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Original Article

EFFECT OF NON-VOLATILE SOLVENT AND EXCIPIENT RATIO ON FLOW AND CONSOLIDATION PROPERTIES OF POWDER BLEND FOR LIQUISOLID COMPACTS

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ABSTRACT

Objective: To study the effect of non-volatile solvent and excipient ratio on flow and consolidation properties of powder blend for liquisolid compacts.

Methods: The effect of non-volatile solvent and excipient ratio on flow and consolidation properties of powder blend for liquisolid compacts was studied. Tween 20, microcrystalline cellulose and colloidal silicon dioxide were selected as non-volatile solvent, carrier and coating material respectively. A central composite statistical design with 2 factors, 5 levels, and 13 runs was selected for the study. Quantity of Tween 20 and excipient ratio were selected as independent factors and an angle of repose, Carr's index and Hausner ratio were selected as responses indicative of flow and consolidation properties.

Results: From the statistical analysis of the data obtained for an angle of repose it was found that the quadratic model was not significant. The response surface quadratic models obtained for Carr's index and Hausner ratio were found to be significant. Both responses were much influenced by the quantity of non-volatile solvent than the excipient ratio. Both the independent factors were observed to have interaction. But the interactions were statistically insignificant.

Conclusion: The selected independent factors were found to be influential on flow and consolidation properties of powder blend for liquisolid compacts. The results of this study could be used for selection of appropriate systems for the preparation of liquisolid blends with tailored flow and consolidation properties.

Keywords: Liquisolid compacts, Non-volatile solvent, Excipients ratio, Central composite design, Contour plot, Response surface plot.

INTRODUCTION

The applications and advantages of liquisolid compacts are well reported [1-4]. The formulation aspects of liquisolid compacts are also well studied [2-5]. A major advantage listed for liquisolid compacts is the improved efficacy of tablet manufacturing [1-4]. Liquisolid compact technology involves the inclusion of appropriate adjuvant required for tabletting. In general the insoluble drug is dissolved in a non-volatile solvent and is transformed to a powder blend with acceptable flow and consolidation properties. Non-volatile solvents are used for solubilizing the insoluble drug and to enhance the solubility and dissolution. The conversion of the liquid to a compressible powder blend is carried out by the use of a combination of carrier and coating material. Large and porous particles are chosen as carrier material. Their function is to provide sufficient adsorption properties for facilitating the formation of a powder blend, along with the coating material, with acceptable flow and consolidation properties when mixed with the non-volatile solvent [6,7]. Microcrystalline cellulose is a widely used carrier material. Coating materials like colloidal silicon dioxide covers the almost wet particles obtained by mixing non-volatile liquid with the carrier material. They provide a dry-looking appearance for the powder blends and enhances the flow considerably. Coating materials with large surface are highly preferred for this purpose. Excipient ratio represents the weight ratio of carrier to coating material and has been widely employed. In addition to the above mentioned formulation excipients, super disintegrants are employed in liquisolid compacts. This is to increase the rate of drug release, water solubility and wettability of liquisolid granules.

Though many studies have been reported on the development of liquisolid compacts no reports have been made on the effect of various formulation factors on liquisolid compacts. Moreover, there are no reports on the effect of non-volatile solvent on flow and consolidation properties for blends for liquisolid compacts. Therefore the aim of the present research work was to study the effect of the non-volatile solvent and excipient ratio on flow and consolidation properties. Here we selected Tween 20 as non-volatile solvent and microcrystalline cellulose and colloidal silicon dioxide as carrier and coating material respectively. Sodium starch glycollate was employed as super disintegrant in the study.

MATERIALS AND METHODS

Materials

Tween 20 was purchased from SD Fine-Chem Ltd., Mumbai, India. Microcrystalline cellulose (Avicel PH 102®) was purchased from Reliance Cellulose Pvt Ltd., Pune, india. Colloidal silicon dioxide (Aerosil®) was obtained as gift sample from Evonik-Degussa India Pvt Ltd., Mumbai, India. Sodium starch glycollate was purchased from Maple biotech Pvt Ltd., Pune, India.

