Research Article

Application of Box-Behnken Design in Optimization of Ibuprofen Ternary Solid Dispersion

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ABSTRACT

The objective of present investigation was to enhance the dissolution rate of ibuprofen by preparing its ternary solid dispersion (SD) using solvent evaporation method. Box-Behnken design was used to scrutinize the combined effect of three independent variables on percentage drug release and flow property of ternary solid dispersion. The independent variables selected were Starcap 1500 (X_1), Polyethyleneglycol4000 (X_2) and drug: polymer ratio (X_3), whereas percentage drug release after 10 minutes (Q_{10}) and angle of repose (AR) were selected as dependent variables. The transformed values of the independent and dependent variables were subjected to multiple regressions analysis to establish full and reduced second order polynomial equations. Using Design of Expert Software the levels of independent variables was predicted [64.65 % Starcap 1500 (X_1 = 1), 10.35 % Polyethylene glycol 4000 (X_2 = 0.4) and 25.00 % drug, i.e. 1:3 ratio of ibuprofen: polymer mixture (X_3 = 0.50)] for maximized response of Q_{10} (81.68 ± 4.22 %) with good flow property (angle of repose = 31°63" ± 1°06"). Dissolution profile of optimized ternary solid dispersion was significantly improved in comparison to pure drug. In conclusion, Box-Behnken design demonstrated the application in predicting the values of independent variables for optimization of ibuprofen ternary solid dispersion.

Keywords: Box-Behnken Design, Solid dispersion, Ibuprofen, Starcap 1500, Polyethylene glycol4000.

1. INTRODUCTION

In the process of drug discovery, approximately 40% of potential new drug candidates (active pharmaceutical ingredients) show low aqueous solubility, which results in poor and variable oral bioavailability (high intrasubject/intersubject) and lack of *in-vitro in-vivo* correlation (IVIVC) [1, 2]. Therefore, developing suitable oral dosage formulation for such drugs, to improve their aqueous solubility and bioavailability, is very challenging task. Numerous techniques have been advanced to develop efficient method to improve solubility and dissolution rate of poorly water soluble drugs like micronization, salt formation, self-emulsifying formulations, solid-lipid nanoparticles, liposomes, use of surfactant, co-solvents, pro-drugs, cyclodextrin, solid dispersion, etc.[3-8].

Solid dispersion technique could serve as a platform to address the issues associated with BCS (Biopharmaceutical Classification System) class II drugs, by increasing their dissolution rate and so oral absorption (bioavailability) [9-11]. Furthermore, the solid dispersion technique is very promising and valuable for pharmaceutical formulators

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because it's easy to prepare, scale up, as well as reproducibility and cost effective [6]. The term solid dispersion refers to dispersion of drug at molecular level in an amorphous solid polymer/matrix by kneading, co-grinding, melting (fusion), co-precipitation, gel entrapment, spray-drying, lyophilization, electrospinning and solvent evaporation method [12]. The solid dispersed state may include eutectic form, crystalline/glass solutions, amorphous/crystalline suspensions forms, etc. When such solid dispersions are exposed to aqueous solution, the polymer/carrier dissolves leaving drug as a fine particles, triggering improvement in dissolution rate of poorly water-soluble drugs [13].

According to BCS, drugs are grouped into four classes with subject to their solubility and permeability. Drugs which belong to class II group are categorized by their low solubility and high permeability [14]. Ibuprofena non-steroidal anti-inflammatory drug belongs to the BCS class II, so poor solubility is the rate limiting step for its oral absorption and bioavailability. Solid dispersions can be used to increase the dissolution rate of poorly soluble drugs like ibuprofen and they have proven to increase the amount of dissolved drug at the site and consequently improve the bioavailability [14-17].

In present study, solvent evaporation method was used for the preparation of ibuprofen ternary solid dispersion, which is simple and easy to scale up at commercial level [9, 18]. Traditional trials for optimization need more effort, time and resources when a complex formulation needs to be optimized. Nowadays response surface methodology (factorial designs) are widely used for optimization of formulation which need less trials, time and offer good relationship between dependent variables and independent variables in the form of polynomial equations and contour plots [19-22]. In the work reported here, a Box-Behnken design was used to optimize ternary solid dispersion, independent variables selected were Starcap 1500 (X_1), polyethylene glycol4000 (X_2) and drug: polymer ratio (X_3) to evaluate their separate and combined effects on percentage drug release after 10 minutes (Q_{10}) and angle of repose (AR).

