

## FORMULATION, EVALUATION AND OPTIMIZATION OF SOLID DISPERSION OF GLIPIZIDE USING FACE CENTERED CENTRAL COMPOSITE DESIGN

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### ABSTRACT

The aim of this study was to increase the solubility and dissolution of glipizide-a practically water insoluble drug. To achieve complete drug release, various batches of solid dispersion of glipizide using water soluble carriers such as PEG (PEG 4000 as  $X_1$  and PEG 6000 as  $X_2$ ), were prepared as per the design expert (8.0.5) to optimize the drug release profile using response surface methodology (Face centered central composite design). DSC and FTIR were used to characterize the solid dispersions. No chemical interaction was found between Glipizide and polymers. The solid dispersion prepared in this study was found to have higher dissolution rate and solubility compared to plain drug and physical mixture of drug and carriers. GZ<sub>s</sub> was found to be optimized batch according to the Face centered central composite design (FCCCD).

**Keywords:** Glipizide, PEG, Solid dispersion, FTIR

### INTRODUCTION

The solid dispersion which was introduced in the early 1970s, is essentially a multi-component system, having drug dispersed in and around hydrophobic carriers. In order to improve the solubility of poorly water soluble drugs, many methods are used. The solid dispersion approach has been widely used for improvement of solubility, dissolution rate and hence bioavailability of poorly water soluble drugs<sup>1-4</sup>.

Solid dispersion technique has been used for a variety of partially aqueous soluble drugs such as nimesulide<sup>5</sup>, paracetamol<sup>6</sup>, tenoxicam<sup>7</sup>, nifedipine<sup>8, 9</sup>, nimodipine<sup>10</sup>. Various hydrophilic carriers such as PEG 4000, PEG 6000, PVP, HPMC, gums, sugars, mannitol have been investigated for improvement of dissolution characteristics and solubility of poorly water soluble drugs.

Glipizide is a second generation sulfonylurea compound used as an oral hypoglycemic agent. It is one of the most potent of the sulfonylurea antidiabetic agents. As per BP, it is practically insoluble in water. Because of its poor aqueous solubility, conventional glipizide dosage forms show absorption problems. Glipizide is a weak acid (pKa = 5.9), and highly permeable (BCS Class II drugs). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100 % and an elimination half life of 2-4 hrs. Glipizide is reported to have a short biological half life (3.4 ± 0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day<sup>11</sup>. High hydrophobicity and hence poor aqueous solubility of Glipizide leads to inadequate dissolution in gastrointestinal (GI) fluids and hence poor absorption, distribution and target organ delivery<sup>12, 13</sup>.

Glipizide (GZ) can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat non insulin dependent diabetes mellitus<sup>12</sup>. The drug is insoluble in water, and its dissolution is considered to be a rate-determining step (*i.e.*, an effective factor) in its absorption from the gastrointestinal fluids. This limits its bioavailability and may be the reason for its delayed absorption. So to improve the aqueous solubility and dissolution of the drug, many techniques have been adopted since decades and solid dispersion is one of those techniques. Two grades of PEG, PEG 4000 and PEG 6000 in combination were used for the formulation of solid dispersion.

The current study aims at developing and optimizing the solid dispersion formulation of glipizide using PEG 4000 and PEG 6000 by fusion method and optimizes the formulation using RSM. Use of response surface methodology has been proved to be useful tool on the development and optimization. Different steps involved in RSM include experimental design, regression analysis, constraint optimization and validation<sup>14</sup>.

### MATERIALS AND METHODS

Glipizide was obtained as a gift sample from Sun Pharmaceutical Pvt. Ltd., Mumbai. PEG 4000 and PEG 6000 were purchased from Loba chemie Pvt. Ltd., Mumbai. All other chemicals used were of pharmaceutical grade. Freshly prepared distilled water used throughout the study.

#### Methods

##### Preparation of physical mixture:-

Physical mixture of Glipizide with the combination of PEG 4000 and PEG 6000 in different ratios obtained from design expert (8.0.5) were prepared by thoroughly mixing the accurately weighed quantity of drug and carrier in glass mortar and pestle for 5 min and sieved through a 0.25 mm sieve (#60) and stored in a dessicator for 24 hr and used for further studies.

##### Preparation of solid dispersion by fusion method:-

Physical mixture was melt in a water bath with gradual increasing of temperature up to the value necessary for the complete melting. The molten mass was rapidly cooled with constant stirring using a glass rod. The resulting solid dispersions were stored in dessicator for 24 hrs, after then the prepared dispersions were grounded in mortar for 2 min. and passed through a 0.25 mm sieve (# 60) and used for further studies<sup>9</sup>.

