



Enhancement of Dissolution of Felodipine; A Thermostable Compound by Hot-Melt Extrusion Solid Dispersion Approach

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ABSTRACT

The objective of this study was to prepare and evaluate the Felodipine (FEL), solid dispersions (SDs) with polyethylene glycol (PEG) 6000, a hydrophilic carrier, by using hot melt extrusion (HME) technique. SDs of FEL and PEG 6000 were prepared in ratios of 1:1, 1:3, and 1:5 (by weight) by HME method. The thermostability of FEL was evaluated by Thermogravimetry analysis (TGA). The change in the nature of FEL and PEG 6000 during SD preparation was evaluated by hot stage microscopy (HSM). These SDs were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared (FTIR) spectroscopy to ascertain whether there were any physicochemical interactions between drug and carrier that could affect dissolution. Dissolution studies were conducted with pure FEL, physical mixture (PMs) and SDs. TGA shows FEL is stable upto 200° C. The results of DSC, PXRD indicated that the drug was in the amorphous state when PEG 6000 was used as carrier. The dissolution rates of FEL in PEG 6000 SDs were much faster than those for the corresponding physical mixtures and pure drug. HME technique is suitable for the SD preparation of thermostable drug. The % yield of SDs was 90.25 ± 2.62 , so can be used appropriate method for SDs in higher scale up. FTIR, DSC and PXRD studies indicate that there was no chemical interaction between FEL and PEG in solid state. In contrast to slow dissolution rate of pure FEL, the dispersion of drug in PEG considerably enhanced the dissolution rate. Therefore, it is concluded that the preparation of SDs of FEL with PEG provides a promising way to increase its dissolution rate.

Keywords: Felodipine; PEG 6000; Solid dispersions; Dissolution; hot melt extrusion.

INTRODUCTION

As per Biopharmaceutics Classification System (BCS), the class II drugs are classify as “low-solubility/high-permeability” and dissolution plays an important role in the absorption of these drugs¹. Improving the solubility and dissolution rate through formulation approaches is the most attractive option for increasing the release rate.

Recently, a variety of methods have been used to enhance the solubility in water, such as solubilization, salt formation, the use of inclusion compounds based on cyclodextrin, and particle size reduction.

The solid dispersion (SD) method, by which a drug is molecularly dispersed in an amorphous state in carriers, is one of the most commonly used pharmaceutical methods to increase the aqueous solubility and bioavailability of poorly soluble drugs.

This method is able to produce an increase in solubility within the SDs and, as the carrier dissolves, the drug comes into close contact with the dissolution medium².

SDs have been prepared by the hot-melt or solvent method.

Hot-melt extrusion (HME) is essentially a combination of melting and mechanical preparation methods, and it has a number of advantages.

(i) HME is a non-solvent technique, so it is not associated with the environmental, toxicological and

financial problems associated with the use of large solvent volumes.

- (ii) The drug degradation is decreased compared with the hot melt method because of the increased input of mechanical energy³ and the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed.
- (iii) HME can be carried out as a continuous process which can be efficient for scale-up during production⁴.
- (iv) HME technique helps in the formation of solid dispersion with thermoplastic polymers which do not melt, such as PVP, which confer increased physical stability on amorphous systems⁵.

Due to these advantages, number of SDs have been developed using the HME technique⁶⁻¹²

Based on the dissolution and absorption properties, Felodipine [FEL] is classified in the BCS as a class II drug, since it has a high permeability, but has solubility in aqueous media which is insufficient for the whole dose to be dissolved in the gastrointestinal (GI) fluids under normal conditions^{13&16}. Because of its poor aqueous solubility, FEL has a low bioavailability and limited clinical efficacy¹⁴.

The purpose of the present study was to improve the dissolution and therefore, the bioavailability of the water-insoluble drug FEL by HME. The SDs of FEL was prepared



with PEG 6000 in different weight ratio. The drug-carrier interactions were studied by Hot stage microscopy (HMS), dissolution studies, PXRD, FTIR, and DSC.

MATERIALS AND METHODS

Materials

FEL was taken from M/s Ranbaxy Ltd. (Gurgaon, India), and PEG 6000 was purchased from Thermo Fisher scientific (Mumbai, India). Purified water was used throughout the experiments. All other chemicals were of Analytical reagent grade and used without further purification.