2. MATERIALS AND METHODS

2.1. Materials

Ibuprofen and Polyethylene glycol4000 (PEG 4000) were purchased from S.D. Fine-Chemical Limited (Mumbai, India). Starcap 1500 was kindly supplied by Colorcon Asia Ltd. (Goa, Mumbai). All other ingredients, solvents and reagents used were of analytical grade. Deionized double-distilled water was used throughout the study.

2.2. Box-Behnken Experimental Design

The traditional approach of optimization were only one variable was changed at a time, reveal nothing about the interactions among the variables. Therefore, a Box-Behnken design with 3 factors, 3 levels and 15 runs was selected for the optimization for ternary solid dispersion. In order to minimize the amount of polymers used in the preparation of solid dispersion, the amount of PEG 4000 and Starcap 1500 and the ratio of drug: polymer mixture was optimized. The independent and dependent variables selected for study, with their transformed values are listed in table 1. The polynomial equation is follow:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

---Equation 1

Where, Y_i is the dependent variable; b_0 is the intercept (arithmetic mean response of 15 runs); b_1 to b_{33} are the regression coefficients; and X_1, X_2 and X_3 are the independent variables that were selected from the preliminary experiments. The main effects of (X_1, X_2 and X_3) represent the average result of changing one factor at a time from its low to high values. The interaction terms (X_{12}, X_{23} and X_{13}) illustrate how the response changes when two factors are simultaneously changed. All the batches were prepared according to the experimental design in table 2. A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses [6].

Table 1: Variables and their levels in Box-Behnken Design

Independent Variables	Levels		
	Low	Medium	High
X_1 = Starcap 1500	0.5	1	1.5
X_2 = PEG 4000	0.1	0.2	0.3
X_3 = Ratio (Ibuprofen: Polymer mixture)	4:1	1:1	1:4
Transformed values	-1	0	+1
Dependent variables	Y_1 = Percentage of drug released in 10 min (Q_{10}). Y_2 = Angle of repose (AR)		

Values of independent variables were taken at three points from contour plot and the theoretical values of Q_{10} and AR were calculated by substituting the values in the polynomial equation. Solid dispersion were prepared experimentally at 3 checkpoints and evaluated for the responses. Optimization was performed to find out the level of independent variables (X_1, X_2, and X_3) that would yield a maximum value of Y_1 with constraints on Y_2.

2.3. Preparation of Ternary Solid Dispersion

According to design, the required amounts of ibuprofen, PEG 4000 and Starcap 1500 were weighed. To prepare solid dispersions by solvent evaporation method, the required amount of ibuprofen and polymers were dissolved in ethanol with constant stirring at 100 RPM for 1 hour. The mixture was then kept in the oven for 48 hours at 45^0C (to evaporate solvent) until a dry cake was obtained. Dry batches were sieved from 100 mesh and stored in a desiccator for the next experiments. All batches were prepared in triplicate.

2.4. Angle of Repose (AR)

To study the flow property of solid dispersion powders, the static angle of repose (θ) for all 15 batches were measured by fixed funnel method. A funnel was clamped and adjusted with its tip 2 cm above a graph paper placed on a flat horizontal surface.

Table 2: Box Behnken Design with transformed values

Batch	X_1	X_2	X_3
1	0	-1	-1
2	0	-1	1
3	0	1	-1
4	0	1	1
5	-1	0	-1
6	-1	0	1
7	1	0	-1
8	1	0	1
9	-1	-1	0
10	-1	1	0
11	1	-1	0
12	1	1	0
13	0	0	0
14	0	0	0
15	0	0	0

The powder was allowed to flow through the funnel freely onto the surface until the apex of the cone just reached the tip of the funnel [23].

Mean diameters of the base of the powder cones were determined and tangent of the angle of repose was calculated using the equation 2. Where, h is the height of the heap of powder and r is the radius of the base of the heap of powder.

$$\theta = \tan^{-1}(h/r) \text{---Equation 2}$$

2.5. Dissolution rate study

A USP dissolution apparatus No. 1, basket method (Electrolab, Mumbai, India) was used to evaluate the dissolution rate profiles of drug-solid dispersion. Solid dispersion equivalent to 100 mg of ibuprofen (Pediatric dose) was filled into hard gelatin capsule. Dissolution was performed using distilled water (900 ml) as dissolution media at 37^oC, and the baskets were rotated at 75 rpm [24]. From the dissolution flask, samples were withdrawn at predetermined time intervals for 40 minutes using a peristaltic pump and the drug was quantified by UV spectrophotometer (Pharmaspec UV-1700, Shimadzu) at 221 nm. The dissolution profiles were established from the concentration after correcting for the change in volume of the dissolution media. The percentage drug dissolved after 10 minutes (Q_{10}) was calculated out from dissolution profile curve.