##### Experimental design for formulations of solid dispersion containing PEG

Two independent variables, the amount of PEG 4000 ( $X_1$ ) and PEG 6000 ( $X_2$ ) were studied at 3 levels each. The central point (0, 0) was studied at quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 1, 2 and 3 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. Solubility (%) and cumulative % drug release (% CDR) were taken as the response variables. Table 1 describes the formulation batches as per the software design expert (8.0.5).

##### Characterization of solid dispersion of Glipizide

The prepared solid dispersions were characterized by solubility analysis, FTIR studies, *In-vitro* dissolution studies, determination of drug content.

##### Solubility analysis

Solubility study was assessed out according to the method of Higuchi and Cannors. The solubility of Glipizide as pure drug and its

solid dispersion were determined in distilled water and phosphate buffer 7.4. Glipizide and solid dispersion equivalent to 10 mg of drug was taken and to this 10 ml of respective medium in 100 ml stoppered volumetric flask and shaken for 25 hrs at  $37 \pm 2$  °C on a magnetic stirrer. The entire samples were protected from light by wrapping the flask by aluminium foil. After 24 hr samples were filtered through Whatman filter and aliquots were suitably diluted and assayed spectroscopically at 274 nm. Each solubility measurement was determined in triplicate and average values were reported<sup>15</sup>.

#### Determination of drug content

The percent drug content of each solid dispersion, was determined using powder equivalent to 10 mg Glipizide and was dissolved in minimum amount of methanol and volume was made up to mark 100 ml using pH 7.4 phosphate buffer. The solution was then filtered through Whatman filter paper and required dilution were being made and assayed for drug content using UV double beam spectrometer at 274 nm. Three replicates were prepared and average value was reported<sup>16</sup>.

**Table 1: Formula used for the formulation of solid dispersion**

Sl. No.	Formulation code	Drug (mg)	PEG 4000 (mg)	PEG 6000 (mg)
1	GZ <sub>1</sub>	30	15	15
2	GZ <sub>2</sub>	30	45	15
3	GZ <sub>3</sub>	30	15	45
4	GZ <sub>4</sub>	30	45	45
5	GZ <sub>5</sub>	30	15	30
6	GZ <sub>6</sub>	30	45	30
7	GZ <sub>7</sub>	30	30	15
8	GZ <sub>8</sub>	30	30	45
9	GZ <sub>9</sub>	30	30	30
10	GZ <sub>10</sub>	30	30	30
11	GZ <sub>11</sub>	30	30	30
12	GZ <sub>12</sub>	30	30	30
13	GZ <sub>13</sub>	30	30	30

#### In-vitro dissolution studies

Dissolution study was carried out by using USP apparatus-II, paddle type for 2 hr. The stirring rate was 50 rpm. Phosphate buffer pH 7.4 and distilled water was used as medium (900 ml) and was maintained at  $37 \pm 5$  °C. Samples equivalent to 10 mg of Glipizide was used for dissolution studies. Samples were collected at regular interval of time and assayed for dissolution spectroscopically at 274 nm. Each dissolution rate test was repeated thrice and average values were reported<sup>17</sup>.

#### FTIR studies

The FTIR spectra of the drug, PEG 4000, PEG-6000, mannitol and solid dispersion in different ratio were recorded with FTIR spectrophotometer. The samples were prepared by using potassium bromide and scanned for the absorbance at 4000-400/cm, Perkin Elmer<sup>18</sup>.

#### Mathematical kinetic assessment for drug release mechanism

Release kinetics is an integral part for the development of a dosage form because if the kinetics of drug release is known, one can also established *in vivo in vitro* (IVIVC) correlation. Mathematical approach is one of scientific methods to optimize and evaluate the error in terms of deviation in the release profiles of formulated products during the formulation development stage. Mathematical model approach important in research and development because of its simplicity and their interrelationships may minimize the number of trials in final optimization, thereby improving the formulation development process. The dissolution profile of the optimized batch was fitted to the different kinetic models.

