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PREPARATION AND CHARACTERIZATION OF TERNARY SOLID DISPERSION OF FLUNARIZINE DIHYDROCHLORIDE

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ABSTRACT

Introduction: The ternary solid dispersion was developed to improve the Solubility and dissolution of drug. **Materials and Methods:** Binary and ternary solid dispersions were prepared by fusion and solvent evaporation method. They were characterized by solubility study, in vitro dissolution and dissolution efficiency. The solid state properties of solid dispersions were characterized by differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). **Results:** Optimized ternary solid dispersion containing ratio 1:2:2 of drug: PEG 6000: Pluronic F68 gave highest solubility with maximum dissolution. The FTIR, and DSC studies of solid dispersions were confirmed the formation of solid dispersion. **Conclusion:** The studies indicated that the solubility and dissolution of drug was improved in the presence of ternary agent (surfactant) as compared to binary solid disersion.

KEYWORDS: Fusion method, PEG 6000, Pluronic F68, Flunarizine Dihydrochloride, ternary solid dispersion.

INTRODUCTION

Flunarizine, a piperazine derivative, is a selective Ca++ channel blocker coupled with its antihistaminic property claimed to be effective in prophylaxis of migraine. It is effective in migraine by reducing intracellular Ca++ overload due to brain hypoxia and thus prevents the deleterious effects of cellular calcium overload. Flunarizine Dihydrochloride has low aqueous solubility and dissolution hence it exhibits poor in vivo bioavailability (18-27%). Several techniques are commonly used to improve dissolution and bioavailability of poorly water

soluble drugs, such as size reduction, the use of surfactants, and the formation of solid dispersions.

Hence, the objective of this study was to improve the solubility of flunarizine Dihydrochloride by preparing the ternary solid dispersion. Mechanisms involved include increased wettability, solubilization of the drug by the carrier at the diffusion layer, and reduction or absence of aggregation and agglomeration. Moreover, transformation of the crystalline drug to the amorphous state upon solid dispersion increases the dissolution rate. Formation of solid dispersions is one of the most widely studied dissolution-enhancing strategies. Phase separation, crystal growth, or conversion from the amorphous to the crystalline state during storage inevitably leads to reduced dissolution rates. To prevent recrystallization, carriers that reduce molecular mobility are added. Moreover, hydrophilic polymers are able to enhance drug supersaturation. In addition, to enhance drug supersaturation, surfactants decrease aggregation, improve wetting, and increase dissolution of drug.

MATERIALS

Flunarizine Dihydrochloride (Adison pharma, Mumbai, India); Pluronic F 68 and Pluronic F127 (BASF chemical company, Germany); Polyethylene glycol 4000 (PEG 4000), Polyethylene glycol 6000 (PEG 6000) and polyvinyl pyrrolidone K30 (PVP K30) (S. D. Fine Chemical Limited, Mumbai, India); Mannitol (Sigma Aldrich, product of China); β-cyclodextrin and HPMC E5 LV (Yarrow chem., Mumbai); (Sodium starch glycolate and crospovidone (Chemdyes corporation, Ahmedabad, India); crosscarmellose sodium (Yarrow chem., Mumbai), and other chemicals and reagent used in the study were obtained commercially and used as received.

METHODS

Preparation of Physical Mixture

A physical mixture of Flunarizine Dihydrochloride with carrier was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier in by glass mortar and pestle. This mixture was then subsequently passed through 80# sieve and stored in a dessicator for 24 hr.

Phase Solubility Study

Phase solubility study was conducted as per the method reported by Higuchi and Connors. Excess quantity (20 mg) of drug was taken for study. Drug and carrier as per the specified

drug: carrier ratio were weighed accurately and added to pure drug with 10 mL of water in screw capped bottles. All the bottles were shaken in incubator shaker at 37 °C and 24 °C for 48 hr. After 24 hrs the solutions were filtered using (0.45 µ) filter and the filtrates were diluted. The absorbance were measured at 254 nm. From the absorbance the solubility of the drug was calculated.

Table 1: Solubility study of Physical mixture in 0.1 N HCL and Distilled water

Carriers	Drug : Polymer Ratio	Solubility in media (mg/mL)	
		DW(n=3)	0.1N HCL(n=3)
Drug	-	0.009±0.000	0.666±0.017
PEG 6000	1:1	**0.113**±0.019	**1.813**±0.019
β-Cyclodextrin	1:1	0.031±0.028	1.554±0.012
PVP K30	1:1	**0.074**±0.019	**1.715**±0.012
Mannitol	1:1	0.056±0.019	1.688±0.012
PEG 4000	1:1	0.045±0.019	1.679±0.017
HPMC E5 LV	1:1	**0.092**±0.019	**1.987**±0.017

Preparation of Solid Dispersion

For optimization of drug: polymer ratio, solid dispersions were prepared by the fusion and solvent evaporation method.

Preparation of Binary Solid Dispersion by Fusion Method

In this method, carriers were melted above 5 °C than their melting point in porcelain dish and to this a weighed amount of Flunarizine Dihydrochloride was added with continuous stirring until homogenization. Solidification was allowed to occur at room temperature. The product was stored in a dessicator for 24 hr and then pulverized using a glass mortar and pestle. The pulverized powders were passed through 80# sieve. The powder equivalents to 10 mg Flunarizine Dihydrochloride was evaluated for solubility study.

