

ENHANCEMENT OF DISSOLUTION RATE OF FENOFIBRATE BY SPRAY DRYING TECHNIQUE: COMPARISON OF EUDRAGIT E-100, SOLUTOL[®] HS15 AND HYDROXYPROPYL CELLULOSE AS CARRIERS

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Abstract

The aim of the present study was the improvement of the dissolution rate of a poorly water-soluble drug fenofibrate (F) by using spray drying technique. Dispersions were prepared using Eudragit E-100 (E), Solutol[®] HS15 (S) and hydroxypropyl cellulose (HPC) at different ratios (1:1 and 1:5) by the spray drying technique. Aerosil[®] 200 was used as anti-sticking agent in FE and FS dispersions. The samples were characterized using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). The morphology of the dispersions was studied by SEM and the dissolution rates of all samples were determined in comparison with their physical mixtures. The flow properties of the dispersions were measured by their angle of repose, Carr's index and Hausner ratio. The stability of dispersions was studied at ambient conditions for a period of 6 months. DSC and XRPD analysis confirmed the presence of the drug in crystalline state in the dispersions. All dispersions showed a higher dissolution rate than the corresponding physical mixtures and pure fenofibrate. Except for HPC that showed higher dissolution efficiency (DE) after 2 hours in the ratio of 1:5, Solutol[®] had higher DE in 1:1 than 1:5 ratio and in Eudragit there was no significant difference between the ratio of 1:1 and 1:5. Dispersions of FEA 1:1 showed crystalline state, better flow ability and compressibility than the other two excipients and showed no remarkable changes in their dissolution profile of the drug after 6 months storage at ambient conditions.

Rezumat

Scopul acestui studiu a fost îmbunătățirea condițiilor profilului de dizolvare a fenofibratului, puțin solubil în apă, folosind o tehnică pulverizării uscate. Dispersiile au fost preparate folosind Eudragit E-100 (E), Solutol[®] HS15 (S) și hidroxipropil celuloză (HPC) în diferite combinații (1:1 respectiv 1:5). Aerosilul[®] 200 a fost folosit ca și agent antiagregant în dispersii FE și FS. Probele au fost caracterizate prin difracție folosind raze X, calorimetrie de scanare diferențială și spectroscopie infraroșu cu transformată Fourier (FTIR). Morfologia dispersiilor a fost studiată prin (SEM) și profilele de dizolvare au fost determinate prin comparație cu proprietățile lor fizice. Proprietățile de curgere ale dispersiilor au fost măsurate prin determinarea indexului Carr și a raportului Hausner. Stabilitatea a fost determinată în condiții ambientale pentru o perioadă de șase luni. Analizele DSC și XRPD au confirmat prezența în produsul medicamentos a formei cristaline din dispersii. Toate dispersiile au prezentat un profil de dizolvare superior celui așteptat din proprietățile fizice ale fenofibratului pur. Cu excepția HPC care a prezentat o eficacitate de dizolvare (DE) superioară după două ore în raport de 1:5, Solutol[®] a avut un raport DE 1:1 mai mare decât 1:5. În Eudragit[®] nu au existat diferențe semnificative între rapoartele 1:1 și 1:5. Dispersiile FEA 1:1 s-au prezentat cristaline, curgerea și compresibilitatea fiind superioare față de cei doi excipienți. Nu au apărut modificări în profilele de dizolvare ale medicamentului după păstrarea acestuia timp de 6 luni în condiții ambientale.

Keywords: Fenofibrate; Spray drying; Eudragit E-100; Dissolution rate; Solid state

Introduction

In orally administered drugs, poor solubility is a major problem posing many issues in formulation development and clinical testing [1]. This is due to the fact that poor solubility results in, poor less bioavailability and increases in the necessary dose to reach the appropriate blood level. Therefore, patient's compliance would decrease because of larger doses and higher administration frequency [2]. Considering the importance of oral drug delivery as the easiest drug administration route,

two strategies are usually applied for solubility and dissolution rate increase: formulation and chemical modification [3, 4]. Some of the formulations and physical modifications for particle engineering include: 1) particle size reduction which leads to surface area increase, 2) utilizing hydrophilic carriers, 3) incorporation of surfactant into the system as a solubilizing agent, 4) application of derivatives of the target drug or its prodrugs, 5) preparing solid dispersion which leads to crystallinity reduction [5].

The increase of drug solubility has two major consequences: proper absorption of the drug after oral administration and making the drug suitable for intravenous injection [1].

Fenofibrate, $C_{20}H_{21}ClO_4$ is a lipid blood level regulating drug, derived from fibric acid and is considered a class II drug according to Biopharmaceutics Classification System (BCS) due to its low solubility and high permeability.

It is clinically used for decreasing the serum levels of low-density lipoprotein (LDL), total cholesterol, triglycerides and apolipoprotein B, as well as increasing the blood concentration of high-density lipoprotein (HDL). It is a white or almost white crystalline powder which is practically insoluble in water [6, 7].

As a result of its poor water solubility, fenofibrate has a low bioavailability after oral administration. If given with food, its bioavailability increases. Other methods applied to improve its bioavailability include manipulating the formulation, focusing on particle size reduction which reduces the given dose from 300 mg of non-micronized fenofibrate to 200 mg of standard micronized powder; therefore, the administered dose of the non-micronized form is between 200-400 mg daily which has been reduced to 267 mg/day for the micronized drug and to 54-160 mg/day for the modified release preparation [8-11]. Different solid dispersion techniques have been reported for modifying the low solubility of fenofibrate with polyvinyl pyrrolidone (PVP) [12], Polaxamer[®] 188, PEG6000 and tocopheryl polyethylene glycol succinate (TPGS) which showed 100% dissolution of solid dispersion with TPGS after 90 min [5]. Enhancement of bioavailability of fenofibrate has been achieved by different solid dispersion techniques using electrospray deposition [13], thin film freezing [14], hot-melt extrusion [15] and a nanomatrix system consisted of colloidal silica and pH-sensitive polymethylacrylate [16]. However, in all of them the crystalline state of the drug has changed to an amorphous form which has limited its stability during the time.

Spray drying technique is another reported method for enhancing the dissolution rate of fenofibrate. Lactose, PVP and sodium lauryl sulphate (SLS) are excipients used in this method [17]. After 10 minutes the spray dried powder containing fenofibrate, SLS and lactose reached a super saturation state, however, it returned to saturation state within 3 hours due to recrystallization precipitation which produced an amorphous state.