Table 3: Measured and predicted values with % error of response Y_1 and Y_2

Batch	Y_1 (Q_{10})	Predicted Q_{10}	% Error	Y_2 (AR)	Predicted AR	% Error
1	**61.91 ± 2.40**	61.36	-0.58	$41^o50'' \pm 2^o40''$	$40^o35''$	2.77
2	65.20 ± 3.45	65.18	0.03	$32^o50'' \pm 3^o34''$	$34^o91''$	-7.42
3	77.40 ± 5.60	77.42	-0.03	$43^o50'' \pm 1^o56''$	$41^o09''$	5.54
4	**85.40 ± 4.67**	85.05	0.42	$34^o00'' \pm 3^o49''$	$35^o15''$	-3.38
5	68.00 ± 4.40	67.08	1.35	**$44^o17'' \pm 1^o78''$**	$45^o59''$	-3.21
6	75.20 ± 6.45	74.66	0.72	$42^o50'' \pm 2^o46''$	$40^o36''$	5.04
7	69.50 ± 2.34	70.04	-0.78	$34^o12'' \pm 2^o23''$	$36^o26''$	-6.27
8	73.00 ± 1.34	73.92	-1.26	**$31^o53'' \pm 3^o23''$**	$30^o11''$	4.50
9	62.50 ± 5.87	63.06	-0.90	$43^o25'' \pm 5^o54''$	$42^o98''$	0.62
10	79.06 ± 6.34	79.96	-1.14	$43^o80'' \pm 2^o40''$	$44^o79''$	-2.26
11	64.00 ± 3.74	63.10	1.40	$35^o50'' \pm 2^o34''$	$34^o51''$	2.79
12	82.70 ± 5.25	82.14	0.68	$33^o41'' \pm 3^o67''$	$33^o68''$	-0.81
13	71.00 ± 2.56	70.83	0.23	$39^o53'' \pm 1^o46''$	$39^o67''$	-0.35
14	70.00 ± 1.89	70.83	-1.19	$39^o68'' \pm 1^o89''$	$39^o67''$	0.03
15	71.50 ± 4.66	70.83	0.93	$39^o80'' \pm 1^o40''$	$39^o67''$	0.33

All values are expressed as mean ± SD, n = 3.

Table 4: Summary of results of multiple regression analysis for Y_1 and Y_2

	$Y_1 = Q_{10}$		Y_2 = AR	
Dependent variables	P-value	Coefficients	P-value	Coefficients
Intercept	0.001	71.69	0.001	38.59
X_1 = Starcap 1500	0.250	0.55	0.001	-4.89
X_2 = PEG 4000	0.001	8.98	0.71	0.25
X_3 = Ratio (Ibuprofen: Polymer mixture)	0.001	2.86	0.001	-2.85
X_{12}	0.371	0.54	0.611	-0.66
X_{23}	0.150	-0.93	0.857	-0.23
X_{13}	0.142	0.95	0.922	-0.12
X_1^2	0.735	0.20	0.859	-0.23
X_2^2	0.129	1.03	0.741	-0.44
X_3^2	0.524	0.39	0.334	1.35

Table 5: Results of ANOVA for Y_1 and Y_2

Y_1 = % Drug release at 10 minutes (Q_{10})					
ANOVA	Df	SS	MS	F	Significance F
Regression	9	725.97	80.66	67.94	0.0001
Residual	5	5.93	1.18		
Total	14	731.90			
Y_2 = Angle of repose (AR)					
Regression	9	266.16	29.57	4.99	0.045
Residual	5	29.59	5.91		
Total	14	295.75			

Dissolution rate study of optimized ternary solid dispersion batch and pure ibuprofen was also performed in distilled water and 0.1N HCl media. The experiment was repeated three times.

2.6. Data Analysis

Contour plots, polynomial models, including interactions and quadratic terms were generated for all the response variables by applying multiple linear regression analysis using Design Expert 9.0.2 software (Trial version).

3. RESULTS AND DISCUSSION

3.1. Data Analysis

In order to investigate the factors systematically, Box-Behnken design was employed. Ternary solid dispersions were evaluated for dissolution study (% release after 10 minutes = Q_{10}) and angle of repose (AR).

