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SOLID DISPERSIONS OF FENOFIBRATE BY DROPPING METHOD

D. Prasanthi *, C. Prakash and K. Lakshmi Aishwarya

G. Pulla Reddy College of Pharmacy, Hyderabad - 500028, Telangana, India.

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Correspondence to Author:
Dr. D. Prasanthi

Associate Professor,
G. Pulla Reddy College of Pharmacy, Hyderabad - 500028, Telangana, India.

E-mail: prasanthidhanu@gmail.com

ABSTRACT: The main objective of the study was to enhance the dissolution of fenofibrate (BCS class II), poorly soluble drug. To improve the solubility of the drug, solid dispersions were prepared by dropping method with PEG 4000 and PEG 6000 in the ratios of 1:1 and 1:2. The formulations were filled into capsules and evaluated for solubility, assay, FTIR, X-ray diffractions, DSC, and *in-vitro* dissolution. The optimized formulation was compared with the marketed formulation. The optimized formulation D4 (containing PEG 6000 (1:2) by dropping method) showed maximum solubility 0.678 ± 0.07 mg/ml when compared to pure drug (0.018 mg/ml), assay, 98.14 ± 12% and practical percentage yield 95.25 ± 0.17%. *In-vitro* dissolution studies of the prepared solid dispersions showed release in 60 min whereas D4 formulation released 99.10 ± 0.18% in 30 min when compared to pure drug 27.38 ± 0.10% in 60 min, and a marketed capsule containing micronized fenofibrate (Lipicard) 93.91 ± 0.12% in 30 min. FTIR studies confirmed that there is no interaction between the drug and the excipients. The solid-state characterization of solid dispersion formulation by XRD and DSC studies confirmed that the drug present in the formulation was in an amorphous state. The optimized formulations were found to be stable. Hence, with the dropping method using the least ratio of the carrier (1:2), the percentage release of drug was increased similar to micronized fenofibrate (Lipicard).

INTRODUCTION: Fenofibrate is an anti-hyperlipidemic drug that is poorly soluble in water, having a biological half-life of 20 h. It lowers lipid levels by activating peroxisome proliferator-activated receptor alpha (PPARα). PPARα activates lipoprotein lipase and reduces apoprotein CIII, which increases lipolysis and elimination of triglyceride-rich particles from the plasma. PPARα also increases apoproteins AI and AII, reduces VLDL and LDL containing apoprotein B, and increases HDL containing apoprotein AI and AII [1].

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Poorly water-soluble drugs are expected to have dissolution-limited absorption. Increasing the drug solubility may substantially improve drug absorption and consequently, drug bioavailability. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs (BCS class-II drugs) [2].

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles in the media [3]. The resulting enhanced surface area shows a higher dissolution rate of [4]. Different methods like fusion method, solvent evaporation, spray - drying, melt - evaporation, kneading method, physical mixture, electrospinning method can be used to prepare solid dispersions [5]. Disadvantages of the use of an organic solvent in the preparation of solid

dispersion led to the development of dropping method [6].

For example, the solvent evaporation method involves dissolving drug and carrier in organic solvent and evaporation for the removal of the solvent. Spray drying and freeze-drying methods are also similar, where the organic solvent is removed by these methods [5]. But the removal of organic solvent is difficult as solid dispersions are viscous, waxy, and amorphous. Other problems associated are residual solvent, further pulverizing, sifting, and cost of recovery. Infusion method and melt-evaporation methods, drugs were mixed with carriers (semisolids and waxes) by melting, and then the melt was solidified using ice or different methods [7]. But developing a dosage form was difficult, as the dispersions were soft and tacky, hard to pulverize, poor flowability and compressibility. In the dropping method, round particles produced from melted solid dispersions could overcome difficulties in other methods. In this method, melted drug-carrier mixture is pipetted and then dropped onto a plate (temperature of the plate is maintained at or below room temperature), it solidifies to round particles. The size and shape of particles depend on the viscosity of melt and size of pipette [8].

