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Original Article

Application of Response Surface Optimization Methodology in Designing Ordispersible Tablets of Antdiabetic Drug

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ABSTRACT

Objectives: The aim of the present investigation is to study the application of Response Surface Methodology (RSM), a mathematical model and graphical representation to formulate and Optimize Orodispersible Tablets (ODTs) of sitagliptin phosphate, a class III BCS drug. **Methods:** ODTs were prepared by direct compression method using dibasic calcium phosphate (DCP), as diluent and croscarmellose sodium sodium (CCS) as super disintegrant. Formulation was designed using design expert software 9.0 version. RSM based 2^2 full factorial design, considering DCP and CCS as variables and dissolution time at 5, 15 and 30 min was taken as response. Mathematical models in the form of regression equations and graphs were developed. **Results:** The adequacy of the developed mathematical models was statistically checked through the analysis of variance **(ANOVA).** The responses were analyzed using ANOVA and polynomial equation was generated for each response using RSM. Responses were mostly affected by the specific combinations of independent variable. R^2 **predicted and** R^2 adjusted values for the constructed models, which revealed the competence for the proposed mathematical model. Based on the results obtained DF1 formulation was optimized. The developed mathematical models can be successfully used for their prediction of measured responses. **Conclusion:** DoE Concept in formulation could pave way for adaptation of Quality Based Design (QbD) in pharmaceutical industry RSM was successfully applied to optimize diluents and disintegrate concentration of ODTs. The variables employed in the study had a great effect on the quality of formulation. Modeling of experimental data allowed the generation of useful equations for prediction of responses.

Key words: Response surface methodology, Optimization, Orally disintegrating tablets, Sitagliptin phosphate.

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INTRODUCTION

In this era of discovery of novel drug delivery systems, ODTs represent a rapidly emerging drug delivery system with industrial popularity and better patient compliance. These are most extensively used and widely acceptable dosage forms. ODTs are commonly known as orally disintegrating tablets, mouth dissolving tablets, fast dissolving tablets, or rapid melt tablets direct compression method is generally used for fast disintegrating tablets with the aid of super disintegrant as an important component.[1,2] The fate of a drug in biological system is determined by the drug fraction that is bioavailable. Hence to deliver the drug and enhance its absorption rate, all the rapid melt tablets are developed using super disintegrants.[3] This delivery system uses the combination of the feasibility of conventional solid dosage form tablets with that of the liquids and specifically desirable to pediatrics and geriatrics.[4] MDTs can be taken without the aid of water as they rapidly disintegrate (in less than 1 min) into the mouth and shows rapid absorption. Sitagliptin phosphate is an anti-diabetic drug and is classified under class III according to BCS (Biopharmaceutical Classification system) indicating high solubility and low permeability with high oral bioavailability, plasma half-life of 12.4 h and has an unpleasant taste. From past decade, there has been an increased demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing day by day.[5,6] Thus, the present study aims to formulate ODTs by application of response methodology of sitagliptin phosphate and understand the variables employed in the study had a great effect on the quality of formulation. RSM is effective statistical method for relating the relationship between and dependent and independent parameters. RSM is particularly appropriate for product development work. The effectiveness of RSM in optimization of ingredient levels, formulations and processing conditions in pharmaceutical technology. RSM uses an experimental design such as central composite design to fit a model using least squares regression analysis. Adequacy of a proposed model is revealed by diagnostic checking provided by ANOVA and 3D response plots. RSM is also a useful tool to minimize the numbers of trials and provide multiple regression approach to achieve optimization.[7] The risk involved in the development of oral disintegrating tablets is assessed by the Quality risk management which minimizes the risk involved during manufacture thereby providing continuous improvement in the development of product and process. This in turn results in high quality product with reduced process variables.[8]

MATERIALS AND METHODS

Materials

The materials used for the experiment include Sitagliptin phosphate, Calcium phosphate dibasic, Croscarmellose sodium, Magnesium stearate, Talc, Aspartame that were gifted from Vergo Pharma Research Laboratories Pvt. Ltd., Verna, Goa.