Preparation of Binary Solid Dispersion by Solvent Evaporation Method

In this method, carriers were dissolved in suitable solvent (Ethyl alcohol) in the petry plate and to this a weighed amount of Flunarizine Dihydrochloride was added with continuous stirring until homogenization. Evaporation of solvent was allowed to occur at room temperature. The product was stored in a dessicator for 24 hr and then pulverized using a glass mortar and pestle. The pulverized powders were passed through 80# sieve.

The powder equivalent to 10 mg Flunarizine Dihydrochloride was evaluated for solubility study.

Selection of Carrier for Binary Solid Dispersion

For the selection and optimization of drug: polymer ratio, different physical mixtures were prepared with the different polymers (β-Cyclodextrin, HPMC E5 LV, Mannitol, PVP K30, PEG 6000 & PEG 4000) in the ratio of 1:1. The prepared physical mixtures were evaluated for solubility study (Table 1). The optimized ratio of drug:polymer was found to be 1:1 of Drug:HPMC E5 LV, Drug:PVP K30, Drug:PEG 6000. Solid dispersion of Drug:HPMC E5 LV, Drug:PVP K30, Drug:PEG 6000 (1:1, 1:2, 1:3, 1:4) was prepared by fusion and solvent evaporation method and evaluated for solubility study (Table 2).From the solubility study, Drug:PEG 6000 (1:2 ratio) prepared by fusion method gives highest solubility in 0.1 N HCL as well as in Distilled water. So, this ratio of solid dispersion was also evaluated for assay, in vitro drug release study and taken for further study.

Table 2: Solubility study for Binary Solid Dispersion

Carriers	Drug : Polymer Ratio	Solubility in media (mg/mL)	
		DW(n=3)	0.1N HCL(n=3)
	Prepared by fusion method		
PEG 6000	1:1	0.116 ± 0.002	1.960 ±0.022
	1:2	**0.208** ± 0.003	**2.047**±0.023
	1:3	0.145 ± 0.004	1.950±0.035
	1:4	0.129± 0.001	1.633±0.018
	Prepared by solvent evaporation method		
PEG 6000	1:1	0.110±0.001	1.612±0.018
	1:2	0.121± 0.001	1.426±0.011
	1:3	0.177±0.001	1.894±0.022
	1:4	0.147±0.001	1.208±0.012
PVP K30	1:1	0.085 ± 0.003	1.564±0.022
	1:2	0.108± 0.001	1.514±0.012
	1:3	0.099± 0.001	1.620±0.012
	1:4	0.089± 0.001	1.728±0.012
HPMC E5 LV	1:1	0.123± 0.002	1.804±0.023
	1:2	0.145±0.003	1.699±0.018
	1:3	0.103±0.002	1.593±0.019
	1:4	0.087±0.003	1.884±0.012

Selection of Ternary Agent for Ternary Solid Dispersion

For the selection of ternary agent, Pluronic F68 and Pluronic F127 were taken as ternary agents in ratio of 1:2:0.5 to 1:2:3 of Drug:PEG 6000: ternary agent. The ternary solid dispersions were prepared by fusion method. They were evaluated for solubility study (Table 3).The screened ternary agent was found to be Pluronic F68 from above study. Pluronic F68 was taken as ternary agent for further study.

Table 3: Solubility study for Ternary Solid Dispersion

Carriers	Drug: Polymer: Surfactant Ratio	Solubility in media (mg/mL)	
		DW (n=3)	0.1N HCl (n=3)
Pluronic F68	1:2:0.5	0.904 ± 0.019	2.026±0.022
	1:2:1	1.193 ± 0.037	2.342±0.017
	1:2:1.5	1.796 ± 0.037	2.560±0.017
	1:2:2	**2.045± 0.045**	**2.922±0.012**
	1:2:2.5	1.889± 0.029	2.660±0.012
	1:2:3	1.606± 0.019	2.435±0.012
Pluronic F127	1:2:0.5	0.853± 0.028	1.979±0.023
	1:2:1	0.899± 0.010	2.191±0.012
	1:2:1.5	1.196± 0.037	2.356±0.028
	1:2:2	1.654± 0.037	2.533±0.022
	1:2:2.5	1.491± 0.028	2.308±0.020
	1:2:3	1.251± 0.019	2.122±0.019

Optimization of Ternary Solid Dispersion Using 3^2 Full Factorial Design

In the present work, a 3^2 full factorial design was adopted to find out the optimum combination of independent variables (Parts of PEG 6000 and Parts of pluronic F68) to obtain desired values of % Drug release. In this design two factors were evaluated by changing their parts simultaneously. The parts of PEG 6000 (X_1) and parts of pluronic F 68 (X_2) were selected as indepdndent variables. Solubility (mg/ml), % Dissolution efficiency at 60 min ($\%DE_{60min}$) and Time required for 85% drug release (Q_{85}) were selected as dependent variable.

Statistical analysis

The statistical analysis of the 3 full factorial design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate contribution of each factor with different levels on response, two way analysis of variance (ANOVA) ($P < 0.05$) was performed using Design Expert 9.0.4.(State Ease, Inc., Minneapolis) demo version software. To graphically demonstrate the influence of each factor on response, the response surface plots were generated using Design Expert 9.0.4.(State Ease, Inc., Minneapolis) demo version software.

