ORIGINAL ARTICLE

Box-Behnken Design for Optimization of Formulation Variables for Fast Dissolving Tablet of Urapidil

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Abstract

Aim: The aim of the present study was to formulate the fast dissolving tablets (FDT) of urapidil by studying the effect of the variable for response with the help of Box-Behnken design (BBD). **Materials and Methods:** A total of 17 formulations were prepared by altering the proportion of cross carmellose sodium, spray dried lactose, and hydroxypropyl methylcellulose K4M by direct compression technique. BBD was employed to study the relations among the variables and to statistically optimize the formulation parameter for FDT tablets of urapidil. Furthermore, the powder mixture characteristics and tablet physiochemical properties such as hardness, friability, drug content, disintegration time (DT), and dissolution test were performed using 900 ml of 0.1N HCl (pH-1.2) at 37 ± 0.5°C. **Results:** BBD successfully provided the significant value for the quadratic model and second order polynomial equation was plotted. Response surface and contour plots were plotted based on BBD and relationship between the variables and response (DT) were established. A perturbation graph was also plotted to identify the deviation of viable from the mean point. An optimized model was prepared based on predicted response, and the resulted response (DT) was close with the predicted value. **Conclusion:** Thus, it can be concluded that the optimized formulation with desirable parameters can be obtained by BBD with the response and variable relation. This study can be implemented and could be used in the large experiment with the involvement of a large number of variables and responses.

Key words: Box-behnken design, direct compression technique, fast dissolving tablet, response surface, urapidil

INTRODUCTION

The most well-liked solid dosage forms area unit being tablets and capsules; one vital downside of those indefinite quantity forms for a few patients such as geriatric, medicine, or medical specialty patients is that the difficulty to swallow. For these reasons tablets which will quickly dissolve or disintegrate within the oral cavity have attracted an excellent deal of attention.[1] A fast dissolving tablet (FDT) system may be outlined as an indefinite quantity type for oral administration that once placed in the mouth, quickly spread, or dissolved and may be enclosed in a type of liquid.[2] Recently, a quick dissolving formulation is popular as novel drug delivery systems as a result of their straightforward to administer and result in higher data patient compliance.[3] As tablet disintegrates in the mouth, this might enhance the clinical result of the drug through pre-gastric absorption through the mouth, tubular cavity and musculature, still as bioavailability of drug will considerably be increased by avoiding first-pass liver metabolism.

Urapidil is a sympatholytic antihypertensive drug. It acts as an α1-adrenoceptor antagonist and as a 5-HT1A receptor agonist. Although an initial report suggested that urapidil was also an α2-adrenoceptor agonist, this was not substantiated in later studies that demonstrated it was devoid of agonist actions in the dog saphenous vein and the guinea-pig ileum. guinea-pig ileum, unlike some other α1-adrenoceptor antagonists.[4,5]

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Response surface methodology explores the relationships between several control variables and one or more response variables.[6] However, an experimental design involves choosing the appropriate combination of factors and the levels of each factor to be tested. Since experimental runs cost time and money, it is pertinent to minimize the number of runs while not compromising the desired goals. To achieve this, some strategies such as full factorial, Box-Behnken (BB), and central composite designs are frequently used optimization with factorial designs and analysis of the response surfaces is powerful, efficient, and systematic tools that shorten the time required for the development of pharmaceutical dosage forms and increases research output.[7] BB experimental design allows the designer to utilize three levels of each factor (with each factor placed at one of each equally spaced value to ensure orthogonality and near rotatability) to adequately quantify second-order response models in 17 runs, inclusive of 5-replicated center points of a cubical design region. BB design can be used to construct a second-order polynomial model to describe the mutual dependency of the studied parameters.[8]

MATERIALS AND METHODS

Materials

Urapidil was procured as a gift sample from, Ahmedabad, India. Cross carmellose sodium (CCS), hydroxypropyl methylcellulose (HPMC)-K4M, and spray dried lactose were purchased from Signet chemical corporation Mumbai, India. All chemicals and solvents were used of the high analytical grade.

Computer-aided modeling

The mathematical relationship in the form of the polynomial equation and Box-Behnken design was plotted for the measured responses obtained with the statistical package of design expert V.11.

Box-Behnken experimental design

Three formulation factors were found to have significant effects on the flowability, compressibility of granules prepared by wet granulation technique and hence the characters of the compressed tablets. These factors are the percent of CCS (A), spray dried lactose (B), and HPMC K4M (C) and were used in the present study. Preliminary studies also provided a set of the levels for each formulation variable [Table 1]. The selected response was DT and cited in Table 2.

A five-level three-factor BB experimental design was used in the present study to evaluate the effects of selected independent variables on the responses, to improve the flowability, the compressibility, to characterize the drug release process, and to optimize the procedure. This design is suitable for exploration of quadratic response surfaces and construction of second-order polynomial models, thus helping to optimize the process using a small number of experimental runs. For the three-level three-factor BB experimental design, a total of 17 experimental runs as cited in Table 2.

