



Formulation and Characterization of Solid Dispersions of Glimepiride through Factorial Design

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Abstract

In order to enhance *in vitro* dissolution and content uniformity of poorly soluble drug glimepiride by preparing solid dispersions using modified solvent fusion method, solid dispersions of drug were prepared by modified fusion solvent method using PEG 6000 and PVP K25 (as carrier). Eight batches (F₁-F₈) were prepared by Factorial design (2³) by taking three factors i.e. the concentration of: drug (X₁), PEG 6000 (X₂) and PVP K25 (X₃). DSC, FTIR spectroscopy, powder X-ray diffraction (XRD) and SEM studies were used to characterize solid dispersions. *In vitro* release was carried out using USP II dissolution apparatus. Multilinear regression analysis was applied to develop mathematical model to estimate cumulative drug release. The batch F₃ was found to be best batch as it showed maximum *in vitro* dissolution after 30 min. Improvement in dissolution behavior of solid dispersion batches was observed due to conversion of crystalline form of drug to amorphous form as confirmed by DSC, FTIR studies and X-RD studies. SEM photographs of batch F₃ showed porous nature of particle surface. Uniformity of content of different batches was found to be in range as specified by IP. Solid dispersion prepared via modified fusion solvent method was proved to be beneficial in enhancement of dissolution rate of poorly-water soluble drug using hydrophilic carriers. Retrospectively, this model can further be utilized to design solid dispersions for desired release characteristics.

Keywords: Factorial design; Glimepiride; PEG 6000; PVP K25; Solid dispersion.

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1. Introduction

Oral drug delivery is the simplest and easiest way of administering drugs. Because

of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development are intended to be used as a solid dosage form that originate an effective and

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reproducible *in vivo* plasma concentration after oral administration [1, 2]. In fact, most NCEs are poorly water-soluble drugs and are not well absorbed after oral administration which can detract from the drug's inherent efficacy [3, 4]. Consequently, if these drugs are not completely released in the gastrointestinal area, they will have a low bioavailability [5]. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [6]. The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes micronization, salt formation, use of surfactants and use of prodrug [7]. However, all these techniques have potential limitations. Solid dispersion is the most successful strategy to improve drug release of poorly soluble drugs. Solid dispersion improves the solubility through decreased particle size, increase surface area, improved wettability and increased amorphous state of water insoluble compound [8]. Sekiguchi and Obi first introduced the concept of using solid dispersions to improve bioavailability of poorly water soluble drug in 1961. Chiou and Riegelman defined the term solid dispersion as "a dispersion of one or more

active ingredients in an inert carrier or matrix, prepared by the melting, solvent, or melting-solvent method [9]. Solid dispersion (SD) technique has been widely used to improve the solubility, dissolution rate and oral absorption of poorly water-soluble drugs [10, 11].

Glimepiride (a BCS class II drug) is a third generation of sulfonyl urea oral anti-diabetic drug having high permeability and low solubility. Low water soluble drugs often exhibit low dissolution profile and oral bioavailability problems [12, 13]. Therefore, the objective of the present study was to improve *in vitro* dissolution profile and content uniformity of glimepiride using solid dispersions by modified solvent fusion through factorial design.

2. Materials and methods

2.1. Materials

Glimepiride was a gift sample from Comed Pharmaceutical Ltd. (India). PEG 6000 was purchased from Glaxo Smithkline Ltd. (India). PVP K25 was purchased from Titan Biotech Ltd. (India). All chemicals used were of analytical grade.