Poloxamer[®] and TPGS are other reported surface active agents applied in the spray drying method [18, 19] which have been used also in the dissolution enhancement of fenofibrate too [5].

TPGS showed synergistic effects when accompanied with Poloxamer[®] 188 to enhance solubility. Dissolution of fenofibrate from solid dispersions containing Poloxamer[®] 188 and TPGS was above 90% after 100 minutes in water, 0.1 N HCl and 0.1 M SLS [5].

Despite the long history of using solid dispersions in pharmaceutical products, the multiplicity of polymeric carriers that have been used is still limited. In the present study it was trying to modify the amorphous state properties of the spray dried fenofibrate reported before by Vogt et al. [17] who used lactose, polyvinylpyrrolidone or sodium lauryl sulphate by co-grinding and spray drying technique for enhancing the dissolution rate of fenofibrate, but reported the production of amorphous form of this drug which may reduce its stability. Therefore, in the present study we took advantage of using the spray drying technique by solid dispersions of fenofibrate to modify its dissolution rate in comparison to the physical mixtures and untreated drug using hydroxypropyl cellulose (HPC), Eudragit[®] E-100, Aerosil[®] 200 and Solutol[®] HS15. To our knowledge this technique has not been reported before with these excipients for particle engineering of fenofibrate.

HPC is partially substituted poly hydroxyl propyl ether of cellulose. HPC is used as a food additive, thickener, a low level binder and as an emulsion stabiliser. In pharmaceuticals it is used as a disintegrant and a binder in tablets. It is freely soluble in water below 38°C and forms a smooth, clear, colloidal solution but precipitate as a swollen flock in hot water, between 40°C to 45°C [20]. The increasing effect of HPC on the solubility of poorly soluble drugs is investigated on nifedipine which increased the apparent solubility of this drug in water to 367 µg/mL [21].

Eudragit[®] E100, based on dimethylaminoethyl methacrylate is a cationic copolymer present in the form of lightly yellow granules which are soluble in gastric fluid and weakly acidic solutions up to pH 5 [20]. Its average molecular mass is 47,000 g/mol, the glass transition temperature (T_g) of 45°C ± 5°C and the alkalin value of 180 mg KOH/ g polymer [20]. Solid dispersions of itraconazole were prepared with pH-dependent hydrophilic excipients, AEA[®] and Eudragit[®] E 100, and resulted in greater increases in drug solubility over those prepared with pH-independent hydrophilic excipients, PEG 20,000, PVP, Poloxamer[®] 188 and HPMC [22].

Colloidal silicon dioxide, Aerosil[®], is widely used in pharmaceutical, cosmetic and food products. Due to its small particle size and large surface area, it improves the flow characteristics in the production processes. Modification of the manufacturing process results in producing different grades of

colloidal silicon dioxide [20]. Aerosil® is one of the commonly used hydrophilic carriers for solid dispersions. Aerosil® 200 is non-porous, hydrophilic adsorbent with a high specific surface area (200 m²/g). Solid dispersions containing Aerosil® 200 have shown good drug dissolution properties and physical stability under dry conditions [23].

Solutol® HS15 or polyoxyl-15-Hydroxystearate is another excipient used in spray dried preparations in order to increase the solubility and dissolution rate of drugs. It is a non-ionic solubilizer and emulsifying agent obtained by reacting 15 moles of ethylene oxide with 1 mole of 12-hydroxy stearic acid. It is soluble in water, ethanol and 2-propanol to form clear solutions. Its solubility in water decreases with increasing temperature and it is insoluble in liquid paraffin. This product has a high chemical stability and toxicology tests have shown that this product is extremely well tolerated. It is a yellowish white paste at room temperature which transforms into a liquid at approximately 30°C. Solutol HS15 is a non-ionic solubilizer for manufacturing aqueous parenteral preparations with vitamins and other lipophilic drugs. It is used in solubility enhancement of biochanin A, a poorly soluble bioflavonoid, *via* the preparation of solid dispersion using Solutol® HS15 and HPMC 2910. The resulted solid dispersion appeared to be promising to improve the dissolution of biochanin A [24].

Materials and Methods

Materials

Fenofibrate was provided by TRICOR SRL Pharmaceutical Company (Remanzacco, Italy), acetone, Tween® 20, HCl, Aerosil® 200 and Isopropyl alcohol were from Merck Chemical Company (Germany). Solutol® HS15 was kindly provided by BASF Company (Germany), Eudragit® E 100 was from Rhöm Pharma (Germany), and HPC from Sigma-Aldrich (USA).

Preparation of spray dried dispersions

Fenofibrate and each of the excipients of Eudragit® E100 or Solutol® HS15 or HPC were dissolved in acetone. Two different ratios of fenofibrate to polymer (1:1 and 1:5) were used in preparation of spray dried dispersions. These ratios were selected in order to have the least amount of excipients. Spray drying was performed in a Büchi Mini Spray Dryer B290 (Büchi Labortechnik AG, Flawil, Switzerland) under the condition of: inlet temperature of 80°C, outlet temperature 50°C, the pump flow rate was 5% (2.5 mL/min), and aspirator was set at 85%. As fenofibrate was not soluble in aqueous solvents, acetone was selected as the common solvent for both the drug and excipients.

In the case of samples containing Eudragit® or Solutol®, it was necessary to use 2% w/w of Aerosil® otherwise the powders would stick into the cyclone and could not be gathered in the collector.

After preparing enough amounts of samples, the spray dried dispersions were stored in a desiccator until used for further studies. Several physico-chemical tests were performed on them including determining of drug loading percent, dissolution rate, flow properties, DSC, SEM, and XRD.

Preparation of physical mixtures

The physical mixtures of sieved fractions of fenofibrate and excipients were prepared by mixing all components of each spray dried formulation using a mortar and pestle.

Drug loading percent

In order to determine the loaded amount of fenofibrate in the dispersions, it was calculated the amount of each powder that should be dissolved in 10 mL of isopropyl alcohol (the suitable solvent for the API) to gain a 300 µg/mL of fenofibrate solution. Afterwards, the dispersions were dissolved in 10 mL of isopropyl alcohol and the absorption of the samples was measured at 285 nm using a spectrophotometer (UV-mini 1240, Shimadzu, Kyoto, Japan). The real concentration of fenofibrate in each sample was calculated using the standard curve of fenofibrate in isopropyl alcohol. The solution containing all components but the drug was used as the blank. The loading percent of fenofibrate in dispersions was calculated using the following equation:

$$\text{Drug loading (\%)} = \frac{\text{entrapped drug in dispersions}}{\text{total weight of the dispersions}} \times 100$$

Particle size analysis

The mean particle size of dispersions was measured by photon correlation spectroscopy (PCS) at a fixed angle of 90°C (Zetasizer, ZEN 3600, Malvern Instrument, UK). Dispersions were suitably diluted to measure mean particle size.

