

Formulation and Characterization of Fenofibrate Loaded Solid Dispersion with Enhanced Dissolution Profile

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Abstract

Fenofibrate (FF) is an anti-hyperlipidaemic drug belonging to BCS class-II (low solubility, high permeability). Its bioavailability is limited by the dissolution rate. This study was aimed to enhance the rate of dissolution of poorly water soluble drug, FF. Initially, solid dispersions of fenofibrate (SDFs) were formulated with Carplex-80 or PEG-4000 or in combination at various weight ratios and were subjected to dissolution study. On the basis of drug release at various time intervals, the formulation producing maximum drug concentration was evaluated physicochemically using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). It was observed that the peak drug concentration was obtained at 120 min of dissolution by formulation SDF-7, which contains a mixture of Carplex-80 and PEG-4000 at weight ratio 1:5:6 of FF:PEG-4000:Carplex-80, respectively. Thus, the extent of drug release by SDF-7 was maximized by 2.5-fold than that of pure FF. Physicochemical characterization revealed the reason for this increased drug release as a conversion of crystalline FF to amorphous form and ensured the chemical compatibility among FF and carriers. The results specified the significant improvement of FF release using solid dispersion technique.

Keywords

Fenofibrate, Solid Dispersion, Dissolution, Solvent Evaporation, Carplex-80, PEG-4000

1. Introduction

Oral administration is the simplest and most convenient method to deliver drugs

[1]. Unfortunately, poor aqueous solubility leading to inadequate dissolution of some drugs is a crucial barrier for oral drug delivery and it causes poor gastrointestinal absorption resulting in low and variable bioavailability [2]. It was reported that 40% of drugs from newly developed chemical entities are poorly soluble in water, among which 10% fail to reach the market, although these drugs possess high membrane permeability [3]. According to Biopharmaceutical Classification System (BCS), drugs with poor aqueous solubility and high membrane permeability are classified as BCS-II category [4]. Therefore, it is always a great challenge for pharmaceutical scientists to improve the aqueous solubility as well as dissolution of these drugs for desired pharmacological effects [5] [6].

Fenofibrate (FF), a fibric acid derivative, is widely used as lipid lowering drug. It is classified as BCS-II drug and its oral absorption and bioavailability is directed by aqueous solubility that is only 0.1 µg/ml [7] [8] [9] [10]. To overcome this limitation, large number of investigations had been conducted. Some reported approaches are development of self-microemulsifying drug delivery system [11] [12], impregnation of drug into various silica [13] [14] [15], impact of fillers [16], oral push-pull osmotic pump [17], electrosprayed nanospherules [18], nanosuspension [19], solid dispersion [10] [20] [21], nanoparticles formations [22], anti-solvent precipitation technique [23], a pair of side by side diffusion cells [24], hot-melt extrusion [25], core shell dual mesoporous silica nanoparticles [28], nanocomposites [26] [27], dry suspension and dry emulsion [28], controlled release matrix [29], lipidic dispersion [30] and co-crystals formation [31]. Among these physical methods, solid dispersion (SD) formulation is comparatively more popular because of its high drug loading capacity and no agglomeration tendency of particles [20] [32]. Hence, solid dispersion were prepared by using a number of comprehensive carriers like mesoporous silica, clay, lactose, macroporous gelatin, octenyl succinic anhydride, polyvinylpyrrolidone, hydroxypropyl-β-cyclodextrin, sodium lauryl sulfate, pluronic F-127 and polyethylene glycol (PEG) [14] [15] [21] [22] [23] [26] [27] [28] [29]. But, PEG and silica are attractive for low melting property, less toxicity, greater hydrophilicity, wide drug compatibility, greater dissolution rate and stability of formulation [9] [33] [34].

Although many SD approaches using various carriers have been examined, but there is no report regarding the use of blend of silica and PEG on dissolution property of FF. Therefore, the objective of this work was to improve the dissolution of FF, using blend of Carplex-80 and PEG-4000 at various weight ratio using solvent evaporation method.

2. Materials and Methods

2.1. Materials

FF was a generous gift from Square Pharmaceuticals Ltd. Pabna, Bangladesh. Carplex-80 and PEG-4000 were purchased from Evonik Pvt. Ltd. Hanua, Germany. Acetone was purchased from Merck, Germany. All other reagents used were of analytical grade.

