

Research Article



Solid Dispersion Adsorbates - A Novel Method for Enhancement of Dissolution Rates of Felodipine

S. Kaushik*, Kamla Pathak

Department of Pharmaceutics, Rajiv Academy for Pharmacy, Mathura (U.P.) India.

*Corresponding author's E-mail: sk.mathura20@gmail.com

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ABSTRACT

The objective of this study was to evaluate the combination of solid dispersion and melt adsorption technologies for enhancing the dissolution rate of Felodipine. Polyethylene glycol (PEG) 6000 was used as hydrophilic carriers in 1:1, 1:3 and 1:5 weight ratios (FEL: PEG 6000) for the preparation of solid dispersions, and mannitol was utilized as an adsorbent for the preparation of solid dispersion adsorbates. The solid dispersion adsorbates were evaluated by differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM) and in vitro drug release study. The dissolution rates of FEL solid dispersion adsorbates were observed much faster when compared to solid dispersions alone and physical mixture. The results were supported by the DSC, FTIR, SEM.

Keywords: Adsorption, Dissolution, Felodipine, Polyethylene glycol 6000, Solid dispersion.

INTRODUCTION

Felodipine (FEL) $\pm$ ethyl methyl 4-(2, 3-dichlorophenyl)-1, 4-dihydro-2, 6-dimethyl-3,5-pyridinedicarboxylate (figure-1) is a calcium channel blocker used as antihypertensive and antianginal drug.¹

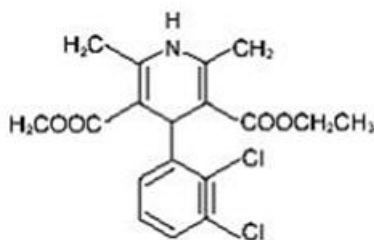


Figure 1: Chemical Structure of Felodipine (FEL)

According to Biopharmaceutical Classification System, FEL is class II drug, i.e., low solubility and high permeability. FEL has poor water solubility and hence poor dissolution and bioavailability after oral administration. FEL undergoes extensive first-pass metabolism with a bioavailability of about 15%.² The major drawback in the therapeutic application and efficacy of FEL as oral dosage form is its low aqueous solubility, which is expressed to be approximately 19.17 mg/L at 25°C. To overcome these difficulties, increasing the aqueous solubility of FEL is an important goal.

The bioavailability of a poorly water-soluble drug is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution.³ The fact that more than 40% of newly discovered drugs have little or no water solubility presents a serious challenge for the successful development and commercialization of new drugs in the pharmaceutical industry. Various techniques that have been employed to increase dissolution rate include micronization, nanosuspensions, polymorphs, complexation, solid dispersion, prodrugs, and salt

formation.⁴ Solid dispersion has become one of the most active areas of research in the pharmaceutical field because of promises in the bioavailability enhancement of poorly water-soluble drugs.⁵ Solid dispersion is defined as “a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent, or melting-solvent method”.⁶ However, the number of marketed products derived from this approach is very limited due to problems of poor compressibility, scale-up, requirement of large amount of carrier, and poor stability.⁵ The processing of solid dispersion can be improved by addition of an adsorbent.⁷

In this study, an amalgamation of solid dispersion and melt adsorption technologies was utilized to prepare solid dispersion of FEL.

MATERIALS AND METHODS**Materials**

Felodipine (Ranbaxy, Gurgaon India) is a thermostable compound with melting point 147–149°C and is poorly water-soluble. PEG 6000 and Mannitol were procured from Thermo Fisher scientific (Mumbai, India). All other chemicals were of Analytical reagent grade and used without further purification.

Preparation of Solid Dispersion Adsorbate (SDA)

SDA of FEL was prepared by the melt adsorption technique as reported by Kinoshita et al. [8]. Accurately weighed FEL was added to molten PEG6000 (65–70 °C) in the ratios 1:1 (SD1), 1:3 (SD2), 1:5 (SD3) with continuous stirring to obtain the solid dispersion. Mannitol was preheated to 70 °C and the solid dispersion was added drop wise to the adsorbent with continuous stirring to obtain the PEG6000-mannitol-adsorbate (PMA). The PEG 6000-mannitol-adsorbate (PMA) was air cooled and passed through sieve #40 ASTM.



FEL: PEG physical mixtures (PMs) were prepared in the ratios 1:1 (PM1), 1:3 (PM2), 1:5 (PM3) of FEL: PEG by homogeneously mixing the ingredients and sifted through sieve #40 ASTM.