Methods

Preparation of FEL solid dispersion

FEL and PEG 6000 were accurately weighed and mixed by hand in a polyethylene bag for 10 minutes to obtain a homogeneous physical mixture (PM). The PM was then extruded using a (Omicron 12 Pharma, Steer, Bangalore) twin-screw extruder. The extruder consisted of a hopper, barrel, die, kneading screw, and heaters distributed over the entire length of the barrel. Materials introduced into the hopper were carried forward by the feed screw, kneaded under high pressure by the kneading screw, and then extruded from the die. The temperatures of the extruder barrel zones and die were set as follows using external temperature controllers: Zone 1 = 140°C, Zone 2 = 150°C, Zone 3 = 150°C, Zone 4 = 150°C, and Die = 80°C. The feed rate and screw rate were both set at 3.5 Hz. The extruded material was collected and allowed to cool at room temperature. The sizing of these extrudes were done by passing through an 80-mesh sieve and stored in a desiccator over fused calcium chloride for further use.

Determination of percent yield

The percent yield of FEL solid dispersions were determined by using the Equation 1:

Eq-1

Yield (%) = (Weight of prepared solid dispersion/ Weight of drug + carriers) x 100

Content uniformity analysis

Drug content of the SDs were evaluated (in ethanol) by UV Spectrophotometer (Perkin Elmer, New Delhi, India) at 362 nm. The absorbance was recorded against a blank solution of an equivalent amount of PEG in ethanol. The % drug content was calculated by using Equation 2:

Eq-2

Drug content (%) = (Actual drug content in solid dispersions / theoretical drug content in solid dispersions) x 100

Thermogravimetric analysis (TGA)

TGA (Perkin Elmer TGA-7 Pyris 1) was used to investigate the thermal decomposition of FEL to see if FEL could tolerate the high temperature during HME. Samples were

crimped in hermetic aluminum pans fitted with lids and each sample was heated from 50°C to 200°C, at a rate of 10°C per minute in an atmosphere of nitrogen.

Differential scanning calorimetry (DSC)

DSC (Perkin Elmer DSC Pyris 1) were used to investigate the thermal properties of FEL, PEG 6000 and SDs. Nitrogen was used as the purge gas at a flow rate of 40 mL/ min. Samples were crimped in hermetic aluminum pans fitted with lids and then examined using a heating rate of 10°C/min from 30°C to 300°C.

Hot stage microscopy (HSM)

HSM (Nikon microscope with linkam hot stage, UK) was used to investigate the change in the nature of FEL and PEG 6000 during SD preparation. The sample was heated with 10°C/ minute rate and microscopic images were taken from the microscope.

Powder X-ray diffraction (XRPD)

The scanning PXRD patterns of FEL and PEG and their SDs were obtained on a X-ray diffractometer (X'PERT-PRO) under the following conditions:

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

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

Infrared spectroscopy

A Fourier Transform Infrared (FTIR) spectroscopy Perkin Elmer FT-IR Spectrometer PARAGON 1000PC was used for the FTIR studies. 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.

Dissolution of SDs and PMs

In vitro dissolution tests of the pure drug, powdered SDs and PMs (equivalent to 25 mg FEL) were performed in triplicate (n=3), using the dissolution apparatus (Electrolab, Mumbai, India) USP 2 paddle method at 37±0.5°C for 2 hours, with a stirring rate of 50 rpm, in 900 mL of a dissolution medium at pH 1.2 buffer and pH 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 0.45 μ m membrane filter, and the concentration of the drug was determined by UV spectrophotometry at 362 nm. All samples were analyzed in triplicate, and release profile data were analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency (DE) at 5 and 10 minutes.

The dissolution efficiency (DE)¹⁵, were calculated by Equation 3:



Eq-3

$$DE = \frac{\int_0^T Y \times dt}{Y_{100} \times T} \times 100\%$$

Where: Y is percent drug released as a function of time

T is the total time of drug release and Y_{100} is 100 percent drug released

RESULTS AND DISCUSSION

The percent yield of various FEL solid dispersions was within the range of 84.52 ± 3.29 to 90.25 ± 2.62 (n=3). The percentage drug content in various FEL solid dispersions ranged from 97.59 ± 2.69 and 98.75 ± 3.15 (n=3). Percent drug content value indicates that the drug was uniformly distributed in SDs. Hence, the method used to prepare SDs was found to be reproducible.