#### In vitro drug release data were fitted to kinetic models

Qt versus t (zero order)

Log (Q<sub>0</sub>-Q<sub>t</sub>) versus t (first order)

Qt versus square root of t (Higuchi)

log %Qt versus log %t (Korsmeyer-Peppas)

Where Qt is the amount of drug released at time t. The criteria for selecting the most appropriate model are lowest sum of square of residuals (SSR) and highest R<sup>2</sup> value. Lowest sum of square of residuals (SSR) indicate the minimum variance between the

predicted and observed dissolution data. Highest R<sup>2</sup> value indicates linearity of dissolution data.

#### RESULT AND DISCUSSION

##### Drug content

The content of glipizide in each formulation was assayed by UV spectroscopy. The assay values were in range 92 % to 99 % of the theoretical value.

##### FTIR

FTIR was performed on Glipizide, PEG 4000 and PEG 6000, solid dispersion of Glipizide with all carriers. The IR spectra of solid dispersion showed all the principal IR absorption peak of Glipizide 3324 cm<sup>-1</sup>, 3051 cm<sup>-1</sup>, 1648 cm<sup>-1</sup>, 1395 cm<sup>-1</sup>. FTIR of solid dispersion of drug and all carriers shows that all the peaks of drug and carrier as it is and drug is present in free form. This indicates that there is no interaction in between Glipizide and the entire carrier employed in solid dispersion. Fig.1 showing the spectra of pure Glipizide and fig. 2 of solid dispersion. The obtained spectrum was compared with the spectrum that was in literature to confirm the authenticity of the given sample.

##### DSC study

The thermograms obtained from DSC study enables us the quantitative detection of all processes in which energy are required or produced. DSC scans of pure drug, physical mixture of drug and PEG and solid dispersion are presented in fig. 3 and 4. The melting endotherms of pure glipizide and PEG alone gave peaks at 220.19°C and 59.6°C respectively corresponding to their melting points. The intensity of peaks in case of solid dispersion was shifted to 63.06°C that shows that glipizide became amorphous during dispersion into PEG matrix.

##### Solubility studies

The solubility of Glipizide in water and in phosphate buffer, without PEG was found to be 0.0312 mg/ml and 0.0346 mg/ml respectively. The solubility of Glipizide increased as a linear function of carrier concentration. All the solid dispersions showed enhanced solubility but higher in case of solid dispersion prepared by PEG 4000 and PEG 6000. The graphical representation of the % solubility from the formulations is given in fig. 5.