Content Uniformity Study

Drug content of the SDs, PMs and SDA were evaluated (in ethanol). The absorbance was recorded against a blank solution of an equivalent amount of PEG in ethanol.

Drug content of the SDs, PMs and SDA was calculated by taken each sample containing an equivalent amount of 5 mg of Felodipine was added to a volumetric flask (25 mL) containing acetonitrile water (1:3 ratio) (20 mL). The flask was shaken for 15 min and final volume was made up using acetonitrile water. The sample was filtered through 0.45 µm filter and assayed for Felodipine by UV Spectrophotometer (Perkin Elmer, New Delhi, India) at 362 nm.

Differential Scanning Calorimetry (DSC) Study

The melting behaviour of the hydrophilic carriers, solid dispersions, and SDA were evaluated by a DSC instrument (Perkin Elmer DSC Pyris 1). Samples were sealed in aluminium pans and scanned from 30 to 250 °C at a heating rate of 10 °C/min.

Fourier Transform Infrared (FTIR) Spectroscopy Study

Infrared absorption spectra of pure Felodipine, PEG 6000, and solid dispersions were obtained by Fourier Transform Infrared (FTIR) spectroscopy Perkin Elmer FT-IR Spectrometer PARAGON 1000PC. The samples were ground and prepared as KBr discs (one part of sample to two parts of KBr) for analysis. The scan range was 4000–400 cm⁻¹ at an instrument resolution of 2 cm⁻¹.

X-ray Diffraction (XRD) Study

The physical characterizations of Felodipine, PEG 6000, and solid dispersions were subjected to X-ray diffractometer (X'PERT-PRO) under the following conditions:

Ni-filtered Cu-Kα radiation; 45 kV voltage: 40 mA current, scan speed 2°/min in terms of 2θ angle.

These PXRD were used to characterize the physical state of the drug in the SDs and PMs. Samples were scanned over a range of 2θ values from 5 to 50°, at a scan rate of 2.0°/min.

Scanning Electron Microscopy (SEM) Study

The surface characteristics of SDA were examined using SEM. The sample was sprinkled on a sample holder using double-faced adhesive tape, a layer of gold palladium was vacuum evaporated onto its surface using agar sputter coater, and each sample was examined with a scanning electron microscope (Philips XL 30 SEM).

In Vitro Dissolution Study

In vitro dissolution tests of the FEL, powdered SDs, PMs and SDA (equivalent to 25 mg FEL) were performed in

triplicate, using the dissolution apparatus (Electrolab, Mumbai, India) type II paddle method at 37±0.5°C for 2 h, with a stirring rate of 50 rpm, in 900 mL of a dissolution medium at pH 1.2 HCl buffer and 6.8 phosphate buffer. Dissolution samples were collected at 5, 10, 15, 20, 30, 45, 60, and 120 min, with replacement of an equal volume of temperature-equilibrated dissolution medium. The samples were filtered through a 0.45µm membrane filter, and the concentration of the drug was determined by UV spectrophotometry at 362 nm. All samples were analyzed in triplicate, and release curves were plotted using calculated mean values of cumulative drug release.

RESULTS AND DISCUSSION

Preliminary studies were carried out to screen a suitable adsorbent. Mannitol was selected owing to good adsorptive capacity and its good water solubility so as to facilitate rapid desorption of drug. The ratio of carrier and adsorbent (1:5) was identified after evaluating angle of repose. The drug, FEL was made to disperse in PEG 6000 in different ratio to obtain solid dispersions (SDs) and physical mixtures (PMs). The DSC thermograms of FEL with PEG 6000 were evaluated to identify the ratio of drug and carrier. The ratio of 1:5 (FEL: PEG6000) were selected for further study, owing to existence of drug at the molecular level as evidenced by the absence of melting endotherms of FEL in the DSC thermograms.

The co-melt of carrier and the drug was adsorbed on to the surface of mannitol to prepare freely flowing granules of SDA, which could be processed into a tablet or directly fill into the capsule.

Content Uniformity Study

The contents of FEL in all the PMs, SDs and SDA were found to vary from 98.50 to 100.25% of the claimed amount of drug.

