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## Formulation and optimization of solid dispersion of Clopidogrel with PEG 6000

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### ABSTRACT

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Clopidogrel, a non competitive inhibitor of adenosine diphosphate at the platelet receptors, is an anticoagulant drug practically insoluble in water. In order to improve the aqueous solubility of drug and its dissolution rate solid dispersions of clopidogrel were prepared with different proportions of the hydrophilic carrier PEG 6000. A two factor three level statistical design was used to quantify the influence of PEG 6000 and Clopidogrel on the dissolution profile of the solid dispersions prepared where PEG 6000 and Clopidogrel were chosen as independent variables while dissolution rate was chosen as dependent variable. Melt fusion method and solvent evaporation method were used for the preparation of solid dispersion. Results obtained showed that there was a significant increase in the dissolution rate of the drug as well as solubility of the drug in comparison to pure drug. Differential scanning calorimetry, X-ray diffraction and scanning electron microscopy analysis revealed the formation of solid dispersion of the drug with PEG 6000.

**Key words:** Clopidogrel, solid dispersion, PEG 6000, Dissolution, Factorial Design

### INTRODUCTION

Clopidogrel, methyl (+)- $\alpha$ -(2-chlorophenyl)-6, 7-dihydrothieno [3, 2-c] pyridine-5(4H)-acetate, is a non-competitive inhibitor of adenosine diphosphate (ADP) at the platelet receptors. It is indicated for the early and long term secondary prevention of atherothrombotic events in patients with acute coronary syndromes (EMEA,2009). Clopidogrel is practically insoluble in water, which results in poor dissolution and poor bioavailability of the drug. Thus increasing the aqueous solubility and dissolution of Clopidogrel is of therapeutic importance. A large number of techniques have been reported over the years to enhance the drug solubility and the dissolution of the drugs. Some of the examples are formation of inclusion complexes with cyclodextrins (Loftsson et al.,2004), formation of solid dispersion with hydrophilic carrier (Waghmare et al., 2008, Dehgan et al.,2006, Rane et al.,2007, Punitha et al.,2010), Micellar drug solubilisation (Carlota et al., 2005), Dendrimers for drug solubilisation (Gupta et al., 2006), spray drying techniques (Chauhan et al., 2005), salt synthesis (Bastin et al., 2000), prodrug approach (Banerjee et al., 2004) and nanoparticle loaded drug molecules (Troy et al., 2006). Solid dispersions are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state (Chiou et al., 1971). Solid dispersion technique has been widely used to incorporate drug in hydrophilic carriers to enhance the dissolution rate of less water soluble drugs often leading to increased bioavailability of the drug. In the present study PEG 6000 was used as a surface adsorbent to formulate solid dispersions of clopidogrel. Polyethylene glycols are addition polymers of ethylene oxide and water. It has a very high affinity towards water and has been used

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extensively for preparing solid dispersions by various research groups.

The aim of the present study was to improve the solubility and dissolution rate of Clopidogrel by formulating a solid dispersion with PEG 6000. Full Factorial experimental designs are one of the best ways to study the effects of different variables on the quality determinant parameters of any formulation. Thus a statistical model was further developed to optimize the solid dispersion formulations. An appropriate statistical model was arrived at and a significant enhanced dissolution rate was observed with the optimized formulation.

## EXPERIMENTAL

### Materials

PEG 6000 was obtained from Merck India Ltd. (Mumbai). The Clopidogrel was obtained as gift sample from Ranbaxy Laboratories Ltd. (Gurgaon, India). All other chemicals and solvents used were of suitable analytical grade.

### Methods

#### *Preparation of solid dispersions of clopidogrel with PEG 6000*

Solid dispersions of clopidogrel in PEG 6000 were prepared using a two factor three level factorial design with clopidogrel and PEG 6000 as independent variables while maintaining the amount of solvent added as constant. The methods used for preparation of these solid dispersions were solvent evaporation method and melt fusion method.

#### *Solvent evaporation method*

The required amounts of Clopidogrel and PEG6000 was dissolved in methanol and thoroughly mixed for 1 hour over a magnetic stirrer. The solvent was then removed at 60° C under vacuum inside a Rotary vacuum evaporator until the solid dispersion was dry. The dried mass was pulverized, passed through sieve and stored in desiccators over anhydrous CaCl<sub>2</sub> until use. A total of nine batches (SF<sub>1</sub> to SF<sub>9</sub>) by solvent evaporation method were prepared (Table 1).

**Table 1.** Design layout of a Two -Factor, Three- level Factorial Design.

BATCH	DRUG	POLYMER
SF <sub>1</sub> ,MF <sub>1</sub>	-1	-1
SF <sub>2</sub> ,MF <sub>2</sub>	-1	+1
SF <sub>3</sub> ,MF <sub>3</sub>	+1	0
SF <sub>4</sub> ,MF <sub>4</sub>	+1	-1
SF <sub>5</sub> ,MF <sub>5</sub>	0	-1
SF <sub>6</sub> ,MF <sub>6</sub>	-1	0
SF <sub>7</sub> ,MF <sub>7</sub>	+1	+1
SF <sub>8</sub> ,MF <sub>8</sub>	0	+1
SF <sub>9</sub> ,MF <sub>9</sub>	0	0