METHODS

Compatibility study between drug and excipients

The pure drug mixture of drug with excipients (1:1) were characterized by Fourier Transform Infrared (FTIR) Spectroscopy after exposure of physical mixture along with drug to 40±1°C/75±5% RH for 1 month to assess compatibility of drug with excipients. The scanning range was 500-4000 cm^{-1} and the IR spectra of samples were obtained using KBr disk method.[9,10]

Formulation design by Design Expert

2^2 Factorial -RSM based Design by varying two quantitative controllable factors (independent variables) DCP (X1) and CCS (X2) as shown in Table 1. API and recipients were mixed in geometrical ratio and passed through sieve #30, magnesium separate and talc was passed through sieve #60. The obtained blend was subjected for compression by using 8mm punch Three dependent variables were selected as responses for representing the main parameters: Dissolution at 5 min (Y1), 15 min (Y2) and 30 min (Y3). After preliminary experiment, the upper and lower limits for the independent variables were established. DCP levels were from 20-60 mg/ tablet and CCS levels were 1-10mg /tablet.[11-13]

Four trials were performed for the evaluation of the optimized formulation (Table 2). The experimental data for each response variable were fitted to the quadratic Model. The regression parameters for the equations are calculated (Table 5 and 6).

Preformulation studies

Angle of repose, bulk density, tapped density and Carr's index was evaluated.[14-17]

Post formulation studies

Weight variation, tablet thickness, friability, wetting time or water absorption ratio were performed.

Table 1: 2^2 level factorial design for orodispersible tablets.

Independent Variables (Factors)	Levels	
	Low	High
Factor 1: Calcium phosphate dibasic	20	60
Factors 2: Croscarmellose sodium	1	10

With 2 factors at 2 levels, a full factorial design, consisting of 4 formulations was designed (2^2=4)

Table 2: Formulation design for orodispersible tablets.

Ingredients (mg/tab)	Formulation code			
	DF1	DF2	DF3	DF4
Sitagliptin Phosphate	62.04	62.04	62.04	62.04
Calcium phosphate dibasic	60	20	60	20
Croscarmellose sodium	10	10	1	1
Microcrystalline cellulose	61.46	101.46	70.46	110.46
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Aspartame	2.5	2.5	2.5	2.5
Total weight	200	200	200	200

Content uniformity was measured by studying the absorbance of aqueous solution at 265nm using UV spectrophotometer. The concentration was calculated by using linear regression equation y=0.04X+0.002, R^2=0.998 with beers range of 5 to 45 µg/ml using pH 6.8 phosphate buffer as reagent blank.[16]

In vitro disintegration time

Six tablets were placed in each tube of disintegration apparatus. The medium was maintained at 37±2°C and the time was noted for the entire tablet to disintegrate completely.[16,17]

In vitro dissolution studies

The *in vitro* drug releases were carried out in USP Type I (basket) dissolution apparatus to suit the physiological conditions of GIT. Aliquots of dissolution medium were withdrawn at predetermined time interval 5, 10, 15, 20, 30 mins and the same volume of medium was replaced to maintain the constant volume.[18,19]

The adequacy of selection of variables was based on mathematical models and was statistically estimated through the ANOVA. The responses were analyzed using ANOVA and polynomial equation was generated.[12] R^2 predicted and R^2 adjusted values for the constructed models, were obtained to check the competence for the proposed mathematical model.[12,20] Based on the results obtained, formulation were optimized.

RESULTS

The linear regression analysis was done on absorbance data. Linear regression equation, Absorbance = 0.004 x concentration + 0.002 (y = mx + c) was generated. Compatibility study between drug and excipients was by characterizing the physical mixture of drug and polymer by FTIR spectral analysis to assess any chemical alteration of the drug characteristics through its functional groups (Figure 1). Powder mixture containing drug with various excipients were subjected for preformulation studies including bulk density, tapped density, % Carr's index, Hausner's ratio and angle of repose (Table 3). Four formulations

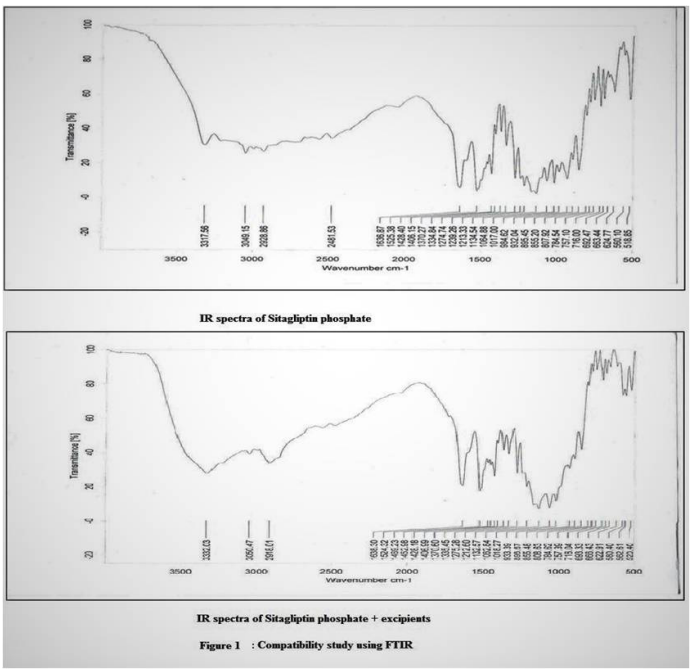

Figure 1: Compatibility studies using FTIR.