Dissolution studies

To meet the sink conditions, 4 mg of pure drug, physical mixtures and spray dried dispersions which was less than or equivalent to 15% of the saturated solubility of fenofibrate in the samples were subjected to dissolution test using USP apparatus II (paddle method). The paddle speed and bath temperature were set at 50 rpm and 37°C, respectively. The dissolution medium was 450 mL of an aqueous medium of deionized water, containing 1% of Tween® 20. The pH and the temperature were adjusted to 1.35 and 37°C. 3 mL samples were taken after 5, 10, 15, 30, 45, 60, 90, and 120 minutes. In order to keep the volume constant, 3 mL of the medium was replaced after each sampling. Samples were centrifuged and absorption of the supernatants was measured at 289

nm spectrophotometrically. The percentage of drug release was calculated as mean $\pm$ SD, using the linear equation of the standard curve of fenofibrate in the aqueous medium, and plotted against time to achieve the dissolution profile. Besides, dissolution efficiency (DE) in 120 min was calculated using the following equation:

$$DE_{120} \% = \frac{\int_0^t y \cdot dt}{y_{100,t}} \times 100$$

Hausner's ratio and compressibility index

Each sample was poured into a graduated cylinder and the bulk volume was measured. Then, the cylinder was tapped by its own weight from the height of 14 ± 3 mm for 500 times. The final volume was measured and divided by the initial volume to calculate the Hausner ratio [25].

Regarding the bulk (V_0) and tapped volume (V_n), the compressibility index was calculated using the following equation [25]:

$$\text{Compressibility } (\%) = [(V_0 - V_n)/V_0] \times 100$$

Angle of Repose

0.2 g of each sample was placed in a funnel which was fixed at the height of 2-4 cm from the top of the cone. The height (h) and diameter (D) of the base was measured when the whole sample poured out of the funnel. The angle of repose was calculated using the following equation:

$$\tan \alpha = \frac{h}{0.5 D}$$

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectra of selected samples were obtained using a Perkin Elmer spectrum BX FTIR (PerkinElmer, Waltham, MA). Samples were prepared by potassium bromide (KBr) and scanned against a blank KBr disk at wave numbers ranging from 4000 to 450 cm^{-1} with resolution of 1.0 cm^{-1} .

X-ray powder diffraction studies (XRPD)

This test was performed to evaluate the crystallinity of the solid samples obtained from spray dryer and physical mixtures, as well as pure fenofibrate, excipients, and Aerosil®. X-Ray powder diffraction patterns were obtained using a Bruker, D8 Advance, Germany diffractometer, with Cu K α radiation ($\lambda = 1.54 \text{ \AA}$). The diffraction pattern was measured with a voltage of 30 kV and a current of 40 mA in the range of 5° - 90° (2θ) in a step scan mode.

Differential scanning calorimetry (DSC)

Calorimetric studies were performed using a DSC 822e Mettler-Toledo (Mettler Toledo, Switzerland) equipped with a refrigerated cooling system. Samples of pure fenofibrate, each of the studied excipients, Aerosil®, dispersions and physical mixtures (3–5 mg) were placed in aluminum pans sealed with a lid. The DSC was calibrated using indium standard. The crimped aluminum pans were

heated from 20 to 250°C at a scanning rate of 10°C/min under nitrogen atmosphere. Onset temperatures and melting points of the samples were automatically calculated using the software provided (STARe Ver. 10.00 Mettler Toledo, Switzerland).

Scanning electron microscopy (SEM)

Morphology of the dispersions was characterized by scanning electron microscopy (SEM). The dispersions were mounted on aluminum stubs, sputter-coated with a thin layer of Au/Pd and examined using an SEM (Hitachi F41100, Japan).

Long term stability

The dispersions of fenofibrate/Eudragit®/Aerosil® 1:1:1 were stored at ambient conditions for a period of 6 months and their stability in dissolution profile were investigated as described previously. Comparison of dissolution profiles were performed by calculating, the difference factor (f_1) and similarity factor (f_2) by the following equations:

$$f_1 = \frac{\sum_{i=1}^n |R_i - T_i|}{\sum R_i} \times 100$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \right\} \times 100$$

Where n is the number of time points, R_t is the percentage of the reference sample that was dissolved at the time point t , and T_t is the percentage of the test samples that was dissolved at the time point t . If the f_1 value was between 0-15 and the f_2 value was between 50 and 100, the dissolution profile of two samples was considered equivalent [26].

Results and Discussion

Drug loading percent

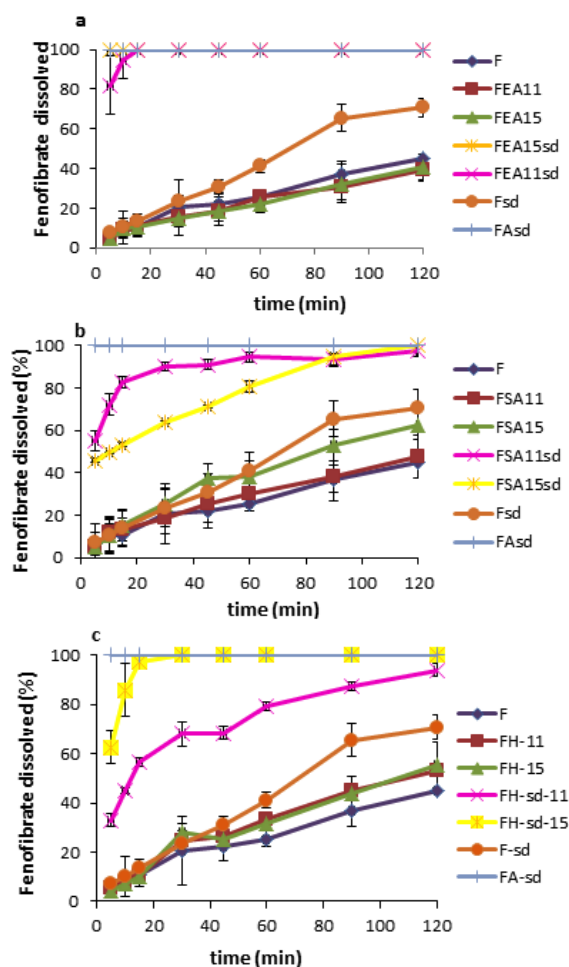
Table I summarizes the drug loading percent and loading efficiency in the spray dried dispersions. As this table indicates the loading efficiency of dispersions prepared with Solutol® and Eudragit® was not significantly different in 1:5 ratio while, the 1:1 ratio of these two excipients were significantly different in their loading efficiency ($p < 0.05$). However, in each type of the studied excipients changing of the excipient ratio did not affect the drug loading efficiency ($p > 0.05$). Among the studied excipients HPC had the highest drug loading percent and efficiency which might be due to the viscous nature of this polymer that when dissolved in the solvent could entrap more drugs by its sticky properties while other studied excipients were not so viscous at similar concentrations compared to HPC.