3.1.1. Data Analysis for Y_1 (Q_{10})

Observed and predicted values for Q_{10} (Y_1) and AR (Y_2) for all the 15 batches are shown in table 3. The Y_1 (Q_{10}) values measured for different batches showed wide variation (i.e. values ranged from a minimum of 61.91 ± 2.4 % to a maximum 85.40 ± 4.67 %).

Table 6: Results of checkpoints and optimized batches for percentage drug release at 10 minutes ($Q_{10} = Y_1$) and angle of repose (AR)

Batch	X_1 (Starcap 1500)	X_2 (PEG 4000)	X_3 (Ratio of drug: polymer)	$\mathbf{Y_1}$ (Q_{10}± SD)	Predicted	% error
Check pt-1	-0.3	-1	0	65.43 ± 4.06	62.88	3.89
Check pt-2	0.1	0	0.1	73.42 ± 6.06	71.16	3.07
Check pt-3	0.5	1	0.3	88.43 ± 5.26	85.06	3.81
Optimized batch	0.92	0.76	0.93	**81.68 ± 4.22**	79.23	-3.00
				$\mathbf{Y_2}$(AR± SD)		
Check pt-1	-0.3	-1	0	40.15 ± 1.06	41.57	-3.53
Check pt-2	0.1	0	0.1	36.32 ± 2.06	37.69	-3.77
Check pt-3	0.5	1	0.3	37.43 ± 3.06	36.49	2.51
Optimized batch	0.92	0.76	0.93	**31.63 ± 1.06**	32.43	2.53

