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Development and Optimization of Solid Dispersion of Olanzapine in Poly Ethylene Glycol by D-Optimal Response Surface Factorial Design.

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Abstract: The aim of present study was to study the effect of molecular weight of polyethylene glycols (PEG) and olanzapine content on the dissolution rates of the solid dispersions with olanzapine by using response surface design. Design indicate that dissolution rate show proportional relation with independent variables (Molecular weight of PEG and drug content).Optimized solid dispersion batch was characterized using infrared spectroscopy, diffrerential scanning calorimetry (DSC) and X-ray diffractometry (XRD). An amorphous form of prepared solid dispersions was indicated in XRD studies and DSC studies. Infra-red spectra suggested that little or no interaction is present between the olanzapine and PEG.
Key word: Olanzapine, Solid dispersion, PEGs, Response surface design and dissolution enhancement.

1. Introduction

Olanzapine (2 – methyl 1- 4 - (4 - methyl -1-piperazinyl)-10*H*-thieno-[2, 3b], [1, 5] benzodiazepine), a thieno benzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. As atypical antipsychotics are generally classified those drugs, which in contrast to classical antipsychotics (e.g. haloperidol), have greater affinity for serotonin 5-HT2 receptors than for dopamine D2 receptors and cause fewer extrapyramidal symptoms (EPS). The efficacy and safety of olanzapine has been demonstrated in randomised, placebo-controlled and comparative trials in positive and negative symptoms of schizophrenia, and also as monotherapy or in combination with mood stabilizers in the treatment of acute manic or mixed episodes associated with bipolar disorder. Olanzapine belong to class II category under the biopharmaceutical classification system (BCS), i.e., it is inherently highly permeable through biological membranes, but exhibits low aqueous solubility. Rate of absorption and/or extent of bioavailability for such insoluble hydrophobic drug are controlled by rate of dissolution in gastro-intestinal fluids. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate (1-3).

Enhancement of bioavailability of hydrophobic drugs is one of the major challenges in drug development. Of the plethora of pharmaceutical technologies available to address this issue *viz*.micronisation, the use of surfactants and the formation of solid dispersions (4). Solid dispersions have been extensively studied to improve oral bioavailability of compounds which in general show poor dissolution characteristics, including those with low aqueous solubility. Solid dispersions are generally prepared by either a solvent method, whereby

the drug and carrier are dissolved in a mutual solvent followed by solvent removal, or by a melting method, whereby drug-carrier mixtures are prepared by co-melting/cooling. The disadvantage of the solvent method is the use of organic solvents with issues of toxicity, safety hazards and solvent residuals and also the possible precipitation of the drug into various polymorphic forms, which have different solubilities and bioavailabilities. Therefore, melting is often the method of choice for the preparation of solid dispersions despite the potential problem of heat-induced degradation of drugs and carriers.

Polyethylene glycols (PEG), polymers of ethylene oxide are widely used as vehicles for solid dispersions because of their low melting point, rapid solidification rate, capability of forming solid drug solutions, low toxicity and low costs (5-7).

The purpose of this study was to compare the ability of three different grade of poly ethylene glycol (PEG), PEG 8000, PEG 20000, PEG 35000 to improve the dissolution of a model poorly water-soluble compound, Olanzapine. Effect of drug content (%) on the dissolution of Olanzapine also studied. The methods of characterization were achieved through using different tools as Fourier transform infra red spectroscopy (FTIR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder X-ray diffractometry (XRD). Moreover, solubility and dissolution rate study were performed to qualify the solid dispersion comparing with the drug alone. Full factorial experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Multiple regression analysis of results gives an equation that adequately describes the influence of the independent formulation variables on the selected responses.

2. Materials and Methods.

2.1 Materials.

Olanzapine was kindly gifted by Micro labs banglore. PEG8000, PEG 20000 and PEG 350000 were obtained from SD Fine Chemicals Ltd. (Mumbai, India). All other materials and reagents were of analytical grade of purity.

2.2 Preparation of solid dispersions.

Solid dispersion containing different drug loading in PEG with different molecular weight were prepared by melted fusion method. The drug and polymer were heated until the polymer melt. The molten mixture was stirred until the drug was dissolved completely in the melt and a homogeneous solution was obtained. The solution was brought to solidification by quick cooling. It was kept in desiccators under vacuum for 24 hr. Then solid dispersion formulation was pulverized using mortar and pestle. The pulverized powder was classified using the sieve # 60.

2.3 Formulation Design.

A D optimal response surface design (**DESIGN EXPERT 8.0.1 demo version software**) was used for the optimization olanzapine solid dispersions. Molecular weight of PEG (A) and olanzapine content were selected as the independent variables whereas dissolution rate was selected as dependent variables. Levels for two factors are presented in Table 1.

Table 1: Level and Factors for factorial design.

