ORIGINAL ARTICLE

Formulation by Design Approach for Fizzy Granules Using Statistical Optimization Methodologies

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Abstract

Context: Patient compliance is a major problem in the administration of medicines to pediatric patients mainly due to bitter taste or fear of medication. Therefore, novel formulation development based on current industrial practices is need of the hour. **Aims:** To prepare fizzy granules of amoxicillin trihydrate using formulation by design (FbD) concept to increase the patient compliance in pediatrics. **Settings and Design:** Critical process parameters were selected using Plackett–Burman design while their concentrations were optimized by application of response surface methodology using 20 confirmatory runs, which indicated very high degree of prognostic ability of statistical optimization. Low and high levels of each factor represented maximal and minimal settings of wide operational ranges. **Materials and Methods:** Formulations were prepared by non-aqueous wet granulation method. **Statistical Analysis Used:** Statistical methodologies were used to screen significant variables and responses, which affect the quality of fizzy formulation. Sodium bicarbonate, polyvinyl pyrrolidone, and lactose were selected as critical excipients, based on *t*-coefficient values as obtained through Plackett–Burman design. Then, 3^3 central composite design was employed to systematically optimize these variables and desired quality attributes, particle size (PS), and fizzy time. Contour plots were drawn, and optimum concentrations of selected excipients were determined using point optimization feature. **Results:** Developed polynomial mathematical models were found suitable to define effervescence time and PS of the optimized formulation with 98.46% and 91.24% validity. **Conclusion:** FbD concept was successfully applied for the development of fizzy granules as per current quality practices prevailing in pharmaceutical industries.

Key words: Amoxicillin, central composite design, design of experiments, fizzy granules, formulation by design, Plackett–Burman, response surface methodology, wet granulation

INTRODUCTION

There are various patient compliance problems in children such as unwillingness to take medicine, vomiting after administration, duration of treatment, parents income, fear of adverse effects, and bitter taste.[1-3] Among these, the most significant problem is an unwillingness to take medicine by children due to bitter taste. Due to this non-compliance usually, children vomit out the drug. Many patients find difficult to swallow solid unit dosage forms; consequently, they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem of ulcer, which results in high incidence of non-compliance and ineffective therapy. Recent developments in the fizzy formulations provide a convenient solution for patients who have difficulties in swallowing tablets and other dosage forms. Fizzy formulations dissolve or disintegrate in the water with effervescence and can be easily swallowed.[4] The time required for this process should be as small as possible because the WHO guidelines for the development of pediatric medicines suggest intake of the fizzy formulation after subsiding the effervescence.[5]

Fizzy granule based formulations have potential advantages over conventional dosage formulation, with improved patient compliance, convenience, bioavailability, and rapid onset of action. This formulation is a very good alternative

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Received: 21-09-2015
Revised: 16-11-2015
Accepted: 25-11-2015

for drug delivery to geriatric and pediatric patients. These dosage forms have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after administration in water. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus fizzy formulation has tremendous scope for being the delivery system for most of the drugs in near future.[6]

The manufacturing process for pharmaceuticals is well-understood when target product profile is defined, product composition and production route are established, critical process parameters (CPPs) are selected, control methods developed, proven acceptable ranges (PARs), and design space are established. The development of pharmaceutical formulation and its process involves a number of variables. So, to manage such number of variables optimization by experimental design and chemometric data evaluation is the best approach. Among many development strategies, statistical formulation by design (FbD) is considered as the most beneficial tool for the scientific knowledge acquisition, since it is relevant for multi-factorial relationships investigation.[7-9]