\*Translation of coded units in actual units

Coded level*	-1	0	+1
A (DRUG) mg	200	300	400
B (PEG 6000) mg	200	400	600

**Table 2.** Drug Content with Solvent Evaporation method.

S.no.	Formulation Code	Percentage of Drug content
1	SF <sub>1</sub>	73.02±0.57
2	SF <sub>2</sub>	98.15±0.23
3	SF <sub>3</sub>	54.7±1.80
4	SF <sub>4</sub>	61.83±0.45
5	SF <sub>5</sub>	93.16±0.40
6	SF <sub>6</sub>	81.28±0.28
7	SF <sub>7</sub>	91.52±0.08
8	SF <sub>8</sub>	94.26±0.48
9	SF <sub>9</sub>	97.48±0.22

**Table 3.** Drug Content with Melt Fusion Method.

S.no	Formulation	Percentage of drug content
1	MF <sub>1</sub>	95.5±0.45
2	MF <sub>2</sub>	82.36±0.37
3	MF <sub>3</sub>	68.44±0.10
4	MF <sub>4</sub>	98.17±0.20
5	MF <sub>5</sub>	92.23±0.32
6	FM <sub>6</sub>	94.16±0.40
7	MF <sub>7</sub>	86.9±0.43
8	MF <sub>8</sub>	91.81±0.25
9	MF <sub>9</sub>	97.55±0.40

#### *Fusion method*

A required amount of PEG-6000 melt in a glass container on a water bath at about 50-60°C. A required amount of clopidogrel dissolved in methanol was added to molten PEG 6000 and mixed thoroughly with a glass rod for 10-15 minutes. Mixture was cooled rapidly by placing glass container in ice bath (0-4° C) for 20-25 minutes. A total of nine batches (MF<sub>1</sub> to MF<sub>9</sub>) by fusion method were prepared (Table 1).

### Evaluation of solid dispersions

#### *Drug content*

Solid dispersion equivalent to 10 mg of clopidogrel were weighed accurately and mixed with suitable quantity of methanol in a 100ml volumetric flask, volume was made up using distilled water. Drug content was analyzed at 240 nm using UV spectrophotometer (Cary 5000). Each sample was analyzed in triplicate.

#### *Solubility studies*

The solubility study of the drug and its solid dispersions was carried out by taking 20 mg of drug and its solid dispersion equivalent to 20 mg of drug in a 25 ml conical flask containing 10ml distilled water, volume was made up to 25 ml and shaken on a mechanical shaker for 24 hrs at room temperature and analyzed at 240 nm using UV-Vis spectrophotometer after suitable dilutions.

#### *In vitro dissolution study*

The dissolution study was carried out using USP Dissolution Apparatus 2. (Rotating Paddle type). Accurately weighed amount of pure drug and solid dispersion were immersed

in a dissolution medium consisting of pH 2.0 HCL buffer maintained at 37° C. The dissolution was carried out for 1 hour and aliquot of 5ml was withdrawn at adequate intervals. An equal volume of fresh dissolution medium was replaced (maintained at the same temperature) in order to keep the total volume constant. The filtered samples were suitably diluted, if necessary, and assayed spectrophotometrically at 240nm.

### Analytical methods

#### Differential scanning calorimetry (DSC)

The DSC thermo grams were recorded using a differential scanning calorimeter (Q10 TA Instruments, USA). Approximately 2-5 mg of each sample was placed in an aluminium pan and heated from 30 to 300° C at a scanning rate of 10° C/min under a stream of nitrogen.

#### Scanning Electron Microscopy (SEM)

The SEM analysis was carried out using a scanning electron microscope (LEO, 435 VP, and UK). Prior to examination samples were mounted on an aluminium stub and then made electrically conducting by coating it with a thin layer of gold (approximately 20nm). The scanning electron microscope was operated at an acceleration voltage of 15kv.

#### Powder X-Ray Diffraction Analysis (XRD)

Powder X-Ray diffraction patterns were recorded using a Powder X-Ray diffractometer under the following conditions: target Cu; filter Ni; voltage 35 kV; current 20mA; receiving slit 0.2 inches. The data were collected in the continuous scan mode using a step size of 0.01° at 20/s. The scanned range was 5-50°.

#### Fourier infrared spectroscopy (FTIR Analysis)

The FTIR spectra were recorded on a FTIR multiscope spectrophotometer (Perkin Elmer, UK) equipped with spectrum v3.02 software. KBr pellets of adequate amount of sample were prepared. The spectrum for each sample was recorded over the 450 to 4000cm<sup>-1</sup> spectral region with a resolution of 4 cm<sup>-1</sup>.

### Experimental Design

A three- level, two factor experimental design as shown in Table no.1 describes the proportion in which the independent variables Clopidogrel (A) and PEG 6000 (B) were used in the formulation of dispersion granules. The dissolution rate, as % drug release in 15 minutes (D<sub>15</sub>) and at 60 minutes (D<sub>60</sub>) was taken as dependent variables. All the nine formulations were prepared and analyzed for dissolution for each method of manufacturing used. Various response surface methodology computations were performed employing Design Expert Software version 8.0.5. Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis approach. In addition contour and surface plots were also obtained by Design Expert to represent the effect of independent variables graphically.