All values are expressed as mean ± SD, n = 3

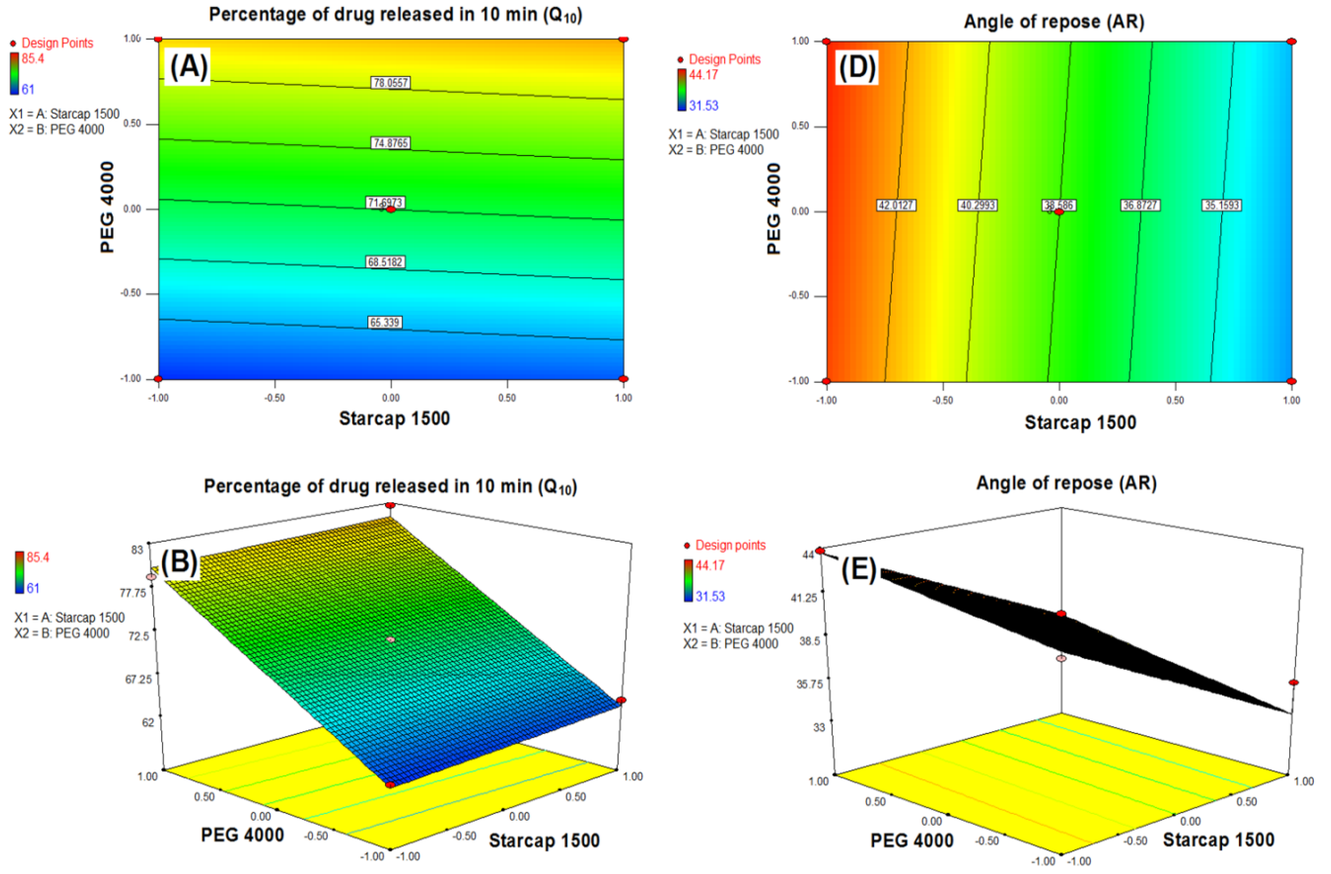

Figure 1: Contour and cube plots showing effects on % drug release after 10 minutes Y_1(Q_{10}) and angle of repose Y_2 (AR).

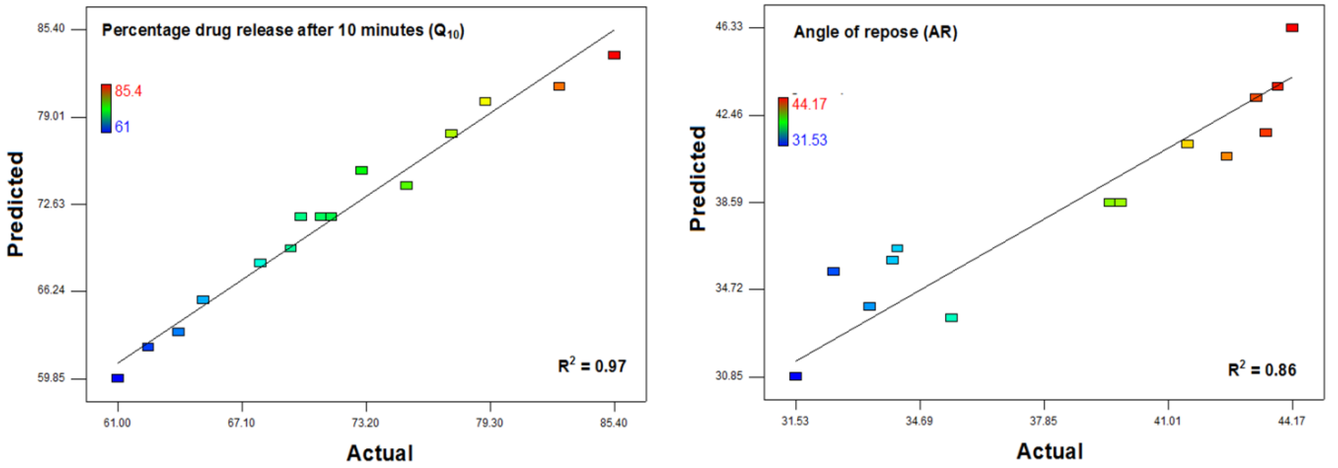

Figure 2:Linear correlation plots between actual versus predicted values for Y_1 = Percentage drug release after 10 minutes (Q_{10}) and Y_2 = Angle of repose (AR).

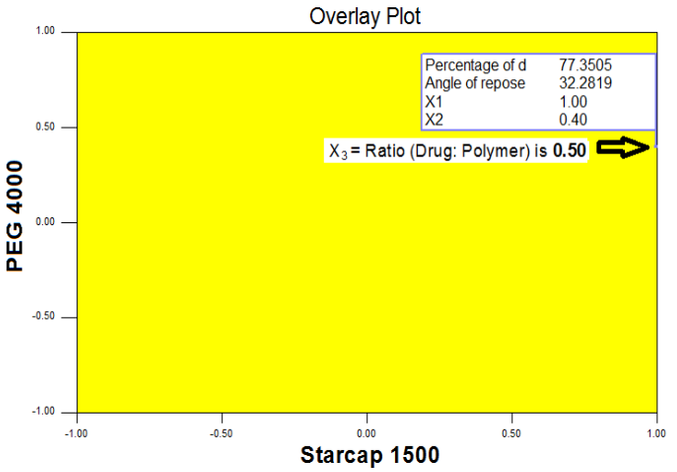

Figure 3: Overlay plot for prediction of optimized batch

Thus, the results clearly indicate that the Q_{10} value was significantly affected by the selected independent variables. The response (Y_1) obtained at various levels of the 3 independent variables (X_1, X_2, and X_3) were subjected to multiple regression to yield a second-order polynomial equation [full model (3) and reduced (4)].