Use of statistical methods is gaining popularity in the pharmaceutical industry to optimize the production process. Specifically, the goal of these methods is to identify the optimum settings for the different factors that affect the production process. Since technological processes have many input and output variables, i.e., operational parameters (speed, time, etc.) and possible product outcomes (loss on drying, flow property, % fines, particle size [PS], and effervescence time, etc.) it looks impossible to test all of them in a structured and organized manner. Therefore, it is accepted to use prior knowledge to establish significant parameters, the so-called CPPs. The CPPs are parameters whose variability in limited range impact drug critical quality attributes (CQA), and hence, should be monitored or controlled to ensure that the process produces the desired quality. Other granule properties (granule size distribution, angle of repose, loose and tap density (Hausner index) and loss on drying) may also be considered to evaluate the fizzy granules.[10] Various methods for optimization are reported in the literature, which includes a Lagrangian method, simplex method, and response surface methodology (RSM). Among these, RSM is having the advantage that it can handle many independent variables at a time. The use of FbD in all areas of drug discovery has steadily increased over the past few years, but it is far from being adopted as standard practice. RSM was applied extensively to optimize formulations using variable excipients, by investigating main and interactive effects of formulation variables. Good correlation between the predicted values and experimental data of the optimized formulation validated the prognostic ability of RSM in these studies.[11-17]

Plackett–Burman design is used for determination of CPPs involved in the process. To avoid such time consuming conventional processes, approaches such as Plackett–Burman design are used to decrease the number of experiments. These approaches are approved by U.S. FDA. This is preferred because only eight experiments are required for evaluation of seven factors by Plackett–Burman design and for a similar number of factors full factorial design requires 128 experiments.[18-20]

The present work summarizes application of FbD approach for formulation of fizzy granules, which leads to increase in patient compliance and will serve as a lead formulation for various drugs and help in the development of numerous formulations with improved patient compliance.

MATERIALS AND METHODS

Materials

Amoxicillin trihydrate (AT) drug was gifted by Ind-swift Pharma, Chandigarh, India and other ingredients such as citric acid, sodium citrate (anhydrous), tartaric acid, sodium bicarbonate (anhydrous), lactose, polyvinyl pyrrolidone (PVP) K-30, and ethanol were used. All other chemicals and solvents used were of analytical grade and were procured from Merck India Ltd. Milli-Q water was used throughout the study.

Methods

Pre-formulation studies

Various parameters of pre-formulation studies such as solubility, Fourier transform infrared (FT-IR) and ultraviolet (UV) spectroscopy, etc. were performed [Figure 1].

Preparation of fizzy granules

Wet granulation method was used to prepare granules because of its ease of manufacture and low cost. AT fizzy granules were prepared by wet granulation method in accordance with Plackett–Burman recipe [Table 1] and central composite design (CCD) recipe [Table 2]. Adequately pre-weighed ingredients were triturated and sufficiently blended with ethanol to obtain a wet mass, so this dough mass was passed through sieve no. 20 and the granules, so obtained, were dried in an oven at 50 ± 5°C until the moisture content was below 1%. The granulation step was being precisely timed, and the ingredients were mixed thoroughly to distribute the solvent evenly in the blend.[21]

FbD based statistical optimization of fizzy formulation

For the optimization of fizzy formulation, Design-Expert® 5.0 Software, Stat-Ease Inc., USA was used to design

Table 1: Selected process variables in the CCD

Process	Levels		
	Low	Center	High
Dependent variables			
Sodium bicarbonate (g)	4.00	10.00	16.00
PVP (g)	0.10	0.55	1.00
Lactose (g)	0.10	0.55	1.00
Independent variables			
Citric acid (g)		3.40	
Tartaric acid (g)		4.00	
Sodium citrate (g)		2.80	

PVP: Polyvinyl pyrrolidone, CCD: Central composite design

Table 2: Plackett–Burman recipe using design-expert software

Run (*n*)	Responses	
	FT (min)	PS (mm)
1	0.658	0.0217
2	0.893	0.030
3	0.664	0.041
4	0.692	0.026
5	0.671	0.033
6	0.531	0.038
7	0.621	0.040
8	0.731	0.040

PS: Particle size, FT: Fizzy time

experimental recipe for statistical optimization. Statistical analysis of experimental data was also performed using this software.[22] Excipients under study were added to the formulation according to the experimental recipes developed by Design Expert software while concentrations of rest of the components were similar.

Plackett–Burman factorial design

The Plackett–Burman factorial design was employed in this study to correlate dependent and independent variables using the following polynomial model:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + \text{----------} + A_n X_n$$

Where, Y is the response, A_0 the constant, and A_1 to A_n are the coefficients of the response values.

