating water uptake into the tablet which is a pre-requisite for disintegration to occur. Rapid volume expansion and hydrostatic pressures allowing tablet disintegration more efficiently were also reported using crospovidone and SSG.[6]

*Author for Correspondence: kamalaparavastu@gmail.com

Fexofenadine HCl (FFH), the carboxylic acid metabolite of terfenadine, is a second generation antihistamine which acts as a reversible and competitive inhibitor at H1 histamine receptor sites that is non sedating and does not cause electrocardiographic effects.[7] It has been approved and widely prescribed for alleviating symptoms of arrhythmia in many countries. Unlike others H1 blockers, this drug does not make person feel drowsy, as it doesn't cross BBB. Anticholinergic side effects were also not displayed by FFH as this drug has less affinity towards cholinergic and alpha-adrenergic receptors.[8]

MATERIALS AND METHODS

Materials

FFH was a gift sample from ESaiPharma, Parawada. Visakhapatnam, India. Crospovidone, SSG and mannitol were procured from Merck laboratories. All other reagents used were of analytical grade.

Methods

Preparation of Oral Disintegrating Tablets

In the present study, oral disintegrating tablets of FFH were prepared by direct compression method, using different polymers. All the required ingredients were weighed accurately and passed through 40 mesh size to get uniform size particles.[7] Measured amount of drug, crospovidone, SSG and mannitol were mixed in increasing order of their weights in a mortar. Talc and magnesium stearate were added later. The final mixture was manually shaken for 10 min in a plastic bag and compressed using tablet punching machine.[9]

Precompression Studies

Fourier Transform Infrared Spectroscopy (FT-IR)

The interaction between the drug and polymer was studied by FTIR (Shimadzu, Japan model–8400S). In order to produce a stable product, there should be no incompatibility between the drug and polymer.[9] IR spectral analysis of pure Fexofenadine hydrochloride, Crospovidone, Sodium Starch glycolate and mannitol was carried out.

Angle of Repose

The angle of repose of the powder blend was determined by employing funnel method. Powder blend which was accurately weighed was taken in funnel and was allowed to flow through the funnel freely onto the surface. A total of three successive determinations were done.

Bulk Density and Tapped Density

Measured quantity of powder was introduced into a measuring cylinder. "After determination of initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals and the tappings were continued until a specified time and the final volume was noted".[9] Lewy body dementia (LBD)and Total body radiation dose (TBD) were calculated. The determination was carried out in triplicate.[9]

Compressibility Index and Hausner Ratio

The compressibility index and hausner ratio of the powder blend for each powder blend was calculated. Three determinations were done for each formula.[9]

Post Compression Parameters

Weight Variation Test

Weight variation was performed according to United state Pharmacopoeia (USP).[10] Twenty tablets of each formulation batch were taken and weighed on an electronic balance.

Thickness

Five tablets were taken and thickness was measured using vernier calipers by placing tablet between two arms and note down the reading.

Hardness

Monsanto hardness tester was used to measure the hardness in Kg/cm^2 of five tablets of each batch.

Friability

Friability of the tablet was checked by Roche friabilator. Tablets were de-dusted, weighed and placed in friabilator at 25 rpm for 5 min. Loss in weight of the tablets was noted and friability was calculated based on the formula:

Friability = [(W0- W1) / W0] 100

where, W0 is initial weight of tablets,

W1 final weight of tablets.

Drug Content Uniformity

Five tablets were randomly selected, crush in mortar pestle and dissolved in 50 mL of 0.1 N HCl in 50 mL volumetric flask.[11] The solution was stirred for 30 min and filtered. 1-mL of the filtrate was further diluted to 100 mL with 0.1 N HCl and measured at an absorbance of 274 nm.

Wetting Time

A piece of filter paper measuring 10 cm diameter was placed in a Petridish. 10 mL of water (containing water soluble dye Eosin) was added to the Petridish. Orodispersible tablet was then placed carefully on the surface of the tissue paper. Wetting time was measured by the time required to wet the upper surface.

Disintegration Time

Disintegration time was measured using disintegrating test apparatus by placing the orodispersible tablet in each tube of the basket rack in a beaker with phosphate buffer at 37 ± 2˚C. The apparatus was operated until no residue of the prepared was left and the time taken to achieve zero residues was recorded.[12]

Modified Disintegration Test

This method mimics standard disintegration time by replacing phosphate buffer with saliva. The time taken for the ODT formulation to disintegrate entirely was noted.

***In-vitro** Drug Release Studies*

Dissolution studies were carried out with USP paddle type apparatus, in phosp/hate buffer, pH 6.8 (900 mL) maintained

Table 1: Summarizes the ranges and constraints of independent and dependent variables, respectively.

Independent variables	*Symbols*	*Levels*	
		Lower limit	Higher limit
Crospovidone	A	10	15
Sodium starch glycolate	B	2	8
Mannitol	C	15	25
		Constraints	
Dependent variables	Y1	in range	
	Y2	in range	
	Y3	in range	

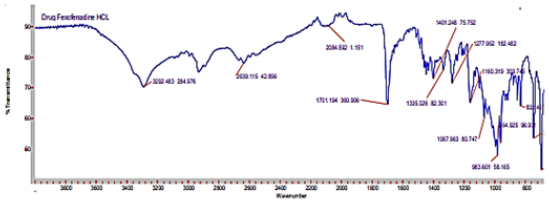


Figure 1: FT-IR spectra of fexofenadine hydrochloride.