S.no	Factor	Type of Factor	Low	High
1	Olanzapine Content (%)	Numeric	5	15
2	M.wt of PEG	Numeric	8000	35000

Different trial formulations of olanzapine solid dispersions were prepared according to the trial proposal of D optimal response surface design. The prepared solid dispersions of Olanzapine were evaluated for dissolution study. The responses were analyzed using ANOVA and the individual response parameters were evaluated using F test and polynomial equation was generated for each response using multiple linear regression analysis (MLRA). The study design including investigated factors and responses is shown in Table 2.

Table 2: D optimal response surface design and their observed response values.

Std	ID	Factor 1	Factor 2	Response 1
		A:PEG(M.Wt)	B:Drug concentration(%)	Dissolution rate (k)
1	SD 1	8000	5	0.403
2	SD 2	20000	5	0.805
3	SD 3	35000	5	1.331
4	SD 4	8000	7.5	0.502
5	SD 5	20000	7.5	0.903
6	SD 6	35000	7.5	1.354
7	SD 7	8000	10	0.605
8	SD 8	20000	10	0.987
9	SD 9	35000	10	1.422
10	SD 10	8000	12.5	0.698
11	SD 11	20000	12.5	1.099
12	SD 12	35000	12.5	1.493
13	SD 13	8000	15	0.796
14	SD 14	20000	15	1.188
15	SD 15	35000	15	1.689

The computation for optimized formulation was carried using software, DESIGN EXPERT 8.0.1. The optimized formulation was prepared which have targeted to the dissolution rate 1.1 mg/min. Constraints for responses and factors are shown in Table 3. By utilizing the software, we got one solution for optimized formulation. The optimized formulation is prepared and evaluated for dissolution rate. Observe response value of the optimized formulation is compared with predicted value. The optimised batch(s) was further investigated by DSC, XRD, and FTIR.

2.4 *In vitro* dissolution study.

Drug dissolution studies was carried out using USP dissolution apparatus 2 using a paddle at a speed of 100 rpm with 900 mL of Phosphate buffer pH 7.4. as dissolution medium at 37^0C. Solid dispersion powders containing 50 mg of olanzapine were dispersed on the surface of the dissolution medium and the time was recorded. At intervals, 5 mL samples were withdrawn through a filter. All the readings were blanked with same media as was used in the dissolution study. The olanzapine content was measured by HPLC method and the percentage of drug released was calculated using calibration curves.

2.5 X-ray diffraction.

Powder X-ray diffraction patterns were obtained with a diffractometer (Geigerflex, RAD-IB, Rigaku, Tokyo). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 40kV; current,20 mA and scanning speed, $2\theta = 4°$:min. Physical mixtures, as control of the solid dispersion, were prepared by simply mixing the powdered olanzapine and polymers at the same composition ratios as those of the solid dispersions.

2.6 Differential scanning calorimetry (DSC).

DSC studies of Olanzapine and optimized solid dispersion batch were conducted using a Perkin Elmer DSC-4 differential scanning calorimeter using aluminium sample pans for volatiles. Samples (about 5 mg) were heated at l0 ^{0}C/min using nitrogen as the purging gas.

2.7 Fourier transform infrared spectroscopy (FTIR).

An approximately minimum quantity (about 1mg) of sample was thoroughly blended with adequate quantity of IR grade KBR (about 5mg) in a mortar. The mix was then made into thin films on a sample plate using a hand operated compression lever. The samples were then analyzed in a Perkin Elmer Model 1330 double beam IR spectrometer using KBr film as negative control (blank).

3. Result and Discussion

3.1 Optimization of Olanzapine solid dispersion.

A total of 15 formulations of Olanzapine solid dispersion were proposed by the D optimal response surface design for two independent variables: Olanzapine content (A) and molecular weight of PEG, which were varied at different levels. The effects of these independent variables on dissolution rate (K) were observed as optimization response parameters in the current investigation. The study design including investigated factors and responses is shown in Table 2. The analyser of obtained data was carried out using ANOVA. The parameter was evaluated using F- test and a polynomial equation was generated for response. The ANOVA test (Table 3) showed ($P<0.0001$) that both molecular weight of PEG and proportion of drug have statically significant influence ($P<0.0001$) on the dissolution rate. The F-value 533.0469 for dissolution rate contributed to the significant model. Mathematically relationship generated using multiple linear regression analysis for the studies variables are expressed in term of coded factor as follow.

Dissolution rate = $1.027672 + 0.4285*A + 0.18612 * B – 0.01297 *A*B – 0.0149 * A^2 + 0.033048 * B^2$
Where A and B indicates PEG M.wt and Olanzapine content (%) respectively.