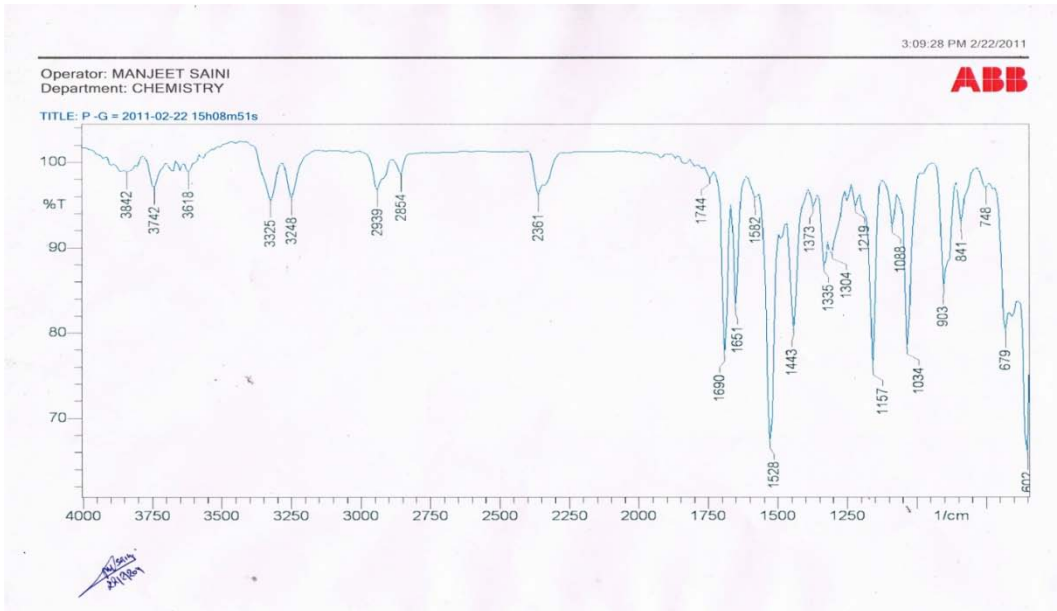


Fig. 1: FTIR of pure glipizide



Fig. 2: FTIR of solid dispersion

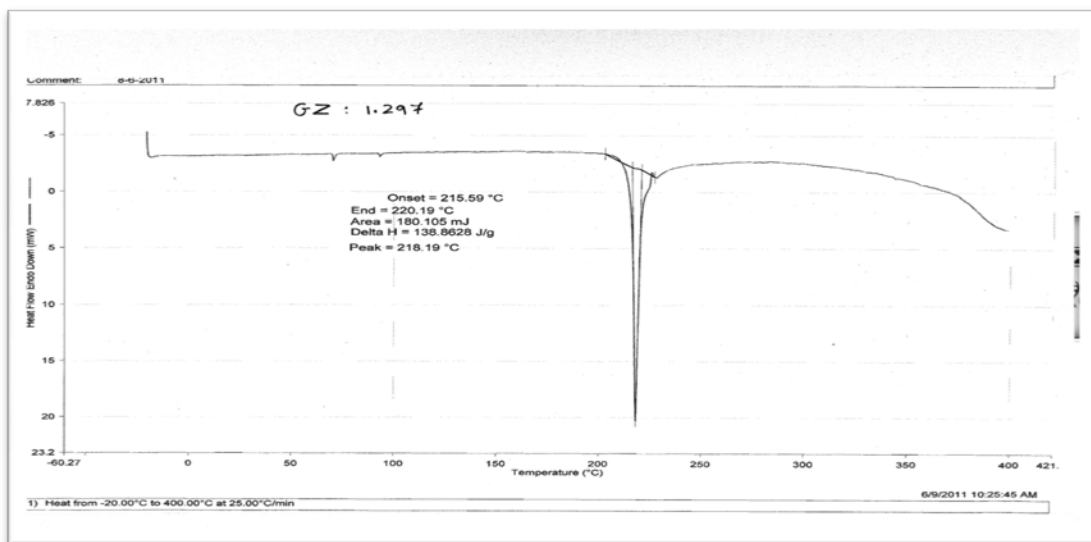


Fig. 3: DSC of pure drug

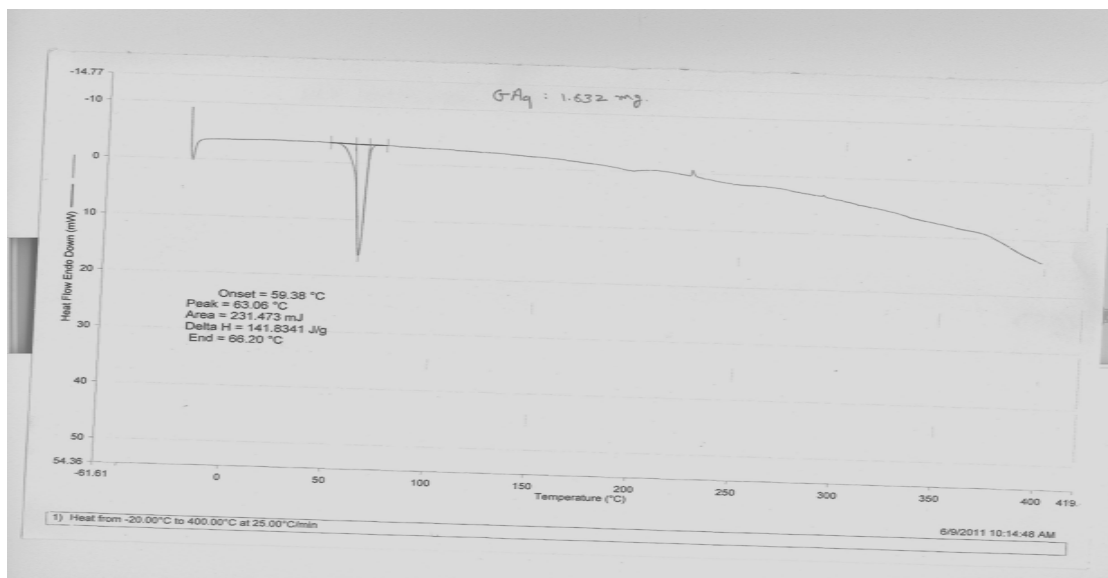


Fig. 4: DSC of solid dispersion

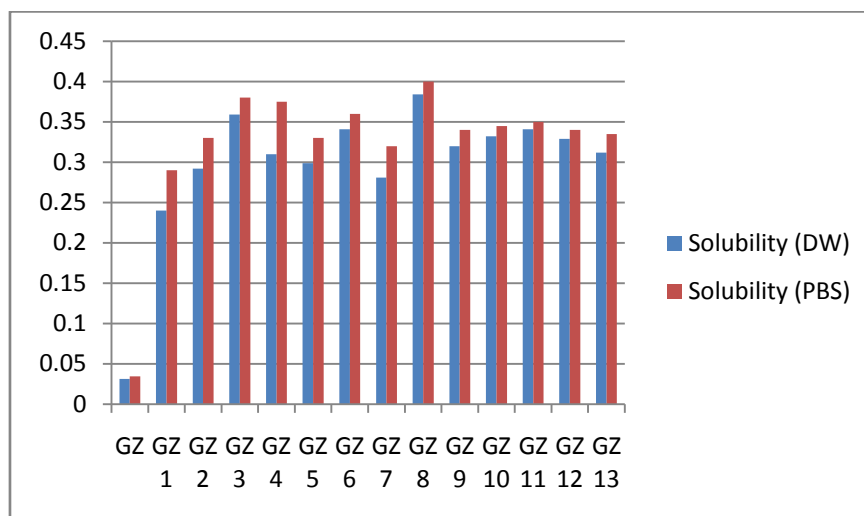


Fig. 5: Graphical representation of solubility of pure drug and solid dispersion formulations

**In vitro drug release**

In vitro dissolution study was carried out for pure drug and all formulations in phosphate buffer pH 7.4. The graphical

representation of the % cumulative drug release from the formulations is given in fig. 6. Table 2 showing the Response parameters solid dispersion of Glipizide prepared as per the experimental design.

Table 2: Response parameters solid dispersion of Glipizide prepared as per the experimental design

Formulation code	PEG 4000 (mg) (X <sub>1</sub> )	PEG 6000 (mg) (X <sub>2</sub> )	CDR (%)	Solubility (mg/ml)
GZ <sub>1</sub>	15	15	60.49	0.29
GZ <sub>2</sub>	45	15	81.25	0.33
GZ <sub>3</sub>	15	45	84.32	0.38