2.2. Preparation of SDFs

SDFs with different weight ratio of drug and carrier (**Table 1**) were prepared by solvent evaporation method. The resultant SDFs were further dried in vacuum for 24 hours. Finally, these were passed through 120 mesh screen to get dried granules of uniform size. Thus, seven SDFs namely SDF1, SDF2, SDF3, SDF4, SDF5, SDF6 and SDF7 were formulated. All the formulations were stored in desiccators for further investigations.

2.3. Determination of Drug Content

The amount of FF in the SDFs was estimated by UV-spectrophotometric method. Briefly, an accurately weighed amount of SDFs equivalent to 25 mg FF was dissolved in 100 ml of methanol. Then the solution was filtered and 5 ml of filtrate was diluted to 50 ml with methanol to obtain a theoretical concentration 25 µg/ml. The drug content was assayed by comparing with a standard solution of pure FF in methanol using UV mini-1240, Shimadzu at λ_{\max} 286 nm.

2.4. In-Vitro Dissolution Study

In-vitro dissolution study was performed for both pure FF and all SDFs according to paddle method (USP Apparatus II) using a dissolution tester (Tianjin Guoming Medicinal Equipment Co., Ltd.). Demineralised (DM) water was used as dissolution medium. The paddle speed and temperature were maintained at 50 ± 2 rpm and $37.0^\circ\text{C} \pm 0.5^\circ\text{C}$, respectively. The analyte samples (2 ml each) were withdrawn and transferred to 25 ml volumetric flasks after 5, 15, 30, 60, 90, and 120 min interval, followed by the replacement of an equal volume of fresh medium. Concentration of FF of the filtrate at each sampling point was assayed against known concentration of FF standard with UV mini-1240, Shimadzu at 286 nm (λ_{\max}). Three replicates of each measurement were carried out and mean value was calculated to obtain dissolution profile.

2.5. Solid-State Characterization of SDFs

2.5.1. Differential Scanning Calorimetry (DSC)

Thermograms of different samples (FF, Carplex-80, PEG-4000, blend of Carplex-80

Table 1. Composition and drug content of formulated SDFs.

Formulation code	Drug: Carrier	Weight ratio	Drug content (%)
SDF1	FF: Carplex-80	1:1	93.2
SDF2	FF: Carplex-80	1:2	92.7
SDF3	FF: Carplex-80	1:3	95.0
SDF4	FF: PEG-4000	1:1	92.9
SDF5	FF: PEG-4000	1:3	91.7
SDF6	FF: PEG-4000	1:5	92.3
SDF7	FF: PEG-4000: Carplex-80	1:5:6	93.6

& PEG-4000, SDF1, SDF6, and SDF7) were obtained from DSC (Exstar, SII DSC7020). Briefly, samples (3 - 5 mg) were placed in sealed standard aluminium pans and heated from 0°C to 300°C, at a scanning rate of 10°C/min, under nitrogen purge, with an empty aluminium pan as reference.

2.5.2. Powder X-Ray Diffractometer (PXRD)

An X-ray diffractometer (RAD-C, Rigaku Denki Co., Ltd.) was used for the diffraction studies. The samples were exposed to CuK α radiation (30 kV, 50 mA) and scanned from 2° - 40°, 2θ at a scanning rate of 5°/min. Samples used for PXRD analysis were FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7.

2.5.3. Fourier Transform Infrared Spectroscopy (FTIR)

FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7 were analysed by FTIR to study incompatible interactions. In addition, to find differences in the spectra, subtractions of the spectrum of Carplex-80, PEG-4000, and blend of Carplex-80 & PEG-4000, was calculated. The samples were measured by the diffuse reflection method using an FT-IR spectrometer (IR-Prestige 21, Shimadzu Co.).

2.5.4. Scanning Electron Microscopy (SEM)

A scanning electron microscope (SSX-500, Shimadzu, Japan) was used to obtain SEM micrographs of the FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7, after coating with gold/palladium in a vacuum beforehand. An accelerating voltage of 15 kV was used.

2.6. Statistical Analysis

Statistical analyses were performed using Dunnett t-test for dissolution results. A probability value of $p < 0.001$ was considered to indicate statistical significance.

3. Results

3.1. Drug Content

FF loading capacity of all SDFs was found more than 90% w/w (**Table 1**). The highest drug loading was obtained from SDF3 (FF:Carplex-80 = 1:3).