Evaluation of solid dispersion

% Drug content

Accurately weighed solid dispersion equivalent to 10 mg of flunarizine dihydrochloride was transferred to 100 ml of volumetric flask and diluted to 100 ml with methanol and sonicated for 30 min for complete solubilization of the drug. The solution was filtered through a 0.45 µ

filter and measured at 254 nm in double beam UV spectrophotometer (UV 1800, Shimadzu, Kyoto, Japan). Concentration of flunarizine Dihydrochloride was determined using the calibration curve of the drug in methanol.

In Vitro Dissolution Study

An amount of solid dispersion equivalent to 10 mg of Flunarizine Dihydrochloride was sprinkled on the surface of the dissolution medium in a dissolution tester, apparatus USP II. Dissolution studies of Flunarizine Dihydrochloride were performed at stirring speed of 50 rpm maintained in 900 ml of 0.1 N HCL at 37 ± 0.5 °C. At appropriate time intervals, aliquots of 10 ml were withdrawn and measured spectrophotometrically at λmax 254nm. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Dissolution Efficiency

Dissolution efficiency (DE) represents the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time.

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

Where y is the drug percent dissolved at time t

Fourier Transform Infrared Spectroscopy (FTIR) Study

Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Fourier transform infrared (FTIR) spectra of drug and physical mixture were recorded using KBr mixing method on FTIR instrument available at central instrument laboratory of the institute.

Differential Scanning Calorimetry (DSC) Study

For checking the solid state property of the drug, polymers and solid dispersions, DSC study was carried out using DCS 60. Samples were placed in pierced aluminum pans and scanned at a heating rate of 10 ^{0}C/ min from 50 to 300 ^{0}C in a nitrogen atmosphere.

RESULTS AND DISCUSSION

Solubility study

The solubility of Flunarizine Dihydrochloride was found to be 0.009 mg/ml in distilled water and 0.666 mg/ml in 0.1N HCL [Table 1]. The physical mixture of Drug: PEG 6000, Drug: PVP K30 and Drug: HPMC E5 LV containing 1:1 ratio shows the highest solubility 0.111, 0.074 and 0.092mg/ml in distilled water and mg/ml in 0.1N HCL respectively as shown in Table 1. Hence, this 1:1 ratio of physical mixture was selected for preparation of binary solid dispersion. The solubility of optimized binary solid dispersion of Drug: PEG 6000 (1:2 ratio) prepared by fusion method was found to be 0.208 mg/ml in distilled water and 2.047 mg/ml in 0.1N HCL (Table 2). Hence, solubility of binary solid dispersion was more compared to physical mixture. The drug content of binary solid dispersion was found to be 99.76%.

Selection of ternary agent for ternary solid dispersion

For the selection of ternary agent, Pluronic F68 and Pluronic F127 were taken as ternary agents in ratio of 1:2:0.5 to 1:2:3 of Drug:PEG 6000: ternary agent. The ternary solid dispersions were prepared by fusion method. Pluronic F68 as ternary agent in ratio of 1:2:2 of drug: PEG 6000: ternary agent shows highest solubility in distilled water as well as in 0.1 N HCL compared to Pluronic F127 as ternary agent as shown in Table 3. The screened ternary agent was found to be Pluronic F68 from the solubility study.

Optimization by 3^2 full factorial design

The parts of PEG 6000(X_1) and parts of pluronic F 68 (X_2) were selected as independent variables. A statistical model incorporating interactive and poly nominal terms was used to evaluate the responses.

$$Y= b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b0 is the arithmetic mean response of the 9 runs, and b1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. All 9 factorial batches were evaluated for assay, in vitro dissolution and % dissolution efficiency.

The data indicate that the release profile of the drug is strongly dependent on the selected independent variables.The results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analyzed using Design Expert 9.0.4.

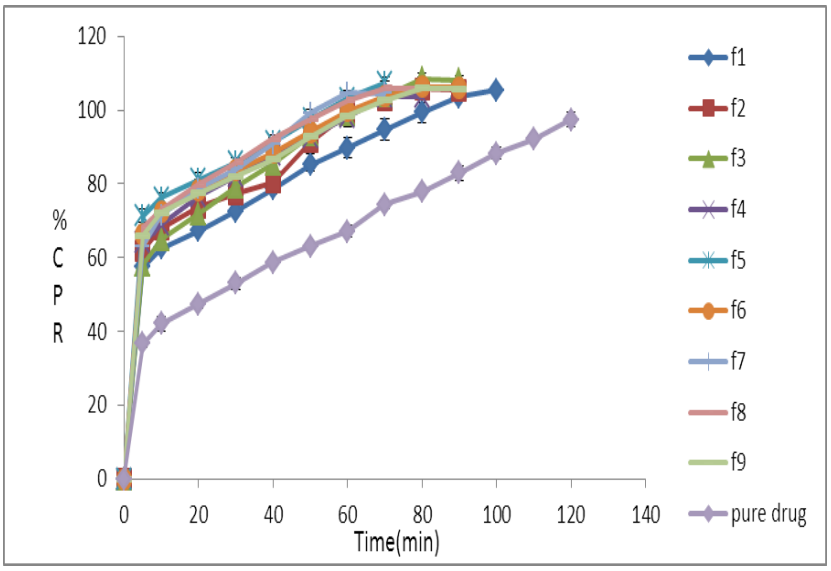

Figure 1: Dissolution profile of factorial batches f1 o f9

Table 4: Statistical Analysis of factorial design batches

Batch Code	X1	X2	Solubility 0.1 N HCL	$\%DE_{(60min)}$	Q_{85}
F1	-1	-1	2.783	68.23	50
F2	0	-1	2.851	73.59	44
F3	1	-1	2.848	73.32	41
F4	-1	0	2.876	75.92	35
F5	0	0	2.925	80.85	30
F6	1	0	2.897	77.41	32
F7	-1	1	2.912	78.21	31
F8	0	1	2.918	80.51	30
F9	1	1	2.889	77.14	35
		Actual Values			
		A		**B**	
Coded Values		**Parts of PEG 6000**		**Parts of Pluronic F 68**	
-1		17.5		17.5	
0		20		20	
+1		22.5		22.5	