Plackett–Burman design was used to establish the degree of significance of selected parameters on effervescence time and PS. Each component was tested at two levels, a high (+) and a low (−) level as given in Table 3. These levels define the upper and lower limits of the range covered by each variable known as PARs. A seven-factor 8-run Plackett–Burman screening design was generated using Design-Expert software (Design expert 5) as shown in Table 4.

Table 3: Factors in the Plackett–Burman screening design

Excipient	Low level (–)	High level (+)
Citric acid (g)	2	8
Tartaric acid (g)	2	8
Sodium citrate (g)	1	8
Sodium bicarbonate (g)	4	16
Lactose (g)	0.1	1
PVP (g)	0.1	1
Flavor (g)	0.02	0.1
Drug (mg)	Constant	

PVP: Polyvinyl pyrrolidone

Each variable was represented at two levels, namely, "high" and "low." In addition to the variables of real interest, the flavor was used as a dummy variable to introduce some redundancy required by the statistical procedure. Incorporation of the dummy variables into an experiment allows an estimation of the variance (experimental error) of an effect.[23] Experiments were done in triplicate and data analysis was done using Design-Expert software and *t* coefficients test for each of the selected parameter were calculated by performing analysis of variance (ANOVA) test.

RSM

CCD of RSM was used in order to investigate the relationship between most effective variables, i.e., X_1: Concentration of sodium bicarbonate, X_2: Concentration of PVP and X_3: Concentration of lactose and to find out their concentration for optimization of critical response variables, i.e., Y_1: PS and Y_2: Effervescence time. Selected dependent and independent variables and their range(s) for the present study are given in Table 1.

A 3^3 factorial design consist of 20 experiments was used for this purpose. The formulation composition and effective variables concentration were selected according to the software-based design and experiments were performed in triplicate. Different combinations of variables and their concentration given by design module of Design-Expert software are shown in Table 5. A multiple regression analysis of the data obtained from an experiment performed was carried out for obtaining respective empirical models that relate the responses measured to the independent variables.[24]

The polynomial equation generated by CCD experimental design was described as equation:

$$Y = b_0 + b_1A + b_2B + b_3C + b_{12}A*B + b_{13}A*C + b_{23}B*C + b_{11}A^2 + b_{22}B^2 + b_{33}C^2$$

Where, Y is the measured response associated with each factor level combination (dependent variable); b_0 is an intercept; b_1 to b_{33} are regression coefficients computed from the observed experimental values of Y from experimental runs; and A, B, and C are the coded levels of independent variables, as shown

Table 4: Plackett–Burman screening design with seven variables in coded values

Run (*n*)	Ingredients						Flavor (g)
	Citric acid (g)	Tartaric acid (g)	Sodium citrate (g)	Sodium bicarbonate (g)	Lactose (g)	PVP (g)	
	1	2	3	4	5	6	7
1	−1	−1	+1	+1	−1	−1	+1
2	−1	−1	−1	+1	+1	+1	−1
3	+1	−1	−1	−1	−1	+1	+1
4	−1	+1	−1	−1	+1	−1	+1
5	+1	+1	−1	+1	−1	−1	−1
6	−1	+1	+1	−1	−1	+1	−1
7	+1	−1	+1	−1	+1	−1	−1
8	+1	+1	+1	+1	+1	+1	+1

Table 5: Proposed experimental recipe by CCD for optimization studies

Run	Type	Sodium bicarbonate (g)	PVP (g)	Lactose (g)
1	Center	10	0.55	0.55
2	Axial	10	0.55	0.55
3	Fact	10	0.55	0.55
4	Fact	10	0.55	0.55
5	Fact	10	0.55	0.55
6	Center	10	0.55	0.55
7	Fact	–0.09	0.55	0.55
8	Fact	20.09	0.55	0.55
9	Axial	10.00	–0.21	0.55
10	Axial	10.00	1.31	0.55
11	Fact	10.00	0.55	–0.21
12	Center	10.00	0.55	1.31
13	Axia	4.00	0.10	0.10
14	Fact	16.00	0.10	0.10
15	Center	4.00	1.00	0.10
16	Axial	16.00	1.00	0.10
17	Center	4.00	0.10	1.00
18	Fact	16.00	0.10	1.00
19	Axial	4.00	1.00	1.00
20	Center	16.00	1.00	1.00