3.2. Dissolution Study

Dissolution study was performed to evaluate the dissolution profile of formulated SDFs in comparison with pure FF. The dissolution profiles of pure FF, SDF1, SDF2 and SDF3 are summarized in **Table 2**. Among these formulations, although SDF2 and SDF3 showed improvement of drug dissolution (1.5-fold higher than pure FF) but, SDF-1 showed the highest (2.0-fold) drug dissolution ($p < 0.001$) than that of pure FF at each sampling point. The dissolution of FF from all formulations namely SDF4, SDF5 and SDF6 was increased than that of pure FF. Among these, SDF6 provided the most significant ($p < 0.001$) dissolution

Table 2. Dissolution of FF and SDFs at various time intervals.

Formulation	Drug dissolved ($\mu\text{g/ml}$)					
	5 min	15 min	30 min	60 min	90 min	120 min
FF	8.8 \pm 0.4	12.6 \pm 0.6	13.3 \pm 0.1	15.0 \pm 0.1	15.0 \pm 0.1	15.0 \pm 0.3
SDF1	21.1 \pm 0.1*	23.9 \pm 0.1*	24.9 \pm 0.1*	26.8 \pm 0.3*	27.8 \pm 0.3*	29.7 \pm 0.2*
SDF2	16.3 \pm 0.1*	18.2 \pm 0.2*	19.2 \pm 0.1*	21.1 \pm 0.2*	21.0 \pm 0.1*	22.0 \pm 0.1*
SDF3	16.3 \pm 0.2*	19.2 \pm 0.2*	19.2 \pm 0.1*	21.1 \pm 0.2*	21.1 \pm 0.3*	21.9 \pm 0.3*
SDF4	10.3 \pm 0.3*	12.9 \pm 0.3*	14.1 \pm 0.6*	18.2 \pm 0.3*	20.7 \pm 0.2*	23.3 \pm 0.3*
SDF5	14.2 \pm 0.2*	14.6 \pm 0.3*	15.1 \pm 0.2*	17.3 \pm 0.3*	23.3 \pm 0.2*	24.8 \pm 0.1*
SDF6	15.9 \pm 0.1*	18.0 \pm 0.2*	18.1 \pm 0.1*	23.2 \pm 0.2*	23.8 \pm 0.1*	26.4 \pm 0.2*
SDF7	29.6 \pm 0.1* ^{††}	30.7 \pm 0.2* ^{††}	34.8 \pm 0.2* ^{††}	35.9 \pm 0.1* ^{††}	38.0 \pm 0.2* ^{††}	38.3 \pm 0.5* ^{††}

Data are expressed in mean \pm SD. *p < 0.001 vs FF, [†]p < 0.001 vs SDF1 and ^{††}p < 0.001 vs SDF6.

(1.5-fold than FF) than others. Depending on these two observations a new formulation SDF7 was made using two carriers together. From newly developed formulation (SDF7) maximum drug release (2.5-fold) than pure FF was obtained. And interestingly, it can be noticed that at 5 min (initial sampling point) the solubility was 3.4-fold higher than that of pure FF, although at 120 min it was 2.5-fold. Moreover, the dissolution improvement by SDF7 was significant (p < 0.001) at each sampling point by 1.4 and 1.7-fold in comparison with the dissolution profiles of SDF1 and SDF6, respectively (**Figure 1** and **Table 2**).

3.3. Solid-State Characterization

3.3.1. DSC Study

Figure 2 depicts the thermal characteristics of pure FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7. Pure FF generated a sharp endothermic peak at approximately 84°C corresponding to its melting point, indicating the crystalline nature. Carplex-80 showed no endothermic peak, but PEG-4000 had a sharp peak at 59.65°C. The mixture of PEG-4000 and Carplex-80 produced a peak with low intensity at 56.23°C corresponding to the peak of PEG-4000 indicating a partial physicochemical interaction between them.

Two narrow endothermic peaks corresponding to that of FF (84°C) could be observed with low intensity by SDF1 and SDF6, indicating minor changes in crystalline behaviour of FF. However, no peak for FF could be observed in the thermogram of SDF7 except for the mixed carrier, signifying that FF might be completely transformed into amorphous state.