GZ <sub>4</sub>	45	45	89.98	0.37
GZ <sub>5</sub>	15	30	72.39	0.33
GZ <sub>6</sub>	45	30	87.38	0.36
GZ <sub>7</sub>	30	15	70.98	0.32
GZ <sub>8</sub>	30	45	91.29	0.40
GZ <sub>9</sub>	30	30	75.49	0.34
GZ <sub>10</sub>	30	30	76.29	0.345
GZ <sub>11</sub>	30	30	76.98	0.35
GZ <sub>12</sub>	30	30	77.67	0.34
GZ <sub>13</sub>	30	30	78.29	0.33

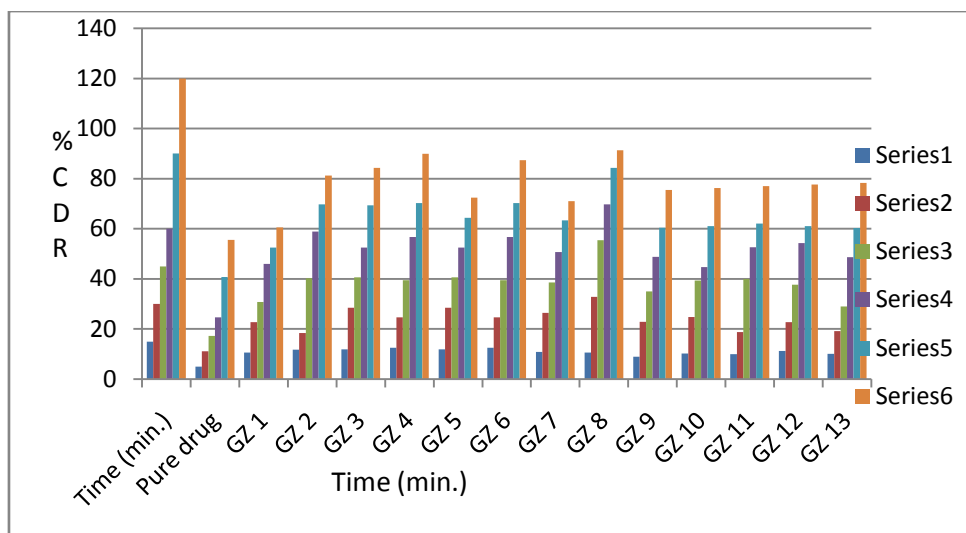


Fig. 6: Graphical representation of % cumulative drug release from pure drug and solid dispersion formulations

**Optimization of formulations using face centered central composite design (FCCCD)**

**Response surface methodology (RSM) for solid dispersion**

Response surface methodology allows understanding of the behavior of the system by demonstrating the contribution of the independent variables. An experimental design organizes the experiments in such a manner that the required information is obtained as efficiently and precisely as possible. Runs or trials

are the experiments conducted according to the selected experimental design.