Table 1: Variables and their constraints for central composite design

Independent factors						
Factor Code	**Factor**	**Levels**				
		-1.414	**-1**	**0**	**+1**	**+1.414**
A	Tween 20 (mg)	39.64	50	75	100	110.36
B	Excipient ratio, R	17.93	20	25	30	32.07
Dependent factors (Responses)						
Response code	Response					
R1	Angle of repose (°)					
R2	Carr's Index (%)					
R3	Hausner Ratio					

Evaluation of the effect of independent factors on responses

In order to achieve the objectives of the study, a central composite statistical design was employed [8]. The variables and the constraints for the central composite design are given in table 1. The levels of independent factors were identified based on pre-optimization studies. A circumscribed central composite statistical design with 2 factors, 5 levels, and 13 runs was selected for the study. This design is suitable for exploring quadratic response surfaces and constructing second-order polynomial models. Design-Expert software (State-Ease Inc, Minneapolis, USA) was used for the evaluation of data. This design is suitable for exploring quadratic response surfaces and constructing second-order polynomial models.

The coded and actual values for the selected central composite experimental design matrix for the study were as given in table 2.

Table 2: The central composite experimental design matrix for the study

Formulation code	Coded values		Actual values	
	Tween 20 (mg)	Excipient ratio, R	Tween 20 (mg)	Excipient ratio, R
B1	-1	-1	50	20
B2	0	0	75	25
B3	0	-1.414	75	17.93
B4	1.414	0	110.36	25
B5	-1	1	50	30
B6	0	0	75	25
B7	1	1	100	30
B8	0	0	75	25
B9	0	1.414	75	32.07
B10	1	-1	100	20
B11	0	0	75	25
B12	-1.414	0	39.64	25
B13	0	0	75	25

The polynomial equation generated by this experimental design is as follows (Eqn. 1).

$R = C_0+C_1A+C_2B+C_3AB+C_4A^2+C_5B^2$-------(Eqn. 1)

Where R is the dependent variable (response), C_0 is the intercept, C_1 to C_5 are the regression coefficients, and A and B are the independent variables.

Preparation of powder blends for liquisolid compacts

Several powder blends for liquisolid compacts were prepared according to the experimental design generated by Design Expert software as follows. The formula expressed in the design was for a 500 mg blend. A binary mixture of carrier-coating materials [microcrystalline cellulose PH 102 (Avicel PH 102®) as the carrier powder and colloidal silicon dioxide (Aerosil®) as the coating material] was added to the non-volatile liquid (Tween 20®) under continuous mixing in a mortar.

Finally, 5% w/w of sodium starch glycolate was added as the disintegrant and was mixed for a period of 10 min. Angle of repose, Carr's index and Hausner ratio of the resultant powder blend were then determined.

Evaluation of the powder blend for liquisolid compacts

The prepared powder blends were evaluated for the selected responses-angle of repose, Carr's index and Hausner ratio [9, 10].

Angle of repose

The angle of repose was determined by the fixed funnel method. This method employed a funnel that was secured with its tip at a given height above a graph paper that was placed on a flat horizontal surface. The powder was poured carefully through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius and the height of the pile were determined.

Bulk density

Weighed accurately 15 g of the powder and transferred to a 50 mL measuring cylinder. The bulk density was calculated using the following equation (Eqn. 2):

Bulk density = weight of the sample/volume of the sample------- (Eqn. 2)

Tapped density

Weighed accurately 15 g of the powder and transferred to a 50 mL measuring cylinder. It was then tapped on a wooden surface from a height of 1 inch about 500 times or until a constant volume was obtained. The tapped density was calculated using the formula (Eqn. 3):

Tapped density = weight of the sample/tapped volume of the sample------- (Eqn. 3)

Carr's index and Hausner ratio

The consolidation properties were studied by determining the Carr's index and the Hausner ratio (Eqns. 4 &5).