Table I

Particle size, drug loading percent and loading efficiency in different spray dried dispersions

Microsphere type	Particle size ($\mu\text{m} \pm \text{SD}$)	Drug loading efficiency ($\% \pm \text{SD}$)	Drug loading ($\% \pm \text{SD}$)
F:S:A (1:5:1)	0.34 ± 0.05	77.57 ± 7.23	9.70 ± 0.90
F:S:A (1:1:1)	0.84 ± 0.05	75.60 ± 1.72	25.20 ± 0.57
F:E:A (1:5:1)	3.67 ± 0.91	77.41 ± 10.12	11.06 ± 1.44
F:E:A (1:1:1)	1.70 ± 0.42	85.55 ± 2.34	28.52 ± 0.78
F:H (1:5)	8.70 ± 0.96	95.76 ± 2.43	15.68 ± 1.14
F:H (1:1)	5.11 ± 2.00	94.09 ± 6.86	47.88 ± 1.21
F	2.20 ± 0.05		
Fsd	1.52 ± 0.23		

F = fenofibrate, S = Solutol® HS15, E = Eudragit® E, A = Aerosil® and H = HPC, "sd" means spray dried dispersions and those formulation codes without "sd" show the physical mixtures, Fsd = fenofibrate spray dried.

**Figure 1.**

Dissolution profiles of spray dried dispersions and physical mixtures of Fenofibrate with **a)** Eudragit® E-100, **b)** Solutol® HS15 and **c)** HPC (n = 3). (F = Fenofibrate, E = Eudragit® E-100, A = Aerosil®, S = Solutol®, H = HPC, sd = spray dried, 11 = excipient/drug ratio of 1:1 and 15 = excipient/drug ratio of 1:5)

Particle sizing measurements

Table I shows the comparison of particle size of different dispersions of fenofibrate compared to the pure fenofibrate powder. As this table shows the particle size of dispersions prepared by Solutol®

HS15 was significantly lower than Eudragit® and HPC used in the preparation of the dispersions ($p < 0.05$). As Solutol® HS15 has surfactant properties the lower particle size of the dispersions prepared from this excipient is probably due to its surface activity effect which reduces the particle size. The dispersions of the other two excipients in both ratios caused particle size growth compared to the pure drug (which was $2.2 \mu\text{m}$) ($p < 0.05$). Increasing in the ratio of the drug/excipients from 1:1 to 1:5 increased the particle size of the dispersions significantly ($p < 0.05$).

Dissolution studies

The dissolution profiles of different spray dried dispersions and their physical mixtures are compared with the untreated pure fenofibrate in Figure 1.

As this figure indicates the untreated pure powder of fenofibrate was dissolved only about 40% after 2 hours and there was not any significant difference between the dissolution profiles of physical mixtures of the drug with all excipients and the pure untreated drug. When the pure drug was spray dried without any excipient the dissolved drug was enhanced compared to the pure untreated fenofibrate (compare F with Fsd) which is possibly due to size reduction of the spray dried form compared to untreated drug (Table I). Eudragit® E-100 (Figure 1a) and Solutol® HS15 (Figure 1b) spray dried dispersions in all studied time points enhanced the dissolution rate of the drug significantly ($p < 0.05$) and the ratio of 1:1 of excipient /drug showed a higher dissolution rate compared to 1:5 ratio (Figure 1a, b). However, in HPC spray dried dispersions there was not any difference between 1:1 and 1:5 ratios (Figure 1c) and both these ratios enhanced the dissolution rate of the pure drug significantly ($p < 0.05$). An interesting finding was that spray dried drug with Aerosil® alone and without any excipient but in the same concentration used in the dispersions of Eudragit® or Solutol® could enhance the drug dissolution rate as much as the dispersions of Eudragit® 1:1, Solutol® 1:1 or 1:5 and HPC 1:5

after 2 hours. This is probably due to hydrophilic properties of Aerosil® 200 which is a hydrophilic type of colloidal silicon dioxide and may cause better wetting of the drug. However, as the obtained dispersions are supposed to be used in tablet dosage forms, the spray dried dispersions produced with Aerosil® alone may cause gellation while when it is covered with other excipients this effect fades. Sadeghi et al. [27] also reported that in the presence of Aerosil® 200 any increase in Aerosil® particle size increased the release rate of propranolol hydrochloride from Eudragit® RS or RL type of matrices. They attributed this effect to the high porosity induced by Aerosil® in the matrices which could control the drug release rate.

On the contrary to Aerosil® 200 which is a hydrophilic type of colloidal silicon dioxide, the hydrophobic type can sustain drug release from different matrices. Walters [28] showed the effect of hydrophobic Aerosil® R974 on propantheline bromide release from Miglyol 829 gels was markedly different from the hydrophilic gel system. Drug release from the Miglyol oil without this type of silicon dioxide was completed within 30 min, whereas it was reduced to 30% and 5% for 1w/w% and 4 w/w% of Aerosil® R974/Miglyol gels after 120 min.

Enhancement of dissolution rate by HPC is not reported before otherwise when it was used for sustaining the drug release of some drugs a reverse effect was seen. For example Billon et al. [29] used some derivatives of cellulose including: microcrystalline cellulose (MCC), sodium carboxymethylcellulose (NaCMC), hydroxypropyl-methylcellulose (HPMC), hydroxyethylcellulose (HEC), HPC, and ethyl cellulose (EC) for the production of time-controlled acetaminophen delivery systems using spray-drying technique. They showed that formulations consisting of a drug/excipient ratio of 1:1 exhibited the slowest drug release, and the spheroids coated with NaCMC and HEC showed the longest $T_{50\%}$ values. A sustained drug release in pH 6.8 medium was reached, showing the following trend: HEC > NaCMC > MCC > EC > HPMC. In other words, HPC in their study not only could not retard the drug release but showed the fastest release profile. In the study of Kundawala et al. [30] also dispersions of isoniazid prepared using chitosan, HPMC and HPC as carrier excipients by spray drying technique all the formulations showed sustained drug release over a period of more than 8 hours except HPC-dispersions which were not able to sustain the drug release.