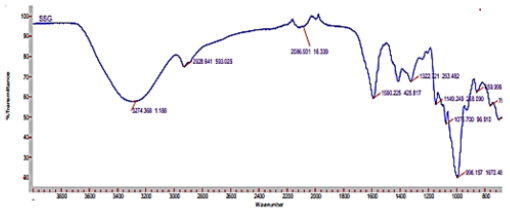


Figure 2: FT-IR spectra of sodium starch glycolate.

at a temperature of 37˚C and paddle velocity of 50 rpm.[12] Aliquots each of 5 mL were taken at 5,10, 15, 20 and 25 min and replenished with equivalent volume of phosphate buffer and the absorbance was measured at 274 nm.

Experimental Design

Box Benkhen Design (BBD) at three factor two level (23) was developed to study the influence of selected independent variables dependent responses[13] using the experimental version of Design-Expert® software 13. The design consisted of replicated center points and a group of points located in the center of each edge of a multidimensional cube that defined the area of interest. This experimental design generates a polynomial equation which is as follows:

$$Yo = bo + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22}$$

where, Yo = dependent variable; X_1, X_2, and X_3= independent variable coded levels;

b0 = intercept; b1 to b9 = regression coefficients.

Three independent variables were chosen after performing preliminary experiments which are as follows; Crospovidone (A), SSG (B) and Mannitol (C). The responses measured were modified disintegration time (Y1), wetting time (Y2) and *in-vitro* drug release (Y3). Corresponding to the independent variables, two different levels were established as the lowest and highest of the tested variables (Table 1). The matrix of 17 experimental formulations was constructed as represented in Table 2. BBD suggesting 17 formulations (including 5 center points) were prepared experimentally in triplicate and characterized. The data were fitted to the various models (linear, 2-FI and quadratic) and analyzed by one-way analysis of variance (ANOVA). Polynomial equations explained the

Table 2: Modeling of the response in the box behnken experimental design

Run	*Factor 1 A: Crosspovidone mg*	*Factor 2 B: Sodium Starch Glycolate mg*	*Factor 3 C: Mannitol mg*	*Response 1 Modified Disintegration Time sec*	*Response 2 Wetting Time sec*	*Response 3 in-vitro drug release %*
1	15	5	15	47	15	91.2
2	12.5	5	20	53	23	95.3
3	10	5	15	49	26	90.2
4	15	8	20	45	16	95.3
5	12.5	8	25	53	24	98.5
6	12.5	5	20	53	24	95.1
7	10	8	20	46	28	95.4
8	10	2	20	54	26	95.6
9	12.5	8	15	54	24	88.4
10	10	5	25	43	28	98.3
11	12.5	2	15	54	24	89.6
12	15	2	20	48	16	94.8
13	12.5	5	20	53	23	94.9
14	12.5	2	25	49	23	98.5
15	15	5	25	40	16	98.2
16	12.5	5	20	54	24	93.6
17	12.5	5	20	53	23	93.8

Table 3: Micromeritic properties of the formulations as per the design

Batch No	*Angle of Repose (Θ)*	*Bulk density (g/mL)*	*Tapped Density (g/mL)*	*Compressibility Index (%)*	*Hausner ratio*
F1	25.85 ± 1.09	0.54 ± 0.09	0.49 ± 1.23	9.26	1.10
F2	29.35 ± 0.74	0.57 ± 0.08	0.51 ± 1.32	10.53	1.12
F3	23.52 ± 0.37	0.57 ± 0.07	0.51 ± 1.05	10.53	1.12
F4	25.60 ± 0.42	0.52 ± 0.65	0.48 ± 0.74	7.69	1.08
F5	29.36 ± 0.52	0.57 ± 0.36	0.51 ± 0.54	10.53	1.12
F6	27.45 ± 0.74	0.38 ± 0.65	0.31 ± 1.13	18.42	1.23
F7	29.26 ± 0.59	0.51 ± 0.54	0.46 ± 2.05	9.80	1.11
F8	24.36 ± 0.54	0.34 ± 1.23	0.29 ± 1.08	14.71	1.17
F9	23.65 ± 0.47	0.42 ± 0.25	0.35 ± 1.2	16.67	1.20
F10	25.34 ± 0.65	0.43 ± 0.53	0.34 ± 0.93	20.93	1.26
F11	25.85 ± 1.23	0.39 ± 0.54	031 ± 0.89	20.51	1.26
F12	26.54 ± 1.25	0.54 ± 0.65	0.46 ± 0.47	14.81	1.17
F13	29.65 ± 0.65	0.37 ± 0.35	0.31 ± 0.29	16.22	1.19
F14	27.25 ± 0.68	0.34 ± 0.54	0.29 ± 0.64	14.71	1.17
F15	24.16 ± 0.75	0.32 ± 0.54	0.27 ± 0.29	15.63	1.19
F16	23.17 ± 0.49	0.41 ± 0.65	0.36 ± 0.65	12.20	1.14
F17	25.37 ± 0.74	0.45 ± 0.64	0.39 ± 1.41	13.33	1.15