In this method, organic solvents are not used, pulverization, sifting, and compressibility are not needed, but only thermostable drugs can be used, and physical instability of solid dispersions is a challenge [6]. Polyethylene glycol (PEG) is used for the preparation of solid dispersions by dropping method. The melting point of PEGs lies below 65 ºC, which is advantageous for the manufacture of solid dispersions. Additional attractive features of PEGs include their ability to solubilize some compounds and also improve compound wettability [9, 10]. In the present study, solid dispersions of fenofibrate were prepared by dropping method using PEG 4000 & PEG 6000 as carriers in 1:1 and 1:2 ratios. The particles were filled into capsules and evaluated for physicochemical properties and dissolution studies. The optimized formulation was compared with solid dispersions prepared by physical mixture and kneading method.

MATERIALS AND METHODS: Fenofibrate was obtained as a gift sample from Suven Life Sciences, Hyderabad. Polyethylene glycol (PEG) 4000, PEG 6000, and sodium lauryl sulfate were purchased from SD fine chemicals limited.

Preparation of Solid Dispersion by Dropping Method (DM): The solid dispersions of the drug were prepared with PEG 4000 and PEG 6000 in the ratio of 1:1 and 1:2. The required amount of carrier was taken in a china dish and melted on a hot plate. Later the drug was added. The melted drug-carrier mixture was pipette and dropped onto a stainless steel plate, where it solidified into particles (as shown in **Photograph 1**) [12].

PHOTOGRAPH 1: SOLID DISPERSION BY DROPPING METHOD- PARTICLES OF FORMULATION

The particles were filled into hard gelatin capsules (size no. 0) for further investigations. Formulations of DMs are given in **Table 1**. The optimized formulation was compared with the physical mixture method and kneading method of PEG 6000 (1:2) solid dispersion filled in capsules. The physical mixture was prepared by blending drug and carrier in the ratio of 1:2 and passing through sieve # 60. The kneading method was prepared using mortar and pestle (glass). The drug and carrier in 1:2 ratio were mixed; methanol was added in small quantity and triturated vigorously until damp granular mass was obtained. The mixture was then dried in a hot air oven at 45 °C to

form dry granules. Then the mixture was taken and passed through sieve #60, and the granules were retained.

TABLE 1: FORMULATIONS OF DROPPING METHOD OF FENOFIBRATE

Formulation code	Drug (mg)	Carriers	
		PEG 4000 (mg)	PEG 6000 (mg)
D1	200	200	-
D2	200	400	-
D3	200	-	200
D4	200	-	400
PM	200	-	400
KM	200	-	400

Characterization of Solid Dispersion:

Assay: Accurately weighed amounts of solid dispersions sample equivalent to 50 mg of drug was weighed and transferred into a 100 ml volumetric flask, 20 ml methanol was added and shaken for 20 min to dissolve the drug. The volume was made to 100 ml with 0.05 M SLS in distilled water. The dispersions were filtered, and 1 ml aliquot of the above solutions was taken and diluted to 10 ml with 0.05M SLS in distilled water. The absorbance of these solutions was determined at 287 nm against the blank as 0.05 M SLS in distilled water using UV-double beam Spectrophotometer [11].

Solubility Studies: An excess of pure fenofibrate drug and prepared solid dispersions were added to screw-capped bottles containing distilled water. Bottles are shaken mechanically inside an orbital shaker bath at room temperature for 24 h [11]. Then the samples were filtered using 0.45µm Whatman filter paper, suitably diluted and analyzed by UV-double beam spectrophotometer at 287 nm.

Percentage Practical Yield: The prepared solid dispersions were weighed accurately, and it was taken as a practical yield. Then the practical percentage yield was calculated by using the formula as follows:

% of practical yield = practical yield × 100 / theoretical yield

Characterization of Fenofibrate Capsules:

Weight Variation Test: 20 capsules were randomly selected, their weight and average weight was determined. The test requirements are met if none of the individual weights is less than 90% or more than 110% of the average [13].

Content Uniformity: 10 capsules are selected and are subjected to assay. The requirements are met if 9 out of the 10 are within the specified potency range of 85 to 115%, and the tenth is not outside 75 to 125% [13].