*****$\%DE_{(60min)}$ (% dissolution efficiency at 60 min), Q_{85} (time required for 85%drug release), X_1 (parts of PEG 6000), X_2 (parts of pluronic F68)

Table 5: ANOVA table for Dependent variables from 3^2 full factorial batches ANOVA table for Response Y1 (Solubility in 0.1 N HCL)

	DF	SS	MS	F	P-value Prob > F
Model	5	0.0159	0.003	55.576	0.0037
Residual	3	0.0001	0.000		
Total	8	0.0160			

Response Y2 (% Dissolution Efficiency at 60 min)

	DF	SS	MS	F	P-value Prob > F
Model	5	125.59	25.12	91.49	0.0018
Residual	3	0.82	0.27		
Total	8	126.41			

Response Y3 [Time required 85% drug release (Q_{85})]

	DF	SS	MS	F	P-value Prob > F
Model	5	396.69	79.34	155.79	0.0008
Residual	3	1.53	0.51		
Total	8	398.22			

*df indicates degree of freedom; SS, sum of square; MS, mean of square; F, Fischer's ratio

The fitted equation relating to the responses Solubility in 0.1 N HCL, % dissolution efficiency at 60 min ($\%DE_{60min}$) and time required for 85% drug release (Q_{85}) to the transformed factors are shown in equations 1 to 3 respectively.

Solubility in 0.1 N HCL

$$\mathbf{Y_1} = 2.92 + 0.01^* \mathbf{X_1} + 0.03^* \mathbf{X_2} - 0.03^* \mathbf{X_1^2} - 0.03^* \mathbf{X_2^2} - 0.02^* \mathbf{X_1X_2} \quad (1)$$

R-Square = 0.9893

($\%DE_{60min}$)

$$\mathbf{Y_1} = 80.27 + 0.89^* \mathbf{X_1} + 3.49^* \mathbf{X_2} - 3.31^* \mathbf{X_1^2} - 2.93^* \mathbf{X_2^2} - 1.49^* \mathbf{X_1X_2} \quad (2)$$

R-Square = 0.9935

(Q_{85})

$$\mathbf{Y_1} = 30.56 - 1.33^* \mathbf{X_1} - 6.50^* \mathbf{X_2} + 2.67^* \mathbf{X_1^2} + 6.17^* \mathbf{X_2^2} + 3.25^* \mathbf{X_1X_2} \quad (3)$$

R –Square = 0.9962

The value of correlation coefficient for Solubility, $\%_{DE60min}$ and Q_{85} indicate good fit (i.e., good agreement between the dependent and independent variables). The polynomial

equations can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative)

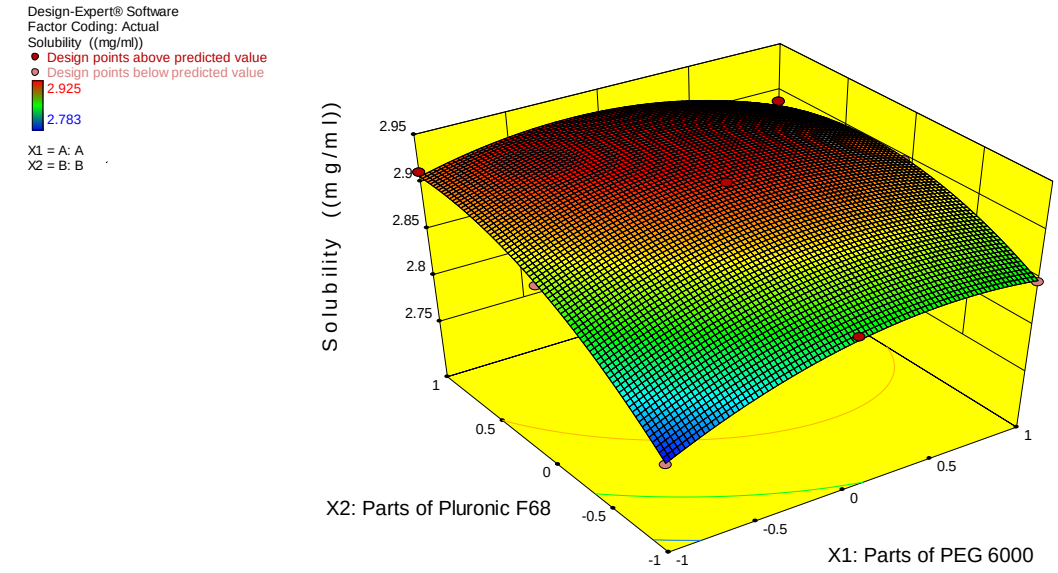

Figure 2: Response surface plot showing the effect of parts of PEG 6000 and parts of Pluronic F 68 on response Y_1 (Solubility in 0.1 N HCL)