Carr's index = [(tapped density–bulk density)/tapped density] × 100------- (Eqn. 4)

Hausner ratio = tapped density/bulk density------- (Eqn. 5)

RESULTS AND DISCUSSION

Effect of independent factors on responses

All the 13 batches proposed by the experimental design were prepared. The powder blend for liquisolid compacts was evaluated for an angle of repose, Carr's index and Hausner ratio. The data thus obtained for these responses of experimental design are displayed in table 3.

Effect of independent factors on angle of repose (R1)

The Model F-value was 1.73, which implied that the quadratic model was not significant. There was a 24.51% chance that a Model F-value this large (1.73) could occur due to noise. The Lack of Fit F-value of 0.25 implied that, the Lack of Fit was not significant (p value = 0.8576). Non-significant lack of fit is good, as the data is required to fit the model. Values of "Prob>F" (p value) less than 0.0500 indicates significant model terms. In this case, there were no significant model terms. A negative predicted R-Squared of–0.0901 implied that the overall mean is a better predictor of the response than the current model. Adequate precision measures the signal to noise ratio.

A ratio greater than 4 is desirable. The obtained ratio of 4.643 indicated an adequate signal. This model can be used to navigate the design space. Table 4 displays the analysis of variance (ANOVA) data for the response.

Fig. 1 shows the plot of actual vs. predicted values of response–angle of repose. From the plot of actual vs. predicted values it can be seen that the points are well scattered away from the model line thus indicating a non significant model.

Table 3: Central composite statistical design data

Formulation code	Independent Factors		Dependent factors (Responses)		
	Tween 20 (mg)	Excipient ratio, R	Angle of repose, θ (°)	Carr's index (%)	Hausner ratio
B1	50	20	45.12	38.3	1.62
B2	75	25	49.81	36.4	1.57
B3	75	17.93	41.50	37.3	1.59
B4	110.36	25	55.49	32.5	1.48
B5	50	30	48.81	37.8	1.61
B6	75	25	46.17	35.3	1.55
B7	100	30	50.12	31.6	1.46
B8	75	25	41.35	35.9	1.56
B9	75	32.87	45.03	35.4	1.55
B10	100	20	56.82	33.9	1.51
B11	75	25	48.34	36.6	1.58
B12	39.64	25	49.11	36.6	1.58
B13	75	25	56.12	36.3	1.57

Table 4: ANOVA for response surface quadratic model–angle of repose (R1)

Source	Sum of Squares	df†	Mean Square	F Value	p-value (Prob>F)	Remark
Model	171.06	5	34.21	1.73	0.2451	Not significant
A-Tween 20	*60.68*	1	*60.68*	*3.08*	0.1229	-
B-Excipient ratio, R	*0.49*	1	*0.49*	*0.025*	0.8791	-
AB	*26.99*	1	26.99	1.37	0.2805	-
A^2	46.30	1	46.30	2.35	0.1694	-
B^2	*26.12*	1	*26.12*	1.32	0.2877	-
Residual	138.11	7	19.73	-	-	-
Lack of fit	*21.85*	3	*7.28*	0.25	0.8576	Not significant
Pure error	*116.26*	4	*29.06*	-	-	-
Cor total	309.17	12	-	-	-	-

†df = degrees of freedom

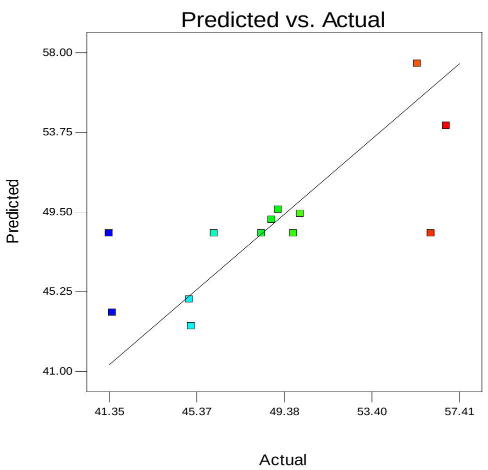

Fig. 1: Plot of actual versus predicted values for angle of repose

In the case of an angle of repose as response, the adequate Precision was satisfactory with a value greater than 4 and lack of fit was not significant. But while considering the fact that the quadratic model suggested by the software was not significant. There for further evaluation of the data was unnecessary.