The dissolution efficiency of each sample is presented in Table II.

This table also confirms the results described of Figure 1. As it is obvious from the DE results there

is no significant difference between the ratio of 1:1 and 1:5 of the drug/polymer ($p > 0.05$) in Eudragit® dispersions. Solutol® had greater DE in 1:1 ratio than 1:5. However, in HPC the 1:5 ratio showed higher DE ($p < 0.05$). The DE of all spray dried samples was significantly bigger than the pure drug and the physical mixtures ($p < 0.05$). The highest DE was seen in FEA11 spray dried dispersions and those prepared just from the Aerosil® (FAsd) ($p < 0.05$). However, their differences were not significant ($p > 0.05$).

Table II

The Dissolution efficiency after 2 hours ($DE_{120\%}$) results of all spray dried dispersions and physical mixtures of Fenofibrate with Eudragit® E-100, Solutol® HS15, HPC, and Aerosil® in different ratios of excipient /drug ratio of 1:1 and 1:5.

Formulation code	$DE_{120\%} \pm SD$
F	26.6 ± 1.9
Fsd	41.6 ± 2.3
FA	20.2 ± 1.4
FAsd	97.9 ± 0.0
FEA11	23.1 ± 4.4
FEA11sd	96.9 ± 1.0
FEA15	23.1 ± 6.0
FEA15sd	97.9 ± 0.0
FSA11	28.4 ± 8.8
FSA11sd	88.2 ± 0.5
FSA15	37.9 ± 1.3
FSA15sd	76.7 ± 0.6
FH11	31.9 ± 1.2
FH11sd	73.4 ± 1.9
FH15	31.8 ± 5.0
FH15sd	95.5 ± 0.9

"sd" means spray dried dispersions and those formulation codes without "sd" show the physical mixtures

Hausner's ratio and compressibility index

Considering the dissolution rate results obtained by spray dried dispersions three formulations with the best results were chosen for further studies on their flow properties. The results of the compressibility index of these dispersions are shown in Figure 2.

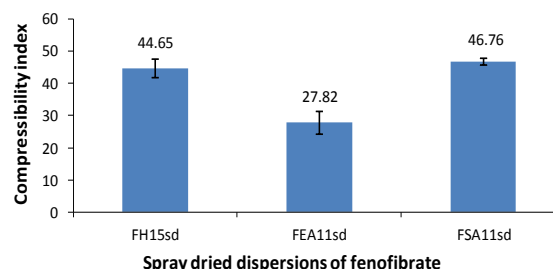


Figure 2.

Compressibility index of three spray dried dispersions of fenofibrate

As this Figure indicates the compressibility index (or Carr's index) of Eudragit® dispersions was significantly lower than the other two excipients (p

< 0.05). However, it was not different in Solutol[®] and HPC ($p > 0.05$). The Carr's index is an indication of the flow-ability of a powder. The lower angle of repose and compressibility index, the better the flow-ability of the powders. A Carr's index greater than 30 is considered to be an indication of poor flow-ability, and below 15, of good flow-ability [31].

Another parameter indicating the flow-ability of a powder is Hausner ratio. A Hausner ratio greater than 1.35 is considered to be an indication of poor flow-ability [31]. The Hausner ratio is related to the Carr's index. Figure 3 shows the Hausner ratio of the spray dried dispersions. The results confirm the Carr's indices of the dispersions. Eudragit[®] dispersions showed almost passable results while Solutol[®] and HPC had very poor flow-ability.

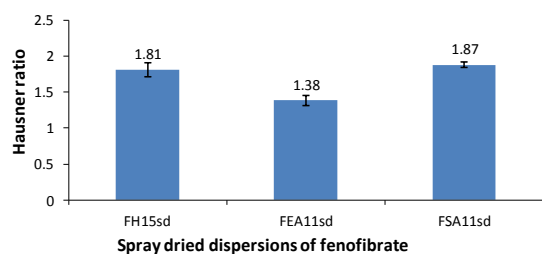


Figure 3.

Hausner ratio results of three spray dried dispersions of fenofibrate

Angle of repose of dispersions

Angle of repose of the powders determines the flow-ability of the sample. The angle of repose of powders up to 40 is fair and those greater than 66 is very poor [31]. The results of Figure 4 show that Eudragit[®] dispersions had fair flow characteristics in contrast to HPC and Solutol[®] which did not have free flow.

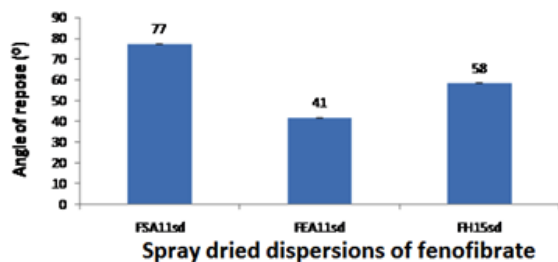


Figure 4.

Angle of repose results of three spray dried dispersions of fenofibrate

Fourier transforms infrared spectroscopy

The interaction between API (active pharmaceutical ingredient) and carrier in a spray dried system usually results in noticeable changes in the FTIR spectra, so this study was performed to investigate if any interaction has been occurred in spray dried

dispersions at the molecular level. The FTIR spectra of pure fenofibrate, Eudragit[®] E, Solutol[®] HS15, HPC, Aerosil[®] their physical mixtures and spray dried dispersions are shown in Figure 5. The FTIR spectra of fenofibrate showed characteristic peaks at 1728 cm^{-1} that was attributed to ketone or C=O group. The aliphatic C-H stretching vibration of was obvious in 2983 cm^{-1} , the C-O stretching vibration of ether group was seen in 1385 cm^{-1} and aromatic C=C group stretching vibration was obvious at 1651 and 1599 cm^{-1} (Figure 5).