PVP: Polyvinyl pyrrolidone, CCD: Central composite design

in Table 5, which were selected on the basis of preliminary experimentation.[25]

Evaluation of granule properties

PS distribution

The fizzy granulate was prepared by sieve and granule size was analyzed by sieve analysis. The size, so determined, was presented as mm.

Fizzy time (FT)

Accurately weighted fizzy granules (5 g) were added in 10 ml of distilled water and the time for *in vitro* effervescence till it ceases was determined and denoted as FT.

Assay of amoxicillin fizzy granules

Drug content of was assayed using Waters, USA HPLC system, having C18 column, 515 pumps, and 2998 detector. The assay was performed in under chromatographic conditions, which involve mobile phase methanol:0.02 M phosphate buffer pH 3.5 (50:50% v/v). The elution was performed at a flow rate of 1 ml/min with UV detector at 229 nm. The retention time of drug was found to be 3.9 min.[26]

Stability studies

The above formulation was packed in high-density polyethylene bottles with silica gel, charged for stability at 25 ± 2°C, 60% relative humidity (RH) and 40 ± 2°C, 75% RH, and evaluated for PS and FT for 3-month at intervals of 1 month. The stability study was performed as per ICH Q1AR2 guidelines which are for stability studies of the new drug product.[27]

Analysis and validation of the model

20 formulations were generated by CCD. All the responses observed were simultaneously fitted to linear and quadratic-models and were evaluated in terms of statistically significant coefficients and R^2 values.[28] Three-dimensional (3D) response surface plots were generated by the Design Expert 5.0 software. "Point optimization" feature of the software was used to determine the most optimum concentration of selected variables. Finally optimized checkpoint formulations were selected to validate the chosen experimental domain and polynomial equations.[29] The resultant experimental values of the responses were quantitatively compared with that of the predicted values to validate experimental design for validation of proposed model.[16]

RESULTS AND DISCUSSION

Pre-formulation studies

From pre-formulation studies, it was found that AT was practically insoluble in water, freely soluble in 0.1 N KOH. It shows λ_{max}, i.e., 245.7 nm in 0.1 N KOH. All the peaks in FT-IR spectra were found to be in compliance with the standard spectra of AT.

Statistical optimization of fizzy formulation

Applications of statistical experimental designs are useful techniques to optimize the formulation and process variables. Traditionally, pharmaceutical formulators used to change one single variable at a time but that did not give an idea about the interaction among the other variables, so optimization of formulations was a tedious process.[30] The statistical experiment designs to overcome the limitations of the conventional approach and require less number of experiments to achieve an optimum formulation, yielding the "best solution" in the presence of competing objectives which results in saving time, cost and manpower. Moreover, it helps in understanding the interactions among factors.

Selection of critical excipients using Plackett–Burman design

The Plackett–Burman screening design was used to screen different excipients based on the magnitude of their effect on CQAs for fizzy formulation. Low and high values for each factor tested in screening design were identified in preliminary experiments to define PARs. The magnitudes of responses for each of the eight experiments are given in Table 2. Values of *t*-coefficients for each of the selected parameter were calculated by performing ANOVA test and are given in Table 6.

Based on obtained values of *t*-coefficients for each of the excipients tested, sodium bicarbonate, PVP, and lactose were selected as main effective excipients while rest of the ingredient, i.e., citric acid, tartaric acid, sodium citrate, and flavor were less significant with respect to selected quality attributes *viz.* FT and PS. After the screening of parameters and ingredients, RSM was applied for optimization of formulation composition.