Table 3: Data of Precompression parameters for formulations DF1-DF4.

Formulations	Angle of repose (θ)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (%)	Hausner's ratio
DF1	25.20±0.015	0.624±0.0005	0.714±0.0005	12.59±0.130	1.143±0.001
DF2	26.31±0.157	0.655±0.0015	0.755±0.0015	13.23±0.026	1.152±0.012
DF3	26.51±0.186	0.608±0.0005	0.734±0.001	17.07±0.062	1.205±0.016
DF4	23.74±0.140	0.624±0.0005	0.734±0.0005	14.93±0.07	1.175±0.001

Table 4: Data Post compression parameters of formulations DF1-DF4.

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Water absorption ratio	Drug content (%)
DF1	200.85±1.136	3.13±0.02	53.66±2.516	0.157±0.0144	94.66±1.246	100±1.000
DF2	200.9±1.209	2.91±0.01	54±1.000	0.182±0.0144	95.83±2.229	99.33±1.527
DF3	200.85±1.182	2.91±0.005	55±1.000	0.172±0.0015	95.68±1.146	97.00±1.732
DF4	200.05±1.234	2.99±0.011	54.33±0.577	0.182±0.02886	96.17±2.557	97.33±1.527

Values are expressed as mean ± SEM (Standard Error Mean);

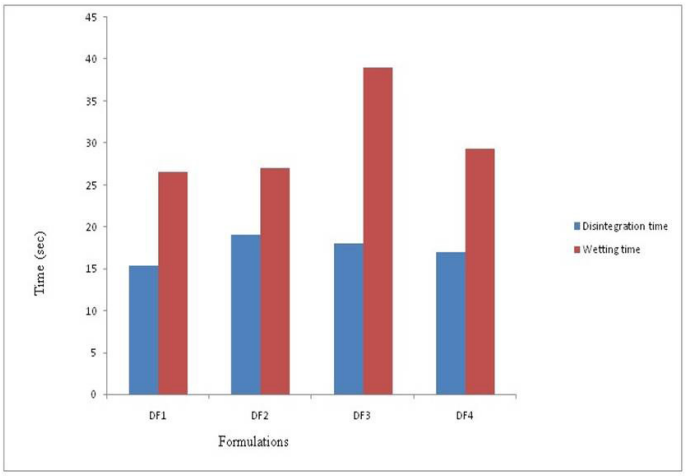

Figure 2: Comparison of disintegration time vs wetting time of formulations DF1-DF4.

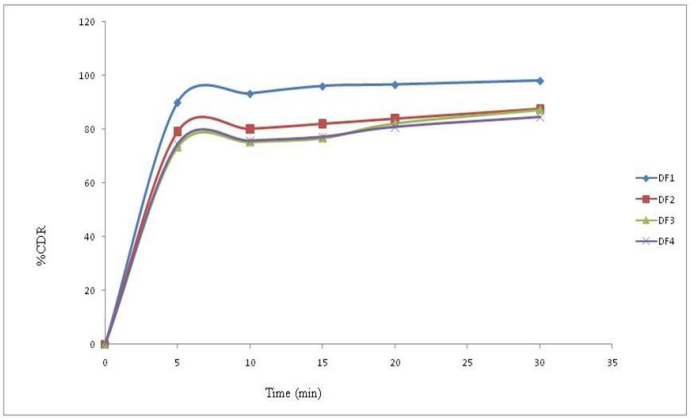

Figure 3: *In vitro* percentage drug release vs time of formulations DF1-DF4.

Table 5: Summary of results of regression analysis for Responses Y1, Y2 and Y3.

Response	R^2	Adjusted R^2	Predicted R^2	SD	% CV	P
Y1	0.9997	0.9990	0.9948	0.29	0.36	0.0180
Y2	0.9992	0.9977	0.9876	0.52	0.61	0.0278
Y3	0.9949	0.9847	0.9183	0.85	0.93	0.0715

SD: Standard Deviation, %CV: Coefficient of variation

were prepared by applying design expert software version 9.0 (Table 1, Table 2). The tablets were prepared by direct compression method.