During the run, the tablets were evaluated for physiochemical characterization and responses were recorded. In our study, it measured the DT, and in response to that the polynomial regression equation was plotted and tested for the significance. After generating the polynomial equations relating the dependent and independent variables, the process was optimized to obtain the levels of A, B, and C, which gives optimum values of Y at constrained conditions. To verify these values, a new formula was prepared according to the predicted levels of A, B, and C. Then, the tablet was prepared as per the optimized value and compared with the predicted value.

Preparation of tablet

Urapidil, CCS, spray dried lactose, and HPMC K4M were passed through #40 mesh and collected separately in a polyethylene bag. Direct compression technique was adopted for the batch preparation of FDTs. The drug and diluents were mixed in a geometrical manner and blended for a period of 20 min. The resulted mixture lubricated with aerosol for 5 min in Octagonal Blender (Mevish engineering, India). Finally, the blend was compressed to formulate tablets using tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with 6.0 mm circular flat punch.[9]

Physiochemical characterization of tablets

The physical properties such as crushing strength, friability, thickness, diameter, weight variation, drug content, and DT for every formulation were determined. Tablet crushing strength determined for 10 tablets victimization digital tablet hardness tester (Erweka TBH-28). Friability determined by

Table 1: Factors and values investigated in BBD

Factor	Name	Unit	Type	Minimum	Maximum	Mean±SD
A	Disintegrating agent (CCS)	mg	Numeric	50	150	100±35.3553391
B	Binder (Spray dried lactose)	mg	Numeric	10	30	20±7.07106781
C	Polymers (HPMC K4M)	mg	Numeric	20	150	85±45.9619408

HPMC K4M: Hydroxypropyl methylcellulose K4M, BBD: Box-Behnken design, SD: Standard deviation

Table 2: Experimental runs and observed values of responses for BBD

Run	Variable factors (mg)			Measured response (s)
	A	B	C	Y
1	100	20	85	435
2	100	20	85	436
3	50	10	85	926
4	50	20	20	582
5	100	20	85	430
6	150	30	85	405
7	100	20	85	553
8	100	30	150	450
9	100	30	20	228
10	100	10	20	274
11	100	20	85	504
12	150	20	20	403
13	50	20	150	1902
14	150	10	85	410
15	50	30	85	398
16	150	20	150	1787
17	100	10	150	1521

BBD: Box-Behnken design

testing 10 tablets in an exceedingly Roche friability tester for 4 min at 25 revolutions per minute. The thickness and diameter of the tablets were measured by Vernier calipers (Mitatoyo, Japan) to check weight variation, 20 tablets were weighed victimization a balance (Contech Instruments CA 224, India). The drug contents in terms of the assay of every batch determined in triplicate. For every batch variety of 20 tablets were weighed and crushed to fine powder victimization mortar and pestle.[10,11] Associate accurately weighed 10 mg of the powder was taken and fittingly dissolved in methyl alcohol and analyzed by high-performance liquid chromatography when creating acceptable dilutions. The procedure was disbursed on Shimadzu LC-10AT (Octadecylsilyl silica gel; 250 × 4.00 mm) with the rate of one.5 ml/min at a close temperature. Double folded tissue was placed in an exceedingly dish having an inside diameter of 6.5 cm to it added six cubic centimeters of refined water.

In vitro, DT was determined using a disintegration test apparatus (Lab Hosp, India). This test was carried out at 37 ± 20C in 900 mL of distilled water.[12]

In vitro dissolution study

The procedure was determined using United States Pharmacopoeia XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl (pH-1.2) at 37 ± 0.5°C and 50 rpm. A sample of 10 ml of the solution was withdrawn from the dissolution apparatus at 5-min interval with the replacement of fresh dissolution medium for 5 min. The samples were passed through a 0.45 μm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 268 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer.[13,14]

RESULTS AND DISCUSSION

Micromeritic study of prepared formulae

Three prime independent variables that have significant effects on preparing tablets have been revealed. These major factors include CCS (X1) as super disintegrating agent, spray dried lactose (X2) as a binder and HPMC K4M (X3) as diluent. Therefore, 17 formulae of different combinations were prepared, by taking values of the major selective variables X1, X2, and X3 at different levels as shown in Table 2.

Response data for all 17 experimental runs of BB experimental design performed in accordance with BBD and mentioned in Table 3. The result showed good compressibility and better flowability for all formulation.