RSM

For optimization of most effective variables (sodium bicarbonate, PVP, and lactose) to get selected responses (FT and PS) in PARs, CCD of RSM was applied using Design Expert software. The recipe of 20 experimental runs of dependent and independent variables and most effective responses, i.e., PS and FT by the CCD is presented in Table 7. Different combinations of sodium bicarbonate, PVP, and lactose resulted in significant variations in effective responses, i.e., PS as low as 0.4009 mm (Run 16) and as high as 2.534 (Run 11) and in FT as low as 0.331 min (Run 8) and as high as 1.815 min (Run 15). This indicated the significance of the interaction of effectors and their effect on overall response.

Statistical analysis

Statistical testing of the models (PS and FT) was done by ANOVA test to check model accuracy, and the results are summarized in Table 8. Goodness of the FT and PS can be checked by the determination coefficient (R^2) and correlation coefficient (R). The coefficient of determination ($R^2 = 0.9846$ and 0.9124) indicated that the sample variation of 98.46% and 91.24% was attributed to the independent variables and only about 1.54%, and 8.76% of the total variation cannot be explained by the selected model. The value of R indicates the degree of correlation between the experimental and predicted values. Values of R as close to 1.0 reflects better agreement for validation of predicted and actual values. In the present study, the value of R (0.9846 and 0.9124) being close to 1.0 indicated a close agreement between the experimental results and theoretical values predicted by the model. Quadratic terms of both PS and FT were highly significant as reflected by $P > F$ values of 0.0001 and 0.0001, respectively.

Model equations

Polynomial equations were generated for both the responses and were given below:

$$FT = 0.57 + 0.041A + 0.024B - 8.977C - 0.13A^2 - 0.032B^2 - 0.021C^2 - 0.036AB + 0.033AC - 0.14BC \quad \text{Equation (1)}$$

$$PS = 0.51 - 0.24A + 0.028B + 0.011C + 0.14A^2 + 0.019B^2 + 0.040C^2 - 0.029AB + 0.031AC + 0.027BC \quad \text{Equation (2)}$$

Where, FT = Fizzy time; PS = Particle size; A = Sodium bicarbonate; B = PVP, and C = Lactose.

Table 6: Statistical analysis based on *t*-coefficient values

Responses	A	B	C	D	E	F
PS	−4.271 Sodium bicarbonate	+1.621 Citric acid	+1.875 Tartaric acid	+3.821 Sodium citrate	+7.917 PVP	+8.056 Lactose
FT	−0.014 Sodium citrate	−3.625 Citric acid	−8.792 Tartaric acid	+0.049 PVP	+0.11 Lactose	+9.271 Sodium bicarbonate

PS: Particle size, FT: Fizzy time

Table 7: Experimental recipe and observed responses of three level center composite design

Run	Point	Process variables			Responses	
		Sodium bicarbonate (g)	PVP (g)	Lactose (g)	PS (mm)	FT (min)
1	Center	10.00	0.55	0.55	0.523	0.554
2	Axial	10.00	0.55	0.55	0.517	0.556
3	Fact	10.00	0.55	0.55	0.513	0.575
4	Fact	10.00	0.55	0.55	0.509	0.566
5	Fact	10.00	0.55	0.55	0.522	0.586
6	Center	10.00	0.55	0.55	0.501	0.599
7	Fact	−0.09	0.55	0.55	1.108	1.027
8	Fact	20.09	0.55	0.55	0.577	0.331
9	Axial	10.00	−0.21	0.55	2.489	0.409
10	Axial	10.00	1.31	0.55	0.532	0.523
11	Fact	10.00	0.55	−0.21	2.534	0.463
12	Center	10.00	0.55	1.31	0.616	0.534
13	Axial	4.00	0.10	0.10	1.022	0.089
14	Fact	16.00	0.10	0.10	0.436	0.445
15	Center	4.00	1.00	0.10	1.108	1.815
16	Axial	16.00	1.00	0.10	0.400	0.353
17	Center	4.00	0.10	1.00	0.913	0.582
18	Fact	16.00	0.10	1.00	2.447	0.396
19	Axial	4.00	1.00	1.00	1.101	1.708
20	Center	16.00	1.00	1.00	0.523	0.411