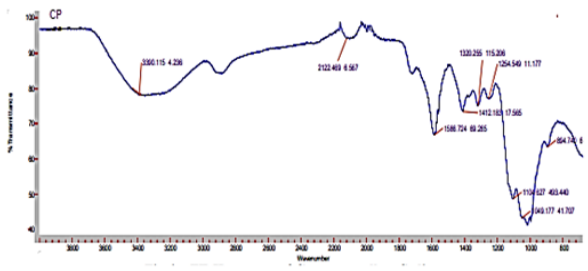


Figure 3: FT-IR spectra of crospovidone

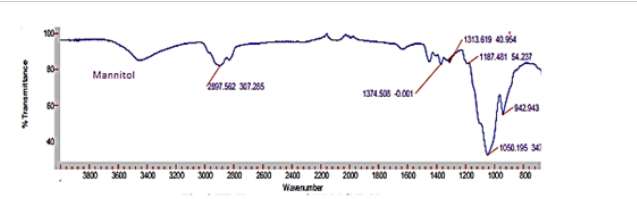


Figure 4: FT-IR spectra of mannitol

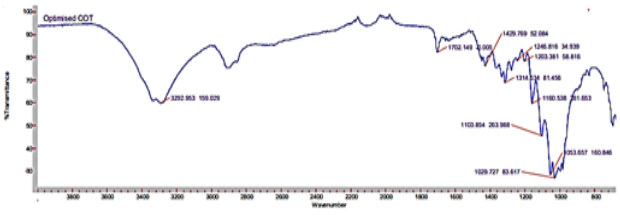


Figure 5: FT-IR spectra of optimized ODT of fexofenadine hydrochloride

models, and their related 3-D response surface plots were created by design-expert® software.[14]

RESULTS AND DISCUSSION

Determination of Drug-polymer Compatibility Studies Using FT-IR

FT-IR techniques have been used to study the physical and chemical interaction between the drug and excipients used.[15] From the FT-IR spectra, the interference was verified and found that FFH did not interfere with the excipients used. Compared with the pure FFH, the absorption peak of the spectra showed no shift and no disappearance of characteristics peaks suggested no interaction between the drug and other additives. No degradation of FFH molecule was observed during its formulation development; hence the drug excipient combinations used in the formulation development were compatible as shown in Figure 1 and 5. No change in peaks of mixture compared to pure drug indicates the absence of interactions.

Precompression Studies

Angle of Repose (θ)

All formulations showed angle of response within 30°C, indicating excellent flow of powder mixture as shown in Table 3.

Bulk Density

Loose bulk density and tapped bulk density for all formulations varied from 0.32 gm/cm^2 to 0.57 gm/cm^2 and 0.27 gm/cm^2 to 0.51 gm/cm^2, respectively. The values were within an acceptable range with minimum difference found between loose bulk density and tapped bulk density (Table 3).

Compressibility Index

Compressibility of all formulations lies within the range of 9.26–20.93, which showed good compressibility. Hausner's ratio was in the range of 1.08–1.26.

Table 4: Evaluation of post compression parameters of orodispersible tablets

Batch No	*Weight variation test**	*Thickness**	*Hardness**	*Friability**	*Drug content uniformity*
F1	300.1 ± 0.07	3.48 ± 0.04	4.2 ± 0.01	0.04 ± 0.0014	100.23
F2	299.9 ± 0.02	3.5 ± 0.02	3.9 ± 0.02	0.02 ± 0.002	99.98
F3	300.01 ± 0.05	3.49 ± 0.05	4.1 ± 0.02	0.03 ± 0.03	99.89
F4	300.12 ± 0.04	3.48 ± 0.06	4.0 ± 0.01	0.01 ± 0.002	99.63
F5	299.98 ± 0.09	3.51 ± 0.02	4.0 ± 0.03	0.05 ± 0.005	98.98
F6	300.21 ± 0.035	3.65 ± 0.03	4.0 ± 0.01	0.06 ± 0.002	99.98
F7	300.01 ± 0.021	3.59 ± 0.05	4.2 ± 0.01	0.04 ± 0.002	100.21
F8	299.98 ± 0.054	3.58 ± 0.06	4.3 ± 0.01	0.02 ± 0.001	100.14
F9	298.36 ± 0.024	3.49 ± 0.02	4.1 ± 0.02	0.11 ± 0.03	99.98
F10	299.98 ± 0.054	3.45 ± 0.01	4.0 ± 0.03	0.05 ± 0.03	99.89
F11	300.12 ± 0.021	3.32 ± 0.04	4.2 ± 0.01	0.06 ± 0.06	100.23
F12	300.24 ± 0.036	3.65 ± 0.06	4.1 ± 0.02	0.01 ± 0.002	99.87
F13	300.12 ± 0.025	3.14 ± 0.02	4.0 ± 0.02	0.22 ± 0.005	99.86
F14	299.98 ± 0.054	3.15 ± 0.06	4.2 ± 0.01	0.24 ± 0.004	100.25
F15	299.88 ± 0.054	3.26 ± 0.04	4.2 ± 0.01	0.03 ± 0.002	99.87
F16	300.12 ± 0.050	3.54 ± 0.04	4.3 ± 0.02	0.05 ± 0.004	98.89
F17	299.68 ± 0.024	3.24 ± 0.06	4.0 ± 0.02	0.04 ± 0.002	100.01

*Values are expressed as mean ± SD (n=3, $p < 0.05$)

Post Compression Studies

The results obtained for weight variation test, thickness, hardness, friability and drug content uniformity were within the limits as shown in Table 4.