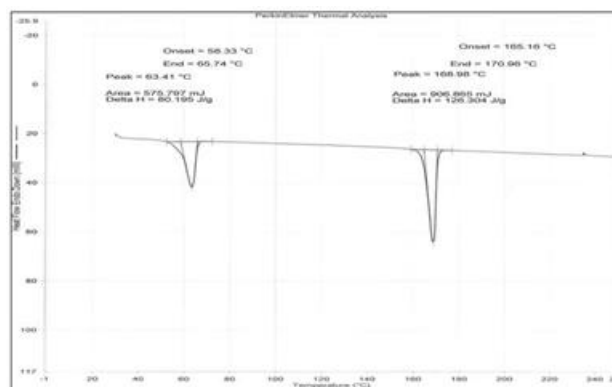


Figure 2: DSC curve of Felodipine, PEG 6000 and Mannitol solid dispersion adsorbate (SDA)

Differential Scanning Calorimetry (DSC) Study

In DSC thermograms of SDA shown in Figure 2, PEG6000 gave peak at 63.41 °C. Mannitol showed an endothermic peak at around 168.98 °C and a peak with decomposition at 240°C findings are similar to those reported by Chidaveenzi et al.⁹ Lack of melting peak of Felodipine (149.66 °C) in the DSC thermograms indicated that the

drug present is amorphous rather than in a crystalline form. The amorphous state in comparison to crystalline form is a high-energy state and is expected to have a high absorptivity.

Fourier Transform Infrared (FTIR) Spectroscopy Study

The infrared spectrum of FEL and solid dispersions exhibited significant differences in the intensities of the absorption peaks shown in Figure 3 and 4 respectively. Broadening of various absorption peaks with a slight shift in the position to a lower wavelength was observed; this is attributed to the intermolecular hydrogen bonding in the solid dispersions.

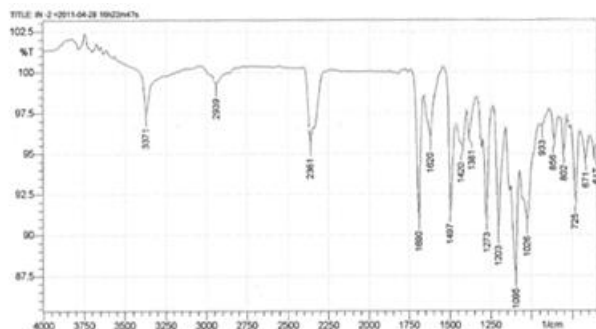


Figure 3: Infra red spectra of Felodipine

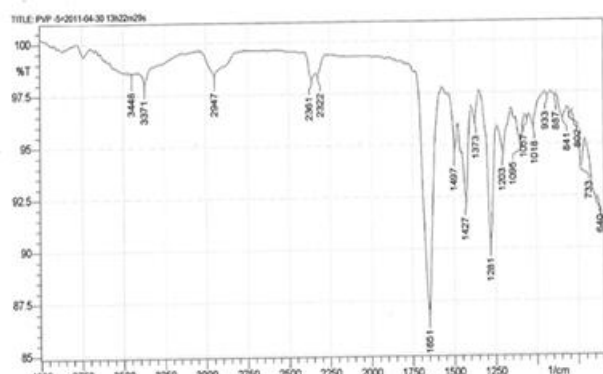


Figure 4: Infra red spectra of Felodipine and SD (1:5 ratios)

X-ray Diffraction (XRD) Study

The X-ray diffraction pattern of FEL revealed high crystallinity of the drug with major diffraction peaks. X-ray diffractograms of solid dispersions confirm the presence of the amorphous form of FEL shown in Figure 5.

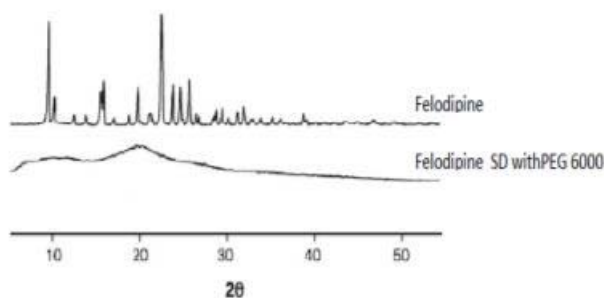


Figure 5: X-ray diffraction pattern of Felodipine and SD (1:5 ratios)

Scanning Electron Microscopy (SEM) Study

The surface morphologies of FEL, PEG 600 and SDA are shown in Figures 6 and 7 respectively. The surface of SDA was seemed to be coated agglomerates of adsorbates and also seemed to be somewhat porous.