## RESULTS AND DISCUSSION

### Content of Clopidogrel

The drug content of the prepared formulations of Clopidogrel was observed to be varying from 54.7 to 98.15% respectively and it was maximum with formulation SF<sub>2</sub> and minimum in formulation SF<sub>3</sub> by Solvent evaporation method, which may be attributed to the fact that insufficient polymer may not be able to entrap the drug moiety into the solid dispersion. For Melt Fusion method the drug content of the prepared formulations varied from 68.44 to 98.17 respectively and it was highest for formulation MF<sub>4</sub> and lowest for formulation MF<sub>3</sub>. It was observed that melt fusion method yielded higher drug content in formulation with respect to solvent evaporation technique.

### Solubility studies

Total aqueous solubility of the formulations is shown in Table 4 and 5. In solvent evaporation method the aqueous solubility of drug was found to be maximum formulation SF<sub>7</sub> (17.57±0.41 µg/ml) and minimum with SF<sub>4</sub>(10.01±0.15µg/ml). In melt fusion method the aqueous solubility of drug was observed to be maximum with formulation MF<sub>7</sub> (17.86±0.32µg/ml) and minimum with MF<sub>2</sub> (10.09±0.08). Studies show that the maximum solubility is achieved when the concentration of the polymer and the drug is highest. It was observed that the formulation prepared by melt method showed greater solubility as compared to solvent evaporation method.

**Table 4.** Solubility of Clopidogrel by solvent evaporation method.

S.no	Formulation Code	Solubility (µg/ml)
1	SF <sub>1</sub>	11.67±1.20
2	SF <sub>2</sub>	11.82± 0.78
3	SF <sub>3</sub>	12.25±0.68
4	SF <sub>4</sub>	10.01±0.15
5	SF <sub>5</sub>	10.62±0.33
6	SF <sub>6</sub>	13.83±0.87
7	SF <sub>7</sub>	17.57±0.41
8	SF <sub>8</sub>	11.9±0.037
9	SF <sub>9</sub>	13.84±0.99
10	Drug	9.92± 0.01

**Table 5.** Solubility of Clopidogrel by Melt fusion method.

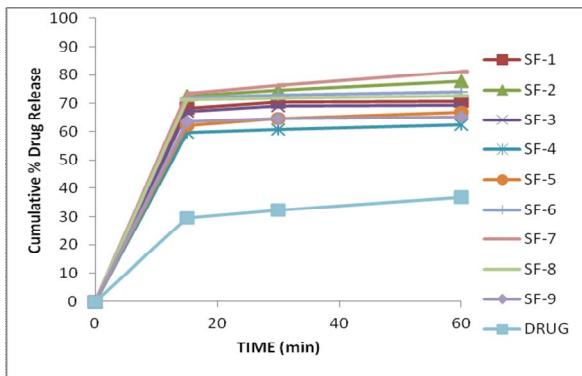
S.no	Formulation Code	Solubility (µg/ml)
1	MF <sub>1</sub>	11.87±1.26
2	MF <sub>2</sub>	10.09±0.08
3	MF <sub>3</sub>	11.09±0.40
4	MF <sub>4</sub>	10.56±0.22
5	MF <sub>5</sub>	11.15±0.14
6	MF <sub>6</sub>	13.34±0.72
7	MF <sub>7</sub>	17.86±0.32*
8	MF <sub>8</sub>	10.76±0.16
9	MF <sub>9</sub>	14.11±0.75
10	Drug	9.92±0.01

### In vitro dissolution study

#### Solvent evaporation method

In vitro dissolution studies of the different formulations of Clopidogrel prepared by solvent evaporation technique, it was

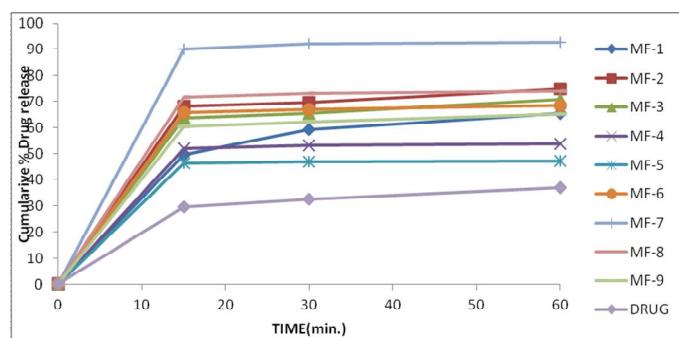
observed that the Solid dispersion of Clopidogrel prepared by this method showed improved dissolution when compared with pure drug. The trend observed was an increase in dissolution rate on increasing the amount of PEG 6000. This could be due to an increase in the effective surface area over which the drug distribution increases accompanied by an enhancement in drug dissolution. Formulation SF<sub>7</sub> (Figure 1) showed the maximum release at the end of 60min with a % drug release of 81.23%. It was observed that for lower drug concentrations the drug release increase with increase in polymer concentration.



**Fig. 1** Effect of PEG 6000 and Clopidogrel content on % drug release by Solvent evaporation method.

#### Fusion method

In vitro dissolution studies of the different formulations of Clopidogrel prepared by Fusion technique, it was observed that the Solid dispersion of Clopidogrel prepared by this method showed improved dissolution when compared with pure drug. The trend observed was an increase in dissolution rate on increasing the amount of PEG 6000. Formulation MF7 (Figure 2) showed the maximum release at the end of 60min with a % drug release of 92.7%.