Table 3. ANOVA for response surface quadratic model.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	2.104589	5	0.420918	533.0469	< 0.0001	**significant**
A-PEG	1.836123	1	1.836123	2325.251	< 0.0001	**significant**
B- Olanzapine content	0.259273	1	0.259273	328.3409	< 0.0001	**significant**
AB	0.000844	1	0.000844	1.069362	0.3281	**Non significant**
A^2	0.000718	1	0.000718	0.909818	0.3651	**Non significant**
B^2	0.002867	1	0.002867	3.630596	0.0891	**Non significant**
Residual	0.007107	9	0.00079			
Core Total	2.111695	14				

Model reduction was carried out by excluding nonsignificant terms ($P > 0.05$) in model equations resulting from the multiple regression analysis (8), giving following equation

$$\text{Dissolution rate} = 1.03 + 0.43*A + 0.19 * B$$

In term of actual value:

$$\text{Dissolution rate} = - 0.020578 + 3.17 \times 10^{-5} \text{ PEG M.Wt.} + 0.037320 \text{ drug content.}$$

Three-dimensional response surface plots and corresponding contour plots to study the effects of the independent variables (factors) on each dependent variable (response) were presented in Figure 1 and 2. The three-dimensional response surface plots and corresponding contour plots pertaining dissolution rate show proportional relation with independent variables (PEG M.Wt and drug content).

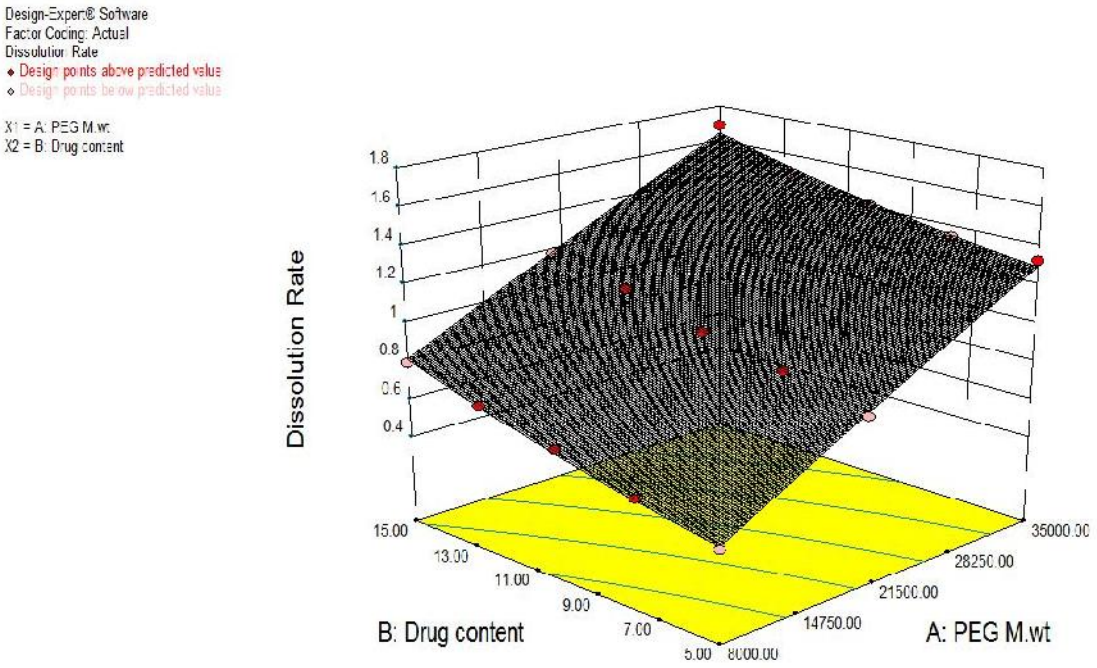

Figure 1. 3 D response surface plot showing the effect of PEG M.Wt & Drug content on dissolution rate.