PVP: Polyvinyl pyrrolidone, PS: Particle size, Fizzy time

Table 8: ANOVA test for PS

Parameter	PS	FT
Model	Quadratic	Quadratic
Root MSE	0.096	0.46
R^2	0.9124	0.9846
Adjusted R^2	0.8496	0.7231
PRESS	0.70	2.34
Sum of squares	0.092	0.26
Mean square	0.018	0.052
$P>F$	0.0001	0.0001

ANOVA: Analysis of variance, RMSE: Root mean square error, PS: Particle size, FT: Fizzy time

The magnitude and direction of the factor coefficient in both equations explained the nature of the effect of factors on the responses. Factors with coefficients of greater magnitude showed a high effect on the response suggesting that concentration of sodium bicarbonate, PVP, and lactose demonstrated the very significant effect on all two responses. The response value is directly proportional to the positive coefficients in the equations and inversely to the negative coefficients.

Contour plots and optimization

The contour diagrams were plotted using the polynomial Equations (1) and (2) to study the interaction of major effective variables and CQAs. The contour plots affirmed unimodal nature of the objective function showing an optimum in the boundaries. These plots also revealed that there were no saddle points within the design space. Contour plots were then generated to study the effect of the interaction of different variables, i.e., sodium bicarbonate, PVP, and lactose on PS and FT. The statistical optimal values of variables were obtained by moving the major and minor axis of the plots and using the "point optimum" feature of the software by independent variation of one parameter at a time. As lactose concentration was not affecting the selected quality attributes significantly, its concentration was kept constant at 0.55 g for further optimization studies. In Figure 2a, PS obtained was in between 0.41 and 0.88 mm, when the concentration of lactose was kept constant at 0.55 g, and concentrations of PVP and sodium bicarbonate were varied from 0.10-1.0 to 4-16 g, respectively. FT obtained was in between 0.40 and 0.54 min under the same conditions. Increase in concentrations of sodium bicarbonate and PVP above 11.3 g and 0.64 g, respectively, were not affected PS and FT significantly. So, the optimum values of the ingredients, as obtained by the design, were: Sodium bicarbonate (11.3 g), PVP (0.64 g), and lactose (0.55 g). The model predicted values of effervescence time and PS by Design Expert Software were 0.586 min and 0.473 mm, respectively. The interrelationships of the two major ingredients PVP and sodium bicarbonate on PS and

FT are shown as two-dimensional contour plots in Figure 2a and 3a and 3D response surface plots [Figure 2b and 3b].

Validation of model

To confirm the optimal concentration, a set of three replicate experiments with the optimal combination of major variables and responses were used as confirmation of the forecasted formulation of fizzy granules. The formulation tested for confirmatory experiment showed 0.576 min FT and 0.435 mm PS [Table 9]. This represented 98.46% and 91.26% similarity of the predicted models for FT and PS, respectively.

Application of FbD by means of statistical design allowed the reliable short listing of a few most significant factors from a long list of probable factors affecting the fizzy formulation process. This method also features studies of the different rare interaction between variables which is not possible by the one-variable-at-a-time procedure. Linear correlation plots between the actual and the predicted response variables of FT and PS are shown in Figure 4a and b. These showed the scatter of the residuals versus actual values for better representing the spread of the dependent variables under present experimental settings. Therefore, it was observed that various responses (FT, PS) are affected by critical parameters up to a certain concentration after that there is no significant change in the value of responses with increase in concentration. So, the obtained results were found to be in agreement with the reported literature.[11,12,31,32]

