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Influence of dependent variables on granule formulation using factorial design: microwave irradiation as one of the factor

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ABSTRACT
As traditional drug delivery poses many disadvantages such as difficulty in consumption, the granules were opted to replace tablet dosage forms available in the market. A 2^3 full factorial design was employed for the formulation and characterization of the granule dosage form of oxcarbazepine. From regression equations we can assess the impact of each factor on the response further contour plots helped to pre-analyze the desired target factor values, in addition optimization process helped to analyze the values of dependent variables. Thus as of the results achieved a preferred response of flow property and drug release was obtained. In the current study, an attempt has been made to minimize possible number of experiments in the formulation of granule dosage forms. Polyvidone is a hydrophilic binder and primellose is a good disintegrate to obtain higher dissolution rate. A part, microwave assisted drying process plays a major role in achieving desired flow properties of granules.

***Key Words*:** Oxcarbazepine, granules, factorial design, flow properties, dissolution.

INTRODUCTION

Mostly 40% of new chemical entities were poorly aqueous soluble, thus the formulation of such compounds for oral delivery is one of the interesting challenges in the pharmaceutical industry. Oxcarbazepine is 10,11-dihydro-10-Oxo-5*H*-dibenz(b,f)azepine-5-carboxamide derivative of carbamazepine with low (0.08g/L) aqueous solubility (Amidon *et al.*, 1995) and 1.31 partition co-efficient. Granules are solid unit dosage form agglomerates of smaller particles of medicament in which powdered drug was mixed with excepients which may be irregular in shape (Cooper and Guns, 2000). Sometimes it is difficult to find a satisfactory preparation for a solid medicament with a large dose as tablets as impracticable because of the size required per dose. Oxcarbazepine is available only in tablet dosage form in the market. In the present work, formulation of oxcarbazepine into granules is a challenging aspect because of the poor flow characteristics of pure drug. During newer dosage form development, it is obvious to review factors influencing formulation and drug release in a short period. It is a common practice in dosage form development process to reduce the cost by developing and optimizing the formulation with minimum number of experiments and optimization using statistical designs can be very powerful, efficient and useful technique (Chowdary *et al.*, 2011; Akhter and Hossain, 2012). The present study was designed with an objective of further evaluating the influence of concentration of polyvidone and primellose and drying heat frequency (F) on various selected responses. Further, it was aimed at optimizing independent variables using statistically designed experiments to achieve selected dependent response.

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MATERIALS AND METHODS

Oxcarbazepine (OXC) was procured as gift sample from Novartis, Mumbai. Polyvidone and Crocarmellose sodium were procured from FMC biopolymer, USA. All other chemicals and solvents used were of analytical/HPLC grade.

Formulation design

This study investigated the utility of a 3-factor, 2-level full factorial design and optimization process for conventional granule formulation using sigma stat® version 12.02.00 (Systat, USA). Amount of polyvidone, amount of primellose and drying heat frequency as the independent variables whereas the angle of repose and $t_{80\%}$ (time required to dissolve 80% drug) were selected as dependent variables (Mangesh *et al.*, 2013). Further the optimization was done by simultaneous (model-dependent) or response surface methodology. The factor levels for the formulation combinations generated by 3 factor 2 level full factorial design.

Preparation of granules

The granules were prepared by the wet granulation method where all the ingredients were weighed and passed through sieve #40. A binder solution of different concentrations was prepared and the mixture of drug blend, spray dried lactose and croscarmellose sodium was blended together and granulated using an aqueous solution of polyvinyl pyrrolidone. The wet mass was passed through 8mm screen and granules were dried using micro - wave oven. The dried granules were then passed through sieve #20. Later they are preserved in containers for further studies.

Determination of flow characteristics of granules

Bulk density

Bulk density was determined by pouring gently 20 gm of sample through a glass funnel into 50 mL graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated using formula:

$$Bulk density = \frac{Weight of\ sample(gm)}{Volume occupied by the sample}$$

Table 1: 2^3 full factorial design for granule formulation.