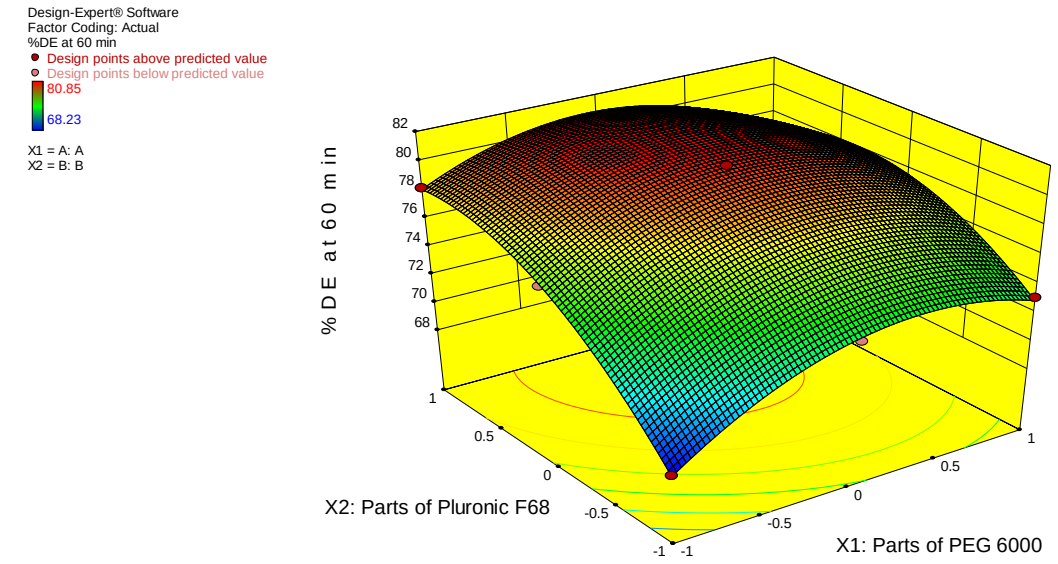

Figure 3: Response surface plot showing the effect of parts of PEG 6000 and parts of Pluronic F 68 on response Y_2 % dissolution efficiency at 60 min (% DE_{60min})

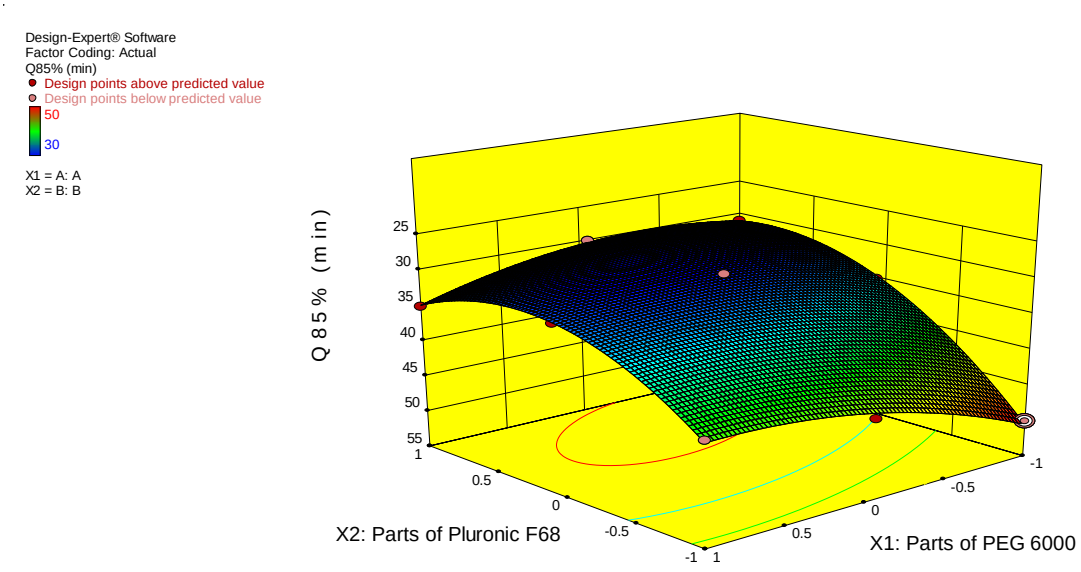

Figure 4: Response surface plot showing the effect of parts of PEG 6000 and parts of Pluronic F 68 on response Y_3 time required for 85% drug release (Q_{85})

From the Statistical analysis it was found that, Variable X_1 i.e. Parts of PEG 6000 and Variable X_2 i.e. Parts of Pluronic F68 shows positive effect on Solubility and % Dissolution Efficiency at 60 min, and negative effect on the Time required for 85% drug release. So, it can be qualitatively concluded that Variable X_1 and X_2 both had significant effect on the response. Compare to other batches F5 batch has high solubility in 0.1 N HCL, high % Dissolution efficiency at 60 min, and shows 85% drug release at 30 min. So, batch F5 is optimized batch.