Effect of independent factors on Carr's index (R2)

The Design Expert® software suggested the quadratic model for the data. The Model F-value was 15.18, which implied that the quadratic model was significant. There was only a 0.12% chance that a Model F-Value this large (15.18) could occur due to noise. The Lack of Fit F-value of 3.63 implied that, the Lack of Fit was not significant (p value = 0.1223). Non-significant lack of fit is good, as the data is required to fit the model. Values of "Prob>F"(p value) less than 0.0500 indicated model terms were significant. In this case, A, B and A^2 were significant model terms. But the predicted R-Squared of 0.5255 was not as close to the adjusted R-Squared of 0.8553. This may indicate a large block effect or a possible problem with the model and/or data. Adequate precision was 11.925. Adequate precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The obtained ratio of 11.925 indicated an adequate signal. Thus, the suggested quadratic model was used to navigate the design space. Table 5 displays the analysis of variance (ANOVA) data for the response.

Fig. 2 shows the plot of actual vs. predicted values of response–Carr's index. From the plot it can be observed that the points are very close to the model line and thus substantiating the fitness of the model.

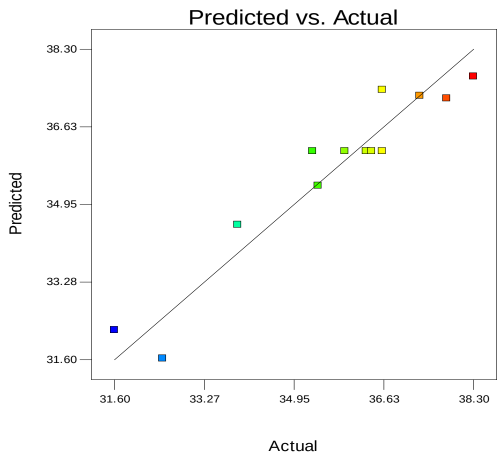

Fig. 2: Plot of actual versus predicted values for Carr's index

Table 5: ANOVA for response surface quadratic model-Carr's index (Response 2)

Source	Sum of Squares	df†	Mean Square	F Value	p-value (Prob>F)	Remark
Model	42.83	5	8.57	15.18	0.0012	Significant
A-Tween 20	33.61	1	33.61	59.59	0.0001	-
B-Excipient ratio, R	3.76	1	3.76	6.67	0.0363	-
AB	0.81	1	0.81	1.44	0.2698	-
A^2	4.31	1	4.31	7.65	0.0279	-
B^2	0.088	1	0.088	0.16	0.7046	-
Residual	3.95	7	0.56	-	-	-
Lack of fit	2.89	3	0.96	3.63	0.1223	Not significant
Pure error	1.06	4	0.27	-	-	-
Cor total	48.78	12	-	-	-	-

†df = degrees of freedom

The model proposed the following polynomial equation (Eqn. 6) in terms of coded factors for Carr's index.

$R2 = 36.10–2.05A–0.69B–0.45AB–0.79A^2+0.11B^2$-------(Eqn. 6)

Where, R2 is the Carr's index, A is the quantity of Tween 20 used (mg) and B is the excipient ratio.

Both the factors A and B (quantity of Tween 20 and excipient ratio respectively) are having a negative value for their coefficient in the equation which implies that an increase in value of factors A and B decreases the value of the response (Carr's index). A high magnitude of coefficient for factor A implies that it has more pronounced effect on Carr's index than that due to factor B. From the p values obtained from the design mode it was shown that A, B and A^2 are statistically significant terms while others are not. From the plots for individual effect of independent factors it was observed that increasing the quantity of Tween 20 decreases Carr's index (fig. 3a) and increasing excipient ratio slightly decreases Carr's index (fig. 3b). But both the independent factors were observed to have interaction. The net response is mainly influenced by the interaction effects rather than individual effects of independent factors. But the effect was not significant statistically as implied by the p value of 0.2698. The overwhelming effect of Tween 20 on Carr's index might have suppressed the individual effect of excipient ratio to much extent in the design.