**Fig.2** Effect of PEG 6000 and Clopidogrel content on % drug release by Fusion method.

#### Differential scanning calorimetry

In order to study the interaction between Clopidogrel and PEG 6000 DSC studies were performed on the individual components. The DSC curve of Clopidogrel showed one endothermic peak at nearly 183.19° C. Pure PEG 6000 showed an endothermic peak at 63.59° C. Thermo grams of solid dispersions using the solvent evaporation method and fusion method showed the absence of a Clopidogrel peak, suggesting that Clopidogrel is

either completely soluble in the liquid phase of the polymer or there is absence of crystalline nature of drug. However, the melting peak of PEG 6000 in solid dispersions was observed at slightly lower temperature (56.97° C to 59.80° C). Absence of an endothermic peak of drug in solid dispersions has also been reported by other research groups.

#### Scanning electron microscopy (SEM)

The surface morphology of Cloidogrel and its solid dispersion was examined by SEM analysis. Figure 4 shows some of the selected SEM images of chosen samples. The clopidogrel crystals appeared with sharp edges and partially agglomerated in bundles. In solid dispersions by solvent evaporation method and Fusion method clopidogrel particles were adsorbed on to the surface of PEG6000 which gives a very rough contour to the surface this contributed to a higher dissolution rate because of enhanced effective surface area of clopidogrel. In addition the SEM images of the batch prepared by melt fusion method showed greater proportion of PEG 6000 evident from the plate like structures characteristic of PEG, which could have contributed to greater dissolution rate of batches prepared by melt fusion method as compared to solvent evaporation method.

#### X-Ray diffraction analysis (XRD)

The XRD pattern of Clopidogrel, PEG 6000 and solid dispersions are given in Figure 5. The XRD pattern of Clopidogrel showed a large number of intense and sharp peaks indicating its crystalline nature. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the solid dispersions prepared with those of the pure drug. It was observed that Clopidogrel showed sharp peaks at 20.7°, 23.3° and 25.7° (2θ) with peak intensities of 5185, 16695 and 5845 cps respectively. However significant decrease in the peak intensities of Clopidogrel was observed in the solid dispersions prepared by using PEG 6000 at the same angles. This indicates a decrease in the crystallinity of the pure drug.

#### Fourier transform Infrared Spectroscopy (FTIR) Analysis

IR spectra of binary system of Clopidogrel showed IR spectra of Clopidogrel and PEG 6000 and no additional peak was observed in binary systems. IR spectrum of Clopidogrel is characterized by principal absorption peaks at 3113.16cm<sup>-1</sup> (C-H aromatic), 1748.41.36cm<sup>-1</sup> (C=O stretching), 1176.36cm<sup>-1</sup> (C-O stretching). The IR spectra of all solid dispersions show disappearance of some peaks of Clopidogrel. The peaks at 2720.89 cm<sup>-1</sup>, 1539.4 cm<sup>-1</sup>, 1070.12 cm<sup>-1</sup> are completely absent. All other peaks appeared with decreased intensity. Rest of the peaks of Clopidogrel were found to be smoothed indicating strong physical interaction of Clopidogrel with PEG 6000. However, no additional peak was observed in the binary system indicating absence of any chemical interaction between Clopidogrel and PEG 6000.

#### Statistical Modelling for Optimization

The statistical evaluation of dependent variables was performed by Analysis of variance (ANOVA) using Design expert