TGA

The Melting point of FEL is 147-149 °C. The TGA shown the weight loss profile [Figure 1], FEL exhibited minimal weight loss < 1.0% up to temperatures of ~200°C. This shows the thermal stability nature of FEL and HME technique is suitable for FEL solid dispersion preparation upto 200°C.

DSC

DSC curve of PEG 6000 [Figure 2,a], FEL [Figure 2,b] and SD in 1:5 ratio shows that the thermogram of FEL exhibited an endothermic peak at about 149.66 °C corresponding to its melting point. The endothermic peak corresponding to melting peak of FEL disappeared in the case of SD with the PEG 6000 [Figure 2,c]. The disappearance of drug melting in lesser amount of drug is due to its dissolution in the melted carrier. Felodipine homogenizes with the carriers in an amorphous form.

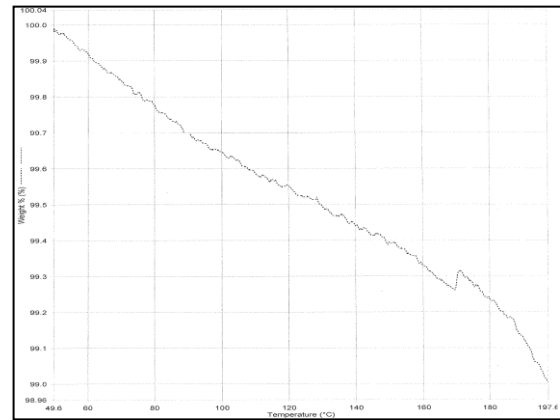


Figure 1: TGA thermogram of FEL

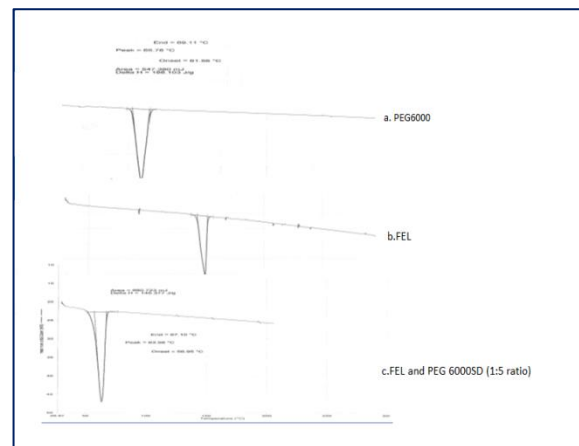


Figure 2: DSC curve a. PEG 6000; b. FEL; c. FEL and PEG 6000 SD (1:5 ratio)

HSM

The effect of the heating was studied on the FEL, PEG 6000 and physical mixture (PM). The microscopic images shows melting behaviour of the PEG 6000 [Figure 3], FEL [Figure 4] and PM mixture of the FEL and PEG6000 [Figure 5]. The results are confirming the DSC data and shows that after melting mixing of PEG6000 and FEL.

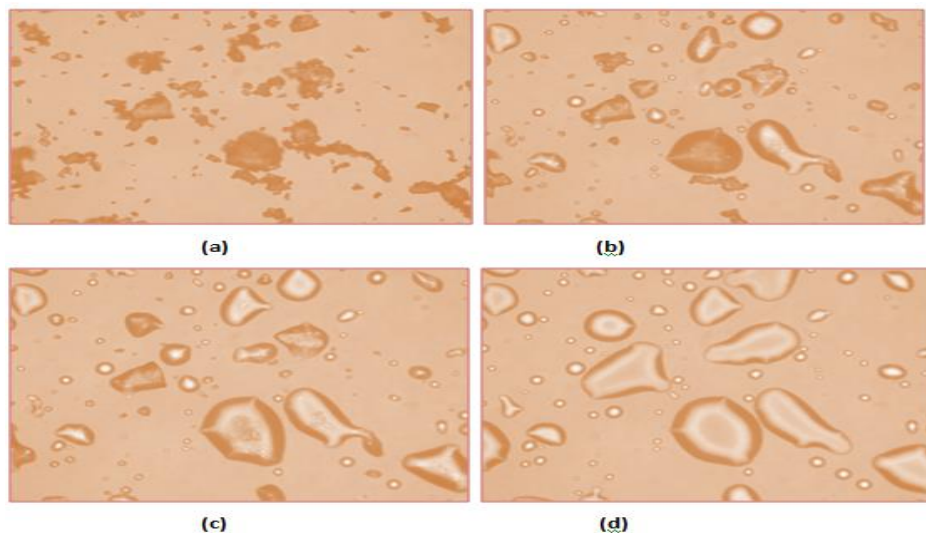


Figure 3: Microscopic images at (20X) of PEG 6000 at different Temperature (a) 30°C; (b) 55°C; (c) 60°C; (d) 65°C