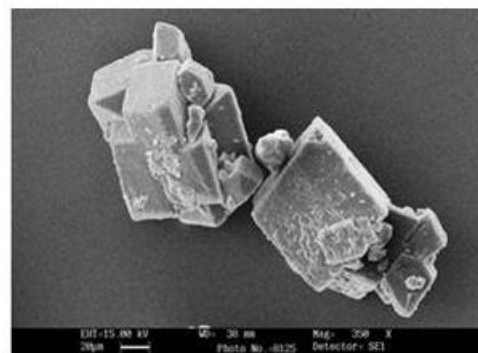


Figure 6: Scanning Electron Microscopy image of Felodipine

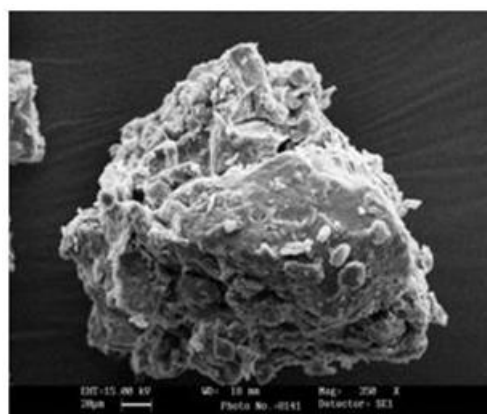


Figure 7: Scanning Electron Microscopy image of solid dispersion adsorbate (SDA)

In Vitro Dissolution Study

The results of *in-vitro* dissolution studies of pure FEL, its PM (1:5 ratio), SD (1:5 ratio) and SDA pH 1.2 HCl buffer and pH 6.8 phosphate buffer are shown in Figure 8 and Figure 9. The *in vitro* dissolution rates of SDA were found to be much faster than the pure drug (FEL), Physical mixture (PMs) and solid dispersions. There was no significant difference in the SDA dissolution rate in pH 1.2 HCl buffer and 6.8 phosphate buffer.

The results obtained give an indication of the relative efficiencies of SDA and its potential immediate-release character. This can be attributed to combination of solid dispersion and melt adsorption technologies, which has resulted in enhancement in dissolution rate due to the combined effect of solid dispersion and increased surface area due to adsorption. Moreover, water solubility of mannitol-selected adsorbent allows the drug to be desorbed completely.

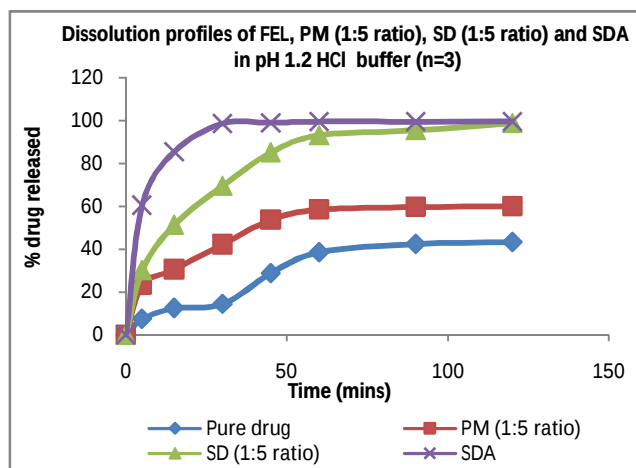


Figure 8: *In vitro* dissolution profile in pH 1.2 HCl buffer

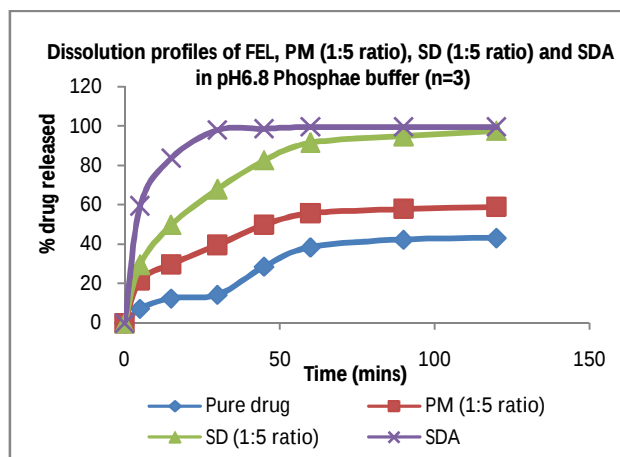


Figure 9: *In vitro* dissolution profile in pH 6.8 Phosphate buffer

CONCLUSION

A combination of solid dispersion and melt adsorption technologies using water-soluble adsorbent has proved to be highly beneficial in the present study for the enhancement of dissolution rate of poorly water soluble drug due to combined effect of solid dispersion and increased surface area due to adsorption. No decrease in dissolution rate observed during the storage of SDA. The solid dispersion adsorbate (SDA) might be evaluated for

the mouth dissolving/ fast dissolving dosage form development for the better utilization of this technique.

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