2.2. Modified Fusion Solvent Method

Solid dispersions were prepared by using the carriers viz. polyethylene glycol (PEG

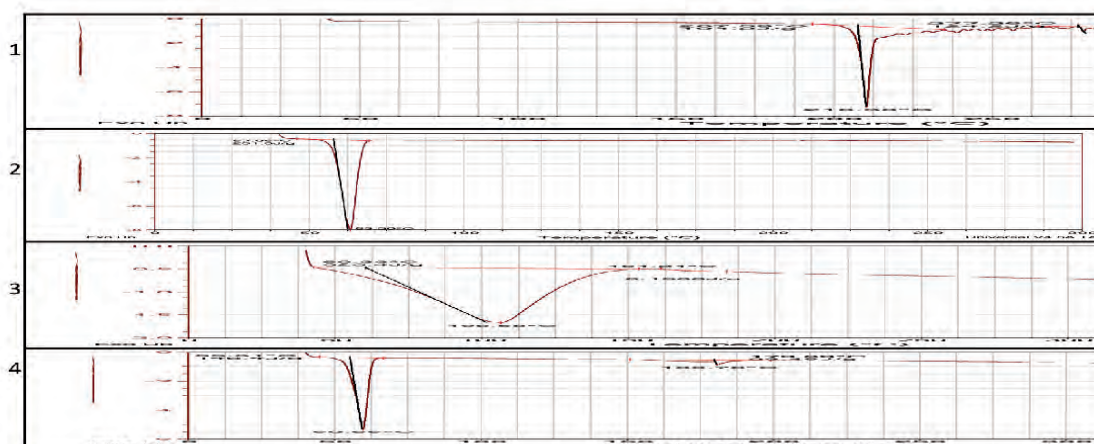


Figure 1. Differential Scanning Calorimetric Thermograms of: Glimepiride (1), PEG 6000 (2), PVP K25 (3) and Solid Dispersion Batch F3 (4).

Table 1. Formulation of different batches of solid dispersion and release profile.

SDs Batch	X_1 (Drug) (mg)	X_2 (PEG 6000) (mg)	X_3 (PVP K25) (mg)	%CDR 30(min.)
				Mean \pm S.D.
F1	-1(1)	-1(5)	-1(2.5)	90.4 \pm 0.8
F2	-1(1)	-1(5)	+1(10)	94.8 \pm 0.5
F3	-1(1)	+1(10)	-1(2.5)	96.5 \pm 0.4
F4	-1(1)	+1(10)	+1(10)	94.1 \pm 1.0
F5	+1(4)	-1(5)	-1(2.5)	41.5 \pm 0.8
F6	+1(4)	-1(5)	+1(10)	53.6 \pm 0.6
F7	+1(4)	+1(10)	-1(2.5)	50.9 \pm 0.5
F8	+1(4)	+1(10)	+1(10)	58.5 \pm 0.4

Values in bracket indicate amounts in mg.

6000) and polyvinyl pyrrolidone (PVP K25) by modified fusion solvent method. PEG 6000 was melted over a thermostatically controlled magnetic stirrer at its respective melting point and drug was incorporated into the molten carrier mass. The polyvinyl pyrrolidone K25 was dissolved in ethanol and mixed in the mixture of PEG 6000 and drug. The whole mixture was kept at the corresponding melting temperature for 10 min, followed by flash cooling on an ice bath. The solidified mixture was pulverized in a pestle mortar and passed through sieve # 44 and stored in desiccator.

2.3. Experimental design

Solid dispersion was formulated according to the (2^3) factorial design to study the effect of three independent variables on *in vitro* dissolution profile of glimepiride. To evaluate three factors at two levels, the factorial design consisted of eight batches (F1-F8). The three factors analyzed during the study were, the concentration of drug (X_1), the concentration of PEG 6000 (X_2) and the concentration of PVP K25 (X_3) (Table 1).