**ANOVA- Analysis of variance**

Analysis of variance of the responses indicated that response surface models developed for % cumulative drug release (2 hr) and % solubility were significant and adequate, without significant lack of fit. Table 3 predicts the data for the analysis of variance.

Table 3: ANOVA for response surface quadratic model

Response factor	Model F-value	p-value Prob>F	Lack of fit	
			F-value	p-value
% CDR	58.02	<0.0001	6.05	0.0528
% Solubility	36.75	<0.0001	3.68	0.1155

**Model Summary Statistics: Influence of formulation variables on the response factors**

Model summary statistics for the selected significant models are shown in table 4. It can be observed that R<sup>2</sup> is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R<sup>2</sup> value is in good agreement with the adjusted R<sup>2</sup> value, resulting in reliable models.

**Mathematical Modeling**

Mathematical relationships generated using multiple linear regression analysis for the studied response variables are expressed as equations given below:

$$\% \text{ CDR} = + 78.68 + 6.90 X_1 + 8.81X_2 - 3.78 X_1 X_2 \dots\dots (1)$$

$$\% \text{ Solubility} = + 0.35 + 0.011 X_1 + 0.036 X_2 - 0.011 X_1 X_2 \dots\dots (2)$$

The polynomial equations comprise the coefficients for intercepts, first-order main effects, interaction terms and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response.

**Response surface analysis**

The 3-dimensional response surface plots and the corresponding contour plots for the studied response parameters, %CDR (2 hr) and

% Solubility revealed the effect of selected independent variables on various responses.

**Solubility (%)**

The polynomial equation (2) for % Solubility denotes that both the coefficients X<sub>1</sub> and X<sub>2</sub> bear a positive sign. Therefore, increasing the concentration of either PEG 4000 or PEG 6000 is expected to increase the % solubility. However, the effect of PEG 6000 is more pronounced as compared to PEG 4000. This was further revealed by the response surface plots (fig. 7 and 8).

**Cumulative drug release (%CDR)**

The polynomial equation (1) for % CDR denotes that both the coefficients X<sub>1</sub> and X<sub>2</sub> bear a positive sign. Therefore, increasing the concentration of either PEG 4000 or PEG 6000 is expected to increase the % CDR. However, the effect of PEG 6000 is more pronounced as compared to PEG 4000. This was further revealed by the response surface plots (fig. 9 and 10).

**Numerical Optimization**

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. The optimum formulation was selected based on the criteria of attaining maximum % cumulative drug release and optimum solubility (%). Table 5 depicts the constraints set and the solution provided by the software.

Table 4: Model Summary Statistics - Influence of formulation variables on the response factors

Response factor	Std. Dev.	R <sup>2</sup>	Adjusted R <sup>2</sup>	Predicted R <sup>2</sup>
% CDR	2.16	0.9508	0.9344	0.9064
% Solubility	8.992	0.9245	0.8994	0.8435