$$Y_1(Q_{10}) = 71.60 + 0.55\,X_1 + 8.98\,X_2 + 2.86\,X_3 + 0.54\,X_{12} - 0.93\,X_{23} + 0.95\,X_{13} + 0.20\,X_1^2 + 1.03\,X_2^2 + 0.39\,X_3^2$$

----Equation 3

$$Y_1(Q_{10})_{\text{reduced model}} = 71.60 + 8.98\,X_2 + 2.86\,X_3$$

----Equation 4

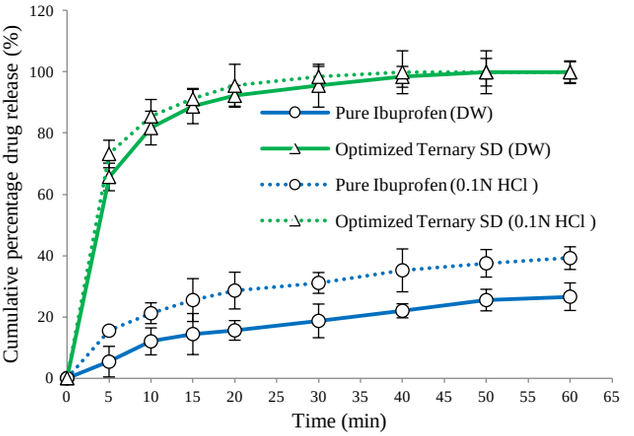

Figure 4: Dissolution profile comparison in distilled water (DW) and 0.1N HCl (pH=1.2) of pure ibuprofen with optimized ternary solid dispersion.

The standardized effect of the independent variables and their interaction on the dependent variable can be investigated by focusing on table 4, which represents the main effect of the independent variables and interactions with their relative significance on the Q_{10} and AR. Among the three independent variables, X_2 (PEG 4000) has prominent effect (b_2 = 8.98 and P = 2.5 × 10^{-06}) on Q_{10}, after that X_3 (ratio) also affects the release profile (b_3 = 2.86 and P = 6.5 × 10^{-04}) and both of them has a positive effect on the dissolution rate. The polynomial equation indicate that, a unit increase in PEG 4000 and drug: polymer ratio cause 8.98 and 2.86 unit increase in % drug dissolution at 10

minutes (Q_{10}). The lowest coefficient value was for X_1 (b_1 = 0.55 and P = 0.25), suggesting that Starcap 1500 has insignificant effect on Q_{10} (P = 0.25).

The interaction effects were not significant in any of the cases, so there is additive effect on results of Q_{10}.

3.1.2. Data Analysis for Y_2 (AR)

Angle of repose (AR) for all the batches were found to be in the range of 31°53" ± 3°23" to 44°17" ± 1°78" (Table 3). A polynomial equation was also developed for Y_2:

$$Y_2(AR) = 38.59 - 4.89\,X_1 + 0.25\,X_2 - 2.85\,X_3 - 0.66\,X_{12} - 0.23\,X_{23} - 0.12\,X_{13} - 0.23\,X_1^2 - 0.44\,X_2^2 + 1.35\,X_3^2$$

---Equation 5

$$Y_2(AR)_{\text{reduced model}} = 38.59 - 4.89\,X_1 - 2.85\,X_3$$

---Equation 6

X_1 (Starcap 1500) and X_3 (ratio) are the variables that have significant effect (P < 0.05), indicating a major contribution on flow property of solid dispersion powder (Table 4). The results showed that, a unit increase in Starcap 1500, cause 4.89 unit decrease in angle of repose, suggesting improvement in flow property of solid dispersion using Starcap 1500 (b_1 = 4.89 and P = 0.0001). While a unit increases in PEG 4000 cause insignificant increase in angle of repose by 0.25 units (b_2 = 0.25 and P = 0.71). PEG 4000 in SD results in more tacky particles, which worsens the flow property. It was also observed that, with increase in ratio i.e. increase in polymer mixture amount in SD, cause improvement in flow property (b_2 = -2.85 and P = 0.001).