Comparison of ternary solid dispersion with binary solid dispersion

Dissolution studies revealed that the dissolution of the drug from ternary solid dispersion was more in comparison to binary solid dispersion as shown in Figure 5.The in vitro drug release from binary and ternary solid dispersions were found to be 93.987% and 103.136%, respectively. This improvement was due to the presence of ternary agent Pluronic F68, which can probably be explained by increased wettability of Flunarizine Dihydrochloride. Indeed Pluronic F68 causes a decrease of the interfacial tension between the drug and the dissolution medium.

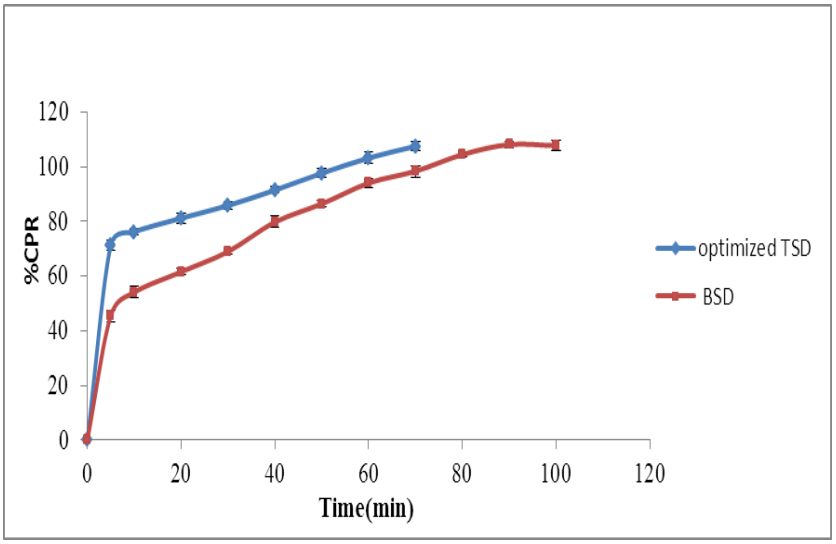

Figure 5: Comparison of dissolution profile of optimized TSD and BSD

Solid state studies

Fourier transform infrared spectroscopy was performed on Flunarizine Dihydrochloride. The prominent peaks were obtained at1514.17, 1236.41, and 2357.09 cm^{-1} because of stretching vibration bands of C-F, C-N, and C-H respectively as shown in Figure 6. It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and excipients (Figure 7). The FTIR study revealed no physical or chemical interactions of Flunarizine Dihydrochloride with PEG 6000 and Pluronic F68.