Physiochemical characterization of tablets

The physiochemical properties of designed formulations are presented in Table 4. Those properties were studied by way of determining hardness, friability, thickness, drug content material, and DT. Hardness or Crushing strength of the prepared drugs ranged from 2.35 ± 1.86 to 2.85 ±1.49 kg/cm^2. It turned into observed that among all formulations containing SSG exhibited better hardness than others. The EU and US pharmacopeias state that a loss up to at least 1% is appropriate for friability. The friability of the prepared pills ranged from 0.12% to 0.49%. The thickness for all tablets ranged from 2.36 to 2.39 mm. In a weight variant test, the pharmacopeial restriction for the share deviation for capsules of extra than 150 mg is ± 3.5%. The average percentage deviation of all tablet formulations become determined to be within the above restriction, and as a result, all formulations surpassed the take a look at for uniformity of weight as in keeping with legit requirements. Uniformity in drug content become observed among unique batches of the tablets, and the percentage of drug content material became extra than 99%.

In vitro dissolution study

Different concentrations of CCS, spray dried lactose, and HPMC K4M were weighed, and tablets were prepared and subjected to *in vitro* drug dissolution studies.

All formulation released 50% of the drug in 30 min and 90% in 90 min, except F17 which released 73% in 90 min. The

Table 3: A micromeritic study of prepared formulae as per the BBD

Formulations	Bulk density	Tapped density	Hausner's ratio	Compressibility index	Angle of repose
F1	0.35±0.09	0.41±1.05	1.17	14.63	37.87±1.09
F2	0.38±0.08	0.42±0.46	1.1	9.52	38.29±0.74
F3	0.42±1.05	0.48±0.36	1.14	12.5	37.64±0.37
F4	0.45±0.65	0.51±1.41	1.13	11.76	38.46±1.17
F5	0.39±0.63	0.48±0.64	1.23	18.75	35.52±1.56
F6	0.46±0.94	0.51±0.97	1.1	9.81	37.64±1.64
F7	0.39±1.76	0.47±0.64	1.2	17.02	34.75±1.3
F8	0.52±0.85	0.56±0.29	1.07	7.14	37.86±1.96
F9	0.47±0.53	0.51±1.08	1.04	7.84	38.54±0.74
F10	0.41±1.07	0.46±1.13	1.12	10.86	33.65±2.01
F11	0.38±0.74	0.46±0.47	1.21	17.39	35.46±2.07
F12	0.39±0.46	0.44±2.05	1.12	11.36	32.86±0.75
F13	0.41±1.5	0.46±0.93	1.12	10.86	34.67±0.49
F14	0.43±0.53	0.47±1.2	1.09	8.51	31.76±1.64
F15	0.42±0.93	0.48±0.74	1.02	12.5	36.74±1.73
F16	0.47±1.85	0.51±1.7	1.08	7.84	38.34±1.41
F17	0.48±1.04	0.56±0.49	1.16	14.28	35.23±1.06

BBD: Box-Behnken design

Table 4: Physiochemical characterization of prepared tablet formulations

Formulation code	Average Weight (mg) (X±Sd)	Thickness (mm) (X±Sd)	Hardness (X±Sd)	Drug content (%) (X±Sd)	Friability (%)
F1	200.1±2.26	2.37±1.87	2.35±1.86	99.64±2.96	0.43
F2	201.1±1.27	2.37±1.06	2.45±2.75	100.76±1.42	0.47
F3	200.8±2.06	2.38±1.8	2.81±2.65	99.75±2.18	0.23
F4	200.9±1.67	2.37±1.06	2.65±1.06	101.86±2.99	0.27
F5	200.5±1.86	2.39±1.5	2.8±2.8	101.74±2.05	0.38
F6	201.9±1.89	2.37±1.05	2.75±1.64	99.64±1.74	0.48
F7	201.7±1.34	2.37±1.8	2.69±2.06	100.18±2.75	0.42
F8	199.9±1.65	2.35±1.09	2.85±1.49	101.62±2.55	0.39
F9	200.7±1.56	2.36±1.58	2.75±1.9	102.87±2.86	0.12
F10	201.8±1.86	2.37±2.98	2.76±1.86	100.3±1.56	0.42
F11	199.7±1.56	2.37±1.97	2.68±2.01	101.6±2.56	0.49
F12	201.4±2.46	2.36±1.45	2.63±2.06	102.8±1.39	0.51
F13	201.5±1.46	2.36±1.98	2.68±1.5	100.2±2.56	0.36
F14	200.4±1.49	2.37±1.12	2.70±1.96	102.8±1.43	0.42
F15	200.4±2.01	2.37±1.34	2.34±2.8	101.6±2.22	0.45
F16	201.8±1.35	2.36±1.9	2.69±2.16	101.2±3.02	0.51
F17	202.9±1.37	2.37±2.08	2.72±1.93	100.7±1.92	0.47

result showed that among all formulation, formulation F9 released 100% drug releases in 30 min. During the study, F6 and F7 were compared as per drug release. It was found that F6 release 100% of the drug in 60 min, whereas F7 released only 96%. This might be due to the higher amount of CCS in F6. It was observed that the number of superdisintegrants such as CCS and binder such as spray dried lactose has a direct effect in the percentage of drug release as shown in F9 and F10 who released 97% at 30 min and 100.76% at 60 min, respectively. A similar pattern was observed in F17 and F10 who released 73% and 99% in 90 and 60 min, respectively [Figure 1 and Figure 2].[15,16]