3.2. Contour Plots and Response Surface Analysis

The relationship between the dependent and independent variables was further elucidated by constructing contour plots (figure 1). As we know X_3 showed positive effect on both Q_{10} and AR, with equal intensity, we decided to keep X_3 at fixed level (medium level, X_1= 0) and the effect of X_1 and X_2 on Q_{10} and AR was studied. The contour plot of Q_{10}, X_1 versus X_2 was found to be linear (R^2 = 0.97), indicating a linear relationship between independent variables and percentage drug release at 10 minutes i.e. Q_{10} (figure 2).It was determined from contour plot that, higher value of Q_{10} (ranging 70-85%) could be achieved with an X_1 level (Starcap 1500) ranging from -1 to 1 and X_2 level (PEG 4000) ranging from 0.5 to 1. The contour plot of AR, X_1 versus X_2 was found to be non-linear (R2 = 0.86), indicating a non-linear relationship between independent variables and angle of repose. Considering factorial design as a tool, we can predict the lower value of AR (i.e. good flow property, θ = 30-35) at X_1 level (Starcap 1500) ranging from 0.5 to 1 and X_2 level (PEG 4000) ranging from -1 to 1.

3.3. Validation of Response Surface Methodology

The accuracy of the obtained polynomial equations was evaluated by preparing three check point batches. All 15 batches and three checkpoint batches were evaluated for Q_{10} and AR. Upon comparison of observed responses with that of predicted, the prediction error varied from -1.26 to + 1.40 and -7.42 to +5.54 for Y_1 (Q_{10}) and Y_2 (AR) respectively (Table 3 and 6). Thus, we can conclude that the obtained mathematical equation is valid and confirms the fitness of the model for predicting Q_{10}, but not for AR, which was also observed by poor regression values for AR (R^2 = 0.86).

3.4. Optimum Formula

After detail analysis on the effects of independent variables on percentage drug release and angle of repose using multiple regression analysis and contour plots, the level of independent variables were selected to obtain the optimum response. It was evident from the polynomial equation and contour plots that PEG 4000 improves the dissolution profile and its higher proportion was required in the mixture with Starcap 1500. While at the same time, higher amount of Starcap 1500 was also required to improve the flow property of solid dispersion. To prepare an economic formulation minimum level of polymer and drug: polymer ratio is preferred. Using the charm of design of ex-

pert software, the range of X_1, X_2 and X_3 was selected as 0 to 1, with target percentage release (Q_{10}) between 65 to 85% and angle of repose between 31 to 33. The software predicted/proposed the optimized batch with 0.99 probability, by selecting X_1 = 1 (Starcap 1500), X_2 = 0.40 (PEG 4000) and X_3 = 0.50 (Ratio of drug: polymer), to achieve Q_{10} = 79.23 % and AR = 32.43 (figure 3). The ternary SD batch was prepared at proposed levels of independent variables. The results showed 81.68 ± 4.22 % drug release after 10 minutes and AR to be 31°63" ± 1°06", which was closed to the predicted values (Error < ± 5%).

3.5. Dissolution Rate Study of Optimized Ternary SD

A significant improvement in the dissolution rate profile of the optimized ternary SD batch was observed in comparison to pure ibuprofen in distilled water and 0.1N HCl (pH=1.2) media (figure 4).Within 10 minutes ternary SD batch showed 81.68 and 85.50% release in respective distilled water and 0.1N HCl, while pure ibuprofen showed only 12.01 and 21.20 % release. The similarity factor f_2 values were found to be 12.12 and 15.20 of ternary SD batch with reference to pure drug in distilled water and 0.1N HCl media respectively, suggesting the dissimilarity in release profiles. The results propose improvement in dissolution release profiles due to molecular dispersion of drug in amorphous state in solid dispersion powder.

4. CONCLUSION

The present study demonstrates the application of Box-Behnken design in optimization of ternary solid dispersion. Optimized formulation was achieved with 64.65 % Starcap 1500 (X_1= 1), 10.35 % PEG 4000 (X_2= 0.4) and 25.00 % drug, i.e. 1:3 ratio of ibuprofen: polymer mixture (X_3= 0.50), to achieve Q_{10} = 81.68 % release of drug after 10 minutes with good flow property (angle of repose = 31° 63"). All the experimental values of Q_{10} and AR including check point batches were in close agreement with the model predicted values, indicating goodness of fit for model. In conclusion, prepared optimized ternary solid dispersion powder exhibited improved dissolution rate in comparison with pure drug. If this technology is scaled-up to commercial level, it holds great potential to provide fast release product with improved bioavailability. However, extensive long term stability and clinical pharmacokinetic studies are required before commercialization.