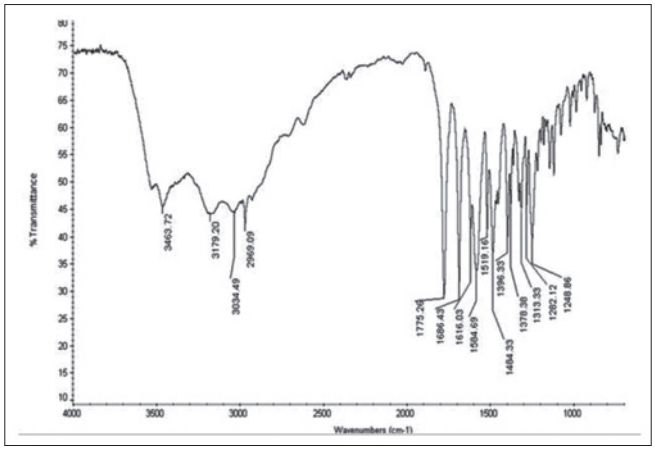

Figure 1: Fourier transform infrared spectrum of amoxicillin trihydrate

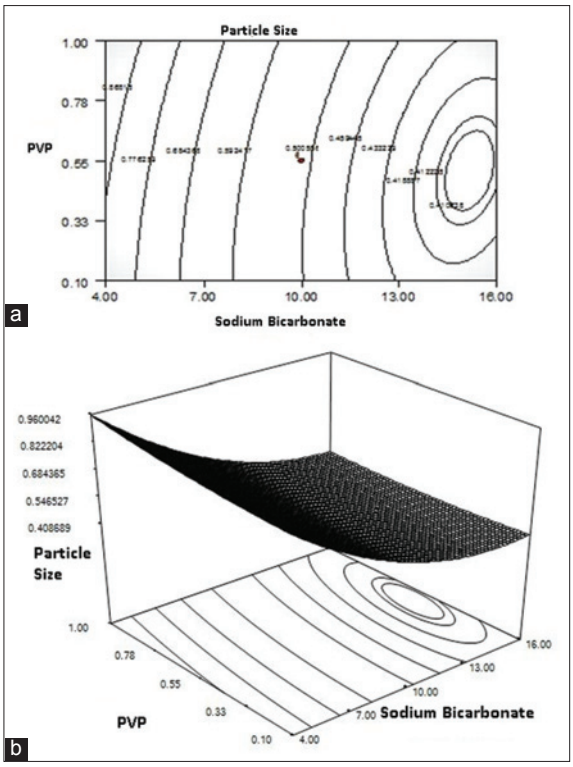

Figure 2: (a) Contour plot of the combined effects of sodium bicarbonate and polyvinyl pyrrolidone (PVP) on particle size (PS), (b) three-dimensional plot illustrating the effects of sodium bicarbonate and PVP on PS

Table 9: Composition of checkpoint formulation, expected and observed values for response variables of PS and FT

Composition			Model predicted values		Observed values	
Sodium bicarbonate (g)	PVP (g)	Lactose (g)	FT (min)	PS (mm)	FT (min)	PS (mm)
11.3	0.64	0.57	0.586	0.473	0.576	0.435

FT: Fizzy time, PS: Particle size, PVP: Polyvinyl pyrrolidone

Table 10: Stability study data of the optimized batch

Parameters	Time (days)						
	0 day	30 days		60 days		90 days	
		25±2°C 60±5% RH	40±2°C 75±5% RH	25±2°C 60±5% RH	40±2°C 75±5% RH	25±2°C 60±5% RH	40±2°C 75±5% RH
PS (mm)	0.5221	0.5324	0.5327	0.5369	0.5378	0.5478	0.5480
FT (min)	0.577	0.584	0.587	0.593	0.597	0.601	0.603