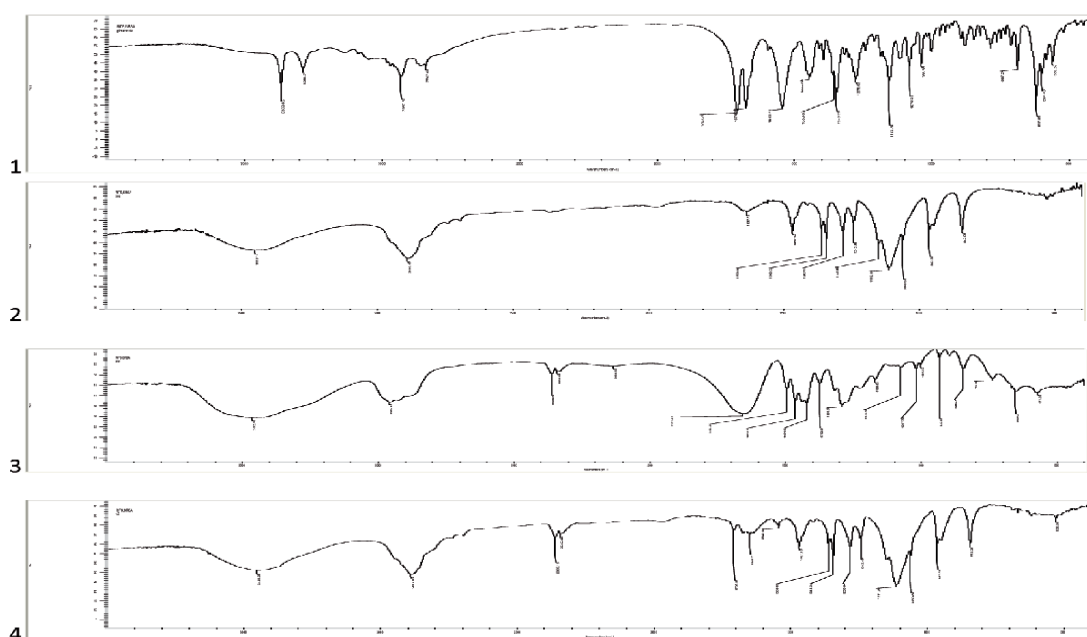


Figure 2. Fourier transform infrared spectrum of: glimepiride (1), PEG 6000 (2), PVP K25 (3) and solid dispersion batch F3 (4).

2.4. Differential scanning calorimetry

The melting behavior of the pure drug, carrier and solid dispersions was evaluated by using DSC instrument (DSC Q10 V 9.9 Build 303). Samples were heated under nitrogen atmosphere on an aluminum pan at a rate of 10 °C/min. over the temperature range of 30 to 300 °C.

2.5. Fourier transform infrared spectroscopy

Infrared spectra of pure glimepiride, carriers and solid dispersions was recorded using FTIR spectrometer (Thermo Nicolet 380, USA) to ascertain the presence of different functional groups. A small amount of the powdered solid (1-2 mg) was added to pure potassium bromide powder and grounded up as fine as possible. This was then placed in a small die and put under pressure mechanically to form KBr pellet. Pellet was then scanned in the range from 400 to 4000 cm⁻¹.

2.6. In vitro dissolution studies

Drug release studies were performed in

triplicate using United State Pharmacopoeia Type I dissolution test apparatus, employing phosphate buffer (pH 6.8) as dissolution media, at a temperature of 37±0.5 °C and at a speed of 75 rpm. Dissolution studies were performed on pure drug (4 mg) and the different solid dispersions containing an equivalent amount of drug. Aliquots of the periodically withdrawn samples (10 ml) were analyzed spectrophotometrically at 226 nm and were replaced with an equal volume of dissolution medium.

2.7. Powder X-ray diffraction studies

Powder X-ray diffraction pattern of solid dispersions were traced employing X-ray diffractometer (X'pert-PRO, PAN Analytical), using Ni filtered CuK (α) radiation, a voltage of 45 kV, a current of 20 mA. The sample was analyzed over 2θ range of 0-50° with scan step size of 0.0170° (2θ) and scan step time of 20 s.