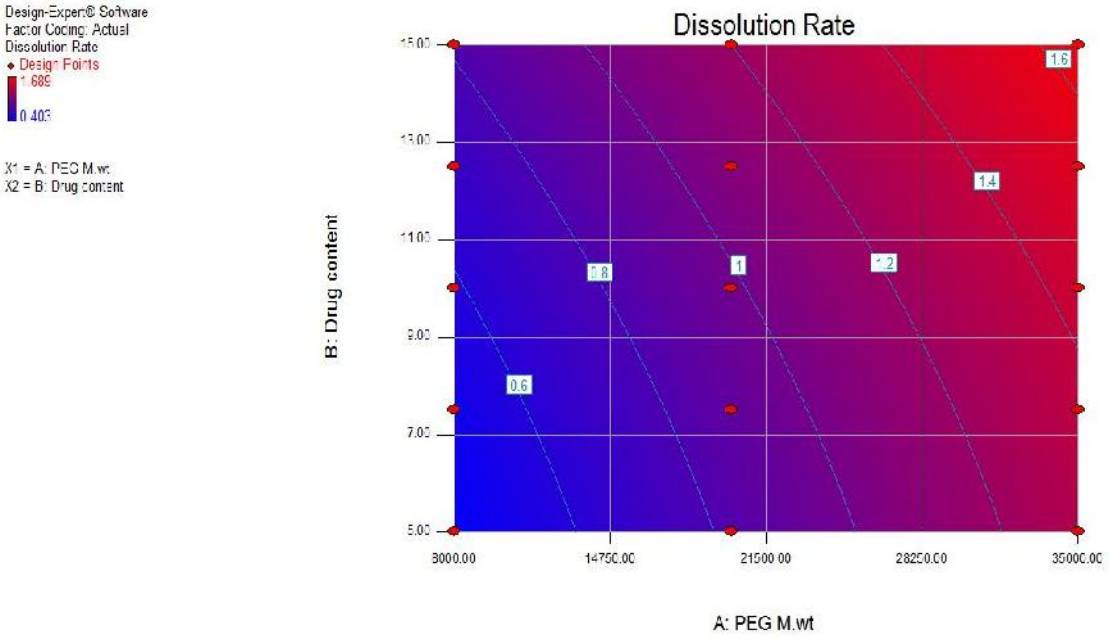

Figure 2. Contour plot showing the effect of PEG M.Wt & Drug content on dissolution rate.

A numerical optimization technique based on the desirability approaches was adopted to achieve new optimized solid dispersion (SD 16) which was also used as the check point. The optimum formulation was selected based on the criteria of high solubility; the following maximizing criteria were adoptful k > 1 mg/ min. For evaluation the optimization capability of response surface factorial design. The variable settling used for the formulation of optimized Olanzapine solid dispersion were PEG M.Wt (A) 20000 and drug content (B) 12.90 % (Fig.3-4 and table 4).The optimized formulations were prepared with the optimized amount of independent variables. The

observed dependent response values were compared with predicted values. From the full model, it was expected that the value of dissolution rate, value of the checkpoint batch should be in close agreement with predicted values. Observed values were found similar to predicted values in SD 16 (Fig.5). Thus, we can conclude that the statistical model was mathematically valid.

Table 4: Constraints for responses and factors.

Name	Goal	Lower limit	Upper Limit
Drug Content (%)	In range	5	15
PEG M.wt	Target ≤ 20000	8000	350000
Dissolution rate (k)	Target ≥ 1.2	0.403	1.689
SOLUTION (SD 16)			
PEG M.wt	**Olanzapine content**	**Dissolution rate**	**Desirability**
20000.00	12.90	1.1	1.0

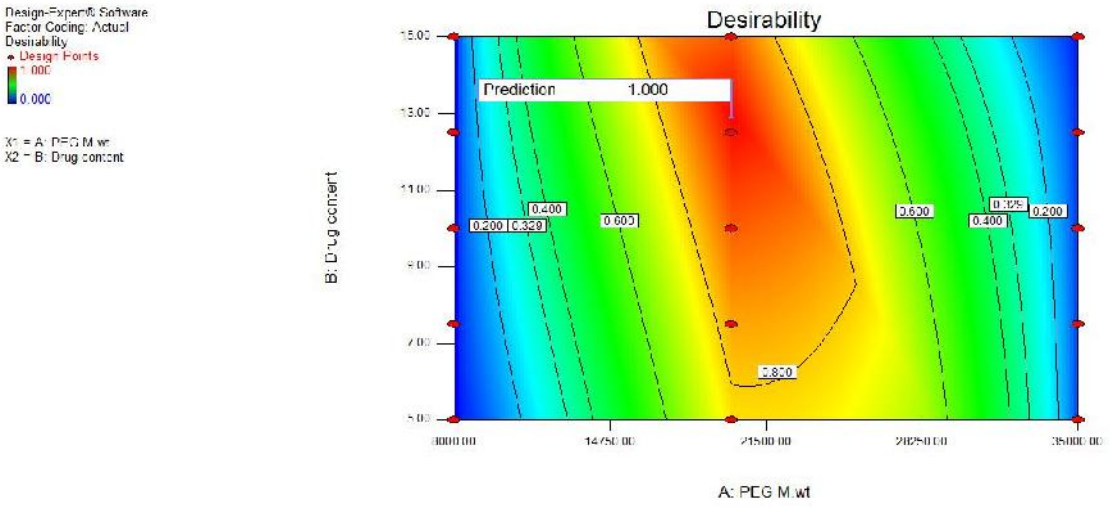

Figure 3. Contour response surface desirability prediction plot.