Formulation	Coded variable			Actual value			Independent variables	
	X1	X2	X3	PVP (mg)	CCS (mg)	Heat frequency	Angle of repose	Dissolution time (min)
F1	-1	-1	-1	17	8.5	2000	31 ± 2.01	48 ± 1.62
F2	-1	-1	0	17	8.5	2500	40 ± 0.34	50.5 ± 1.04
F3	-1	0	-1	17	25.5	2000	32 ± 0.99	15 ± 1.48
F4	-1	0	0	17	25.5	2500	34 ± 1.23	26 ± 1.22
F5	0	-1	-1	42.5	8.5	2000	29 ± 0.85	55.5 ± 1.85
F6	0	-1	0	42.5	8.5	2500	40 ± 1.89	56 ± 1.96
F7	0	0	-1	42.5	25.5	2000	25 ± 0.41	37.5 ± 1.9
F8	0	0	0	42.5	25.5	2500	28 ± 1.88	47 ± 1.42

Tapped density

Tapped density was determined by using a graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted, and the sample was tapped on a horizontal base. The tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density was calculated by:

$$Tapped\,density = \frac{Weight\,of\ sample(gm)}{Tapped\,volume}$$

Hausner ratio and compressibility index

Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density and the tapped density of the powder.

$$Hausner\,ratio = \frac{Tapped\,density}{Bulk\,density}$$

$$Compressibility\,index = \left(1 - \frac{V}{V_\circ}\right) \times 100$$

V = volume of powder blend before tapping;
$V_\circ$ = volume of powder blend after 100 tappings

Angle of repose

Drained angle of repose is determined by allowing an excess quantity of material positioned above a fixed diameter base to drain from the container. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose (Carr, 2003).

Dissolution test

Dissolution test was carried out using USP type II (paddle) apparatus for 1h. The stirring was kept at 50rpm, 0.75% SLS as dissolution medium (900mL) and the temperature was maintained at 37±1°C. 5mL of samples were collected at regular time intervals of 0, 5, 10, 15, 20, 30, 45 and 60min and were assayed spectrophotometrically at 256nm. A triplicate number of experiments were performed for each formulation.

Experimental designing and Statistical analysis

A quadratic model was obtained after analyzing data later results of optimization were statistically proven for significance by ANOVA studies. Calculated F ratio was obtained from the ratio of mean squares of regression to the mean squares of residuals. Values of $p<0.05$ indicate model terms were significant. The statistical model comprising incorporated interactive and polynomial terms was utilized to evaluate the response. The relationship between the dependent and independent variables was further elucidated using contour plots. The results were graphically depicted using contour plots for geometric illustration of responses, obtained by plotting one independent variable vs. other while holding the other variables constant. The exact amount of CCS and PVP of liquid for achieving the desired response was found out from optimization. Finally the optimum formula was determined and the predicted optimal formulation was formulated and the responses were evaluated and verified.

RESULTS AND DISCUSSION

The drug blend of solid dispersions consists of 150 mg of OXC-API and 600 mg of mixture of urea, sodium citrate and sodium acetate promoted enhanced solubility of up to 0.8 mg/mL as previously discussed by Prameela and Hema (2012). The use of hydrophilic binders also enhances the dissolution rate of drug (Pandey *et al*., 2013). Further formulated into granules, these solid dispersions were used. Granules prepared with synthetic hydrophilic binder as PVP with water as granulating liquid till capillary or funicular stage was obtained and droplet stage was avoided as if powder mixture is over wetted, the granules will be hard and if they are not wet sufficiently, the resulting granules will be soft (Joseph 2006) thus PVP K-30 binder concentration was important that contribute to reduce friability of granules (Tejas et al., 2010). Povidone and primellose selected as per acceptable daily intake and is Regulatory Authorities (GRAS) listed (Raymond 2006). Influence of drying temperature (Elham *et al*., 2013) and granulation liquid concentration are most essential to maintain good flow properties and drug distribution in granules (Kiekens *et al*., 2000) this criterion was satisfied by selecting a microwave where its intensity may not affect drug degradation (Patel *et al*., 2011), friability and size distribution of granules (Chee *et al*., 2005). Thus used 2000 MHz frequency creates rapid changes in the field, the orientation of the field changes 2000 million times per second cause rapid (di-pole rotation) reorientation of the molecules in the microwave field, resulting in friction and heat creation for granules served to obtain granules of desired characteristics (Garcia and Lucisano, 1997). Granules prepared by wet granulation technique using factorial design that helps to minimize the number of experiments (Amelia *et al*., 2011) and to interpret all the possible effects by all the factors as given in table 1 resulted in good flow characteristics and dissolution profile of dissolution in water of pure liquid non-Ionic surfactants was observed (Jinhua *et al*., 2003).