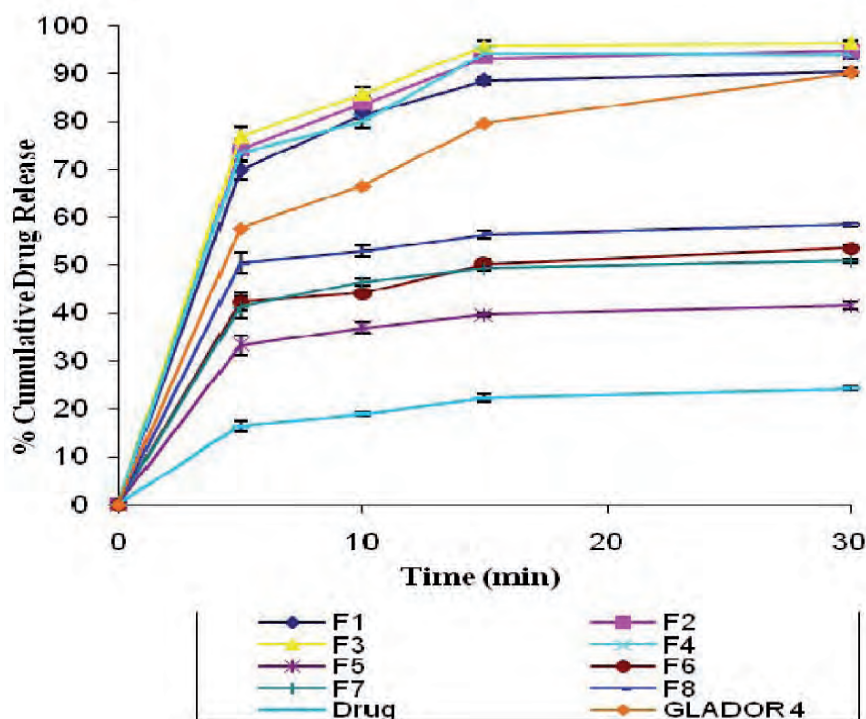


Figure 3. Dissolution profile of pure drug glimepiride, solid dispersions (F1-F8) and marketed product (GLADOR 4).

Table 2. ANOVA of the regression (%CDR).

	Degree of freedom	Sum of Squares	Mean Square	F	F-Significance
Regression	3	3841.932	1280.644	68.99823	0.00067
Residual	4	74.240	18.560		
Total	7	3916.175			

2.8. Scanning electron microscopy

Sample of pure drug and solid dispersions were mounted onto the stubs using double-sided adhesive tape and then coated with gold palladium alloy (150-200 Å) using fine coat ion sputter (Joel, JPC-1100). The samples were subsequently analyzed under the scanning electron microscope for external morphology.

2.9. Content uniformity

Solid dispersions containing an equivalent amount of 4 mg of glimepiride was added to a volumetric flask containing methanol. The flask was shaken for 10 min. and final volume was made up using buffer of pH 6.8. The sample was diluted and analyzed spectrophotometrically at 226 nm.