The formulations were subjected for post formulation evaluations including thickness, hardness, friability, weight variation, *in vitro* disintegration time, wetting time, water absorption ratio, drug content, *in vitro* dissolution studies (Table 3 and 4, Figure 2 and 3) Based on the responses the data obtained was subjected to statistical analysis. 3D surface plots and polynomial equations were used to analyze effect of independent variables on dependent variables (Table 5-6, Figure 4-6).

Table 6: Results of analysis of variance (ANOVA) for measured responses.

Parameters	DF	SS	MS	F	Significance
		% CDR at 5 min			
Model	2	267.84	133.92	1538.87	0.0180 Significant
Residual	1	0.087	0.087	-	
Total	3	267.93	-	-	
		% CDR at 15 min			
Model	2	355.32	177.76	644.93	0.0278 Significant
Residual	1	0.28	0.28	-	
Total	3	355.79	-	-	
		% CDR at 30 min			
Model	2	140.78	70.39	97.43	0.0715
Residual	1	0.72	0.72	-	Not Significant
Total	3	141.50	-	-	

DF: Degrees of Freedom, SS: Sum of Square, MS: Mean Sum of Square, F: Fischer's ratio

CDR-Cumulative drug release

Note: *P* values less than 0.05 indicates model is significant

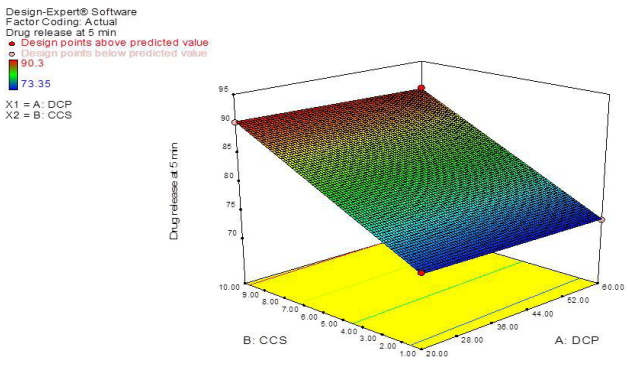

Figure 4: 3D response surface plots for *in vitro* drug release at 5 min.

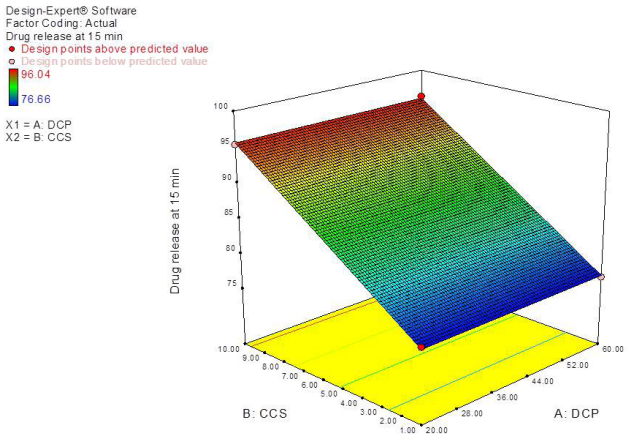

Figure 5: 3D response surface plots for *in vitro* drug release at 15 min.

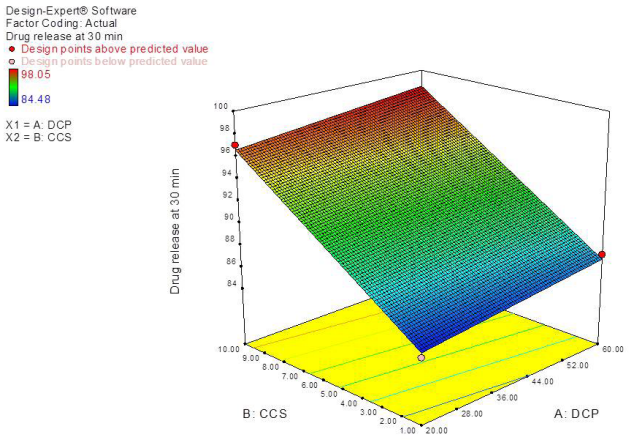

Figure 6: 3D response surface plots for *in vitro* drug release at 30 min.