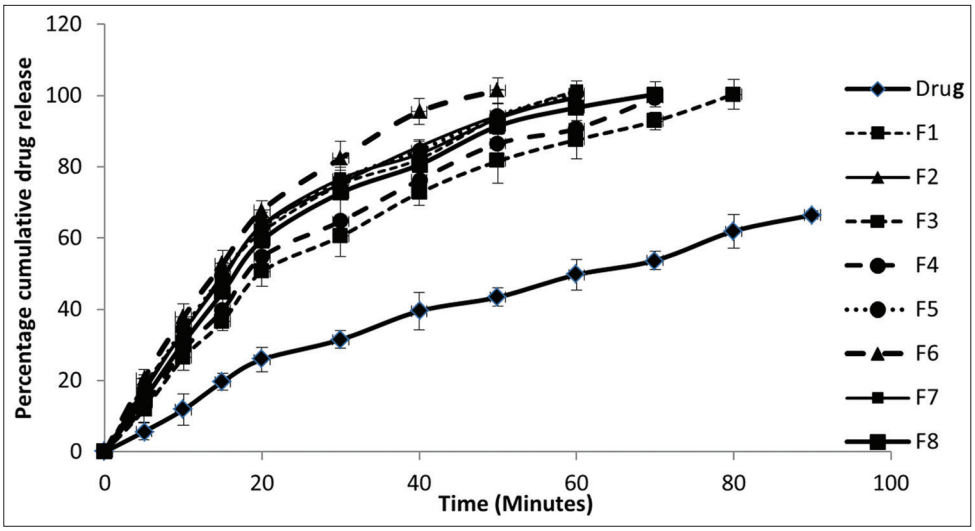

Figure 1: *In vitro* drug release for formulation F1 to F8 and pure drug. Data shown are the mean ± standard deviation (n = 3)

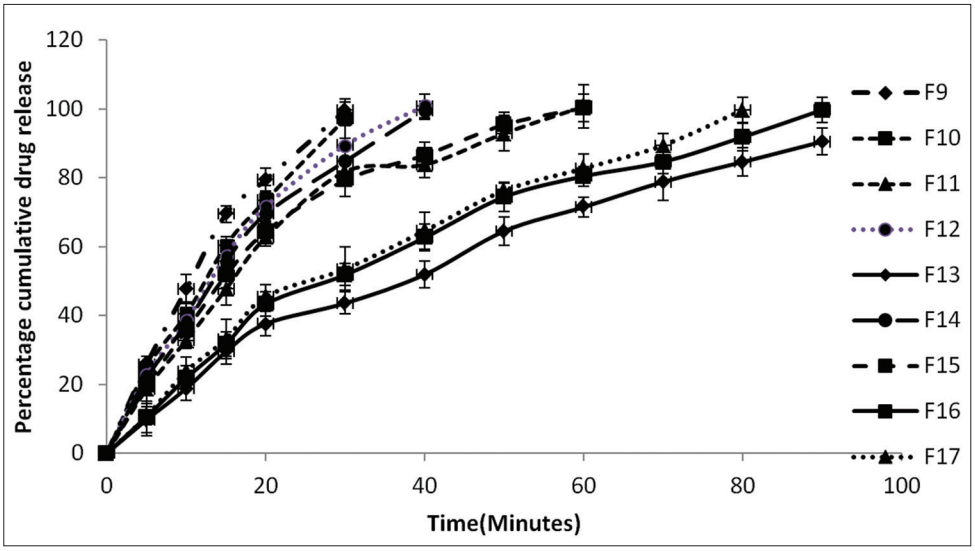

Figure 2: *In vitro* drug release for formulation F9 to F17. Data shown are the mean ± standard deviation (n = 3)