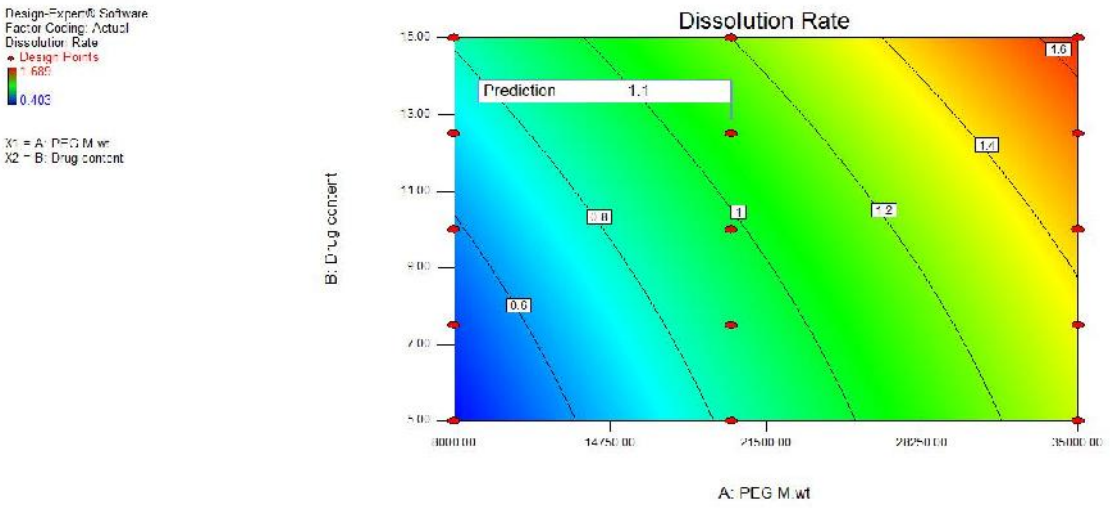

Figure 4. Contour response surface dissolution rate prediction plot.

3.2 Effect of PEG Molecular weight and Olanzapine content on dissolution rate.

Dissolution of pure olanzapine and solid dispersions was carried out in phosphate buffer 7.4 dissolution studies were profound for 60 minutes. Dissolution rate constant (k) were calculated by linear regression from the data provided by the apparently linear segment of dissolution profile. Dissolution profile of olanzapine solid dispersion were shown in figure 5-7.

Release from PEG-8000 formulation were linear for the entire dissolution study for all proportion of olanzapine. The dissolution rate reaches a maximum at maximum drug proportion (15%).

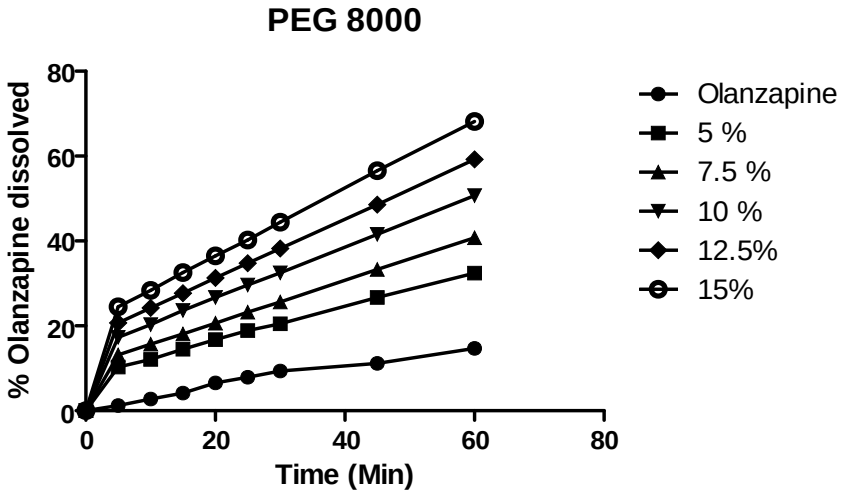

Figure 5. Dissolution profiles of the dispersions containing different amount of Olanzapine in PEG 8000.

With PEG 2000 dissolution profile are linear for all proportion of olanzapine as for PEG 8000 though release rate with PEG 20000 were greater than with PEG 8000 (fig. 6). If may be due to inhibition of crystalline growth of Olanzapine by the high viscous solution formed by PEG 20000.