5. ACKNOWLEDGEMENT

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6. REFERENCES

1. Stegemann S, Leveiller F, Franchi D, De Jong H, Lindén H. When poor solubility becomes an issue: from early stage to proof of concept. European Journal of Pharmaceutical Sciences. 2007;31:249-61.
2. Di L, Kerns EH, Carter GT. Drug-like property concepts in pharmaceutical design. Current Pharmaceutical Design. 2009;15:2184-94.
3. Perrut M, Jung J, Leboeuf F. Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes: Part I: Micronization of neat particles. International Journal of Pharmaceutics. 2005;288:3-10.
4. Maulvi FA, Dalwadi SJ, Thakkar VT, Soni TG, Gohel MC, Gandhi TR. Improvement of dissolution rate of aceclofenac by solid dispersion technique. Powder Technology. 2011;207:47-54.
5. Thakkar FMV, Soni T, Gohel M. Supercritical fluid technology: a promising approach to enhance the drug solubility. Journal of Pharmaceutical Sciences and Research. 2009;1:1-14.
6. A Maulvi F, T Thakkar V, G Soni T, R Gandhi T. Optimization of Aceclofenac Solid Dispersion Using Box-Behnken Design: in-vitro and in-vivo Evaluation. Current Drug Delivery. 2014;11:380-91.
7. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics. 2000;50:47-60.

8. Goddeeris C, Coacci J, Van den Mooter G. Correlation between digestion of the lipid phase of smedds and release of the anti-HIV drug UC 781 and the anti-mycotic drug enilconazole from smedds. European Journal of Pharmaceutics and Biopharmaceutics. 2007;66:173-81.
9. Démuth B, Nagy Z, Balogh A, Vigh T, Marosi G, Verreck G, et al. Downstream processing of polymer-based amorphous solid dispersions to generate tablet formulations. International Journal of Pharmaceutics. 2015;486:268-86.
10. Huang Y, Dai W-G. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharmaceutica Sinica B. 2014;4:18-25.
11. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences. 1971;60:1281-302.
12. Nikghalb LA, Singh G, Singh G, Kahkeshan KF. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs. Journal of Applied Pharmaceutical Science. 2012;2:170-75.
13. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II: Experimental evaluation of a eutectic mixture: Urea-acetaminophen system. Journal of Pharmaceutical Sciences. 1966;55:482-87.
14. Wu C-Y, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceutical Research. 2005;22:11-23.
15. Yang G, Zhao Y, Feng N, Zhang Y, Liu Y, Dang B. Improved dissolution and bioavailability of silymarin delivered by a solid dispersion prepared using supercritical fluids. Asian Journal of Pharmaceutical Sciences. 2014.
16. Moneghini M, Bellich B, Baxa P, Princivalle F. Microwave generated solid dispersions containing ibuprofen. International Journal of Pharmaceutics. 2008;361:125-30.
17. Newa M, Bhandari KH, Li DX, Kwon T-H, Kim JA, Yoo BK, et al. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. International Journal of Pharmaceutics. 2007;343:228-37.
18. Mohammadi G, Hemati V, Nikbakht M-R, Mirzaee S, Fattahi A, Ghanbari K, et al. In vitro and in vivo evaluation of clarithromycin–urea solid dispersions prepared by solvent evaporation, electrospraying and freeze drying methods. Powder Technology. 2014;257:168-74.
19. Ferreira SC, Bruns R, Ferreira H, Matos G, David J, Brandao G, et al. Box-Behnken design: An alternative for the optimization of analytical methods. Analytica Chimica Acta. 2007;597:179-86.
20. Karnachi AA, Khan MA. Box-Behnken design for the optimization of formulation variables of indomethacin coprecipitates with polymer mixtures. International Journal of Pharmaceutics. 1996;131:9-17.
21. Patil P, Khairnar G, Naik J. Preparation and statistical optimization of Losartan Potassium loaded nanoparticles using Box Behnken factorial design: Microreactor precipitation. Chemical Engineering Research and Design. 2015;104:98-109.
22. Dizaj SM, Lotfipour F, Barzegar-Jalali M, Zarrintan M-H, Adibkia K. Box-Behnken experimental design for preparation and optimization of ciprofloxacin hydrochloride-loaded $CaCO_3$ nanoparticles. Journal of Drug Delivery Science and Technology. 2015;29:125-31.
23. Kaur P, Singh SK, Garg V, Gulati M, Vaidya Y. Optimization of spray drying process for formulation of solid dispersion containing polypeptide-k powder through quality by design approach. Powder Technology. 2015;284:1-11.
24. Nokhodchi A, Al-Hamidi H, Antonijevic MD, Owusu-Ware S, Kaialy W. Dissolution and solid state behaviours of carbamazepine-gluconolactone solid dispersion powders: The potential use of gluconolactone as dissolution enhancer. Chemical Engineering Research and Design. 2015;100:452–66.