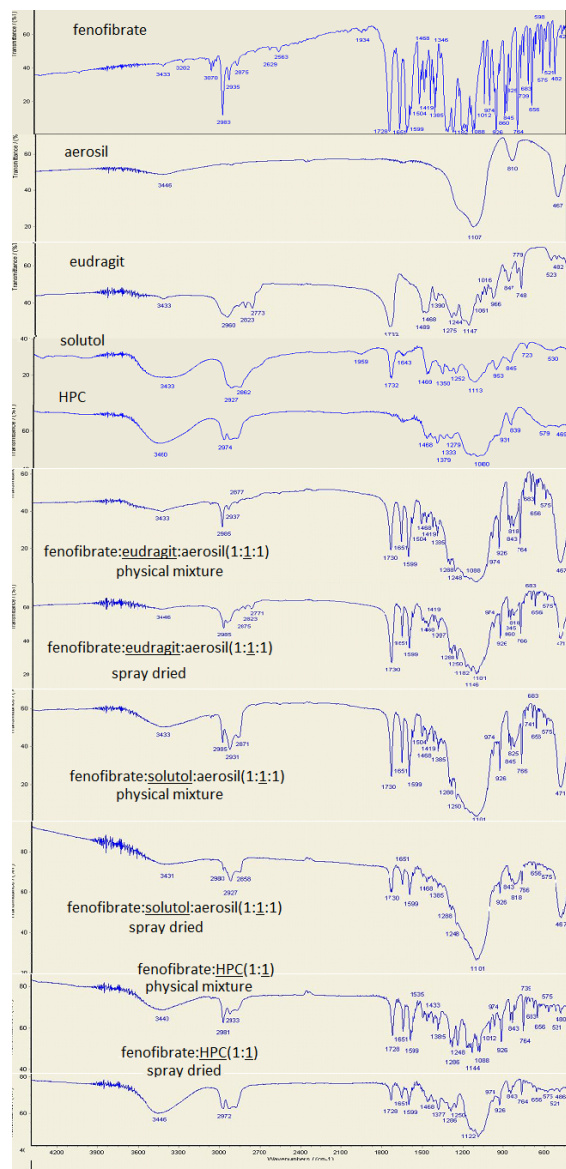


Figure 5.

FTIR spectra of spray dried dispersions and physical mixtures of Fenofibrate with Eudragit[®] E-100, Solutol[®] HS15 and HPC

For Aerosil[®] or colloidal silicone dioxide no special characteristic peak was seen (Figure 5) and for Eudragit[®] E-100 the C-N stretching vibration of the amines of type three were seen at 1275 or 1147 cm^{-1} .

Another characteristic peak attributed to the esteric bond of C=O group of Eudragit® E-100 was seen at 1736 cm^{-1} and the aliphatic C-H stretching vibration at 2960 cm^{-1} .

Solutol® HS15 which is the polyoxyl 15 hydroxyl stearate, showed the characteristic stretching vibrations of C=O at 1732 cm^{-1} and the OH at 3425 cm^{-1} . The most important characteristic peak for HPC related to the ether bond of C-O which was seen as a broad band at 1000 cm^{-1} .

All characteristic stretching bands of each ingredient in the spray dried dispersions or physical mixtures were seen indicating no special interaction between them.

X-ray powder diffraction

Further characterization of solid states of samples was carried out by XRPD studies. The patterns obtained for pure fenofibrate, Eudragit® E, Solutol® HS15, HPC, Aerosil® their physical mixtures and spray dried dispersions are displayed in Figure 6.

The untreated fenofibrate exhibited sharp diffraction peaks at 2θ values of 14° , 17° , 19° , 20° , 21° , 25° , 26° and 30° indicating crystalline nature of the drug corresponding to the reported crystal lattice parameters for fenofibrate [32]. None of the excipients or Aerosil® did not show any peak and exhibited amorphous state. The physical mixtures of fenofibrate and excipients or Aerosil® showed peak positions similar to fenofibrate, but at lower intensities, indicating that fenofibrate has retained its crystallinity. Similarly, distinct peaks of the drug were observed in the diffraction patterns of the spray dried dispersions but with very lower intensities compared to the pure fenofibrate especially for Eudragit® dispersions. The presence of fenofibrate peaks with lower intensity in the spray dried dispersions indicates keeping the crystalline state of the drug but as it is mixed with equal proportions of the excipients the intensity of distinctive peaks were reduced. These results were in good agreement with DSC studies (Figure 7). Voget et al. [17] reported a spray drying technique for drying the nanosuspension of fenofibrate. They prepared a nanoparticulate dispersion of fenofibrate by a media milling process operating in the circulation mode. A suspension containing fenofibrate, lactose and SLS in water was pre-treated in an ultra-homogenizer before processing in the mill for 90 min. A spray dryer was connected directly to the mill, enabling the continuous transfer of the suspension from the milling chamber outlet to the spray nozzle. The mill was kept operating during the spray-drying process in order to maintain the homogeneity of the suspension. In contrary to our study their obtained particles had an amorphous structure.

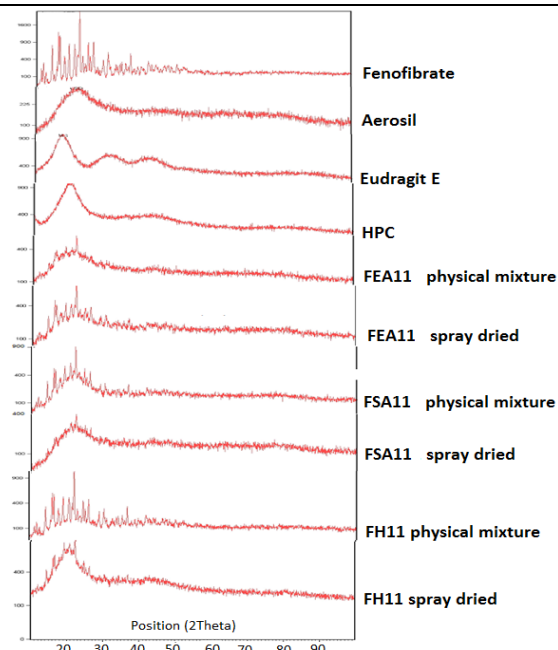


Figure 6.

XRD pattern of spray dried dispersions and physical mixtures of Fenofibrate with Eudragit® E-100, Solutol® HS15 and HPC (11=polymer/drug ratio of 1:1)

Therefore the method of preparation of the nanoparticles of fenofibrate by Voget et al [17] was quite different from ours. In our method we dissolved the drug and the polymers in the organic solvent (acetone) in the presence of Aerosil® without any aqueous dispersion of the drug. Moreover, the gas used in our spray dryer was nitrogen which is not the same as the Voget et al [17] study. These may be the reasons of the different crystalline forms of fenofibrate obtained in these two experiments. Although in many cases the spray drying technique results in production of amorphous state of drugs but there are some cases also reporting the crystalline forms obtained from this technique. An example is the spray drying of sulfathiazole in two different configurations of the spray-drying process which resulted in a highly crystalline or an amorphous form [33]. Powders of metastable sulfathiazole polymorph were produced by using the closed cycle mode configuration of the lab-scale spray drier using nitrogen as the drying gas, whilst amorphous powders of sulfathiazole were obtained from ethanolic solutions in the opened cycle mode configuration. These results agreed with the findings of Islam and Langrish [34] who demonstrated how the selection of different spray drier configurations and drying gas could affect the properties of spray dried lactose. Different equipment configurations and the use of different solvents will lead to different pressure, temperature and humidity environments inside the

spray dryer, causing variations in the heat-mass transfer which could affect the properties of the spray-dried materials.