3.3.2. PXRD Study

Figure 3 expresses the X-ray diffraction patterns of pure FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7. As a crystalline compound, FF furnished a series of sharp peaks with high intensity at 2 θ angles 12.0°, 14.46°, 16.26°, 16.72°, 19.3°, 20.9°, 22.22°, 24.74° and 26.24°. Carplex-80

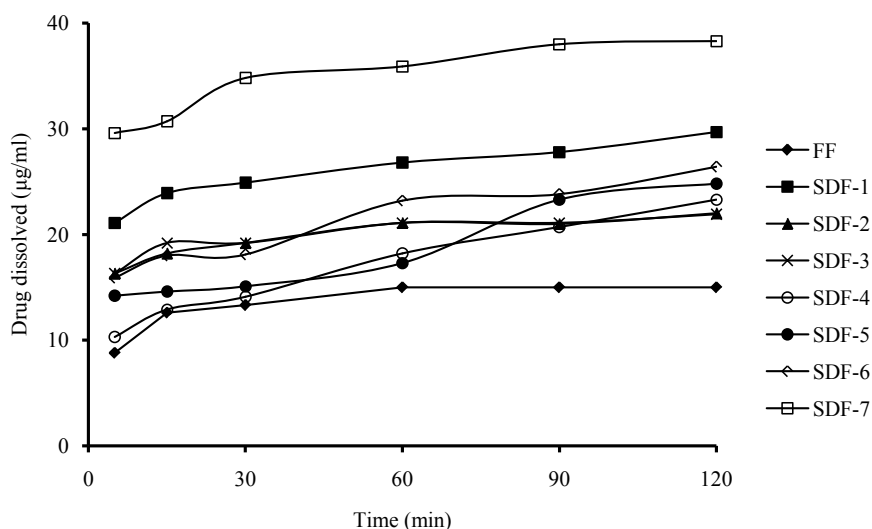


Figure 1. *In-vitro* comparative drug dissolution profiles of FF and SDFs.

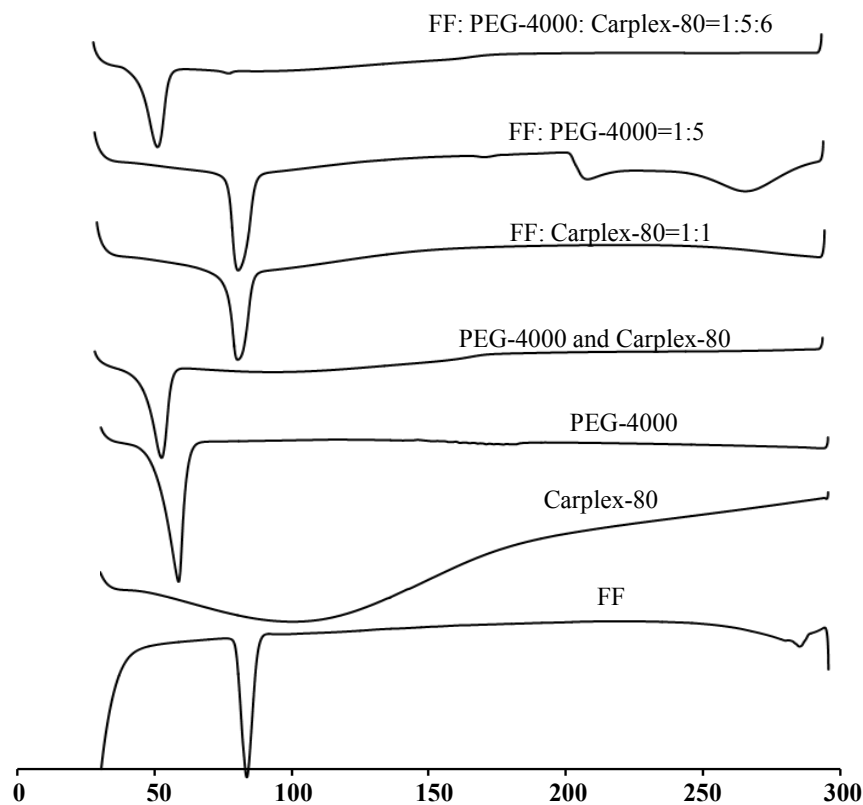


Figure 2. DSC thermograms of pure FF, Carplex-80, PEG-4000, mixture of PEG-4000 and Carplex-80, SDF-1 (FF: Carplex-80 = 1:1), SDF-6 (FF: PEG-4000 = 1:5), and SDF-7 (FF: PEG-4000: Carplex-80 = 1:5:6).

showed no peaks for crystallinity. But PEG-4000 had two intense sharp peaks at 19.44° and 23.7°. The blend of Carplex-80 and PEG-4000 demonstrated two dull peaks corresponding to that of PEG-4000 but with low intensity indicating a physical or weak chemical interaction. FF separately formulated with Carplex-80