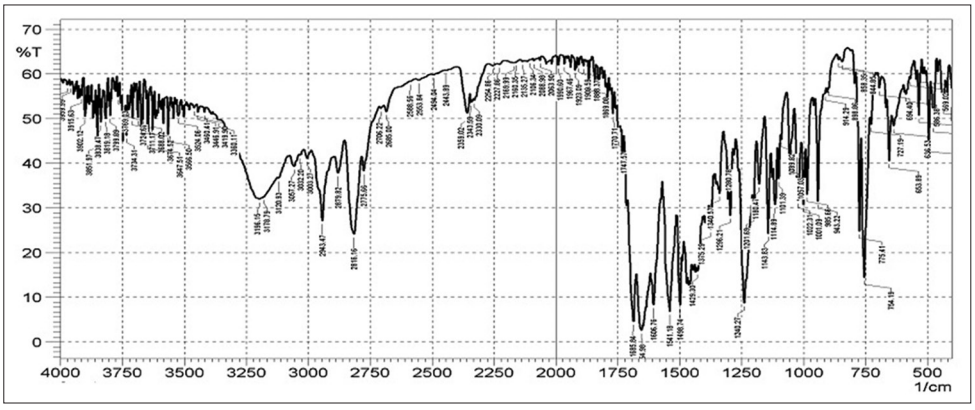

Figure 3: Fourier transform infrared spectrum of pure drug

Drug-polymer interaction study

The drug - excipient interaction was studied using Fourier transform infrared (FTIR) (FTIR 8400S, Shimazu). IR spectra for drug and powdered tablets were recorded in a FTIR spectrophotometer with KBr pellets. The spectra were scanned over the 3600–400 cm^{-1} range. The FTIR spectrum of Urapidil [Figure 10a] exhibited a broad intense band at 3196.15 and 3178.79 cm^{-1} assigned to C–H