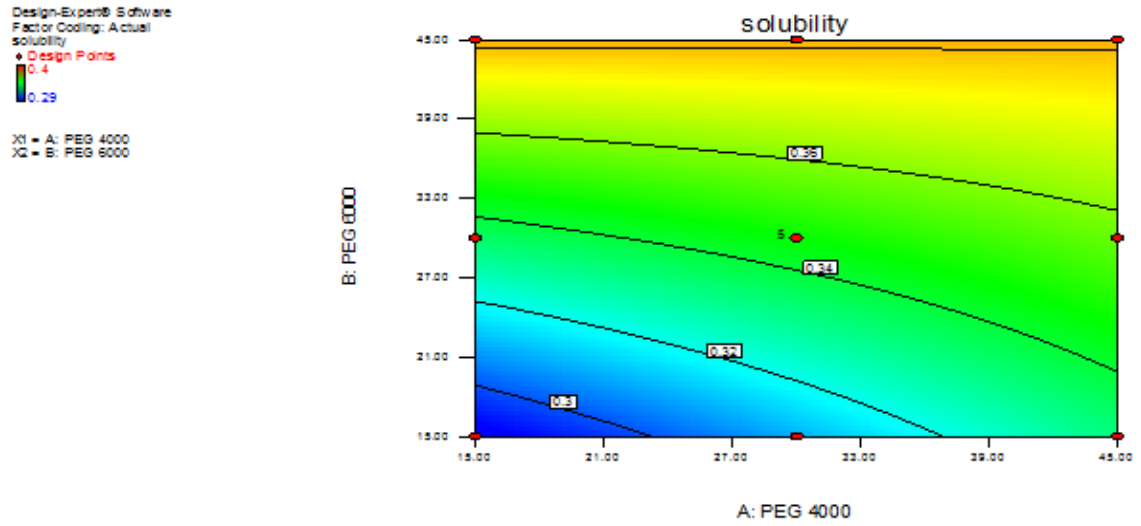


Fig. 7: Contour plot showing the influence of two factors on % Solubility

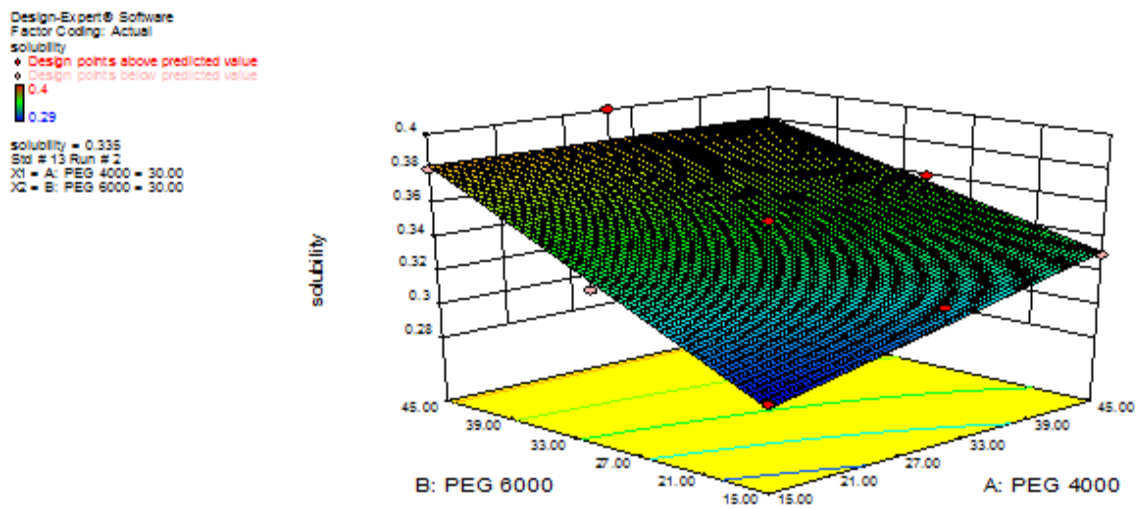


Fig. 8: 3D response surface plot showing the relationship between various levels of two factors on % Solubility

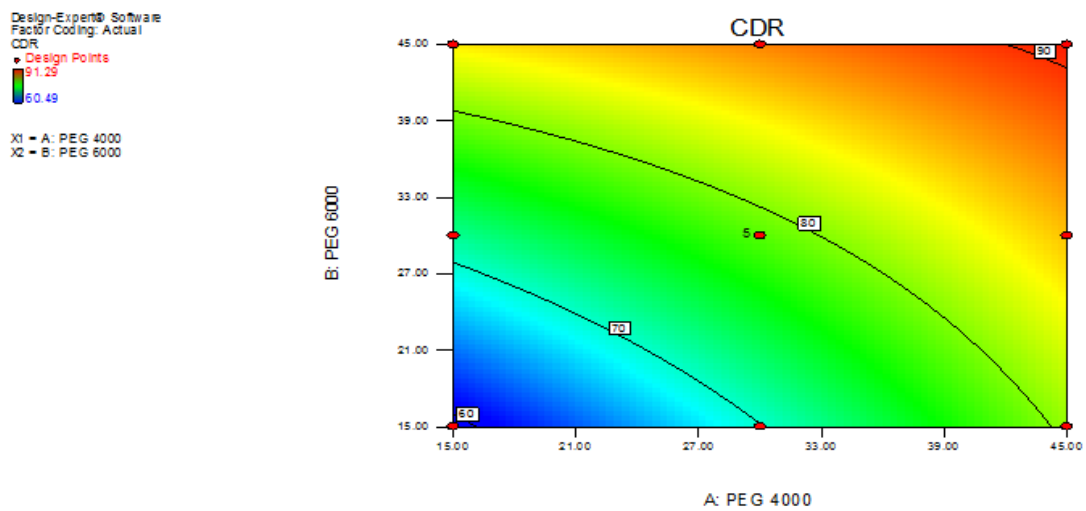


Fig. 9: Contour plot showing the influence of two factors on % Cumulative Drug Release (% CDR)