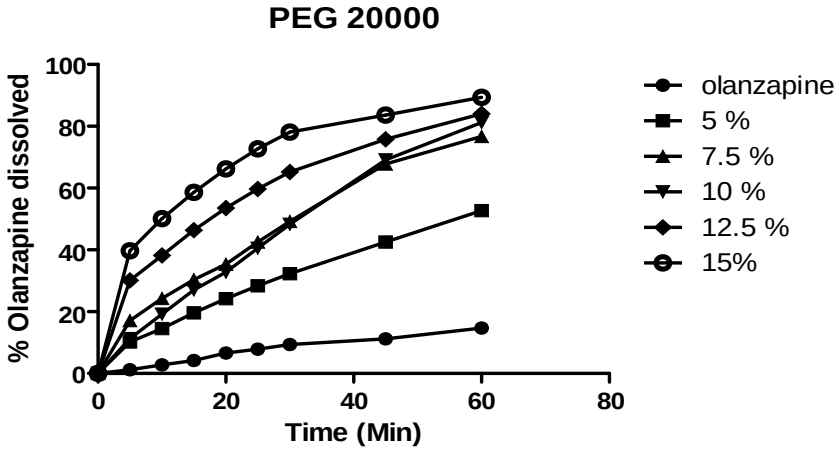

Figure 6. Dissolution profiles of the dispersions containing different amount of Olanzapine in PEG 20000.

Release from PEG 35000 solid dispersion were found linear for first 30 minute after which the rate decrease and the profile became biphasic and irregular (Fig 7). This irregularity increase with the proportion of drug. In all case drops of the dissolved drug were observed in dissolution after 30 minutes it dissolution rate reached a maximum at a proportion of 10% and rate constant decrease in higher olanzapine proportion.

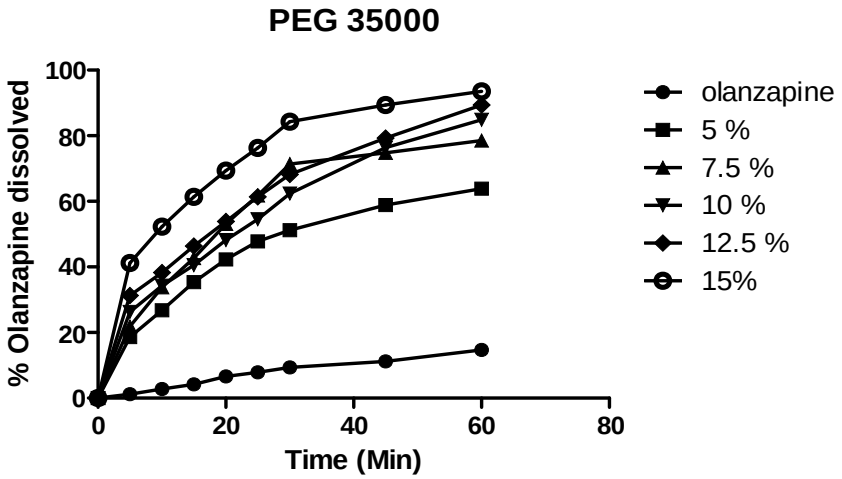

Figure 7. Dissolution profiles of the dispersions containing different amount of Olanzapine in PEG 35000.

The dissolution rate constant (k) determined by linear regression analysis, are plotted as function of olanzapine proportion (Fig.8). A linear relationship existed between dissolution rate constant and olanzapine proportion for PEG 8000 and PEG 20000 with r^2 Value 0.999 and 0.998 respectively. The result shown that drug proportion affect the dissolution rate of solid dispassion and not brings out any change in dissolution mechanism. Some other studies show a similar effect relation between dissolution rate and drug content (9). With PEG 35000, the relation between dissolution rate & olanzapine proportion was not clearly understood. It is postulated that PEG 35000 solid dispersion was not sufficiently homogenous due to high viscosity of molten.

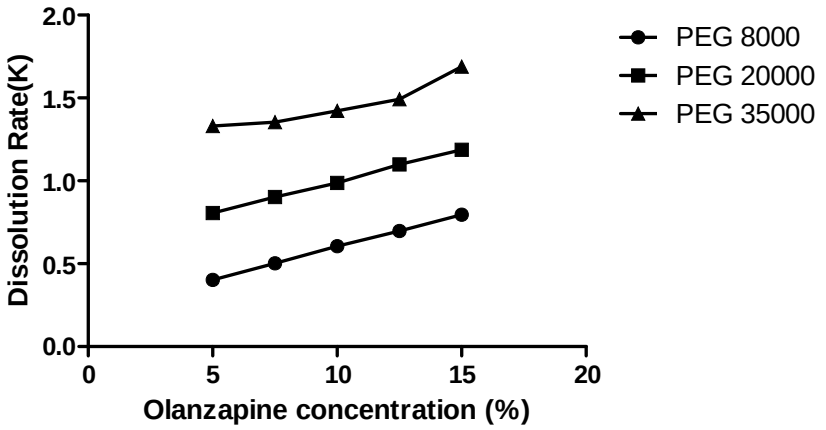

Figure 8 . Dissolution rate composition profiles of olanzapine-PEG solid dispersions.

3.3 Powder X-Ray diffraction study.

The x-ray powder differtometry (XRD) study of olanzapine and optimized solid dispersion is done in the following manners. The angular range is 5 to 50^0, 2θ counts are accumulated for 1 sec at each step. A typical x ray diffraction of olanzapine & solid diserssionn are shown in table 5 & figure 9. Wherein d represents the inter planer spacing & I/I_0 represent the typical relative intensity. In the table peaks are Listed whose relative intensity in equal or greater than 10%.