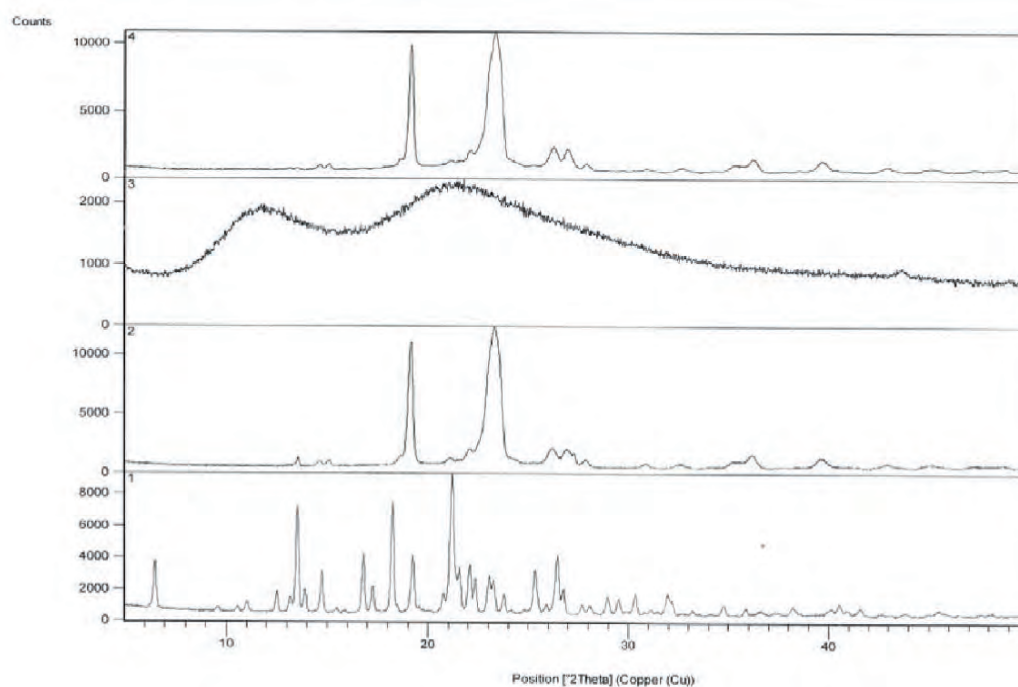
3. Results and discussion

Preliminary studies were carried out to

select the factors affecting formulation of solid dispersion. Three factors i.e. amount of drug and carriers (PEG 6000 and PVP K25) were studied at two levels (+1 and -1) and eight batches (F1-F8) of solid dispersion were formulated using (2^3) factorial design (Table 1). All the batches were first subjected to DSC, FTIR and *in vitro* release studies.

3.1. Differential scanning calorimetry

The DSC curve of glimepiride shows a sharp endothermic peak at 210.30 °C with enthalpy of fusion 194.2 J/g corresponding to its melting point, indicating its crystalline nature. Similarly, the endothermic peak of PEG 6000 was found at 63.29 °C with enthalpy of fusion 251.3 J/g and DSC of PVP K25 showed endothermic peak at 106.58 °C with enthalpy of fusion 323.4 J/g (Figure 1). Absence of endothermic peak of drug (corresponding to its M. Pt. i.e. 210.30 °C) in

**Figure 4.** Powder X-ray diffraction spectra of: glimepiride (1), PEG 6000(2), PVP K25 (3) and solid dispersion batch F3 (4).

thermograms of batches F1- F8 indicate that entire drug has been converted to its amorphous form.

3.2. Fourier transform infrared spectroscopy

An IR spectrum of sample was recorded as to ascertain the presence of different functional groups. FTIR of pure glimepiride showed characteristic sharp peaks at 3369 cm^{-1} and 3288 cm^{-1} due to N-H stretching, 1707 cm^{-1} and 1674 cm^{-1} due to carbonyl group, 1345 cm^{-1} showing C-N stretching vibration, 1153 cm^{-1} showing S=O stretching vibration [19]. PEG 6000 showed a C-H stretching at 2886 cm^{-1} and C-O stretching at 1112 cm^{-1} . PVP K25 showed a C-H stretching at 2955 cm^{-1} and broad peak due to C=O in tertiary amide at 1654 cm^{-1} (Figure 2). The IR spectrum of different batches (F1-F8) of solid dispersion exhibited significant decrease in the intensity of N-H and S=O stretching vibration of glimepiride. This is attributed to formation of hydrogen bonds between the primary amino group of drug and the carbonyl group of PVP or the backbone oxygen atoms and the

chain end hydroxyl groups of PEG. The absence of characteristic peaks of drug (3369 cm^{-1} and 3288 cm^{-1}) in solid dispersion batches indicates H-bonding between drug and carrier thereby increasing the solubility leading to enhanced dissolution.

3.3. In vitro dissolution

Studies of *in vitro* dissolution rates allow a comparison to be made between pure drug, solid dispersion and marketed product (GLADOR 4). The dissolution profiles of pure drug, solid dispersion batches (F1-F8) and marketed product (GLADOR 4) are shown in Figure 3. The *in vitro* dissolution rates of all solid dispersions were found to be much faster than the pure drug. Solid dispersion batch F3 showed highest release rate out of all and it was compared with marketed product. The results obtained give an indication of potential immediate release characteristics of solid dispersion. Solid dispersion batch F3 was selected for further SEM and X-RD studies owing to the existence of drug at molecular level as evidenced by