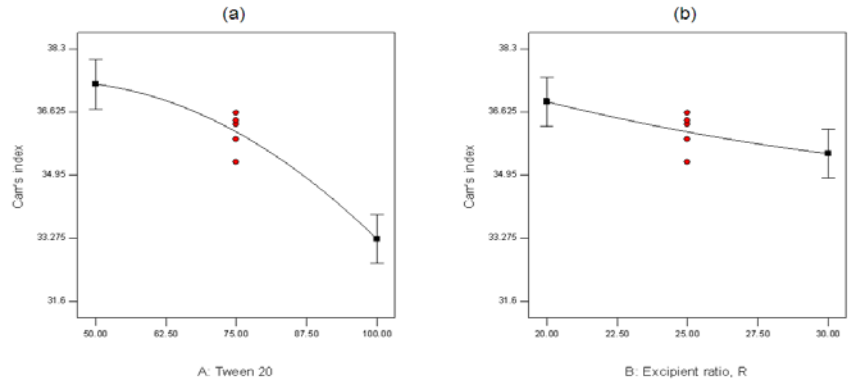

Fig. 3: Plot of individual effect of the quantity of (a) Tween 20 and (b) excipient ratio on Carr's index

Fig. 4a shows the contour plot and fig. 4b shows the response surface plot for the effect of independent factors on the response–Carr's index. From the plots it can be observed that the iso-value curves in the contour plot and the response surface in the response surface plot are most influenced by the quantity of Tween 20. The iso-value curves are more towards like parallel to the y-axis (of excipient ratio) which implies that the response is most dependent on the quantity of Tween 20 used. Similarly a rapid inclination of the response surface on changing the values of Tween 20 shows that it has much influence on the response, Carr's index. Since the response surface inclines down on increasing the value of Tween 20, we can conclude that increased value of Tween 20 causes decrease in Carr's index. There was only a slight inclination of the response surface in response to change in excipient ratio. This suggested that the effect of excipient ratio on Carr's index is feeble.

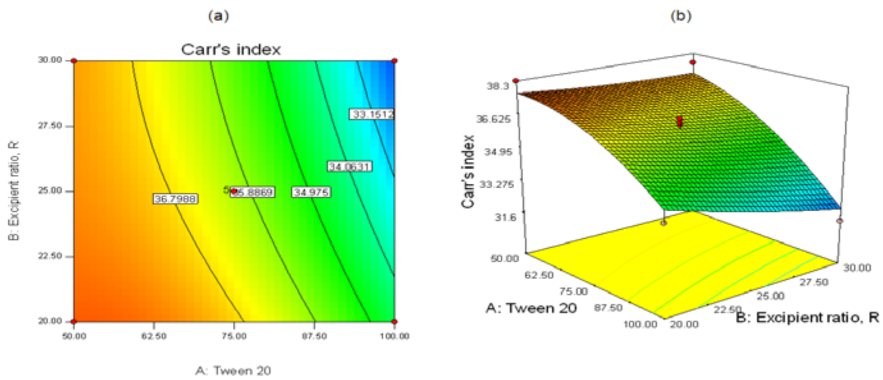

Fig. 4: Effect of independent factors on Carr's index (a) Contour plot and (b) Response surface plot

Effect of independent factors on hausner ratio (R3)

The Design Expert® software suggested quadratic model for the data. The Model F-value was 15.13, which implied that the quadratic model was significant. There was only a 0.12% chance that a Model F-value this large (15.13) could occur due to noise. The Lack of Fit F-value of 4.51 implied that, the Lack of Fit was not significant (p value = 0.0898). Non-significant lack of fit is good, as the data is required to fit the model. Values of "Prob>F"(p value) less than 0.0500 indicated model terms were significant. In this case, A and A2 were significant model terms. But here also, as in the case of Carr's index, the predicted R-Squared of 0.5049 was not as close to the adjusted R-Squared of 0.8548. This may indicate a large block effect or a possible problem with the model and/or data. Adequate precision was 11.887. Adequate precision was 11.887. Adequate precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The obtained ratio of 11.887 indicated an adequate signal. Thus, the suggested quadratic model was used to navigate the design space. Table 6 displays the analysis of variance (ANOVA) data for the response.