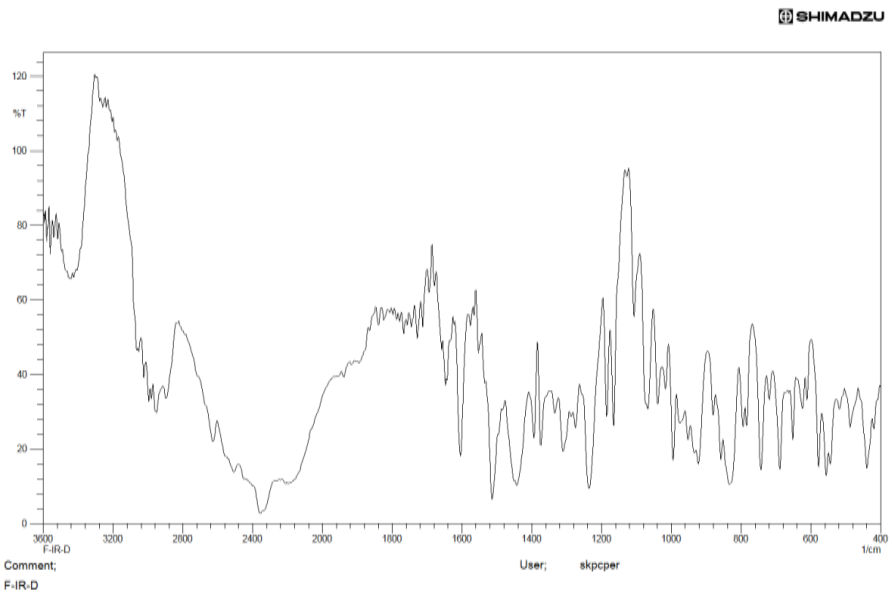

Figure 6: Fourier transform infrared spectroscopy spectrum of pure drug

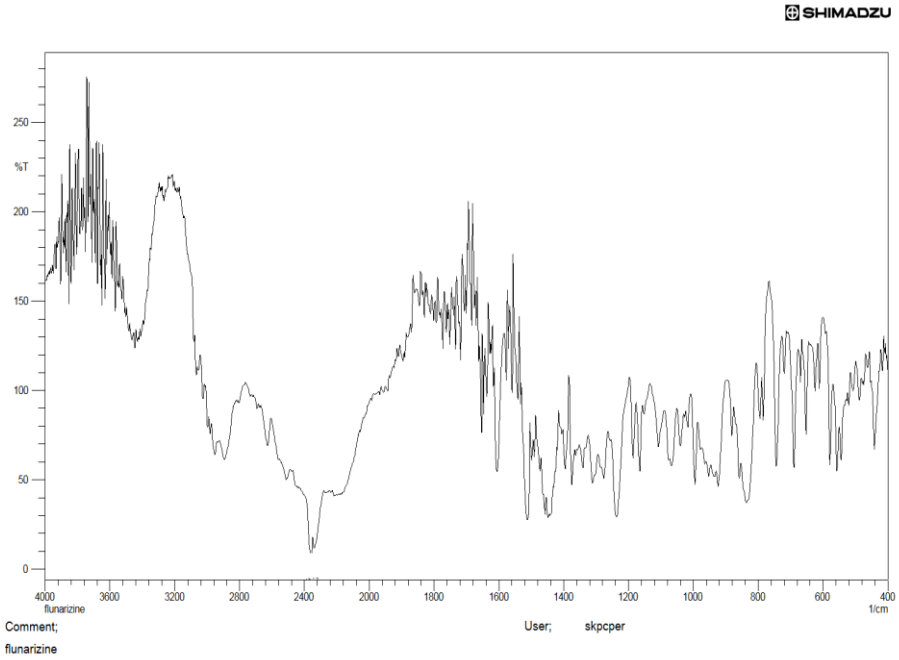

Figure 7: Fourier transform infrared spectroscopy spectrum of the ternary

System containing PEG 6000 and Pluronic F68

The DSC thermograms of pure drug, polymer and carrier systems are depicted in Figures 8-12. The thermogram of drug was characterized by melting endotherm at 223.28 °C. DSC analysis shows that Flunarizine Dihydrochloride was rendered entirely amorphous in the ternary solid dispersion as compared to binary solid dispersion as indicated by the absence of the melting endothermic peak for Flunarizine Dihydrochloride at approximately 223.28 °C.