(SDF1) and PEG-4000 (SDF6) presented some sharp peaks at 16.98°, 22.32°, 22.68°, 25.12°, 26.76° and at 12.22°, 16.84°, 22.26°, 22.32°, 26.4°, respectively, corresponding to that of pure FF. Elimination of other peaks at 12.0°, 14.46°, 16.26°, 19.3°, 20.9° and 14.46°, 16.26°, 19.3°, 20.9° by SDF1 and SDF6, respectively, indicated the partial conversion of drug crystals to amorphous state. However, no peaks corresponding to FF were found in SDF7 suggesting the inclusive transformation of drug crystal to amorphous form.

3.3.3. FTIR Study

The compatibility study of pure FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7 was performed by FT-IR study (Figure 4). FF produced major distinguishing peaks at 1730 (due to the ester group), 1651 (due to C=O stretching) and 1600 cm^{-1} (due to the lactone carbonyl group). Carplex-80 produced a broad peak at 1103.28 cm^{-1} might be due to O-H group bonded with silica. PEG-4000 showed peaks at 842.89, 1111 and 2895 cm^{-1} possibly due to =CH₂, C-O and O-H group, respectively. Peak at 1105.21 cm^{-1} corresponding to that of Carplex-80 was shown by blend of PEG-4000 and Carplex-80, which abolished the peak at 2895 cm^{-1} for O-H group of PEG-4000, indicating that Carplex-80 had a strong chemical bonding with PEG-4000. Besides,

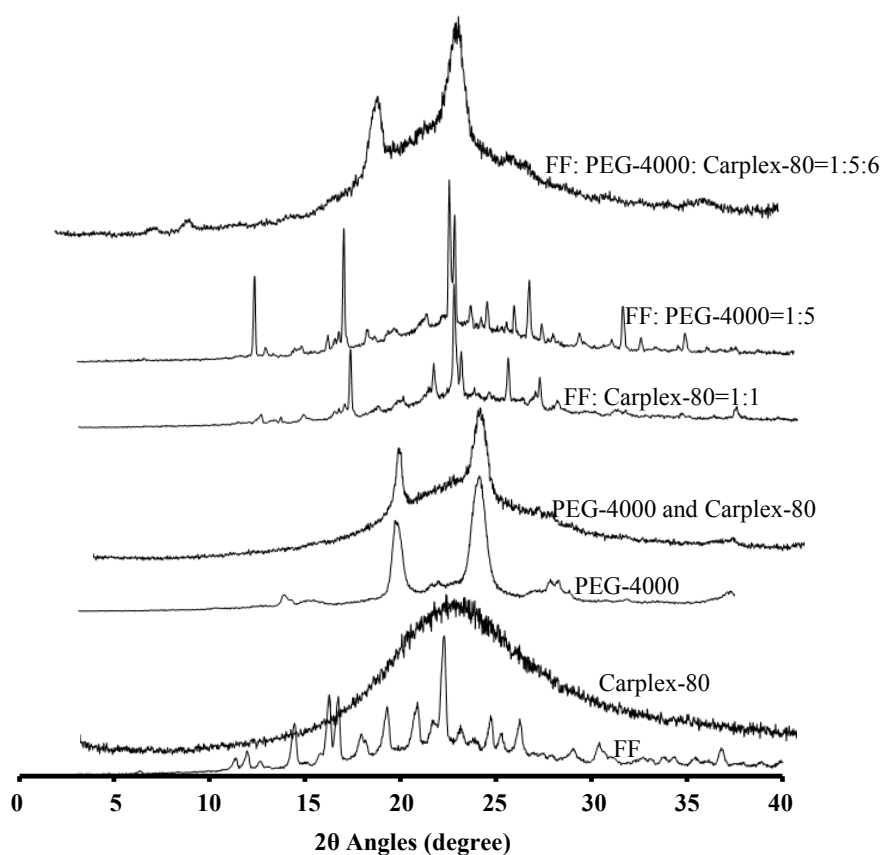


Figure 3. PXRD patterns of pure FF, Carplex-80, PEG-4000, mixture of PEG-4000 and Carplex-80, SDF-1 (FF: Carplex-80 = 1:1), SDF-6 (FF: PEG-4000 = 1:5), and SDF-7 (FF: PEG-4000: Carplex-80 = 1:5:6).