Weight Variation

The % weight variation was calculated for all formulations. All the formulations passed the weight variation test as the percentage weight variation was within the pharmacopoeia limits of ± 5%. The weights of all formulations were found to be uniform with low standard deviation values.

Thickness

Thickness of all the formulations was found to be 3.14 ± 0.02 to 3.65 ± 0.03 mm with low standard deviation values.

Hardness

The crushing strength of the uncoated tablets of each batch ranged between 3.14 ± 0.02 to 3.65 ± 0.03 kg/cm^2.

Friability

The values of friability test were in the range from 0.01 ± 0.002 to 0.24 ± 0.004%. The percent friability of all the formulations was less than 1% ensuring that the tablets were stable.

Content Uniformity

The drug content of the tablets was found between to 99.63 mg to 100.23 mg. The results indicated that, in all the formulations, the drug content was uniform. The percentage drug released by each tablet in the *in-vitro* release studies were based on the mean content of the drug present in the respective tablet.

Wetting Time

Wetting time of the formulations was within 1-min showing significance of the dispersion of the tablet within minutes.

Table 5: Wetting time, disintegration and modified disintegration time

Batch no	*Wetting time (secs)*	*Disintegration time (secs)*	*Modified disintegration time (secs)*
F1	22.0 ± 3.08	48.39 ± 2.3	51.23 ± 3.58
F2	32.02 ± 3.21	46.32 ± 2.0	48.36 ± 1.54
F3	26.35 ± 3.1	50.21 ± 2.01	52.34 ± 1.53
F4	18.36 ± 3.21	52.30 ± 2.6	54.39 ± 1.16
F5	17.54 ± 0.05	46.32 ± 2.4	48.36 ± 1.23
F6	24.32 ± 0.5	45.39 ± 1.1	49.34 ± 1.34
F7	23.56 ± 2.5	48.36 ± 2.1	52.34 ± 1.43
F8	22.32 ± 1.0	49.54 ± 1.6	53.24 ± 1.24
F9	18.96 ± 1.1	52.34 ± 1.9	56.57 ± 1.25
F10	20.32 ± 2.3	54.32 ± 1.8	57.21 ± 1.54
F11	30.00 ± 2.25	48.21 ± 2.03	52.49 ± 1.64
F12	15.36 ± 2.4	47.54 ± 1.5	53.96 ± 1.54
F13	18.36 ± 1.6	46.21 ± 2.3	54.31 ± 1.36
F14	19.35	42.24	52.10
F15	25.31	45.37	50.34
F16	22.01	44.35	49.36
F17	25.30	42.30	46.54

Disintegration Time and Modified Disintegration Time

All formulations completed disintegration at simulated salivary pH of 6.8 within the acceptable limit of 1-min.

In-vitro drug release studies

All the formulations showed cumulative drug release of greater than 88.4% in 20 mins. Formulation batches F5, F10, F14 and F15 showed more than 98% drug release in 20 mins.

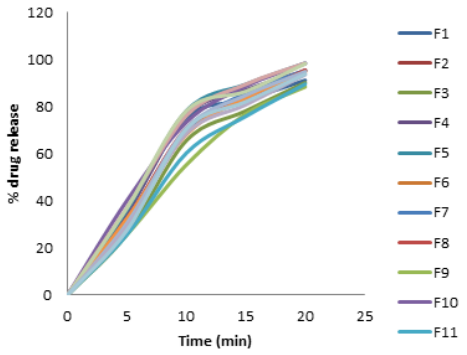


Figure 6: Drug release profile of orodispersible tablets

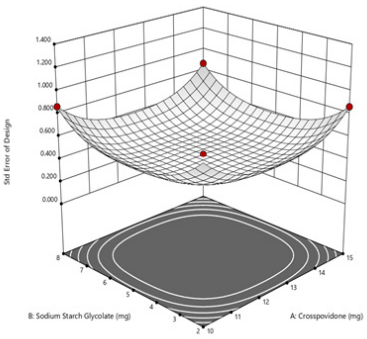


Figure 7: Standard error graph of BBD design in 3D view.

The formulation batches F9 and F11 showed lesser dissolution rate below 90%. It was observed that amount of disintegrating agent influences the dissolution rate and disintegrating time. The graphical representation of *in-vitro* drug release as shown in Figure 6.

Experimental Design

Statistical Analysis of Data

The design was validated by standard error graph which indicates the values of standard error of prediction for areas in the design space as shown in Figure 7.[16] It was satisfactory to obtain relatively minimum values of standard error close to 1 or lower across the area of interest. The results revealed that the standard error was ranged between 0.800 and less than 1, implying the efficient potential of prediction of the design.