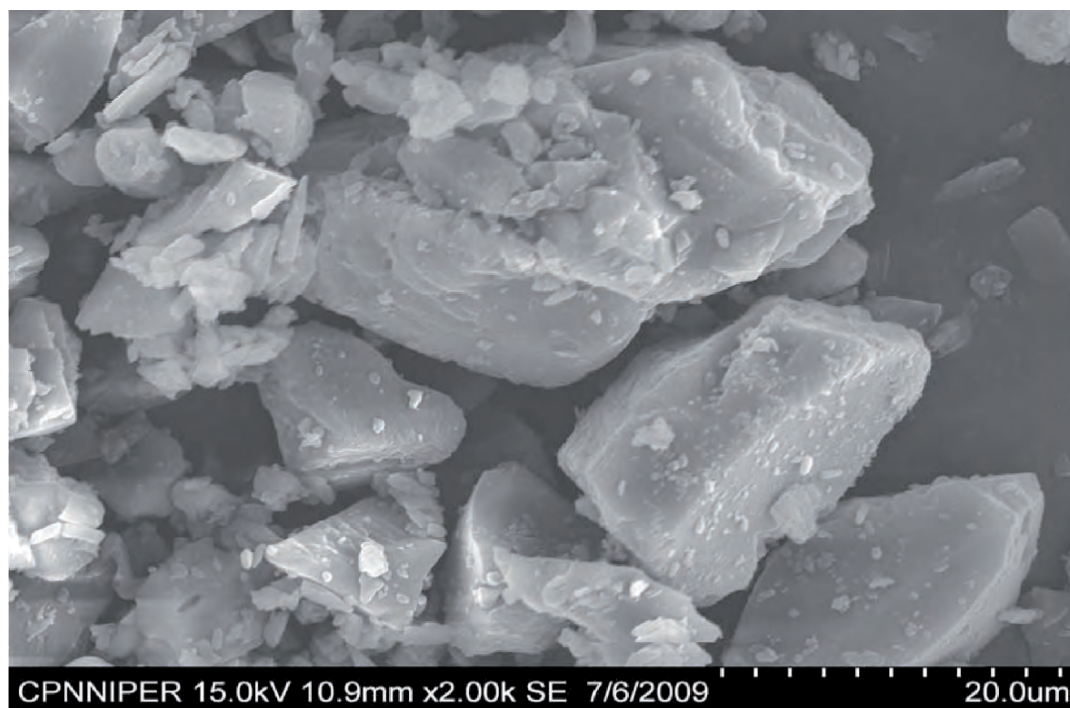


Figure 5. Scanning electron microscopic photomicrograph of pure drug glimepiride at 2000x.

absence of endothermic peak of drug (corresponding to its M. Pt. i.e. 210.30 °C) during DSC studies, absence of characteristic peak of drug in IR spectrum and maximum cumulative drug release during *in vitro* dissolution studies.

3.4. Powder X-ray diffraction studies

Crystallinity was further confirmed by comparing some representative peak heights in the diffraction of the solid dispersion with those of the pure drug glimepiride. Glimepiride showed sharp peak of the diffraction angle of 2θ at 13.52, 18.23 and 21.18° with peak intensities of 1216.66, 1293 and 1667.11, respectively. PEG 6000 showed distinct peak at 19.18 and 23.27° at 2θ with peak intensities of 2920.35 and 2649.77, respectively, which is a characteristic of its crystallinity. PVP K25 showed the characteristic peak at 11.18 and 21.38 with intensity of 135.55 and 104.53, respectively (Figure 4).

Diffractionograms of solid dispersion batch F3 showed fewer, broader and less intense

peaks. Lack of characteristic peaks of glimepiride (13.52, 18.23 and 21.18°) confirms the presence of amorphous form of drug (Figure 4).

3.5. Scanning electron microscopy

Figure 5 and 6 illustrates the surface morphologies of pure drug and solid dispersion batch F3, respectively. Glimepiride appeared as smooth-surfaced rectangular crystalline structure. Whereas the topological changes observed in drug particles of the solid dispersion batch F3 and the drug surface seems to be more porous in nature. Solid dispersion appeared as uniform and homogeneously mixed mass with wrinkled surface.