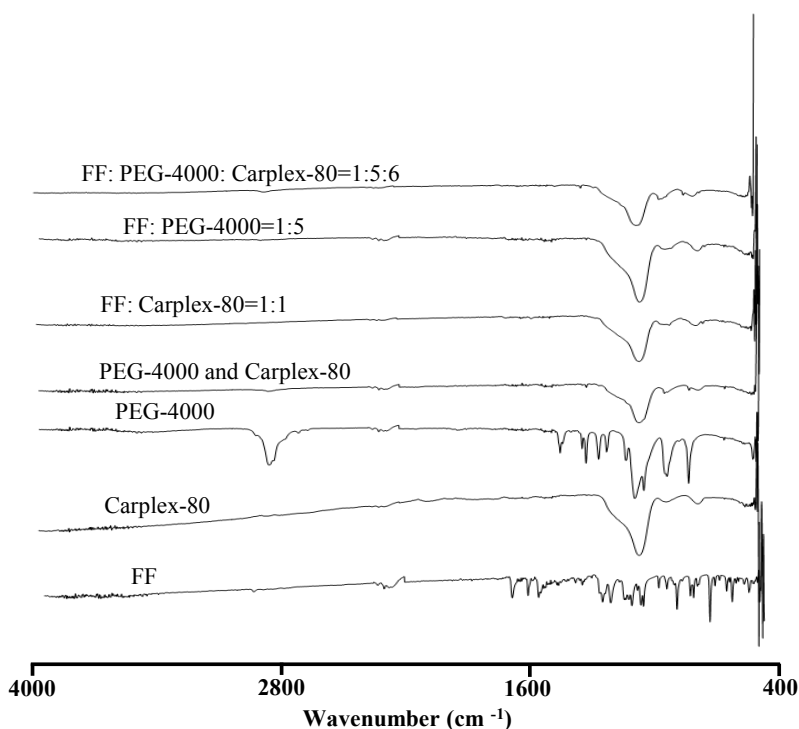


Figure 4. FTIR spectra of pure FF, Carplex-80, PEG-4000, mixture of PEG-4000 and Carplex-80, SDF-1 (FF: Carplex-80 = 1:1), SDF-6 (FF: PEG-4000 = 1:5), and SDF-7 (FF: PEG-4000: Carplex-80 = 1:5:6).

SDF1, SDF6 and SDF7 demonstrated peaks at same frequency (1101 cm^{-1}) corresponding to that of Carplex-80 with varying in shapes and intensity, suggesting that either the formation of weak bond by FF with blend of carriers or chemical adsorption of FF onto surface of the blend was occurred which facilitate level of dissolution improvement of the drug. In spectra of SDF7 no peak within the range of $2700 - 3300\text{ cm}^{-1}$ was observed suggesting the possibility of O-H bridging between C = O of FF and O-H of PEG-4000. This might be one of the key mechanisms for highly significant dissolution improvement by SDF7.

3.3.4. SEM Study

The SEM images of FF, Carplex-80, PEG-4000, blend of Carplex-80 & PEG-4000, SDF1, SDF6, and SDF7 are demonstrated in **Figure 5**. The micrograph of the drug exhibited the presence of a crystalline solid. Carplex-80 appeared with discrete and smooth surfaces. PEG-4000 exhibited as large crystal. In the blend of Carplex-80 & PEG-4000, the crystalline nature of PEG-4000 was abolished and formed new smooth surfaces probably due to the interaction between O-H group of Carplex-80 and of PEG-4000. The SEM images of SDF1 and SDF6 exhibited their surface morphology discrete and regular in shape that might be responsible for solubility improvement of FF. But, SDF7 presented a SEM image not only with discrete and regular surface morphology but also smooth surfaces that ensured the absence of drug on it; rather the drug is entrapped within the blend of carriers.