ANOVA at 95% confidence level was applied to evaluate the model significance in the current study. The model p-values observed for Y1, Y2 and Y3 responses were 0.0132, 0.0025 and 0.0002, respectively. This implies that the independent variables manifest major effects on the tested responses away from experimental errors or chances. Besides, this illustration would be confirmed by greater values of F-ratio where their low values elucidated more error in the model. The rank order of the model predicting the capability of responses was determined as follows; Y3 > Y2 > Y1 which was based on small p-values and high values of F-ratios. Lack of fit values was used to predict the efficiency by consideration of p-values and it should be non-significant for a model to be good and fitted. The values of lack of fit for the observed dependent responses were 0.0009, 0.1985 and 0.3636 as shown in Table 6. This concluded that lack of fit values were not significant and the chance for these large values due to noise were 0.09%, 19.58 and 36.36% respectively. Total 17 formulations were prepared for optimization of the 3 independent variables (A, B and C) and then characterized to analyze the influence exerted on the observed dependent responses (Y1, Y2 and Y3).

Effect of Independent Variables on Modified Disintegration Time (Y1)

Results mentioned in Table 6 showed the significance of the model because of the high F-ratio (6.09) with *p*-value of 0.0132. This revealed that the chance for this large F-ratio to occur due to noise is only 1.32%. In our study, C, A2 were significant terms owing to their significant *p*-values. *p*-values greater than 0.1 were insignificant. The predicted R^2 of 0.7760 was in feasible agreement with the adjusted R^2 of 0.7410 where the difference between them was less than 0.2. The desirable adequate precision of 9.3294 (greater than 4) indicated an adequate signal and the model could navigate the design space as shown in Figure 8. C, A^2, C^2 are significant model terms in this model. If there are many insignificant model terms, model reduction may improve your model. Lack of Fit *f*-value of ($p > 0.05$) implies that it is not significant. The polynomial equation attained for this model was:

Disintegration time = 53.20-1.50*A-0.8750*B-2.38*C+1.25*AB-0.2500*AC+1.00*BC-6.35*A2+1.40*B2-2.10*C2

This equation stated that the variables have lesser impact on disintegration time.[17] The relationship between independent and dependent variables on disintegration time was studied by plotting the 3D response surface graphs as shown in Figure 8.

Effect of Independent Variables on Wetting Time (Y2)

As presented by Table 6, the high F-ratio of 62.40 with *p*-value of <0.0001 implied that the model was significant and there was only a 0.01% chance that this F-ratio occurred due to

Table 6: Summary of results of quadratic model for regression analysis of responses Y1, Y2 and Y3

Dependent Variables	*p*-value	F-ratio	Best fitted model	Lack of fit	Adequate Precision	Predicted R^2	Adjusted R^2	R^2
Y1 (Modified Disintegration time)	0.0132	6.09	Quadratic	Insignificant (p > 0.05)	9.3294	0.7760	0.7410	0.8867
Y2 (Wetting time)	0.0025	62.40	Quadratic	Insignificant (p > 0.05)	22.9831	0.8648	0.9719	0.9877
Y3 (*in vitro* drug release)	0.0002	23.29	Quadratic	Insignificant (p > 0.05)	15.2706	0.7099	0.9261	0.9677

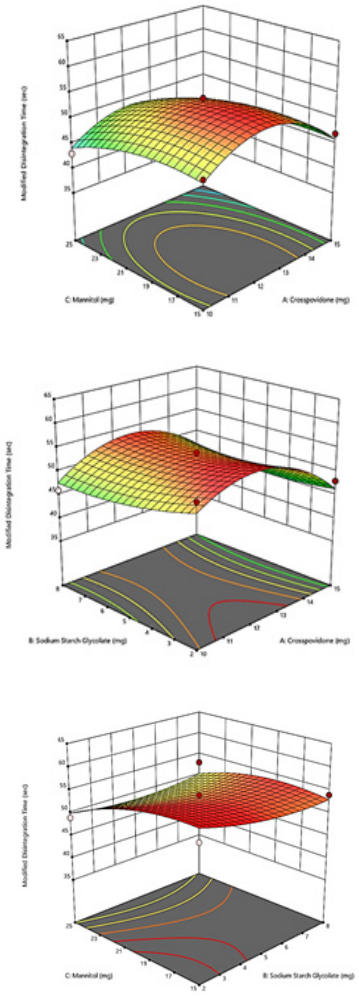


Figure 8: Response surface graphs showing the effect independent variables on modified disintegration time (Y1)

noise. In this model, A and A2 were significant model terms because of their significant *p*-values, while other terms were not significant. Also, the predicted R^2 (0.8648) was in reasonable agreement with the adjusted R^2 (0.9719) as the difference was less than 0.2. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. In this case 22.983 indicate an adequate signal. The effect of independent variables on *in-vitro* drug release along with linear correlation between predicted and actual response as shown in Figure 9. The polynomial equation was determined as follow:

Wetting time =23.40-5.62*A+0.3750*B+0.25*C-0.5*AB-0.25*BC-2.20*A2+0.3*B2+0.05*C2

Effect of Independent Variables on *in-vitro* Drug Release (Y3)

As presented by Table 6, the high F-ratio of 23.29 with *p*-value of 0.0002 implied that the model was significant and there was only a 0.02% chance that this F-ratio occurred due to noise. In this model, C and C2 were significant model terms because of their significant *p*-values, while other terms were not significant. Also, the predicted R2 (0.7099) was in reasonable