FT: Fizzy time, PS: Particle size, RH: Relative humidity

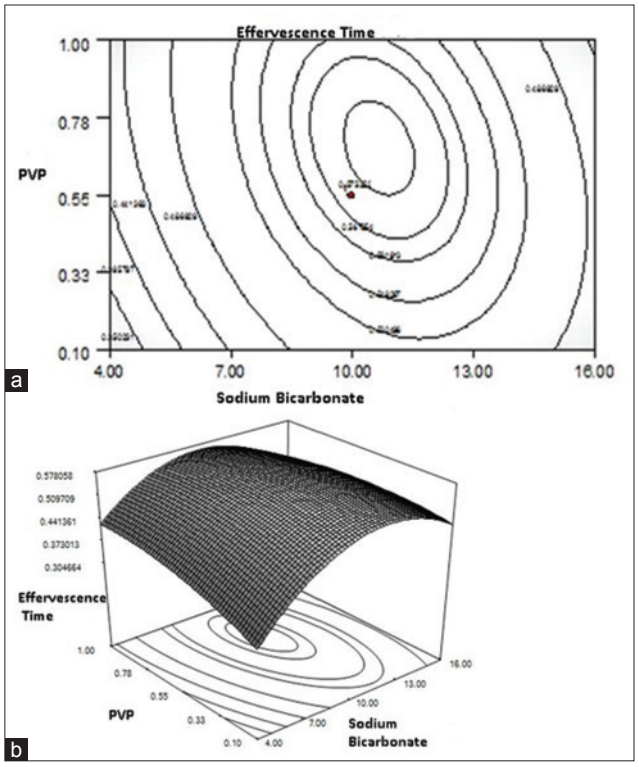

Figure 3: (a) Contour plot of the combined effects of sodium bicarbonate and polyvinyl pyrrolidone (PVP) on fizzy time (FT), (b) three-dimensional plot illustrating the effects of sodium bicarbonate and PVP concentration on FT

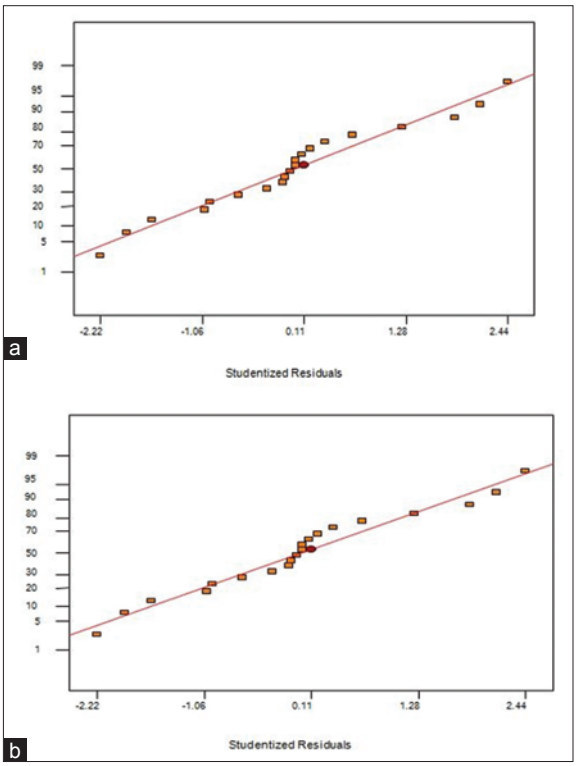

Figure 4: (a) Linear correlation plots between the actual and the predicted response variables of fizzy time, (b) linear correlation plots between the actual and the predicted response variables of particle size

Stability study

Stability studies of 100 g batch of fizzy granules were performed w.r.t. quality attributes *viz*. PS and FT for consecutive 3 months. Storage under tested conditions did not affect the selected quality attributes as given in Table 10. The results showed that there was no significant change in the PS and FT. No significant change in response values indicated that the prepared formulation was stable. This study is in agreement with the ICH guideline Q1A (R^2), i.e., no significant change (5%).

CONCLUSION

Present work may be considered as a model study to identify and understand the effect of CPPs on desired product quality attributes for selected formulation. The concept of FbD was successfully applied for development and optimization of the fizzy formulation. The Placket–Burman design was chosen for the screening of CQAs and ingredients. From the factors examined, sodium bicarbonate, PVP, and lactose were found to have a most critical effect on the quality attributes, i.e., PS and FT of fizzy granules. RSM was used to generate a highly significant mathematical model, which can adequately describe or predict the formulation optimization of fizzy granules for desired quality. Overall the concept of FbD was successfully applied to develop a fizzy formulation by critical analysis of process variables. This formulation is having tremendous commercial potential so by extrapolating current study large number of formulations can be developed for various drugs which will be having more patient compliance. This formulation also involves FbD approach so it can be easily extrapolated to scale up for industrial acceptance.

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Source of Support: Nil. **Conflict of Interest:** None declared.