***In-vitro* Drug Release Studies:** *In-vitro* drug release of fenofibrate capsules was determined using USP dissolution apparatus II (Paddle type) (Electrolab TDL-08L). The dissolution test was performed using 900 ml of 0.05 M SLS in distilled water at 37 ºC ± 0.5 °C. A winder was used to retain the capsules in the dissolution basket. The speed of rotation of paddle was set at 75 rpm. 5 ml samples were withdrawn at time points of 5, 10, 15, 20, 30, 45, 60 min, and the same volume was replaced with fresh media. The absorbance of the solution was checked by UV spectrophotometer (Chemito 2600 double beam spectrophotometer) at a wavelength of 287 nm. The dissolution studies of optimized formulation were compared with pure drug, physical mixture method formulation (PM), kneading method formulation (KM), and marketed capsules of micronized fenofibrate (Lipicard).

Drug-Excipient Compatability Studies:

Fourier Transformed Infrared Spectroscopy (FTIR): The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for the preparation of solid dispersions were studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu corporation (model – 8400S Kyoto, Japan). Potassium bromide (KBr) disks were prepared by mixing few mg of the sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure [14]. The resultant disc was mounted in a suitable holder in IR spectrophotometer, and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 min. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in a compound.

Differential Scanning Calorimetry (DSC): The physical nature of the drug, polymer, and optimized formulations were studied by DSC. DSC analysis was performed using Shimadzu DSC-60 differential scanning calorimeter (DSC). The instrument was calibrated with indium standard. 3-5 mg samples were weighed and placed in a closed, hermetic sample pan with pinhole. Thermograms

were obtained by heating the sample at a constant rate of 10 °C/ min. A dry purge of nitrogen gas (50 ml/min) was used for all runs. Samples were heated from 0˚C to 350 ºC. The melting point, heat of fusion, disappearance of the sharp crystalline peak of the drug, and appearance of any new peak were noted [15].

X-Ray Diffraction Analysis (XRD): The crystallinity of the drug, polymer, and optimized formulations were studied by XRD. The XRD analysis was performed using Shimadzu XRD-7000, X-Ray diffractometer using copper K α (λ=1.5406 Aº) radiation [15]. The data were recorded over a scanning 20 range of 5º to 50º at a step time of 0.045 steps/0.5sec.

Stability Studies: The optimized formulation was subjected to stability studies according to ICH guidelines for three months. The samples were evaluated for weight variation, content uniformity, and dissolution studies [14].

RESULTS AND DISCUSSION: Solid dispersions of fenofibrate by the dropping method were prepared according to **Table 1**. The solid dispersions were evaluated for assay, solubility, and percentage yield. Assay values ranged from 92.71 ± 0.19% to 95.42 ± 0.14%. The decrease in the assay value could be due to losses in the procedure as the drug is melted and then pipette onto a plate to form round particles [12]. Solubility ranged from 0.552 ± 0.11 mg/ml for D1 formulation to 0.678 ± 0.07 mg/ml for D4 formulation. As the ratio of carrier increased the solubility also increased. All the formulations showed enhanced solubility when compared with the pure drug (0.018 mg/ml). The results are given in **Table 2**. The percentage yield of formulations ranged from 89.16 ± 0.11% to 95.25 ± 0.02%. The decrease in the yield is due to the losses occurring in the procedure of preparation.

TABLE 2: CHARACTERIZATION OF SOLID DISPERSIONS OF FENOFIBRATE BY DROPPING METHOD

Formulation code	Assay %	Solubility (mg/ml)	% Yield
D1	91.65 ± 0.23	0.552 ± 0.11	93.5 ± 0.25
D2	94.47 ± 0.17	0.604 ± 0.13	89.16 ± 0.11
D3	95.42 ± 0.14	0.626 ± 0.09	90.25 ± 0.19
D4	92.71 ± 0.19	0.678 ± 0.07	95.25 ± 0.02

Values are expressed as mean ± SD, n = 3

The solid dispersions were filled into size 2 capsules and evaluated for weight variation and content uniformity. The weight variation tests for the formulations D1 to D4 were found to be within the limits of 90% to 110% of the average. Content uniformity test based on the assay of ten capsules was also within limits. The capsules characterization complied with the official limits [13].