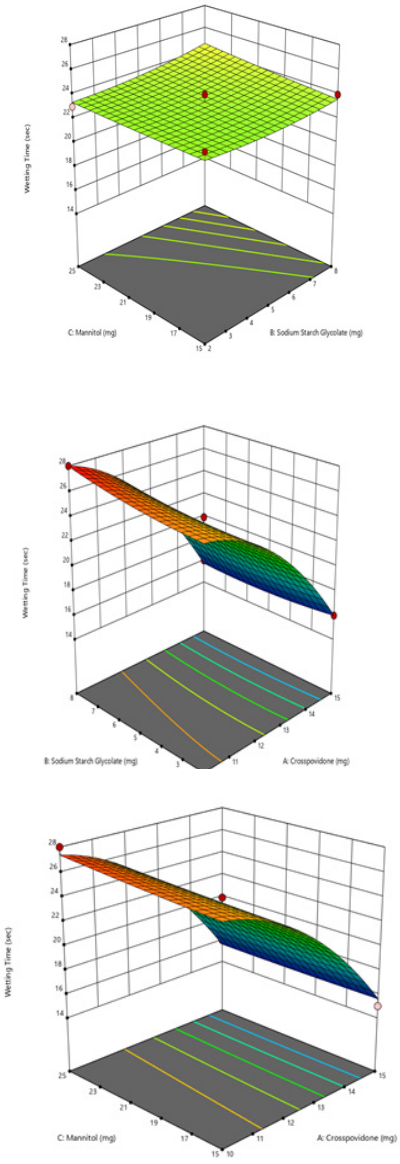


Figure 9: Response surface graphs showing the effect independent variables on wetting time (Y2)

agreement with the adjusted R2 (0.9677). Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. In this case 15.271 indicate an adequate signal.

The effect of independent variables on *in-vitro* drug release along with linear correlation between predicted and actual response as shown in Figure 10.

The polynomial equation was determined as follows:

in-vitro drug release = 94.54-0.1125*B+4.26*C+0.1750*AB-0.2750*AC+0.3*BC+0.73*A2+0.0050*B-0.7950*C2

Surface Plot for Each Response

Surface plots were obtained for the measured response based on the model using Design-Expert® software. A response surface graph shows the response as a function of factor level.

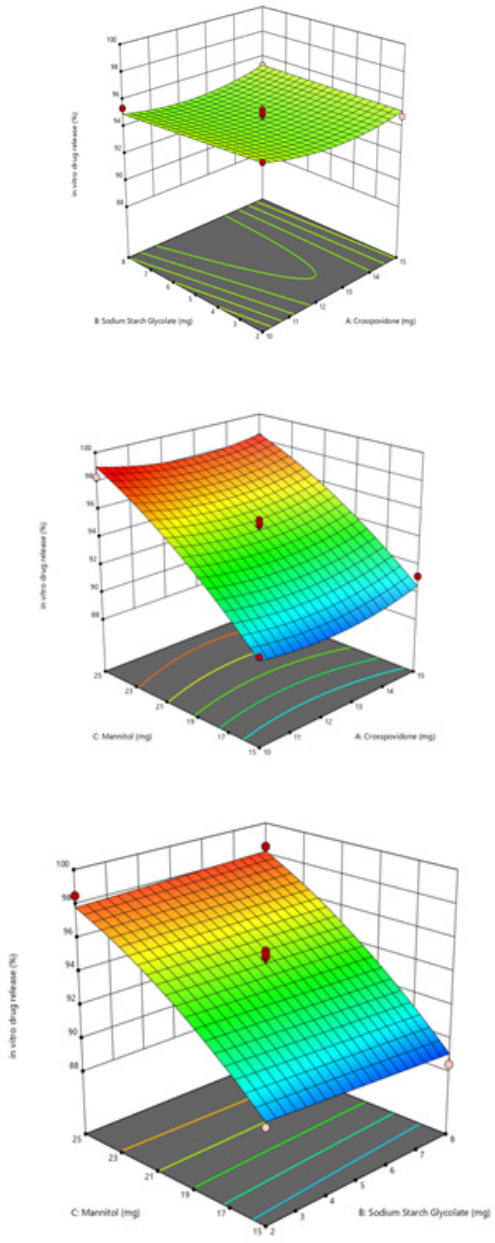
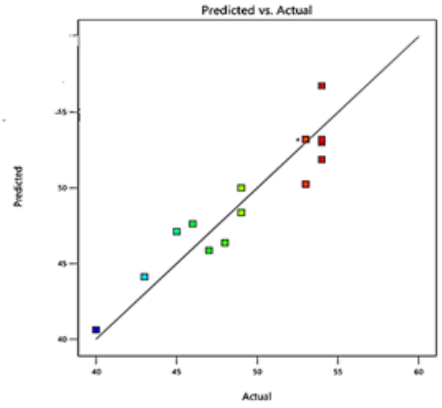


Figure 10: Response surface graphs showing the effect of independent variables on *in-vitro* drug release (Y3)

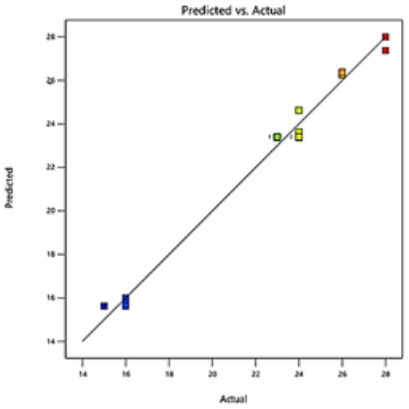
Three-dimensional response surface graphs for Y1, Y2 and Y3 were drawn for two factors only keeping the third factor constant. Significant influences of each independent variable on dependent variables were observed from all response surface graphs. The relationship between the independent variables and the response can be further explained by using these surface plots.