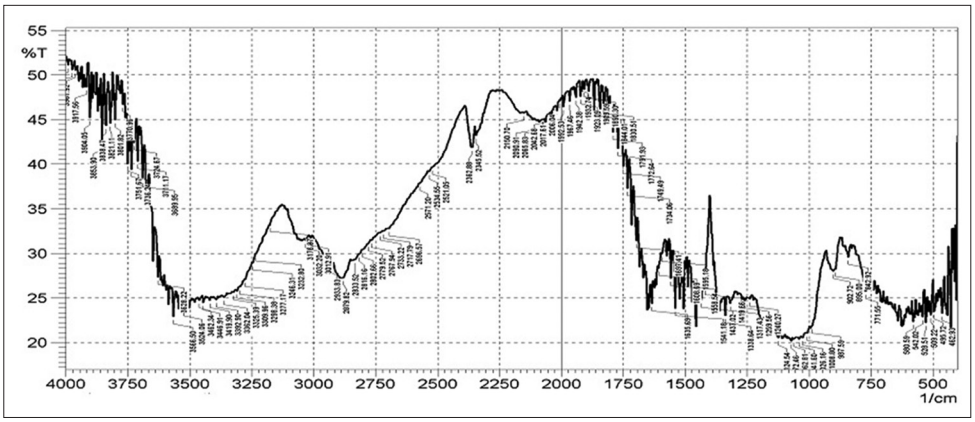

Figure 4: Fourier transform infrared spectrum of the formulation

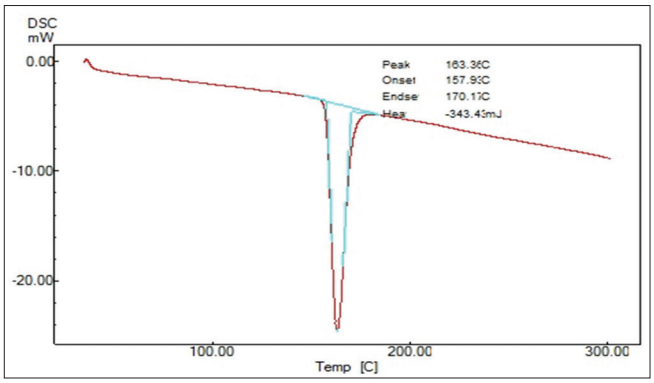

Figure 5: Differential scanning calorimetry of pure drug

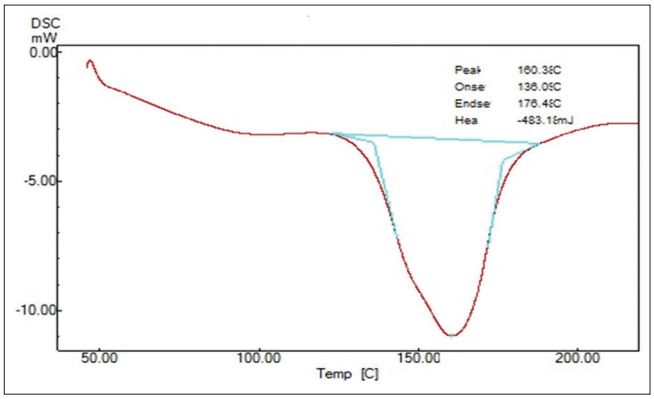

Figure 6: Differential scanning calorimetry of formulation mixture

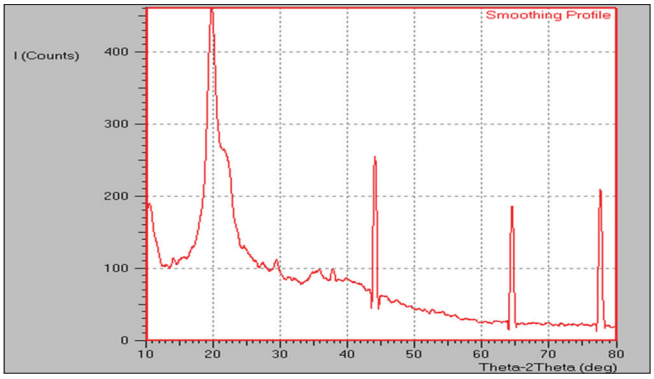

Figure 7: X-ray powder diffraction spectrum of pure drug

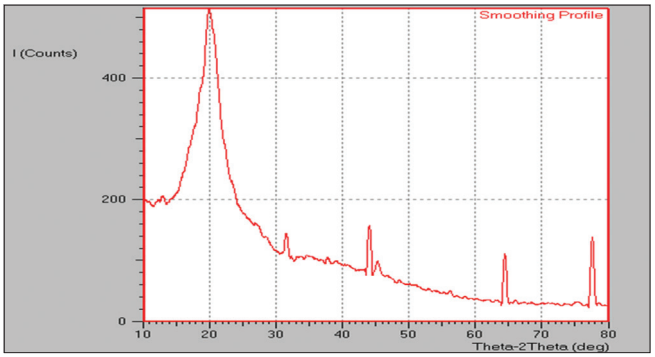

Figure 8: X-ray powder diffraction spectrum of drug mixture formulation on storage for 24 h

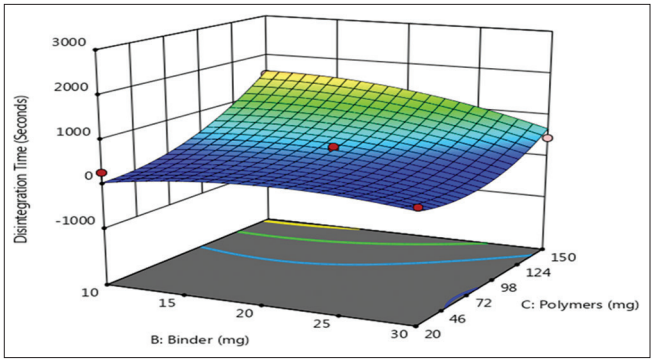

Figure 9: 3D response surface plot showing the effect of B and C on response Y (disintegration time)

vibrational stretching in the aromatic ring, "overtone" (2000–1665 cm^{-1}) and Oop band (900-675 cm^{-1}) are characteristic peaks for an aromatic ring. It was found that there was no remarkable change and chemical interaction found between Urapidil and excipients used as cited in Figures 3 and 4.

Differential scanning calorimetry (DSC) study

DSC has shown to be an important tool to quickly obtain information about possible interactions between the active and the excipients, according to the appearance, shift or disappearance of endothermic or exothermic peaks. DSC study was performed using DSC 8000 Perkin Elmer instruments to

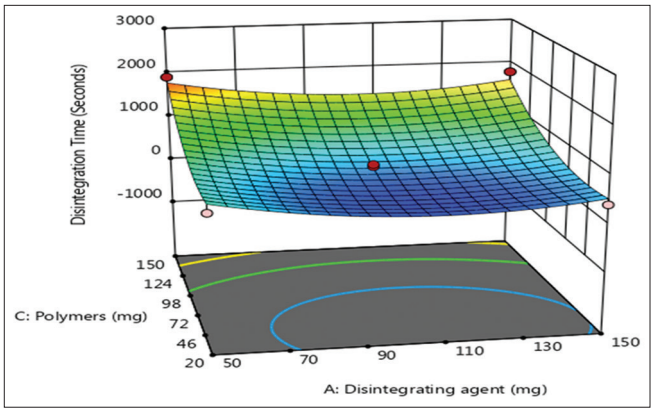

Figure 10: 3D response surface plot showing the effect of A and C on response Y (disintegration time)

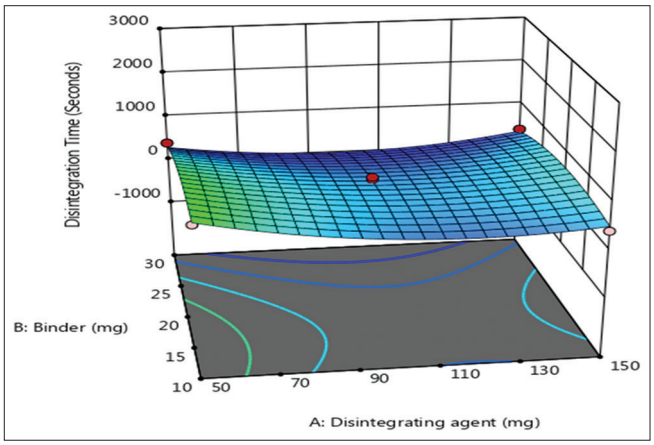

Figure 11: 3D response surface plot showing the effect of A and B on response Y (disintegration time)