In theory, in the closed-loop system, the solvent contained in the gas stream is cooled and consequently condensed. The regenerated flow is then returned to the spray dryer. However, it is possible that a certain amount of the organic vapour contaminates the regenerated carrier gas. In contrast, in the open-loop system, the solvent vapour is diluted by the environmental air (which contains water vapours) and exhausted into the atmosphere, thus affecting the crystallization process to a lesser extent. The crystallinity in the spray-dried drug can also be related to the use of an over-saturated solution. It is possible that the initial evaporation of solvent results in the drug precipitating from the supersaturated solution, resulting in a suspension and, subsequently, a crystalline dried solid, in contrast to solvent evaporation from an under-saturated solution which results in amorphous solids. In the present study we also used a closed cyclone mode due to the usage of acetone and perhaps the obtained crystalline state of the drug may be due to the aforementioned reason.

Differential scanning calorimetry (DSC)

The DSC analysis was performed in order to investigate the thermal behavior of the components in the spray dried and physical mixtures. Figure 7 shows the DSC thermograms of untreated crystalline fenofibrate, each studied excipients, Aerosil[®], samples of physical mixture and spray dried dispersions at 1:1 drug: carrier ratio.

This figure shows the melting endothermic peak for fenofibrate at 83.1 °C, for Aerosil[®] at 76.8°C, and for Eudragit[®] E-100 two endothermic peaks at 65.7°C (possibly its T_g) and 237°C (possibly due to degradation of the polymer) were seen. For the physical mixture of FEA11 just the melting point of the drug was seen at 82°C and for its spray dried dispersions (FEA11sd) the same endothermic and exothermic peaks aforementioned are obvious but with a partial shift and are seen in 72.3°C (probably the melting point of the drug) and at 197°C (the crystallization exothermic temperature of the excipient). The presence of the endothermic melting point denotes the crystalline form of the drug in the dispersions and the shift of peaks may be due to the hydrogen bonding of the hydroxyl groups of the polymer with the ketone, carboxyl and ether functional groups of the drug.

Solutol[®] showed the T_g of 93.1°C which is reported in literature around 70°C [35], and two exothermic

peaks at 190° and 229°C probably related to the crystallization and degradation of the excipient. For the physical mixture of fenofibrate with this excipient i.e., FSA11, the small endothermic peak at 81.2°C relates to the melting point of the drug and the exothermic one at 188°C is the same seen at the pure Solutol[®] mentioned earlier. The presence of all characteristic peaks of the pure drug and excipient indicates the crystalline form of the drug in the physical mixture. In the spray dried dispersions of FSA11 a very small exothermic peak at 207°C was observed with no melting temperature of the drug which indicates the amorphous state of the drug. This is almost in accordance with the XRPD results for these dispersions (Figure 6). The shift of exothermic peak at 197°C (the degradation exothermic temperature of the polymer) may be due to the hydrogen bonding of the polyoxyethylene groups of the excipient with the ketone, carboxyl and ether functional groups of the drug.

HPC pure polymer showed no T_g but an exothermic peak at 214.8°C. Kararli et al. [36] also reported no T_g peak for HPC. The physical mixture of fenofibrate and HPC (HF11) showed a distinct endothermic peak at 83.5°C which is assigned to the melting point of the drug and its crystalline form. A small endothermic peak at 243°C with very low enthalpy of fusion may indicate the hot melting of the crystalline polymer which was also reported by Kararli et al. [36] for HPC at about 195°C. In the spray dried dispersions of FH11 this peak is still obvious at 81.2°C and the two other endothermic peaks are present at 221.5 and 237.4°C. The new endothermic peaks may indicate the melting points (T_m) for the blend samples. The variations in shape and area were attributed to the different degrees of crystallinity found in the sample [37, 38]. As well known by the previous reported works, a change in the crystalline structure may result from polymer-polymer interactions in the amorphous phase, therefore, the disorder in the crystals is created, reducing the temperature of the phase change [39, 40].

Therefore, generally the results of XRD (Figure 6) and DSC thermograms (Figure 7) show the crystalline form of fenofibrate dispersions while other reported methods of production of solid dispersions like solvent, kneading and fusion methods used for enhancing the solubility of nimodipine using different drug: polymer ratios showed the disappearance of the characteristic peak of the melting point of the drug which may be due to decrease the crystallinity of the drug [41].