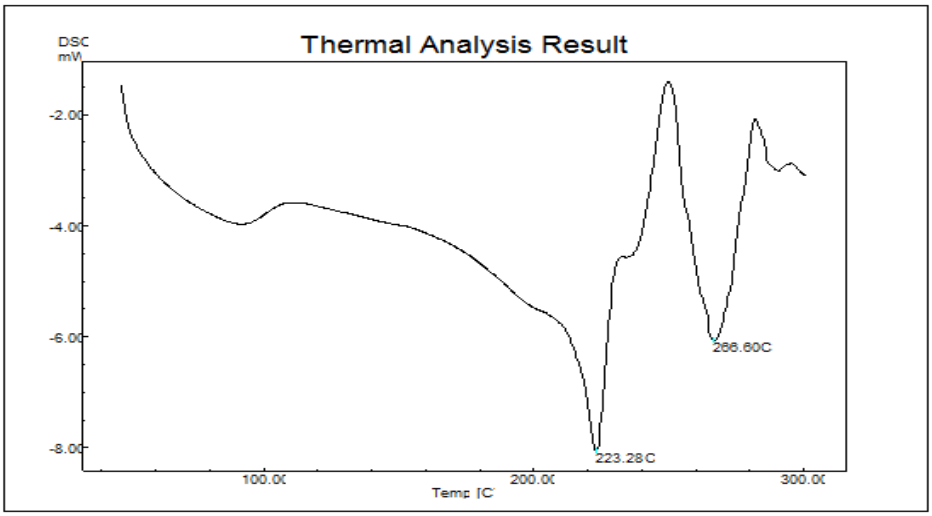

Figure 8: Differential Scanning Calorimetry thermogram of pure Drug

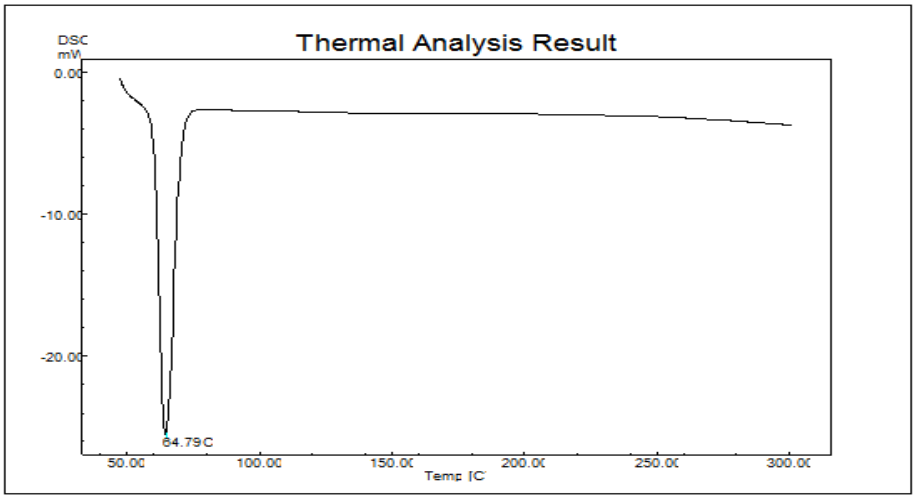

Figure 9: Differential Scanning Calorimetry thermogram of PEG 6000

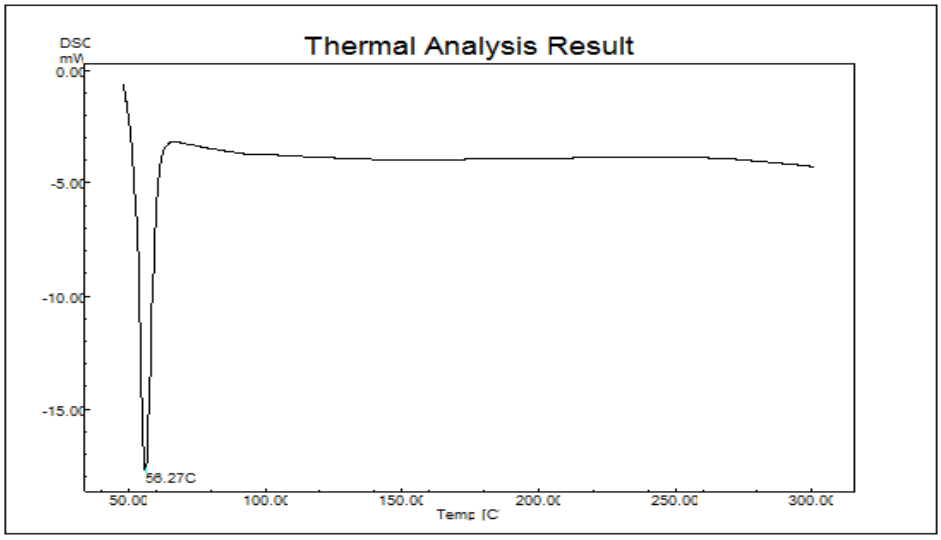

Figure 10: Differential Scanning Calorimetry thermogram of Pluronic F68

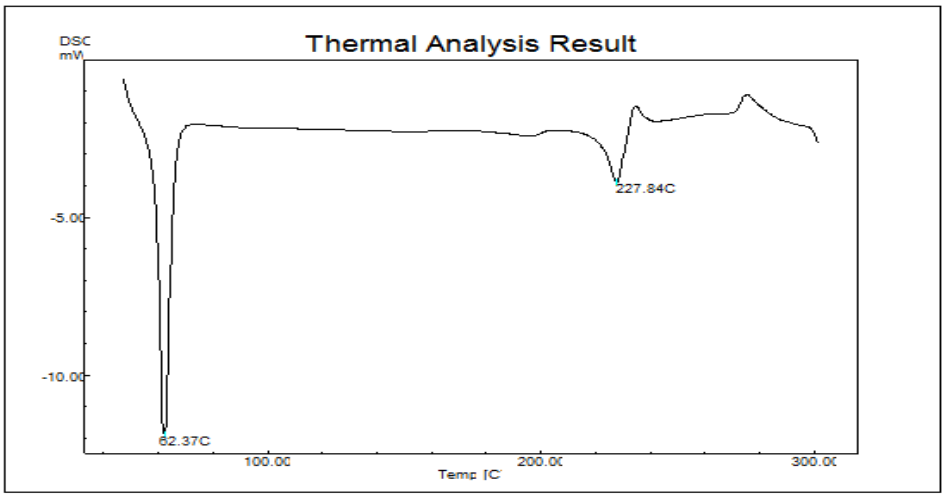

Figure 11: Differential Scanning Calorimetry thermogram of Binary Solid Dispersion

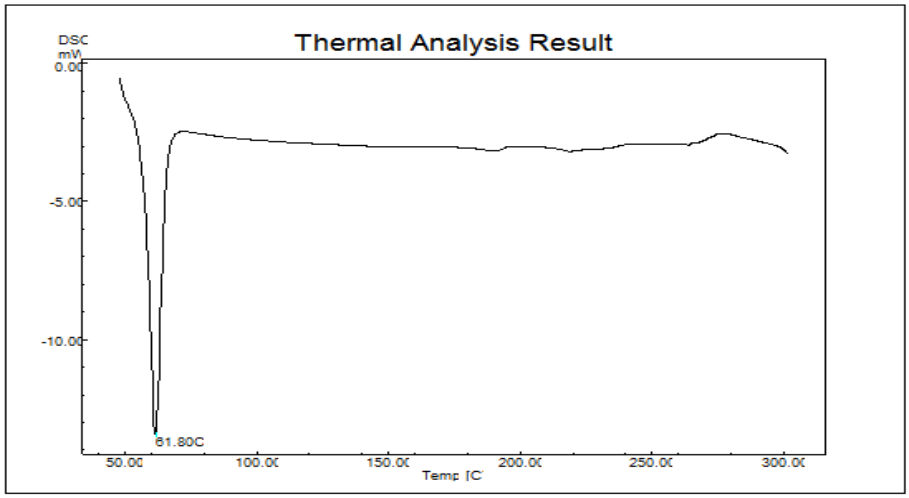

Figure 12: Differential Scanning Calorimetry thermogram of Ternary Solid Dispersion

It can be concluded that the binary dispersions of poorly water soluble drug Flunarizine Dihydrochloride with the PEG 6000 and its ternary dispersion with PEG 6000 and surfactant (Pluronic F68) were successfully prepared by the fusion method. This study demonstrated that the ternary dispersion system of the Flunarizine Dihydrochloride with the polymer (PEG 6000) and the surfactant (Pluronic F68) possessed dramatically higher dissolution rates as compared to pure drug and also their binary dispersion. The FTIR study indicated there was no intermolecular interaction between excipients and drug. Due to presence of surfactant in ternary system, there was more amorphizing effect as compared to binary solid dispersion as confirmed by the DSC study. The solubility and dissolution rate of Flunarizine Dihydrochloride was increased by dispersing it in the PEG 6000 and a further dramatic increase was noted when the surfactant (Pluronic F 68) was added to the dispersion system. The dissolution of the drug solid dispersions depended on the type of carrier. The ternary dispersion with Pluronic F 68 presented higher solubility than those with Pluronic F127.

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