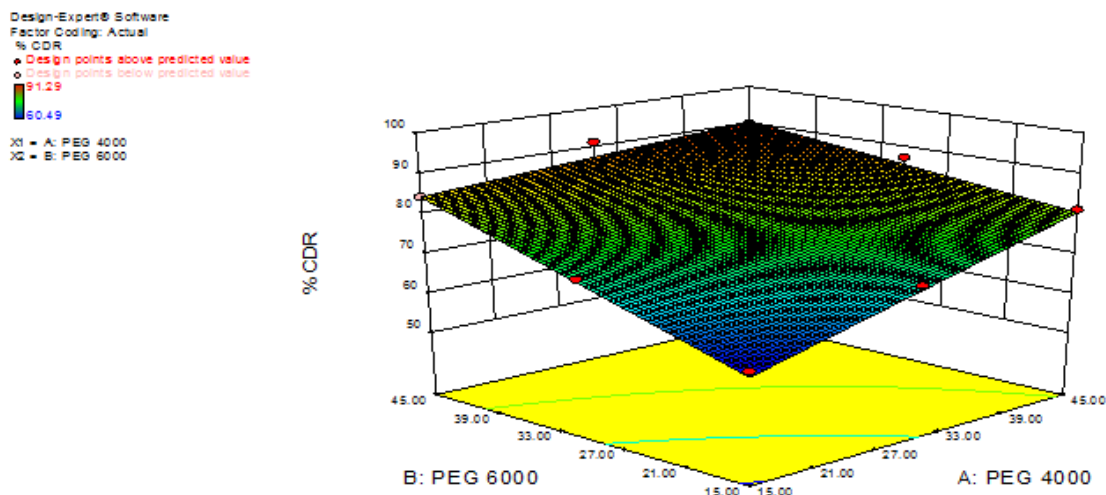


Fig. 10: 3D response surface plot showing the relationship between various levels of two factors on % Cumulative Drug Release (% CDR)

Table 5: Solution provided by face centered central composite design (FCCCD)

Constraints						
Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
PEG 4000	Is in range	15	45	1	1	3
PEG 6000	Is in range	15	45	1	1	3
% CDR	Maximize	60.49	91.29	1	1	3
% Solubility	Maximize	0.29	0.4	1	1	3

Solution						
Formulation code	PEG 4000 (mg)	PEG 6000 (mg)	CDR (%)	Solubility (%)	Desirability	Solution
GZ <sub>8</sub>	30	45	91.29	0.4	0.9	Selected

**Mathematical modeling to study the *in-vitro* release kinetics of optimized batches**

To establish the order and mechanism of drug release, dissolution data of the optimized batches were fitted to four different kinetic models, namely. Zero order model, first order model, Higuchi model and Korsmeyer peppas model. The model for best fit was predicted

from the value of R<sup>2</sup>. For an ideal fit, value of R<sup>2</sup> was 1. Hence, the model which gives the R<sup>2</sup> value nearest to 1 describes the order of drug release (table 6). From the results of data fitting to various models, it was found that the optimized batch GZ<sub>8</sub> showed first order of drug release, i.e. mechanism of drug release from the glipizide solid dispersion is concentration dependent.

Table 6: Value of R<sup>2</sup> obtained from different kinetic models

Formulation Code	R <sup>2</sup>			
	Zero order	First order	Higuchi model	Korsmeyer Peppas model
GZ <sub>8</sub>	0.884	0.997	0.956	0.923

**CONCLUSION**

In the present study it can be concluded that the release was directly proportional to the concentration of polymer used for the formulation of solid dispersion. The result of dissolution study showed that Glipizide: PEG 4000 + PEG 6000 solid dispersion had faster dissolution rate than glipizide itself. From the results of data fitting to various models, it was found that the optimized batch GZ<sub>8</sub> showed first order of drug release, i.e. mechanism of drug release from the glipizide solid dispersion is concentration dependent.

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