Linear Regression Plots and Perturbation Plots

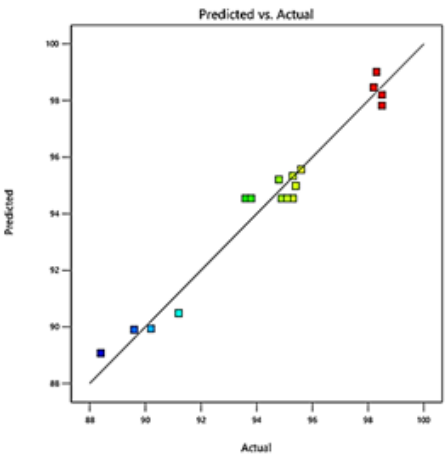
Linear regression plots were drawn between the observed and predicted values of the response properties. The linear correlation plots demonstrated high values of R- squared



a): Modified disintegration time



b): Wetting time



c): *in-vitro* drug release

Figure 11: Actual and predicted values of the responses

for all the three responses drawn between the predicted and experimental values. The effects of factors at a certain point in the design can be compared by perturbation plots in the design. The response is plotted by changing only one factor while holding all the other factors constant. The plot was plotted by Design Expert software version 13.0. This plot provided the information related to significant contribution and effect of factors to response. It was observed that wetting time and

Table 7: Effect of factors and p-values

	Intercept	*A*	*B*	*C*	*AB*	*AC*	*BC*	*A2*	*B2*	*C2*
Modified Disintegration Time	53.2	-1.5	-0.875	-2.375	1.25	-0.25	1	-6.35	1.4	-2.1
p-values		0.1018	0.3084	0.0205	0.3039	0.8307	0.4043	0.00007	0.2431	0.0975
Wetting time	23.4	-5.625	0.375	0.25	-0.5	-0.25	0.25	-2.2	0.3	0.05
p-values		< 0.0001	0.1746	0.3474	0.1973	0.4994	0.4994	0.0004	0.4096	0.8879
In vitro drug release	94.54	3.93205E-15	0.1125	4.2625	0.175	-0.275	0.3	0.73	0.005	-0.795
p-values		1.00	0.7188	<0.0001	0.6923	0.5375	0.5023	0.1208	0.9907	0.0960

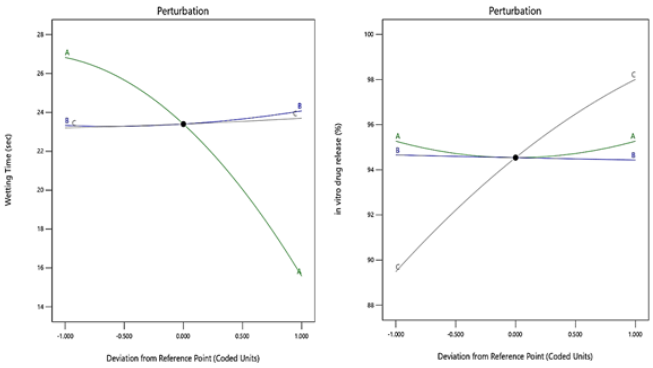


Figure 12: Perturbation plot showing the deviation from the reference point

in-vitro drug release had a major impact on orodispersible tablets because of maximum deviation from the reference point as shown in Figure 11 and 12.

Quantitative Effect of a Factor

Table 7 presents the factor effects of the BB model and associated *p*-values for response. A factor is considered to influence the response if the effects significantly differ from zero and $p < 0.05$. A positive sign indicates a synergistic effect, while a negative sign represents an antagonistic effect of the factor on the selected response. The table shows that A, B and C have a significant effect on the responses modified disintegration time, wetting time and *in-vitro* drug release. It was found A, B and C have an antagonistic effect on modified disintegration time with p values of 0.1018, 0.3084 and 0.0205, respectively, while the interaction effect AB and BC have a synergistic effect on modified disintegration time with *p*-values of 0.3039 and 04043 respectively. Similarly, B, C, BC has a synergistic effect on wetting time with *p*-values of 0.1746, 0.3474 and 0.4994, respectively. B, C, AB, BC all have a synergistic effect on *in-vitro* drug release with p-values of 0.7188, <0.0001, 0.6923 and 0.5023, respectively.

Optimizing the Formulation

Model quadratic polynomial equations were generated to relate the dependent and independent variables for the optimization of responses Y1, Y2 and Y3. The final optimal experimental parameters were calculated using the canonical analysis, which allows the compromise among various responses and searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the set. The optimally calculated parameters are shown in Table 8 and 9. The optimized formula predicted for the optimized formulation of orodispersible tablets through Box-Behnken statistical design consisted of Crospovidone, SSG and mannitol at optimum level of 14.30, 2.33, and 21.70, respectively.