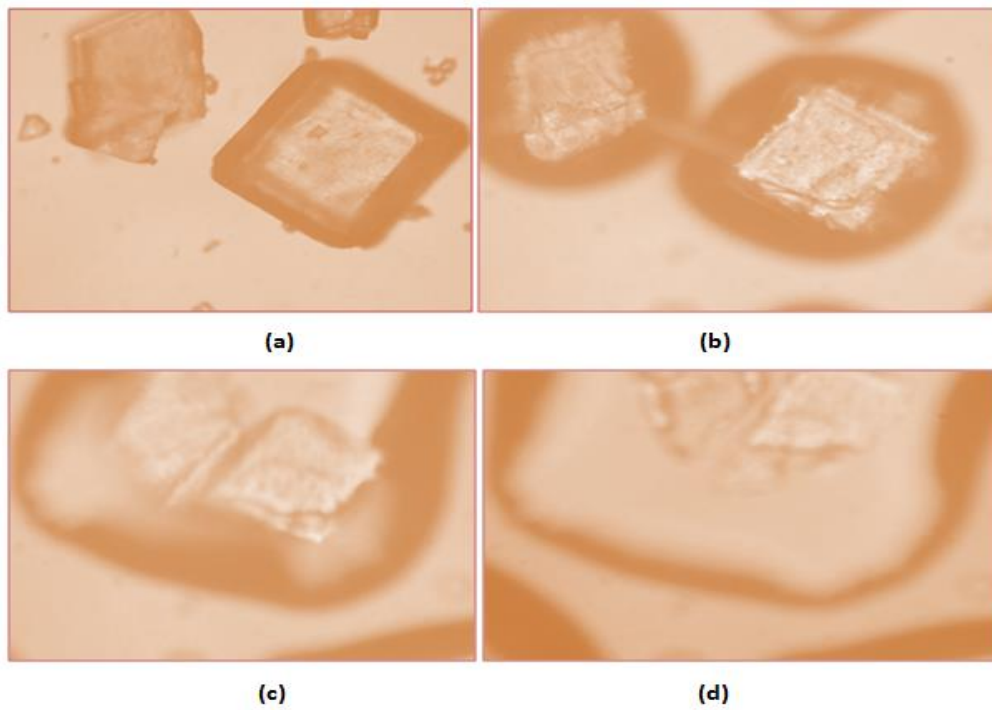


Figure 4: Microscopic images at (20X) of FEL at different Temperature (a) 30°C; (b) 140°C; (c) 145°C; (d) 147°C