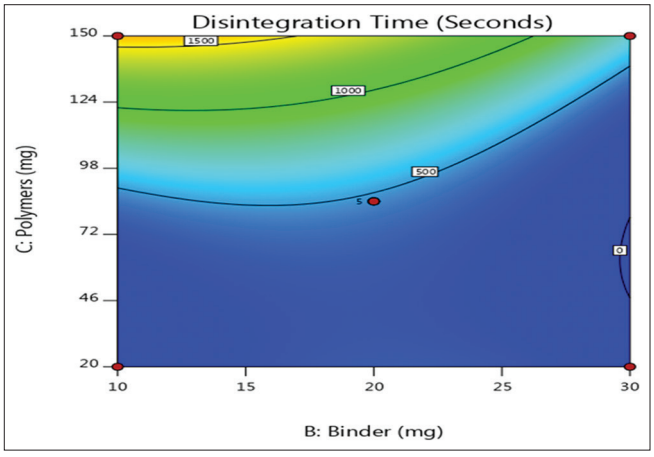

Figure 12: Contour plot showing the effect of B and C on response Y (disintegration time)

determine the drug excipient compatibility study. During the study, a sharp endothermic peak for Urapidil was obtained at 163°C corresponding to the melting point. However, in the formulation, there was a slight change in peak temperature and peak shape as seen in Figure 5 and Figure 6, which might be due to the reduction of the purity level of component and interaction with excipients.

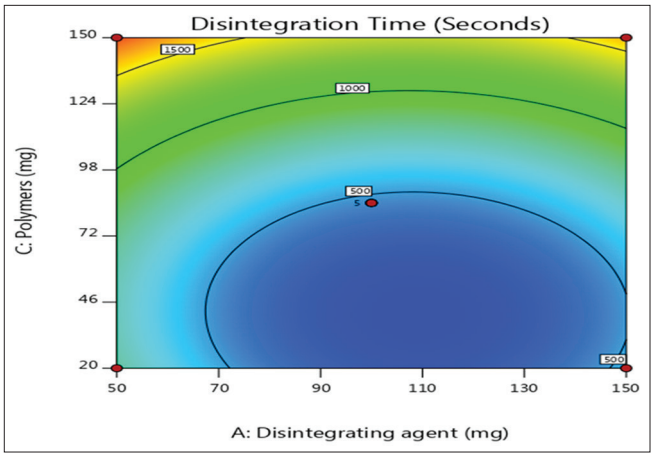

Figure 13: Contour plot showing the effect of A and C on response Y (disintegration time)

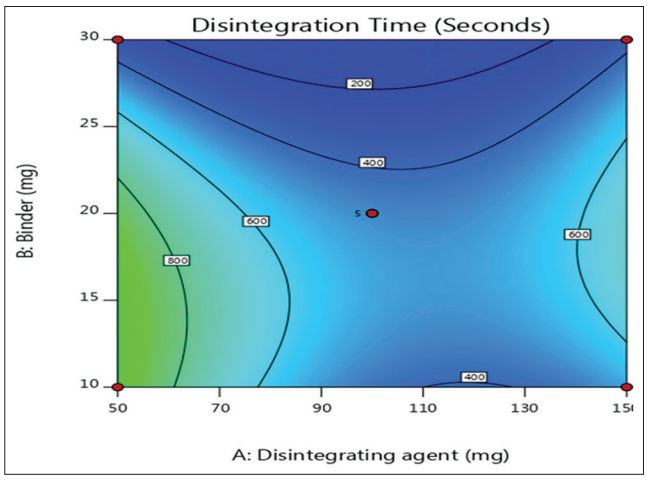

Figure 14: Contour plot showing the effect of A and B on response Y (disintegration time)

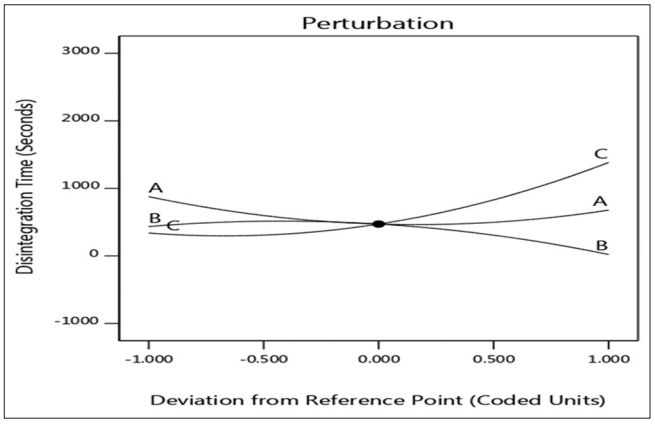

Figure 15: Perturbation plot showing the deviation from the reference point

X-ray powder diffraction (XRD) study

Change in crystallinity of the drug can be determined by this technique. Pure drug and components mixture was analyzed with the help of XRD 7000, Shimadzu. Pure Urapidil showed

the classical diffractogram of the crystalline substance. The drug mixture did not show and remarkable change in crystallinity, but slightly decreased in peak heights were observed due to moisture and impurity as cited in Figure 7 and Figure 8.[17]