The pure olanzapine XRD showed numerous sharp narrow and intense peaks indicating its high crystallnity. Solid dispersion of olanzapine did not show the characteristic peak indicating reduction in crystalline and phase transition from crystalline to amorphous from in the solid dispersion sample.

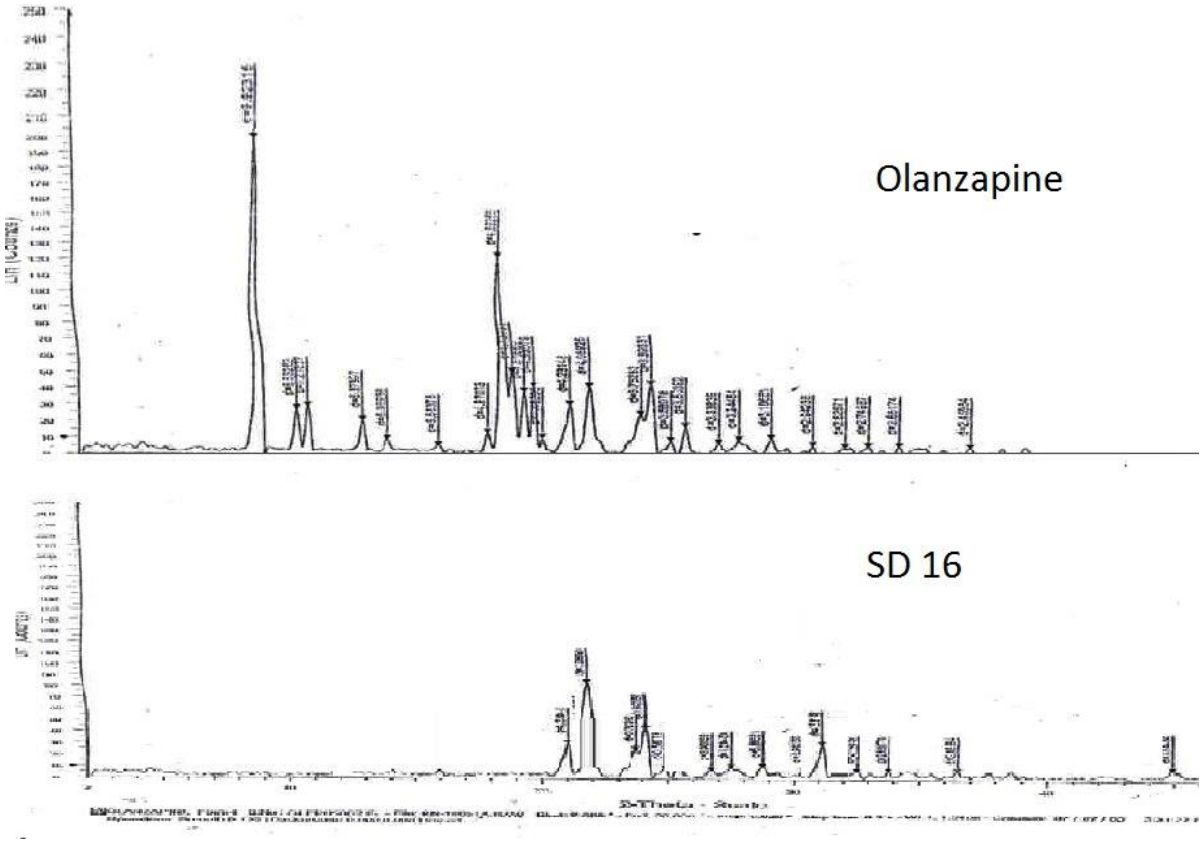

Figure 9. Powder XRD of Olanzapine and Olanzapine solid dispersion (SD 16).

Table 5. Powder XRD of Olanzapine and Olanzapine solid dispersion (SD 16).

Olanzapine			**Solid dispersion (SD 16)**		
2θ	**D value**	**I/I_0(%)**	**2θ**	**D value**	**I/I_0(%)**
8.904	9.923	100	21.535	4.1268	34.37
12.868	6.7397	10.4	22.3775	3.973	100
18.382	4.8228	60.9	27.1527	3.2842	26.88
19.209	4.61689	19.3	27.9557	3.19167	25.25
20.977	4.23148	15.4	31.8018	2.81391	46.73
21.716	4.08926	20.9	45.814	1.99281	15.95
23.689	3.75283	12.4			
24.077	3.69331	21.8			

3.4 Differential scanning calorimetry (DSC).

DSC curve obtained for pure olanzapine and solid dispersion prepared by melting method. Pure olanzapine showed a melting endothern 197.5^{0}C. The DCS of solid dispersion showed melting point for the PEG around 59^{0}C with no endothermic peak corresponding to the Olanzapine (Figure 10). The absence of peak at temp corresponding to the melting of the drug could potentically be assigned to the solubility and distribution of the drug within the polymer matrix resuting in the conversion of crystalline drug form into amorphous form.