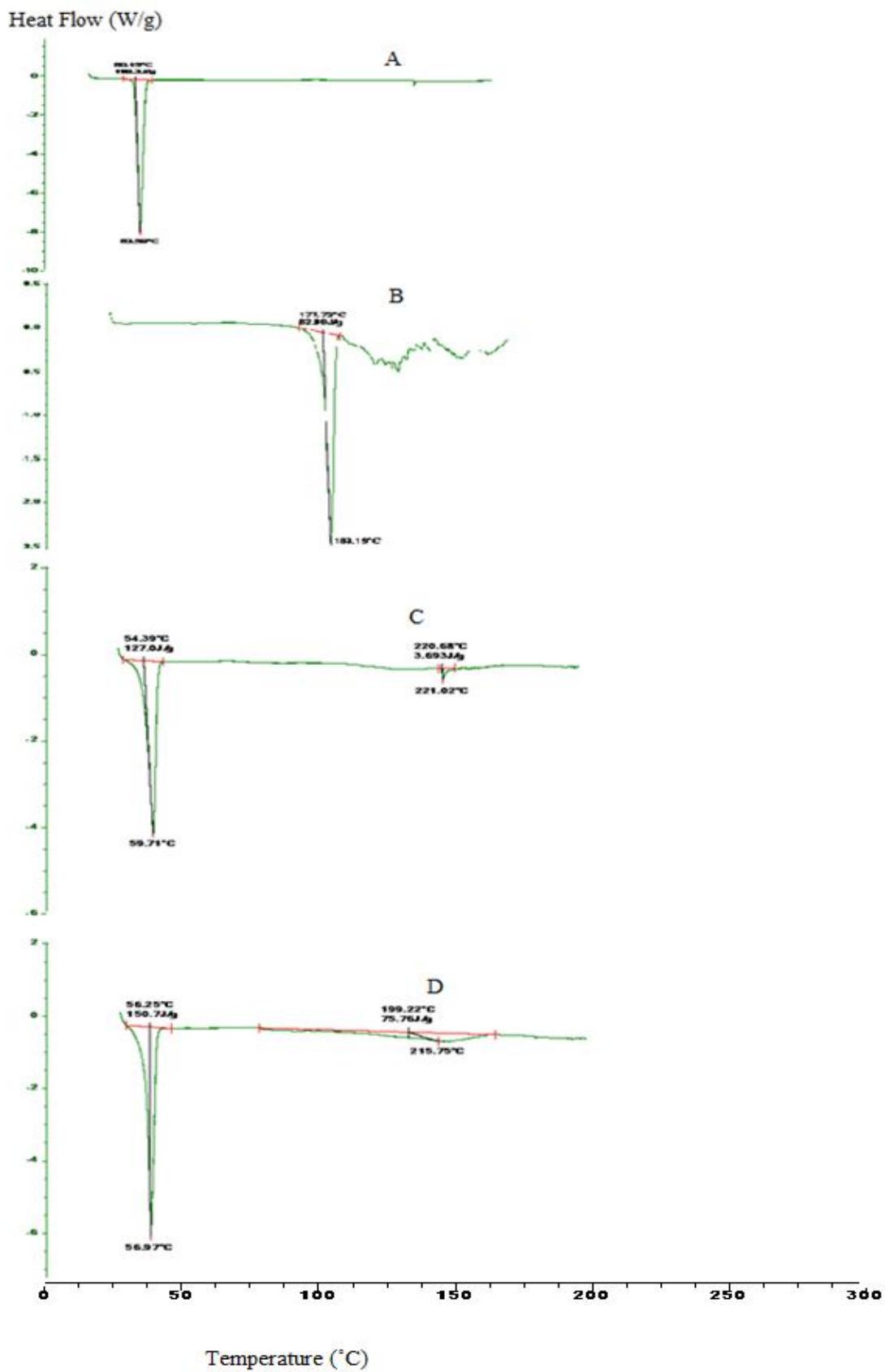
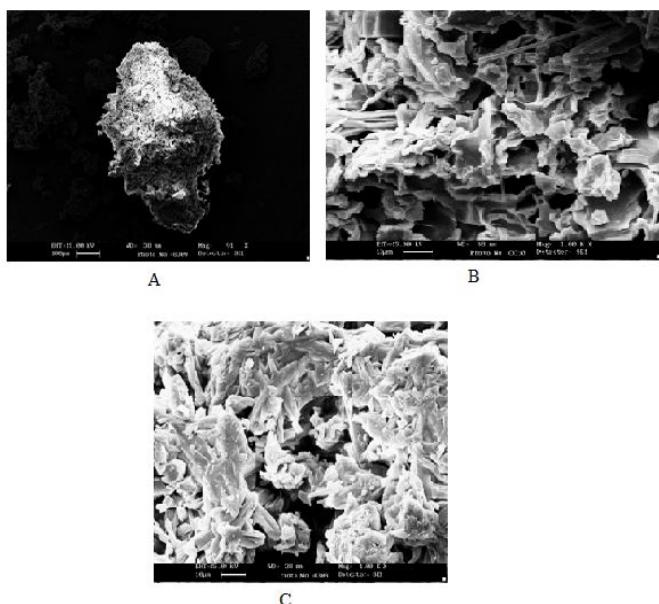


Fig.3 DSC Spectra of (A) PEG 6000, (B)Clopidogrel , (C) MF<sub>2</sub> , (D) SF<sub>2</sub>.



**Fig. 4** SEM photographs of (A) Clopidogrel (91X), (B) Solid dispersion by Fusion method (1000X), (C) Solid dispersion by solvent evaporation method (1000X).

Software version 8.0.5. The ANOVA results of the variables on the percent drug dissolved in 15 and 60min from the Solid dispersions prepared by both the Fusion method and Solvent evaporation method are shown in Table 6 & 7.

**Table 6.** ANOVA results of dependent variables for the fusion method.

Response	Sum of squares	df	Mean square	F value	P-value Prob>F	R <sup>2</sup>
% DR in 15min(D <sub>15</sub> )	1444.87	7	206.41	665.10	<0.0001	0.9989
% DR in 60min(D <sub>60</sub> )	1340	5	268	55.21	<0.0001	0.9753

**Table 7.** ANOVA-influence of dependent variables for the solvent evaporation method.

Response	Sum of squares	df	Mean square	F value	P-value Prob>F	R <sup>2</sup>
% DR in 15min(D <sub>15</sub> )	250.57	5	50.01	25.90	0.0002	0.9487
% DR in 60min(D <sub>60</sub> )	373.20	5	74.64	17.40	0.0008	0.9255

The effects of independent variables upon the responses were modelled using the following general form of the equation 1.

$$Y = b_0 + b_1 A + b_2 B + b_3 AB + b_4 A^2 + b_5 B^2 + b_6 AB^2 + b_7 A^2 B \quad (1)$$

Where Y is the predicted response,  $b_0$  is the arithmetic mean response of 13 runs where  $b_1$  and  $b_2$  are the estimated coefficients for the factors A and B respectively. The main effects (A and B) represent the average result of changing one factor at a time from its low to high value.

Coefficients with one factor indicate the effect of that particular factor on the desired response, while the coefficients with more than one factor and those with second-order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign of the term indicates additive effect, while negative sign indicates antagonistic

effect of the factor on the response. The polynomial terms ( $A^2$  and  $B^2$ ) are included to represent the nonlinearity and the interaction term (AB) shows how the values of the percent drug dissolved in 15 and 60 minutes changes when the two factors are changed simultaneously. The fitted equations relating the responses D<sub>15</sub> and D<sub>60</sub> to the transformed factors for both the fusion method and solvent evaporation method are shown in equation 2,3,4,5 respectively.