Table 6: ANOVA for response surface quadratic model-hausner ratio (Response 3)

Source	Sum of Squares	df†	Mean Square	F Value	p-value (Prob>F)	Remark
Model	0.025	5	4.93×10^{-3}	15.13	0.0012	Significant
A-Tween 20	0.020	1	0.020	61.87	0.0001	-
B-Excipient ratio, R	1.7×10^{-3}	1	1.7×10^{-3}	5.22	0.0563	-
AB	4.0×10^{-4}	1	4.0×10^{-4}	1.23	0.3043	-
A^2	2.254×10^{-3}	1	2.254×10^{-3}	6.92	0.0339	-
B^2	2.783×10^{-5}	1	2.783×10^{-5}	0.085	0.7785	-
Residual	2.279×10^{-3}	7	3.256×10^{-4}	-	-	-
Lack of fit	1.759×10^{-3}	3	5.864×10^{-3}	4.51	0.0898	Not significant
Pure error	5.2×10^{-4}	4	1.3×10^{-4}	-	-	-
Cor total	0.027	12	-	-	-	-

†df = degrees of freedom

Fig. 5 shows the plot of actual vs. predicted values of response–Hausner ratio. From the plot it can be observed that the points are very close to the model line and thus substantiating the fitness of the model.

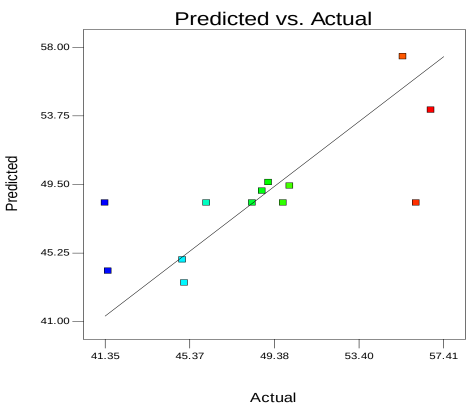

Fig. 5: Plot of actual versus predicted values for hausner ratio

The model proposed the following polynomial equation (Eqn. 7) in terms of coded factors for Hausner ratio.

$R3 = 1.57 - 0.050A - 0.015B - 0.010AB - 0.018A^2 + 0.002B^2$-------(Eqn. 7)

where R3 is the Hausner ratio, A is the quantity of Tween 20 used (mg) and B is the excipient ratio.

Both the factors A and B (quantity of Tween 20 and excipient ratio respectively) are having a negative value for their coefficient in the equation which implies that an increase in value of factors A and B decreases the value of the response (Hausner ratio). A high magnitude of coefficient for factor A implies that it has more pronounced effect on Hausner ratio than that due to factor B. These results are similar to those observed for Carr's index. From the p values obtained from the design mode it was shown that A and A^2 are statistically significant terms while others are not. From the plots for individual effect of independent factors it was observed that increasing the quantity of Tween 20 decreases Hausner ratio (fig. 6a). Increasing excipient ratio also decreases Hausner ratio but slightly (fig. 6b) when compared to the quantity of Tween 20. But both the independent factors were observed to have an interaction affect as indicated by the significance of factor AB in the proposed quadratic equation. The net response is mainly influenced by the interaction effects rather than individual effects of independent factors. But the effect was not significant statistically as implied by the p value of 0.3043. Thus it can be see that the effect is most influenced by the presence of Tween 20.