CONCLUSION

Orodispersible tablet prepared using combination of two superdisintegrants, Crospovidone and SSG, showed satisfactory tablet properties. The factorial design and BBD revealed that superdisintegrant concentration has significant influence on wetting time, modified disintegration time, and *in-vitro* drug release from Orodispersible tablet. Corresponding to the independent variables, two different levels were established as the lowest and highest values of the tested variables. The matrix of seventeen experimental formulations was constructed. Minimum values of standard error close to 1 across the area of interest was satisfactory by elucidating the standard error graph. The optimized formula predicted for the optimized formulation of orodispersible tablets through Box-Behnken

Table 8: Optimizing the value of factors

Factor	*Name*	*Level*	*Low level*	*High level*	*Std. Dev*
A	Crosspovidone	14.30	10.00	15.00	0
B	Sodium Starch Glycolate	2.33	2.00	8.00	0
C	Mannitol	21.70	15.00	25.00	0

Table 9: Point prediction

Response	*Predicted*	*Observed*	*Std Dev*	*SE Mean*	*95% CI low*	*95% CI high*	*95% TI low*	*95% TI high*
Modified disintegration Time	48.4877	48.12	2.25357	1.48886	44.9671	52.0084	35.2349	61.7406
Wetting time	18.3763	17.998	0.702038	0.463815	17.2796	19.4731	14.2477	22.5049
In-vitro drug release	96.109	94.364	0.848486	0.560568	94.7835	97.4345	91.1192	101.099

CI: Confidence interval TI:Tolerance interval

statistical design consisted of crospovidone, SSG and mannitol at optimum level of 14.491, 4.2329, and 15.5481, respectively.

REFERENCES

1. Kolluru LP, Gala RP, Shastri PN, Ubale R. Design of experiments: a valuable "Quality by Design" tool in formulation development. Nanopart. Vaccine Deliv. Syst. 2015;61.
2. Beg S, Al Robaian M, Rahman M, Imam SS, Alruwaili N, Panda SK, editors. Pharmaceutical drug product development and process optimization: effective use of quality by design. CRC Press; 2020.
3. Myers RH, Montgomery DC, Anderson-Cook CM. Response surface methodology: process and product optimization using designed experiments. John Wiley & Sons; 2016
4. Lawrence XY, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. The AAPS journal. 2014;16(4):771-83.
5. Kannuri R, Challa T, Chamarthi H. Taste masking and evaluation methods for orodispersible tablets. International Journal of Pharmacy & Industrial Research. 2011;1(3):201-10.
6. Türkmen Ö, Şenyiğit ZA, Baloğlu E. Formulation and evaluation of fexofenadine hydrochloride orally disintegrating tablets for pediatric use. Journal of Drug Delivery Science and Technology. 2018;43:201-10.
7. Chaturvedi S, Agrawal VK, Singh S. Impact of superdisintegrants on the release of oro-dispersible tablets of losartan potassium: A comparative analysis. Sch Res Lib. 2012;4:1768-76.
8. Sivadasan D, Sultan MH, Madkhali O, Javed S, Jabeen A. Formulation and *in vitro* evaluation of orodispersible tablets of fexofenadine hydrochloride. Tropical Journal of Pharmaceutical Research. 2020;19(5):919-25.
9. Kaushik D, Dureja H, Saini TR. Formulation and evaluation of olanzapine mouth dissolving tablets by effervescent formulation approach. Indian Drugs. 2004;41:410-2.
10. Kumari PVK, RAO YS. Formulation and Evaluation of Orodispersible Tablets of Donepezil Hydrochloride. Int. J. Curr. Pharm. Res. 2020;12:45-51.
11. United States Pharmacopeia 24/NF19 (2000) The official compendia of standards. In: Asian Rockville MD (Ed), United States Pharmacopoeia Convention Inc, pp 1913–1914
12. Banker GS, Anderson NR. Tablets. Lachman L, Lieberman HA. The theory and practice of industrial pharmacy (Special Indian. 1987:229-345.
13. Ferrero C, Munoz N, Velasco MV, Muñoz-Ruiz A, Jiménez-Castellanos R. Disintegrating efficiency of croscarmellose sodium in a direct compression formulation. International journal of pharmaceutics. 1997;147(1):11-21.
14. Mehta DM, Dave DJ, Dadhaniya DV, Shelat PK, Parejiya PB, Barot BS. Application of Box-Behnken design to formulate and optimize multipolymeric fast dissolving film of rizatriptan benzoate. Asian J Pharm. 2014;8(1)
15. Roy H. Box-Behnken design for optimization of formulation variables for fast dissolving tablet of urapidil. Asian J Pharm. 2018;12(03).
16. Ismail S, Khattab A. Optimization of proniosomal itraconazole formulation using Box Behken design to enhance oral bioavailability. Journal of Drug Delivery Science and Technology. 2018;45:142-50.
17. Kumari PV, Yarraguntla SR, Sharmila M, Gulibindala E. Application of Box-Behnken Design for Formulation Parameters of Eslicarbazepine Tablets. Indian Journal of Pharmaceutical Sciences. 2021;83(3):575-83.
18. Abedullahh MH. Box-behnken design for development and optimization of acetazolamide microspheres. India. 2014;5:1228-39.