### Fusion method

$$(D_{15}) = 60.35 - 1.03 * A + 12.69 * B + 4.91 * A * B + 5.09 * A^2 - 0.77 * B^2 + 1.45 * A^2 * B + 7.12 * A * B^2 \quad (2)$$

$$(D_{60}) = 64.32 + 1.38 * A + 12.51 * B + 7.40 * A * B + 7.66 * A^2 - 1.37 * B^2 \quad (3)$$

### Solvent evaporation method

$$(D_{15}) = 64.04 - 2.12 * A + 4.66 * B + 2.46 * A * B + 4.03 * A^2 + 1.17 * B^2 \quad (4)$$

$$(D_{60}) = 65.36 - 1.59 * A + 5.27 * B + 2.97 * A * B + 5.11 * A^2 + 3.14 * B^2 \quad (5)$$

It may be concluded from the equations and the contour and 3D plots obtained that the high level of polymer PEG 6000(B) has a more profound effect on the percent drug release at 15 and 60 min than factor A (drug concentration).

Three dimensional response surface plots and two dimensional contour plots were obtained from the data with Design expert version 8.0.5 to estimate the effects of the independent variables (A and B) on each response, as depicted in Fig.7 and 8.

## CONCLUSION

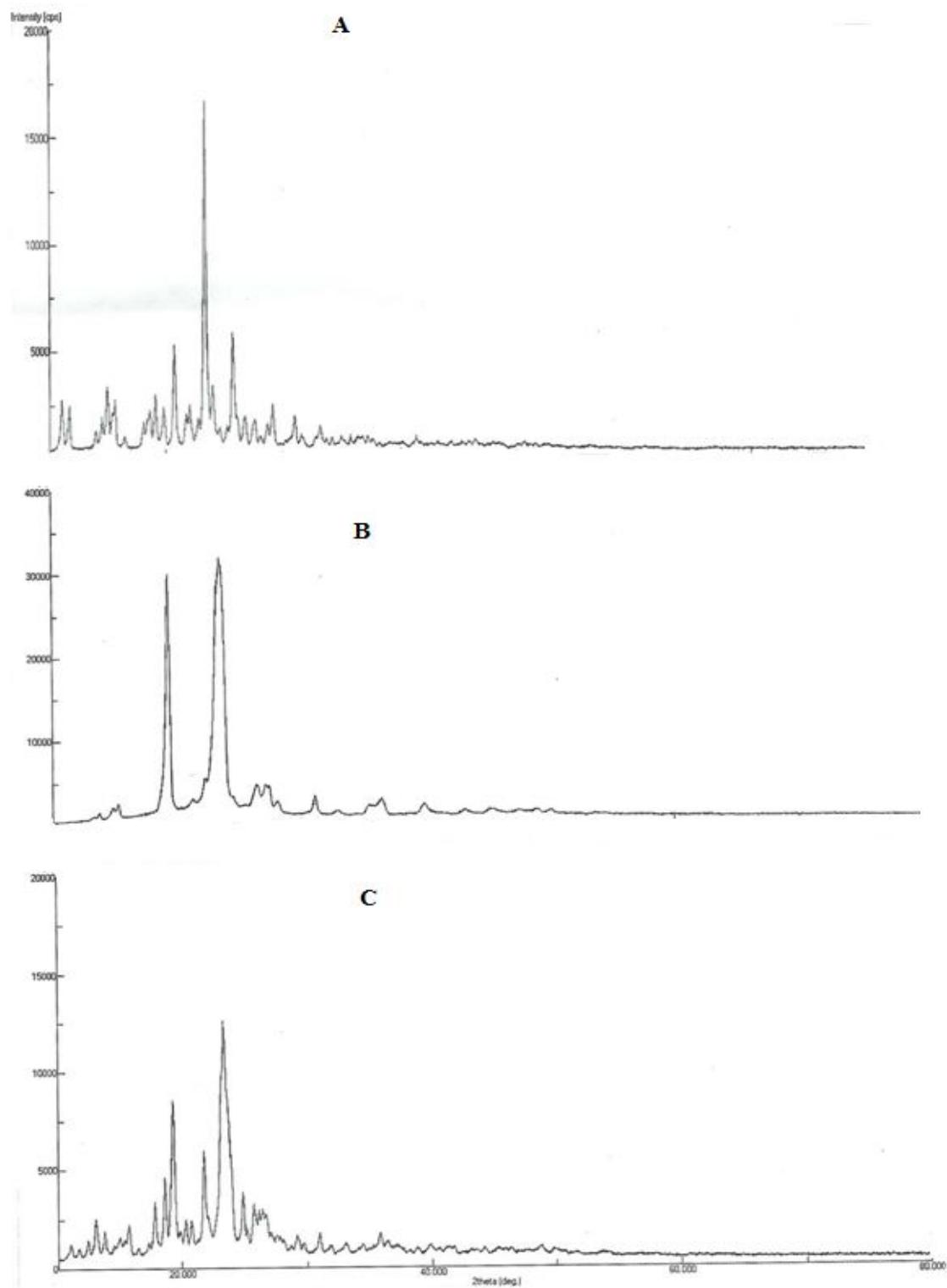
The enhancement of solubility of a poorly soluble drug Clopidogrel from its solid dispersion with PEG 6000 has been investigated. The solid state properties of the binary system were characterized by powder XRD, DSC, SEM and FTIR studies showed decrease in the crystallinity of the drug in the solid dispersions prepared. The study showed that the dissolution rate of the drug can be enhanced to a great extent by solid dispersion technique using both the solvent evaporation and Fusion method.