All the prepared formulations were evaluated for flow properties and shown in table 2. Formulation F3 showed poor flow character probably due to high binder concentration. Remaining all formulations showed almost good flow characteristic. 20gm of powder was taken to evaluate for each formulation. Almost all the formulations showed good flow properties with Hausner ratio <1.28 and compressibility index <15 and passable flow character

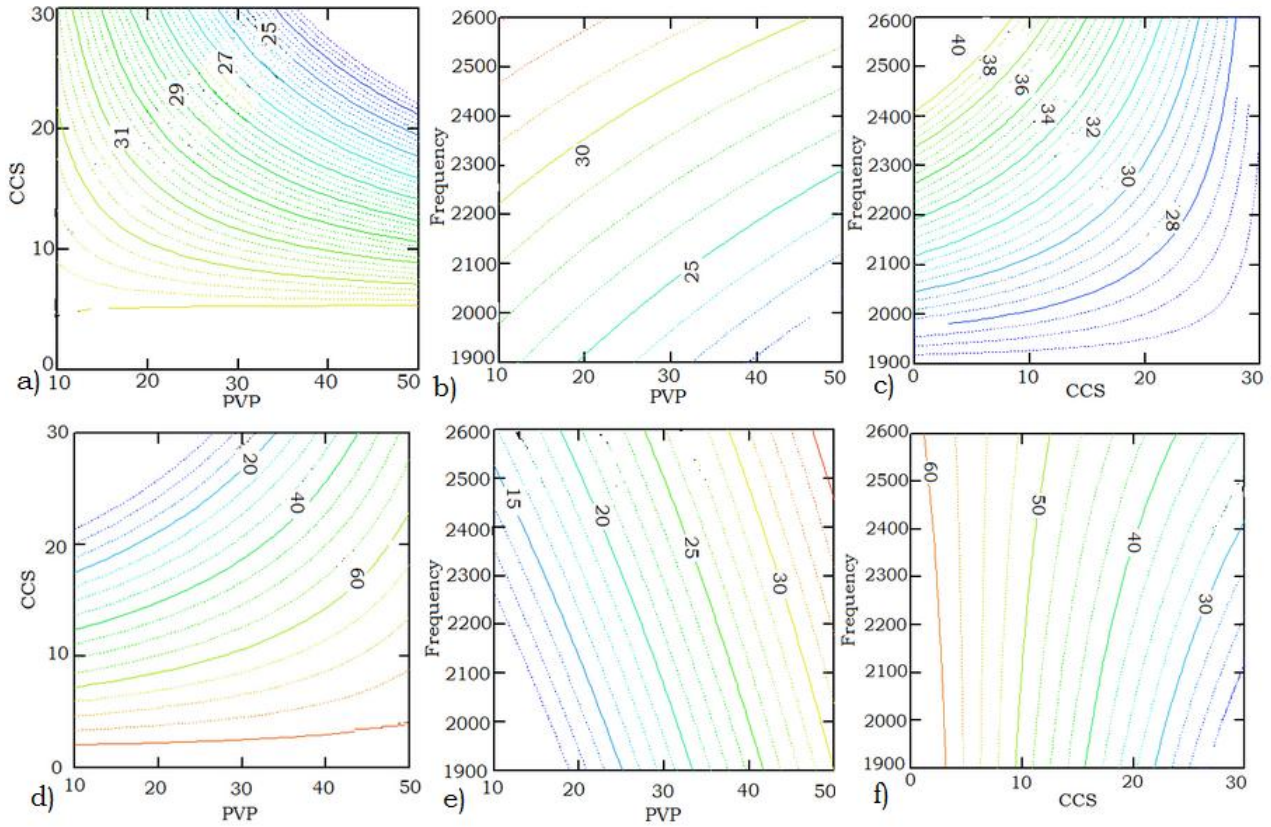

Figure 1: Contour plots showing the influence of interaction of CCS, Heat frequency and PVP on angle of repose and dissolution; *CCS- Croscarmellose sodium; PVP- Polyvinyl pyrrolidine.