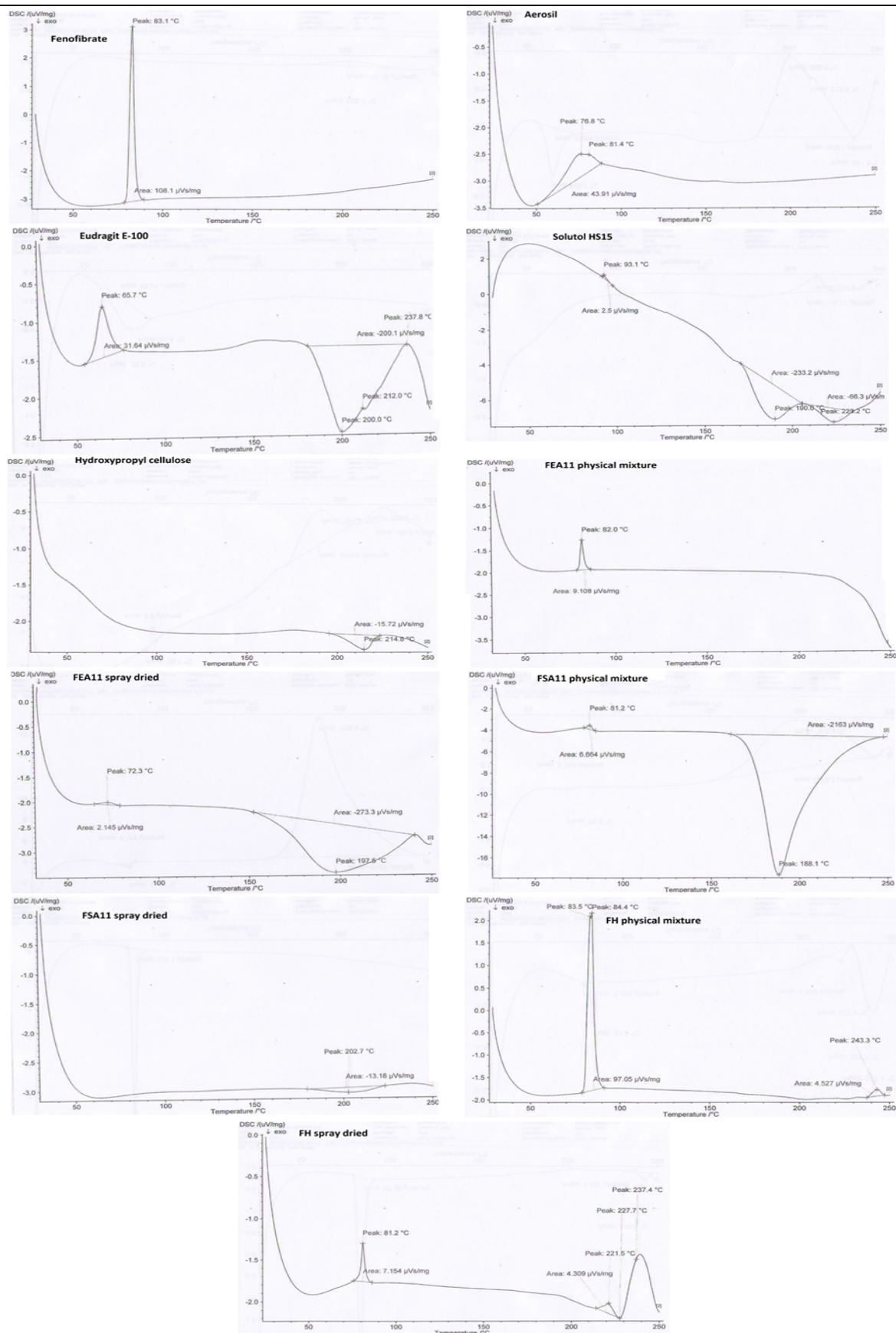


Figure 7.

DSC thermograms of spray dried dispersions and physical mixtures of Fenofibrate with Eudragit® E-100, Solutol® HS15 and HPC (11 = excipient / drug ratio of 1:1)

Morphological studies of dispersions by scanning electron microscopy (SEM)

The SEM pictures of spray dried dispersions of drug-loaded Eudragit® E-100 formulation are presented in Figure 8. It can be seen that dispersions are spherical with wrinkles on their surface which may be due to drug crystallinity that

decreased the surface smoothness of the spray-dried dispersions. Moreover as Aerosil® 200 was added to the excipient -drug solution for preventing the stickiness, the surface of the dispersions was affected by this additive to some extent and their smoothness was reduced a little.

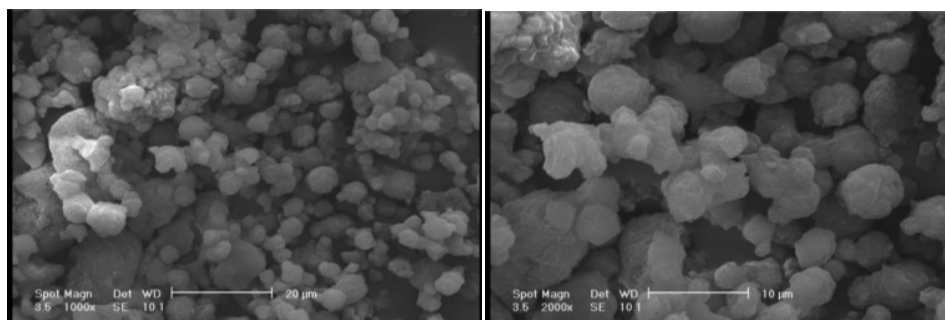


Figure 8.

SEM micrographs of spray dried dispersions of fenofibrate-Eudragit® E-100-Aerosil®

Long term stability

Amorphous systems are thermodynamically unstable and have a more accentuated tendency to convert to stable (crystal) forms. Recrystallization of amorphous drug is the main disadvantage of solid dispersion systems. Any change in crystallinity of the drug could be reflected in dissolution profiles. The dispersions of fenofibrate prepared in the present work all showed that the drug was somewhat in the crystalline form which is the distinctive property of the method for enhancement of dissolution rate of fenofibrate so far. However, the superior flow-ability of the dispersions of FEA11 to the other dispersions caused in suggesting these type of dispersions for further stability tests. Figure 9 shows the dissolution profiles of these spray dried dispersions stored at ambient conditions. The comparison of dissolution profiles showed the values for f_1 was 2.46 (< 15) and f_2 was 74 (> 50) indicating that there is no considerable change in drug dissolution after six months.

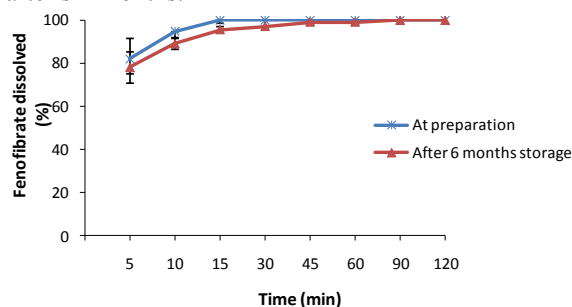


Figure 9.

Dissolution profiles of spray dried dispersions of Fenofibrate / Eudragit® E-100 / Aerosil® at the time of preparation and six months after storage at ambient temperature ($n = 3$)

Conclusions

It could be concluded that the spray drying technique is a suitable method for the production of solid dispersions of fenofibrate while keeping the crystallinity of the drug without changing its solid state to a metastable crystalline form II. Although the present method used an organic solvent that may be mentioned as a disadvantage aspect of this method, but considering the production of stable crystalline forms of the drug it is superior to the recently developed methods of nanonisation of fenofibrate by the bead-milling method [42]. In the developed spray drying method Eudragit® E-100 in a ratio of 1:1 to the drug showed faster dissolution efficiency than Solutol® HS15 and HPC. The enhancement of dissolution rate of the drug was probably due to particle size reduction compared to the untreated drug. The dissolution profile of fenofibrate didn't change after 6 months storage at ambient temperature.

Acknowledgements

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