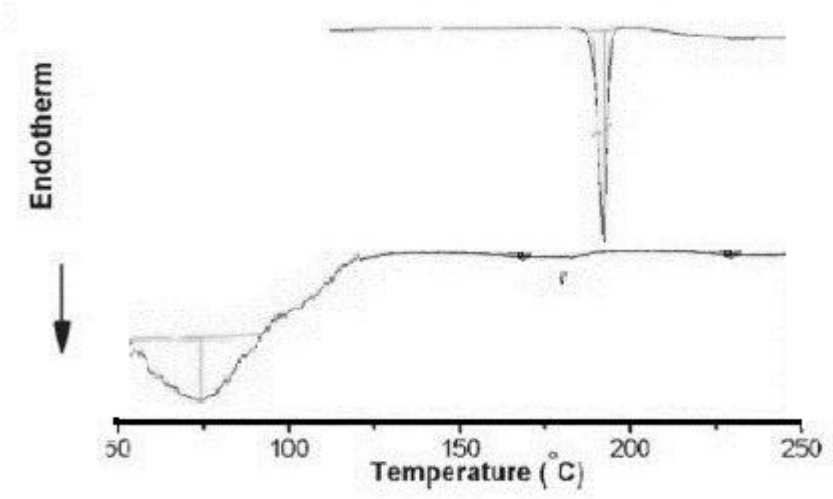

Figure 10. DSC thermogram of Olanzapine and solid dispersion(SD 16).

Fourier transforms infrared spectroscopy (FTIR).

The IR spectra for olanzapine was characterised by sharp transition occurring at 1033, 2225, 1559 and 745 cm^{-1} corresponding to the bond stretching associated with O-H bending, N-H stretching, C = N stretching and C-S bending respectively. Analysis of the spectra for the solid dispersion of olanzapine(figure 11) did not reveal any changes for the specific absorption bands for the drug suggesting a lack of interaction between the two moieties.

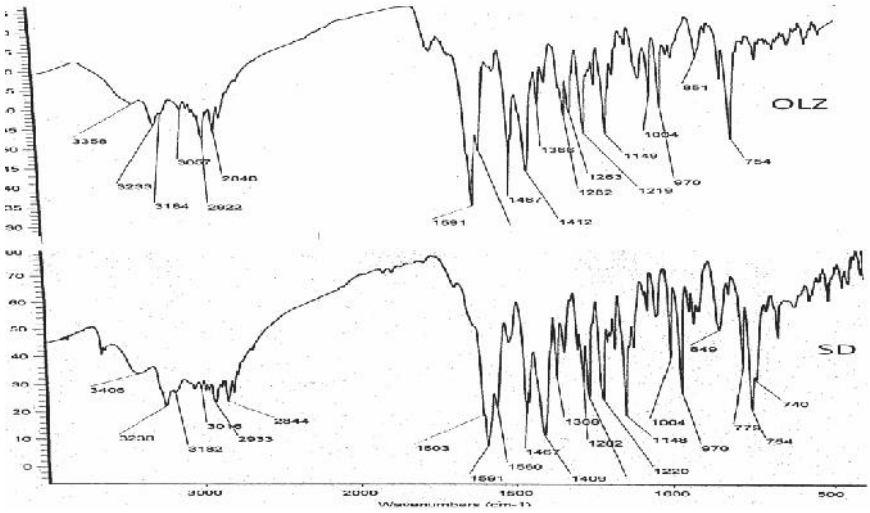

Figure 11. FTIR spectra of Olanzapine and solid dispersion (SD 16).

Conclusion.

Olanzapine solid dispersion was successfully developed by response surface methodology based on D-optimal design. The effect of PEG M.wt and amounts of olanzapine, on the dissolution rate of olanzapine solid dispersion were analyzed and optimized. The multiple linear regression analysis and three-dimensional response surface plot indicate that dissolution rate show proportional relation with independent variables (PEG M.Wt and drug content). The optimized Olanzapine solid dispersion (SD 16) showed 1.16 mg/min. The dissolution rates of olanzapine increased as the molecular weight of PEG increased, but the best results were obtained with PEG 20000. Although the dissolution rate increased with the drug content. The amorphous form of Olanzapine found in powdered solid dispersions as demonstrated by X-ray diffraction and DSC may offer an explanation of

better dissolution rate from solid dispersion. The proposed solid dispersion ensures an increase in dissolution rate of Olanzapine.

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