Table 2: Flow properties of granules.

Formula-tion code	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compress-ibility index
F1	0.542	0.603	1.112	10.18
F2	0.539	0.587	1.089	8.15
F3	0.567	0.638	1.260	21.06
F4	0.559	0.629	1.125	11.06
F5	0.553	0.625	1.30	21.55
F6	0.529	0.603	1.139	12.22
F7	0.533	0.590	1.106	9.69
F8	0.542	0.608	1.122	10.89

Table 3: Analysis of Variance (ANOVA) of dependent variables.

Dependent variables	Source of variation	Degree of freedom	Mean square	F-ratio calculated (tabular)	P-value
Angle of Repose	Regression	6	34.292	274.333	0.046
	Residuals	1	0.125	(234)	
	Total	7			
	R^2	1.000			
Dissolution ($Y_{80\%}$)	Regression	6	252.783	8089 (234)	0.009
	Residuals	1	0.031		
	Total	7			
	R^2	1.000			

Table 4: Desirability analysis for formulation optimization.

Factor	Stationary point	
	Coded	Uncoded
PVP (mg)	-0.271	29.75
CCS (mg)	1.000	17.00
Heat frequency	-1.000	2000

Table 5: Achieved responses for the target formulation

Response	Lower value	Target	Upper value	Achieved value
AOR	25	25	40	27 ± 1.32
Y80%	14	15	56	16 ± 0.54

Table 6: Cumulative percent drug released and log percent drug remain over time for optimized formulation.

Time (min)	Optimized formulation	
	Percent drug dissolved (mean ± SD)	Log percent drug remain undissolved (mean ± SD)
0	0.0 ± 0.00	2.0 ± 0.00
5	46.76 ± 0.07	1.73 ± 0.005
10	63.33 ± 0.15	1.56 ± 0.002
15	78.84 ± 0.3	1.32 ± 0.006
20	84.43 ± 0.73	1.19 ± 0.02
30	87.44 ± 2.02	1.09 ± 0.07
45	93.12 ± 3.02	0.81 ± 0.18
60	96.95 ± 0.15	0.48 ± 0.02

with Hausner ratio 1.30 and compressibility index of 21.55. From ANOVA table 3, the treatment sum of squares is a measure of treatment differences, here large sum of squares means that treatment differences are large (dissolution and angle of repose). Mean squares are variance estimates and higher values indicate random variation in groups (dissolution and angle of repose). From null hypothesis of F distribution, the calculated F value is greater than the tabulated value of $F_{6,1}$ at the 5% level of significance indicates the significant difference between the groups. Values of "Prob>F" less than 0.05 indicate model terms are significant. In this case PVP, CCS and F are significant model terms. This model provides a way to describe factor- response relationship where the response for all showed good correlation co-efficient of 1.000.

$$Y_{AOR} = 18.417 - 0.196PVP + 0.054CCS - 2.024F - 0.013PVP \times CCS - 0.001CCS \times F$$

$$Y_{80\%} = 68.125 + 0.265PVP - 4.605CCS - 0.002F + 0.035PVP \times CCS + 0.001CCS \times F$$

From the regression equation of the angle of repose, a negative sign for F indicates increase of the micro wave frequency decrease angle of repose. From the regression equation of dissolution, positive sign on PVP and interaction terms PVP-CCS, CCS-F means their combined increase in value increases the dissolution while raise in CCS, F, PVP-F reduces the dissolution time. The interaction terms showed how the response changes when two factors were simultaneously changed. The target value lies in the range of lower and upper values and to obtain the desirable value, uncoded levels of three factors were used during formulation. The relationship between the dependent and independent variables was further elucidated using contour plots. Contour plots help to logically predict values of the angle of repose of 25 and T80% from formulating products as shown in figure 1. The final selection of the optimized batch would be done after considering the other requirements of dosage form i.e. flow properties and drug release through desirability analysis as given in table 4. The obtained results were similar to the predicted values as shown in table 5. Thus Optimized formulation (OF) was selected due to excellent flow properties and higher dissolution rate of 96.9% of drug release in first 60 minutes as shown in table 6.

CONCLUSION

A favorable response of flow property and drug release was obtained by using hydrophilic binder and disintegrates along with microwave irradiation for optimal drying of the granules as dependent factors.

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