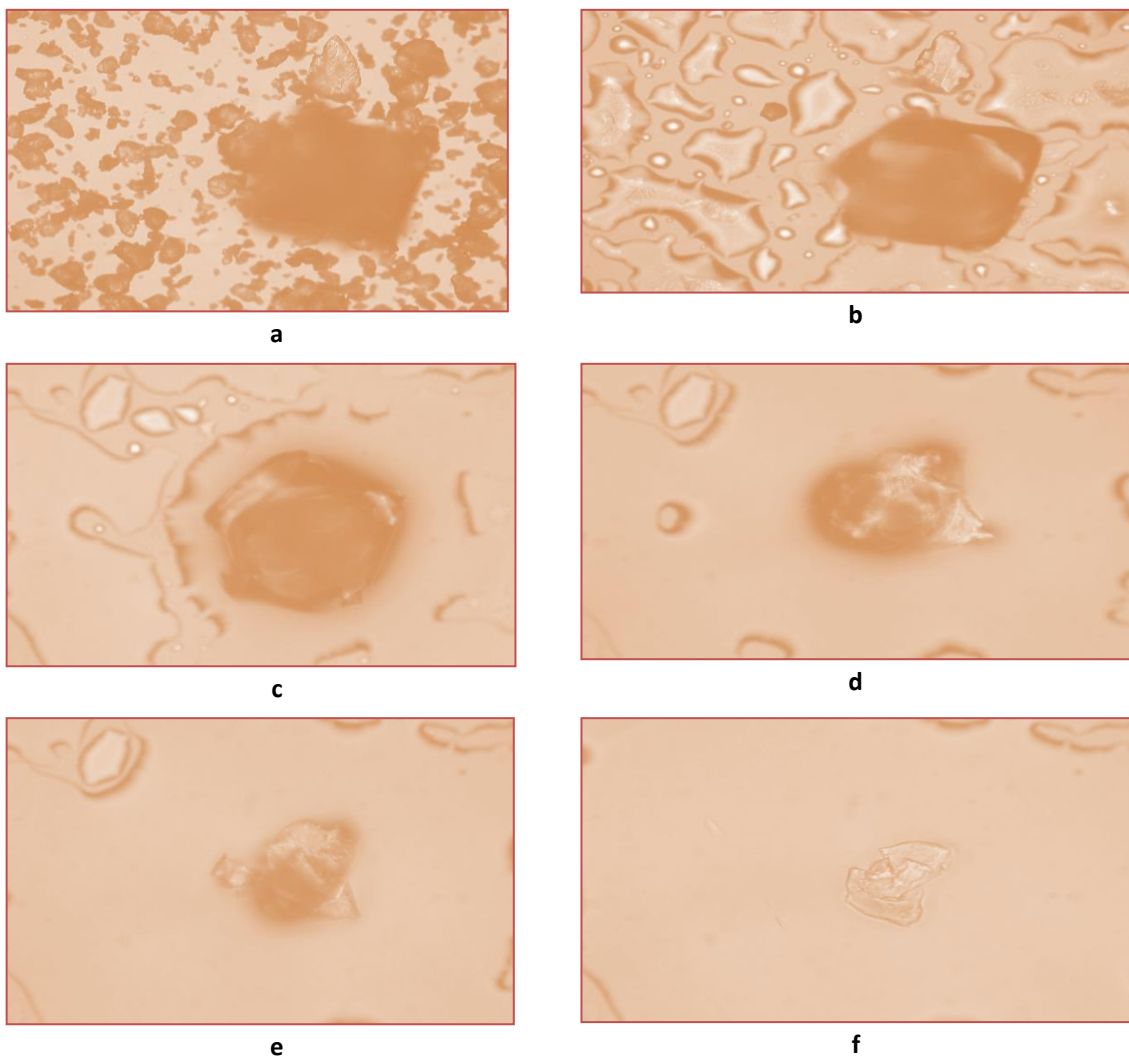


Figure 5: Microscopic images at (20X) of FEL and PEG 6000 (1:5 ratio by weight) at different Temperature (a) 30°C; (b) 55°C; (c) 110°C; (d) 115°C (e) 120°C; (f) 125°C

XRPD

In order to verify the DSC and HSM results and to exclude the possibility of the existence of crystalline material into solid dispersions, the XR-diffraction were performed. A characteristic X-Ray Diffraction of pure FEL (a) and another of a solid dispersion system 1:5 of FEL/PEG (b) is shown in [Figure 6].

The intensity of FEL peak at 10.087 remarkably reduced in SD of FEL with PEG 6000 at ratio 1:5 indicating amorphous state of the drug. XRPD data shows that a structural modification occurred in molecular state FEL. The physical state of FEL is crystalline, but that of carrier is amorphous. The molecular state of FEL prepared as drug carrier SD changed from crystalline state to microcrystalline state, and the presence of some peaks of the drug might be due to some amount of drug that was present outside the SD, i.e., it was not dispersed monomolecularly. The diffused peaks in SD shows entrapped drug molecules that were monomolecularly dispersed in the carrier bed.

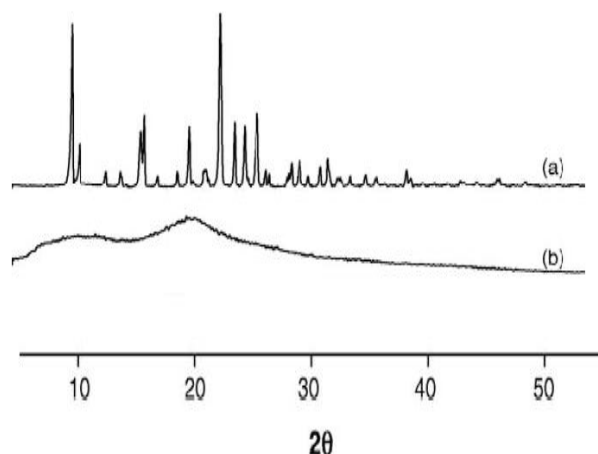


Figure 6: X-ray diffraction pattern of (a) Felodipine. (b) SD

FTIR

FTIR spectroscopy was used to further characterize possible interactions between FEL and PEG 6000 in the solid state. Comparing the spectra of SDs of FEL with PEG, no difference was shown in the position and trend of the absorption bands. Hence, provided the evidence for the absence of any chemical incompatibility between PEG with FEL under investigation, the spectra can be simply regarded as the superposition of those of FEL and PEG.