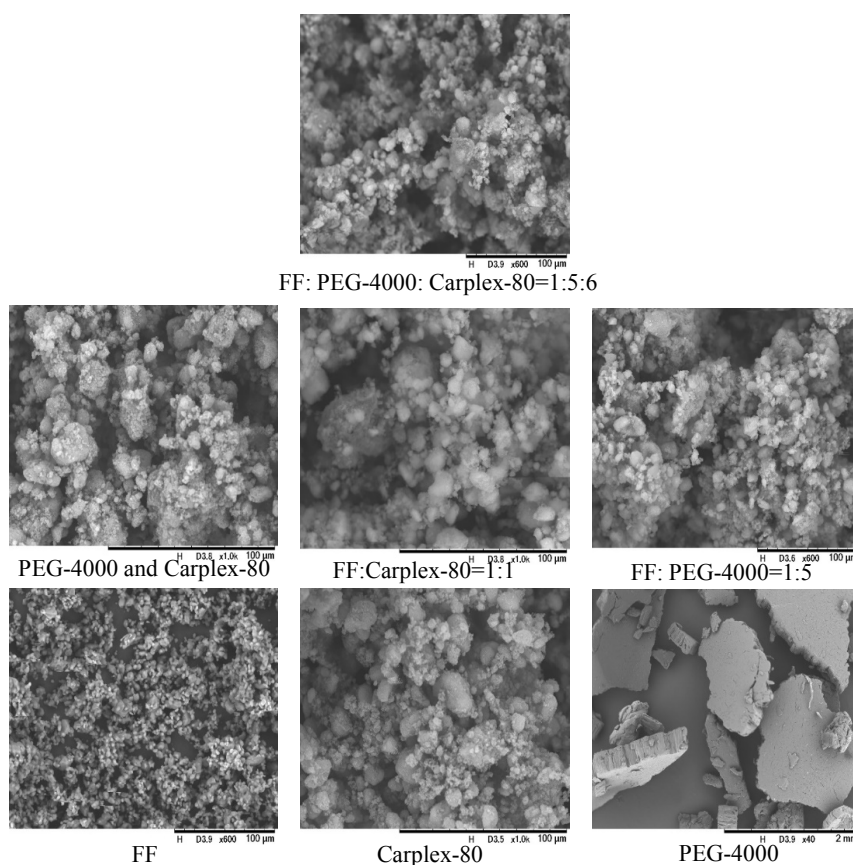


Figure 5. SEM images of pure FF, Carplex-80, PEG-4000, mixture of PEG-4000 and Carplex-80, SDF-1 (FF: Carplex-80 = 1:1), SDF-6 (FF: PEG-4000 = 1:5), and SDF-7 (FF: PEG-4000: Carplex-80 = 1:5:6).

4. Discussion

Fenofibrate is a BCS Class II drug having very poor aqueous solubility that plays a limiting role on its bioavailability [35]. To overcome this limitation solid dispersion technique was used to enhance the dissolution and oral bioavailability of hydrophobic drugs [18] [22].

The drug loading in the prepared SDFs was within the range of 91.7% - 95.0%. Our result resembled with the study of Harendra Prasad *et al.*, who reported the percent of drug content in SDFs prepared by solvent evaporation method [36] [37]. In our study, the most significant ($p < 0.001$) improvement of drug dissolution initially after 5 min and after 120 min was obtained by SDF7, which might be a noticeable improvement than that of pure FF at corresponding sampling points. The improved dissolution of FF might be due to achieving the higher level of wettability by PEG-4000 and entrapment of drug molecules by the blend of carriers converting the drug crystals to amorphous form which was authenticated together with DSC thermograms, PXRD data and surface morphology studies by SEM. Another possibility for this conversion might be the polymorphic transformation by reducing T_g (glass transition temperature) of PEG-4000 [38], which might be one of the causes of enhanced dissolution that also reported in

previous studies [21] [39] [40]. The anticipated mechanism for increased wettability of the drug might be noticed as a strong interaction of silica with PEG-4000 and formation of reversible chemical bonding by FF with Carplex-80, suggesting the improvement of wettability property of the drug, which resulted its improved dissolution [41] [42] [43].

Finally, taken together with DSC, PXRD, FTIR and SEM results it is revealed that the crystalline behaviour of FF was abolished using the combination of Carplex-80 and PEG-4000 as carriers. Thus, the enhanced dissolution profiles of SDFs correspond with transformation of drug from crystalline to amorphous state. Therefore, the formulation SDF7 can be designated as the best formulation for dissolution enhancement of FF considering its dissolution study, DSC, PXRD, FTIR and SEM.

5. Conclusion

This study reveals the significant improvement of dissolution of FF that is mainly attributed to the use of carriers blend (FF:PEG-4000:Carplex-80 = 1:5:6). Therefore, solid dispersion of fenofibrate, thus prepared, would be promising for oral drug delivery of fenofibrate with enhanced drug dissolution performance.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding this research work.

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