3.5. Data analysis

To determine the magnitude of contribution of different factors towards dissolution, multiple linear regression analysis was performed. Microsoft excel worksheet was used for the implementation of multiple linear regression. The real values of the factors were

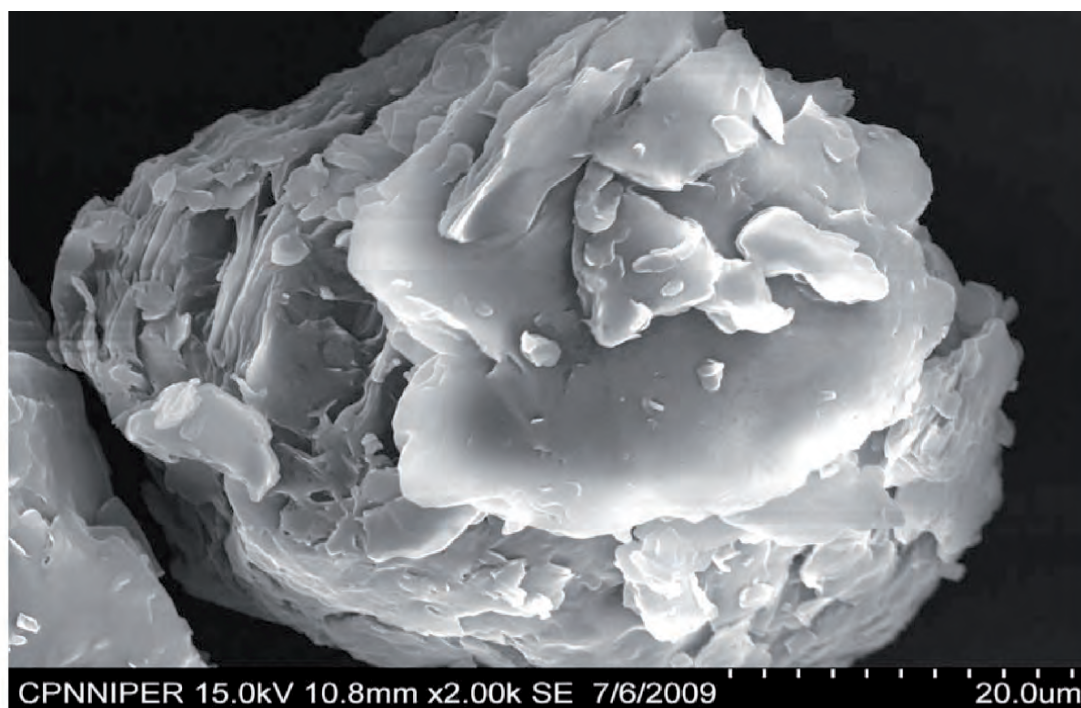


Figure 6. Scanning electron microscopic photomicrograph of solid dispersion batch F3 at 2000x.

transformed to facilitate orthogonality of results and easy calculations. The model, developed from multiple linear regression, to estimate cumulative drug release (Y) can be represented mathematically as:

$$Y = 71 - 21.6625 \times X_1 + 2.225 \times X_2 + 2.455 \times X_3$$

Where, Y=% Cumulative drug release, X₁=Amount of drug, X₂=Amount of PEG 6000, X₃=Amount of PVP K25.

Analysis of variance (ANOVA) was applied (Table II) to study the fitting and significance of the mathematical model to estimate cumulative drug release. The ratio F=68.993 shows regression to be significant. The estimated model, therefore, may be used as response surface for cumulative drug release.

3.6. Content uniformity

All the solid dispersion batches comply with uniformity of drug content (97-99%) as specified in I.P.

4. Conclusion

Solid dispersions can be used to improve the solubility of poorly-water soluble drugs. Modified fusion solvent method was proved to be beneficial in enhancement of dissolution rate of poorly-water soluble drug glimepiride using the carriers, PEG 6000 and PVPK25. The improvement in the drug release might be due to improved wettability of the drug particles, significant reduction in particle size during the formulation of solid dispersions and to the presence of amorphous form of glimepiride, as confirmed by DSC, FTIR and XRD studies. Retrospectively, this model can further be utilized to design solid dispersions for desired release characteristics.

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