DISCUSSION

ODTs were formulated by application of response surface methodology of sitagliptin phosphate and understand the variables employed in the study had a great effect on the quality of formulation.

Experimental data for each response variable were fitted to the quadratic model and regression equation were generated to predict the responses.[7]

ODTs were prepared by direct compression method using DCP, as diluent and CCS as super disintegrant using design expert software 9.0 version, dissolution time at 5(Y1), 15(Y2) and 30(Y3) min was taken as response. Mathematical models in the form of regression equations and graphs were developed.[7-10] FTIR compatibility studies of drug with excipients were carried out prior to tablet preparation and it reveals that there was no physico-chemical interaction between drug and excipients. All the characteristic peaks of drug were present in the spectra of formulation, thus indicating compatibility between drug and excipients. The FTIR spectra of pure drug and formulation are shown in Figure 1.

Four formulations were formulated by using 2^2 level factorial design (Table 1, 2) using design expert software version 9 and evaluated for precompression parameters like angle of repose, bulk density, tapped density, Carr's index and results shown in Table 3. All the parameters were carried out to study the powder flow characteristics in order to achieve tablets of uniform weight and were found to be well within the permissible limits.

The tablets were subjected to post compression evaluation parameters weight variation, thickness, hardness, friability, *in vitro* disintegration time verses wetting time and *in vitro* drug release (Table 4) (Figure 2,3) and all the formulations the results were found to be well within the permissible limits. The tablets had good mechanical strength with sufficient hardness and low friability. The drug content was also within pharmacopoeial limit (90–110 %). The wetting time was optimally low. The disintegration time of the DF3 formulation was high when compared to other formulations as shown in Figure 2.

Drug dissolution studies were performed for all four formulations. The DF1 formulation has shown minimum disintegration time 15.33 s and a maximum drug release 96.04% at 15 min as shown in Figure 3.

Statistical Optimization of formulations was validated by using ANOVA. Adequacy of the models at a confidence level of 90% is summarized in Table 5. The coefficient of determination (R^2), indicates the proportion of total variability of the model explained and suggested that good fit model.[12,13] R^2 value should be as close to as 1 or at least 0.8.[21] Hence the R^2 reflected to be goof fit between the predicted and the observed response values and can be used to assess model adequacy. ANOVA variance statistics is shown in Table 5. The suggested sequential model sum of squares, lack of fit test (Showing Degrees of freedom, mean square, *f* Value, *p* value), model summary statistics is given in table 6. The model was found to be statistically significant for responses Y1 and Y2 since $p<0.05$ and for response Y3 with $p>0.05$ the model is non-significant. Hence, dissolution at 5 min. As shown in equation below, a statistical model incorporating interactive and polynomial terms was used to evaluate the responses. Y=b0+b1A+b2B, Where Y is measured response associated with each factor level combination; b0 is an intercept representing arithmetic average of all quantitative outcomes of four runs; b1and b2 are regression coefficient computed from the observed experimental values of Y. A and B are the coded levels of independent variables.[13]

The polynomial equation was used to draw conclusions after considering the magnitude of coefficients and the mathematical sign it carries, i.e. positive or negative. A positive sign signifies a synergistic effect, whereas a negative sign stands for an antagonistic effect.[12,13] Regression equations for each response are as follows, Y1 = +72.57278 – 0.014875*A + 1.81722*B, Y2 = +74.71500 + 0.001875*A + 2.09500*B, Y3 = +82.67778 + 0.046250*A + 1.30222*B (Table 5). The results of ANOVA in the Table 6 for the dependent variables demonstrate that the model was significant for both the response variables Y1 (Dissolution at 5 min) and Y2 (Dissolution at 15 min) whereas response variable Y3 (Dissolution at 30 min) was found to be non-significant. It was observed that the two independent variables viz. A (DCP concentration) and B (CCS

concentration) had a negative effect on dissolution at 5 min and positive effect on dissolution at 15 min (Y2) and 30 min (Y3). The DF1 formulation has shown minimum disintegration time 15.33s and a maximum drug release 96.04% at 15min.

CONCLUSION

DoE Concept in formulation could pave way for adaptation of Quality Based Design (QbD) in pharmaceutical industry. RSM was successfully applied to optimize diluents and disintegrant concentration of orally disintegrating tablet of sitagliptin, capable of fast disintegration within the buccal cavity within 16 s. The variables employed in the study had a great effect on the quality of formulation. Modeling of experimental data allowed the generation of useful equations for prediction of responses and was according to acceptance criteria for dissolution of ODT's.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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