BB experimental design

Effect on DT by the combined influence of binder and a disintegrating agent

The Y response was ranged from 228 s to 1521 s. It was found that the role of the polymer has a major contribution in determining the disintegrating time. It was observed that as the amount of CCS increased the DT time gradually decreased as cited in F12 and F14 with a value of 403 s and 410 s, respectively.[18] During the study, it was also observed to have the direct effect of HPMC K4M on DT time. As the amount of HPMC K4M increased progressively, the DT Time also increased as in formulation F16 and F17 with a value of 1787 and 1521 s, respectively. From the study, it can be assumed that the HPMC K4M have additive binding character and tightly hold the particles and progressively increased the DT time.

Contour and response surface plot

Three-dimensional response surface plots with contour below for the measured response were constructed based on the model polynomial functions to assess the change of the response surface. The relationship between the dependent and independent variables can be further understood by these plots.

The figure shows the response surface plot, which displays the effect of A, B, and C on the DT time response. From the figure, it observed that when X1 value wax 118.5 and X2 value 29.8 the response value was 91.03. Similarly, as the value changed for X1 at 107.09 and X2 at 26.86, the response recorded was 220.09 s. During the study, it observed that as the amount of X1 and X2 increased gradually the Y value also increased as found in Figures 9, 10 and 11. It was also found that the effect of C has major importance in DT time. The value for DT time increased as the X1 and X2 increased. From the point of the experiment, it can be concluded that all the three variables have a significant contribution on DT time as also confirmed in the 2D contour plot as seen in Figures 12, 13 and 14.

Formation of the second order model

For the estimation of coefficients in the approximating polynomial function, applying uncoded values of factor levels, the least squares regression method was performed using the design expert software.

$$\text{Disintegration time (DT)} = 471.6\text{-}100.37\ A\ \text{-}206.2\ B\ +521.6\ C\ +130.75\ AB\ +16.0\ AC\text{-}256.25\ BC\ +\ 306.7\ A^2\text{-}\ 243.5\ B^2+\ 390.2\ C^2 \quad (1)$$

Quantitative effect of a factor

In Table 5, the factor effects of the BB model and associated *P*-values for response are presented. 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.

From the table, it observed that B and C have a significant effect on the response (DT). It found C have a synergistic effect and B have an antagonistic effect on DT with a *P*-value of 0.0001 and 0.0178, respectively, while the interaction effect (BC) has significant antagonistic effect with *P*-value of 0.0304. During the study, it found that the quadratic effect by A^2, B^2, and C^2 has a significant effect on response DT.

Perturbation plot

The perturbation plot helps to compare the effects of all the factors at a particular point in the design space. The response

Table 5: Effect of factors and *P*- values

Response	Intercept	A	B	C	AB	AC	BC	A^2	B^2	C^2
DT	471.6	−100.375	−206.25	521.625	130.75	16	−256.25	306.7	−243.55	390.2
P-values		0.1775	0.0178	0.0001	0.2098	0.8706	0.0304	0.0127	0.0335	0.0039

DT: Disintegration time

Table 6: Optimizing the value of factors and a point prediction

Factor	Name	Level	Low Level	High Level	Std. Dev.
A	Disintegrating agent	100	50	150	0
B	Binder	24.1058248	10	30	0
C	Polymers	99.8450829	20	150	0

Point prediction

Response	Predicted	Observed	Std. Dev.	SE Mean	95% CI low	95% CI high	95% TI low	95% TI high
DT	461.315983	467.48	189.3887	83.1627	264.667	657.964	−572.95	1495.58

CI: Confidence interval, DT: Disintegration time

is plotted by changing only one factor over its range while holding all the other factors constant. The plot was plotted by design expert V 11.0 software. This plot provided the information related to significant contribution and effect of factors to response. It observed that, the effect of polymer had major contribution on prepared dosage form as found in Figure 15.

Optimizing the formulation

After generating the model polynomial equations to relate the dependent and independent variables, the process was optimized for responses. 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 6.

CONCLUSION

Urapidil FDT was prepared using the statistical parameter. The use of BB with three factors and two levels significantly helped to found the relationship between factors and response (DT time). The final formula prepared by based on predicted values and the observed value was pretty close with predicted one.

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