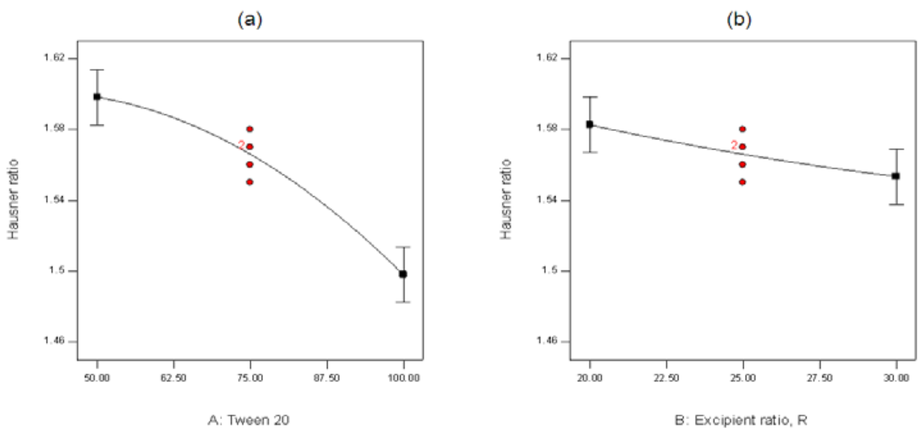

Fig. 6: Plot of individual effect of the quantity of (a) Tween 20 and (b) excipient ratio on Hausner ratio

Fig. 7a shows the contour plot and fig. 7b shows the response surface plot for the effect of independent factors on the response-Hausner ratio. From the plots, it can be observed that Tween 20 has the most influence on the iso-value curves in the contour plot and the response surface in the response surface plot. The iso-value curves are more towards like parallel to the x-axis (of excipient ratio) which implies that the response is most dependent on the quantity of Tween 20 used. Similarly a rapid inclination of the response surface on changing the values of Tween 20 shows that it has much influence on the response, Hausner ratio. Since the response surface inclines down on increasing the value of Tween 20, we can conclude that increased value of Tween 20 causes decrease in Hausner ratio. There was only a slight inclination of the response surface in response to change in excipient ratio. This suggested that the effect of excipient ratio on Hausner ratio is feeble. These results were much similar to those obtained for Carr's index.

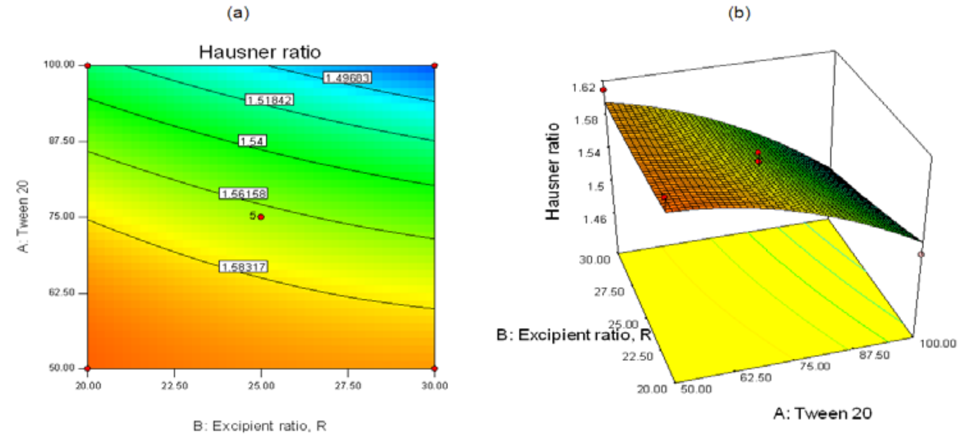

Fig. 7: Effect of independent factors on Hausner ratio (a) Contour plot and (b) Response surface plot

CONCLUSION

The effect of the non-volatile solvent and excipient ratio on flow and consolidation properties of powder blend for liquisolid compacts was studied. Tween 20, microcrystalline cellulose and colloidal silicon dioxide were selected as non-volatile solvent, carrier and coating material respectively. A circum scribed central composite statistical design was selected for the study. From the statistical analysis of the data obtained for an angle of repose it was found that the quadratic model was not significant. The response surface quadratic models obtained for Carr's index and Hausner ratio were found to be significant. Both responses were much influenced by the quantity of non-volatile solvent than the excipient ratio. Tween 20 and excipients ratio were found to decrease Carr's index and Hausner ratio. But the effect of Tween 20 was much pronounced that of excipients ratio. The results of this study could be used for selection of appropriate systems for the preparation of liquisolid blends with tailored flow and consolidation properties.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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