The incorporation of FEL into PEG did not modify their peaks positions and trends.

These results further indicate the absence of a well-defined interaction between FEL and PEG as already confirmed from the x-ray diffraction study.

Dissolution of SDs and PMs

The results of *in-vitro* dissolution studies of FEL, its PM and SD with PEG 6000 in pH 1.2 HCl buffer and pH 6.8 phosphate buffer [Figure 7] and [Figure 8].

The dissolution profile shows that there is no significant difference on the *in vitro* dissolution at pH 1.2 buffer and pH 6.8 phosphate buffer and the drug release increased in the following order.

SD > PM > pure drug

Cumulative amount of FEL dissolved from pure FEL was lower compared with SDs and physical mixture. At the end of 5 minutes in pH 1.2 buffer, approximately 7.38, 23.27, 40.35, 45.63 and 50.26 % of FEL and in pH 6.8 phosphate buffer, approximately 7.25, 22.95, 39.65, 44.84 and 49.69 % of FEL was released from FEL physical mixture (PM3) and SD1 (1 : 1), SD2 (1 : 3) and SD3 (1 : 5) (w/w) SDs, respectively.

Enhanced solubility, dissolution efficiency, dissolution rate of FEL SDs from physical mixtures could be due to the fact that surface area and wettability of FEL has been increased due to the conversion of the FEL crystalline state to amorphous state with hydrophilic carrier PEG6000 by hot melt extrusion technique.

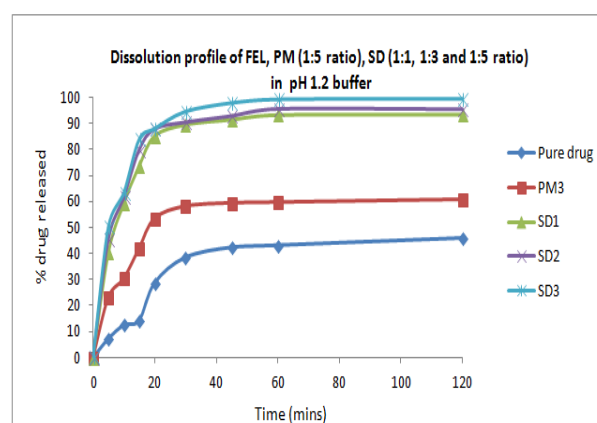


Figure 7: Dissolution profile in pH 1.2 buffer

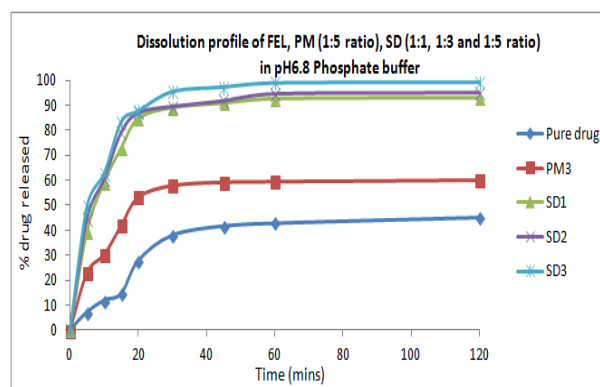


Figure 8: Dissolution profile in pH 6.8 phosphate buffer

CONCLUSION

The solubility of a poorly water-soluble compound, FEL, was increased by preparation of amorphous SDs via hot-melt extrusion with PEG 6000.

FTIR, DSC and PXRD studies indicate that there is no chemical interaction between FEL and PEG in solid state.

In contrast to slow dissolution rate of pure FEL, the dispersion of drug in PEG considerably enhanced the dissolution rate. Therefore, it is concluded that the preparation of SDs of FEL with PEG provides a promising way to increase its dissolution rate.

Also, HME technique is suitable for the SD preparation of thermostable drug and it can be used appropriate method for SDs in higher scale up.

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