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**Fig.5** XRD Spectra of (A) Clopidogrel, (B) PEG 6000, (C) Formulation.

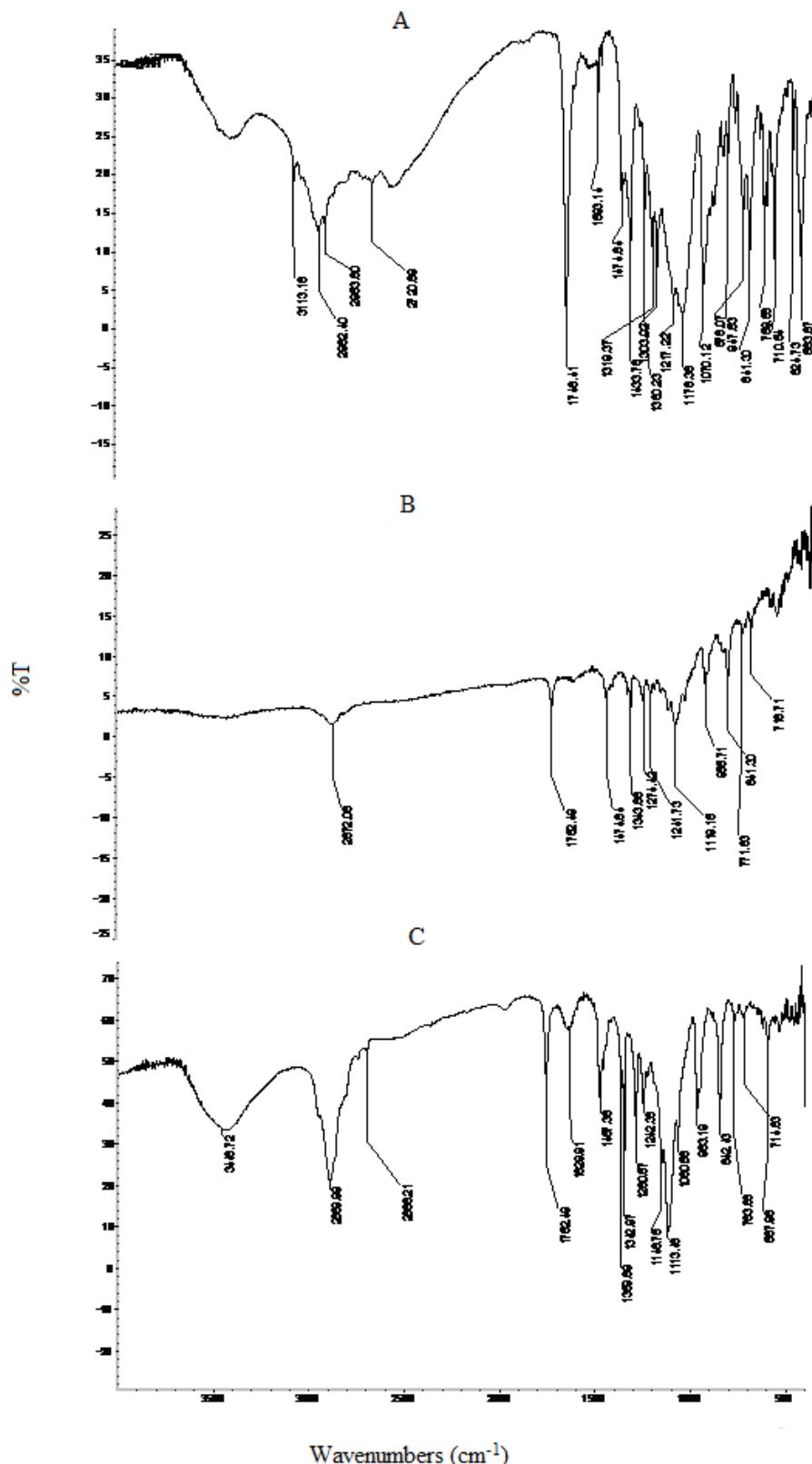
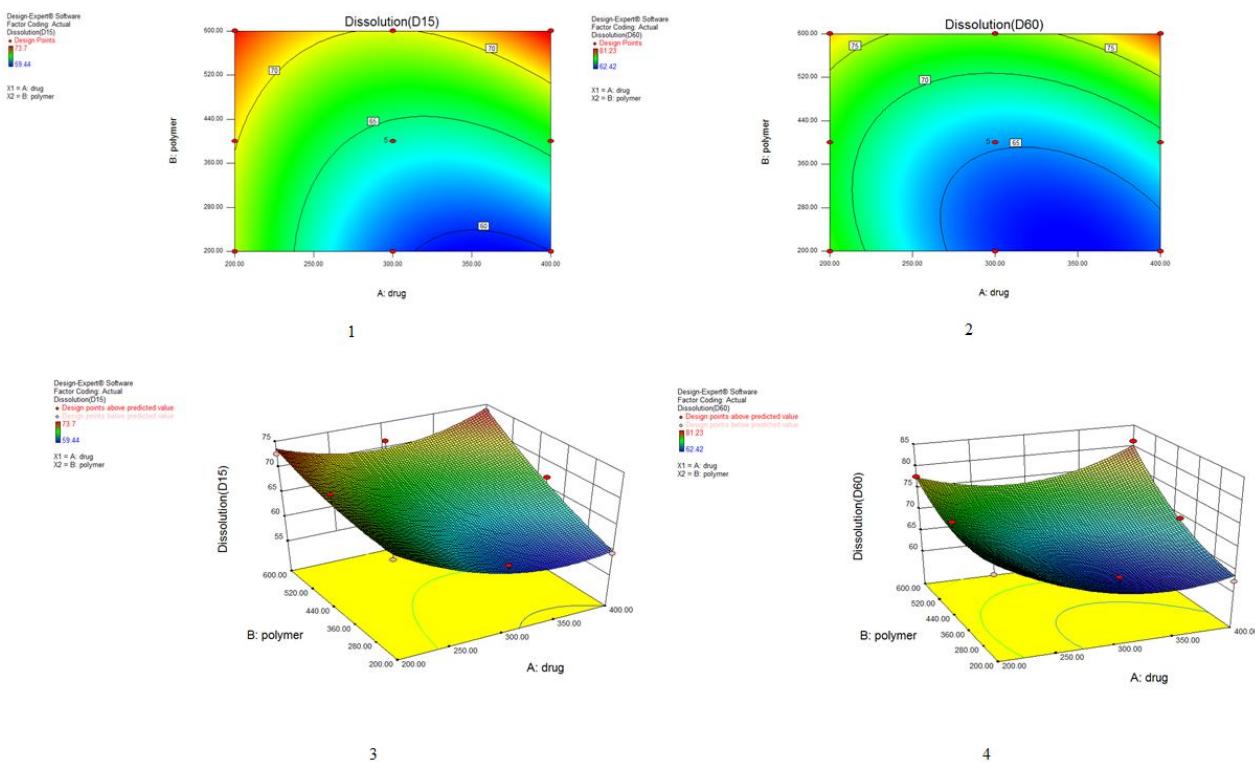
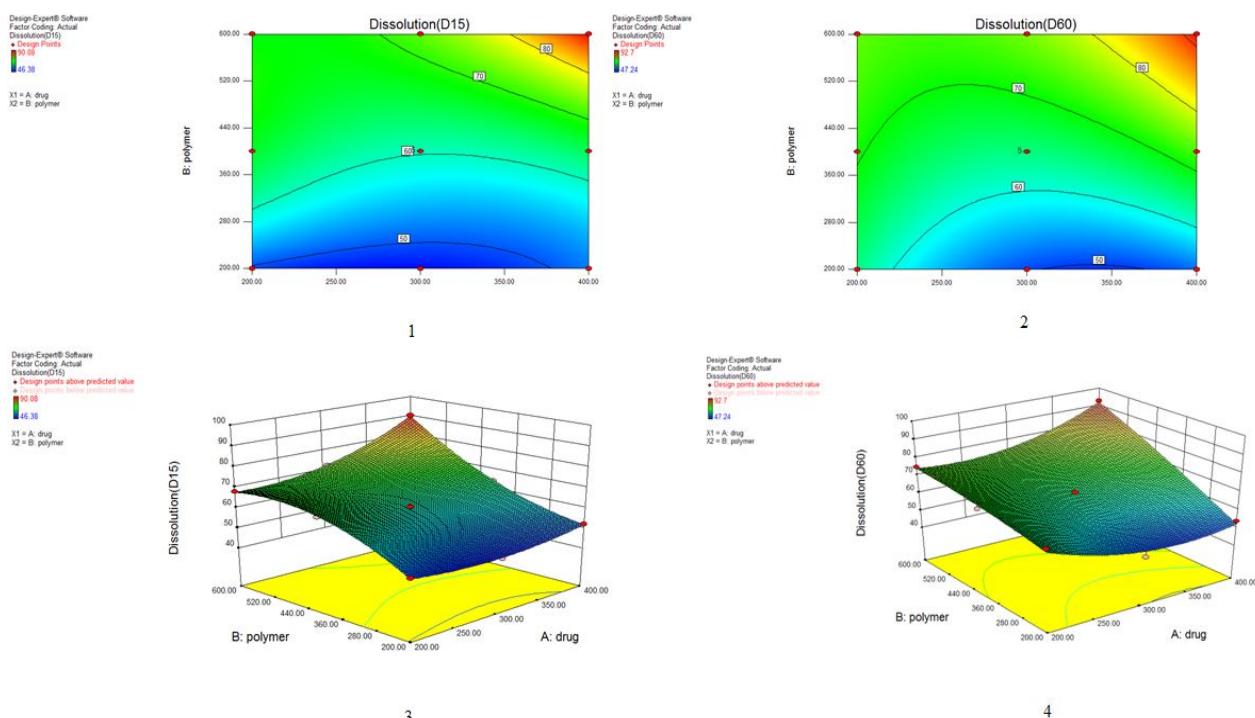


Fig.6 FTIR Spectra of (A) Clopidogrel, Formulation (B) MF<sub>5</sub> & (C) SF<sub>2</sub>.



**Fig.7** Contour and surface plots showing % drug release in 15 minutes and 60 minutes of solid dispersions as a function of PEG 6000 and Clopidogrel for Solvent evaporation method.



**Fig.8** Contour and surface plots showing % drug release in 15 minutes and 60 minutes of solid dispersions as a function of PEG 6000 and Clopidogrel for Fusion method.

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