In-vitro dissolution studies of fenofibrate solid dispersions filled into capsules were performed using dissolution USP apparatus II (paddle type). The drug release was maximum with D4 formulation (99.10 ± 1.42% in 30 min) when compared to the pure drug in a capsule (27.38 ± 1.42% in 60 min) as shown in **Fig. 1**. D2 formulation showed 87.04 ± 1.41% release and D1 (60.3 ± 1.39%) in 60 min. As the ratio of carrier increased, faster release of the drug was observed. D3 formulation released 79.59 ± 1.43% in 60 min. When compared with PEG 4000, PEG 6000 showed faster release.

A similar pattern of increase in the ratio of the carrier enhanced the release with PEG 6000 also. Only 1:1 and 1:2 ratio were tried due to the limitation of capsules size used for human beings. Where size 0 is the maximum optimum size for use in humans. The dose of the drug was 200 mg, so the ratio of 1:2, with a total weight of 600 mg only could be tried. The optimized formulation D4 release was compared with PEG 6000, 1:2 ratio in the physical mixture (PM, 67.24 ± 1.88% in 60 min) and kneading method (KM, 72.15 ± 1.75% in 60 min). Faster release of drug was observed with the dropping method. Formulation D4 showed a similar percentage of release with marketed capsule Lipicard (93.91 ± 0.22% in 30 min) containing micronized fenofibrate shown in **Fig. 2**.

The increased dissolution rate is due to several factors such as reduction of crystalline size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability, and dispersibility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier, drug conversion to an amorphous state. Pure fenofibrate due to its hydrophobic nature and poor solubility tend to form aggregates and floats on the surface, leading to reduced effective surface area and thereby

decreased dissolution. It was also evident that as the PEG 6000 concentration got increased, the release of fenofibrate from the solid dispersion by dropping method got increased due to more carrier available for coating [12].

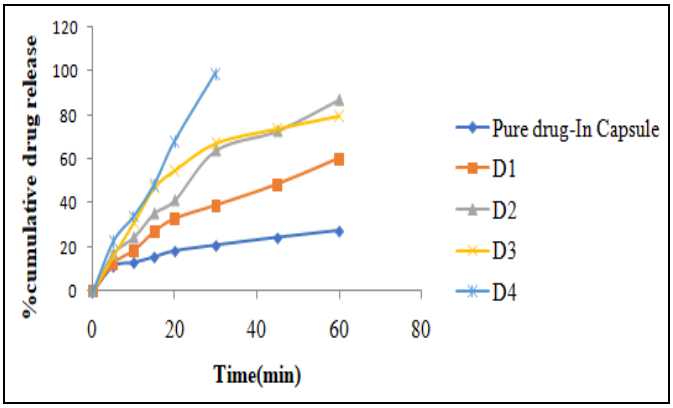

FIG. 1: PERCENTAGE RELEASE PROFILES OF FENOFIBRATE SOLID DISPERSIONS DROPPING METHOD

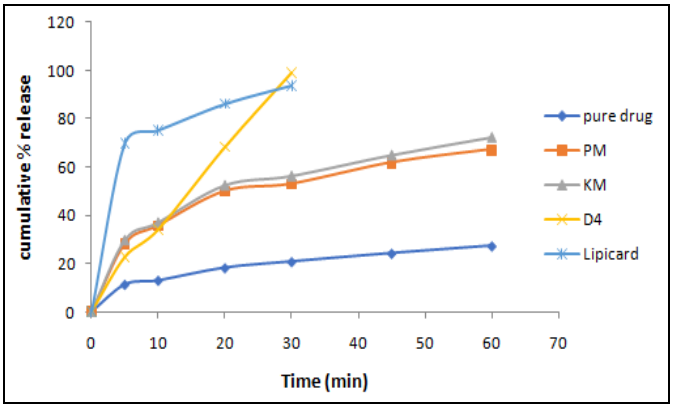

FIG. 2: COMPARISON OF RELEASE PROFILES OF D4, PHYSICAL MIXTURE (PM), KNEADING METHOD (KM), PURE DRUG AND MARKETED (LIPICARD)

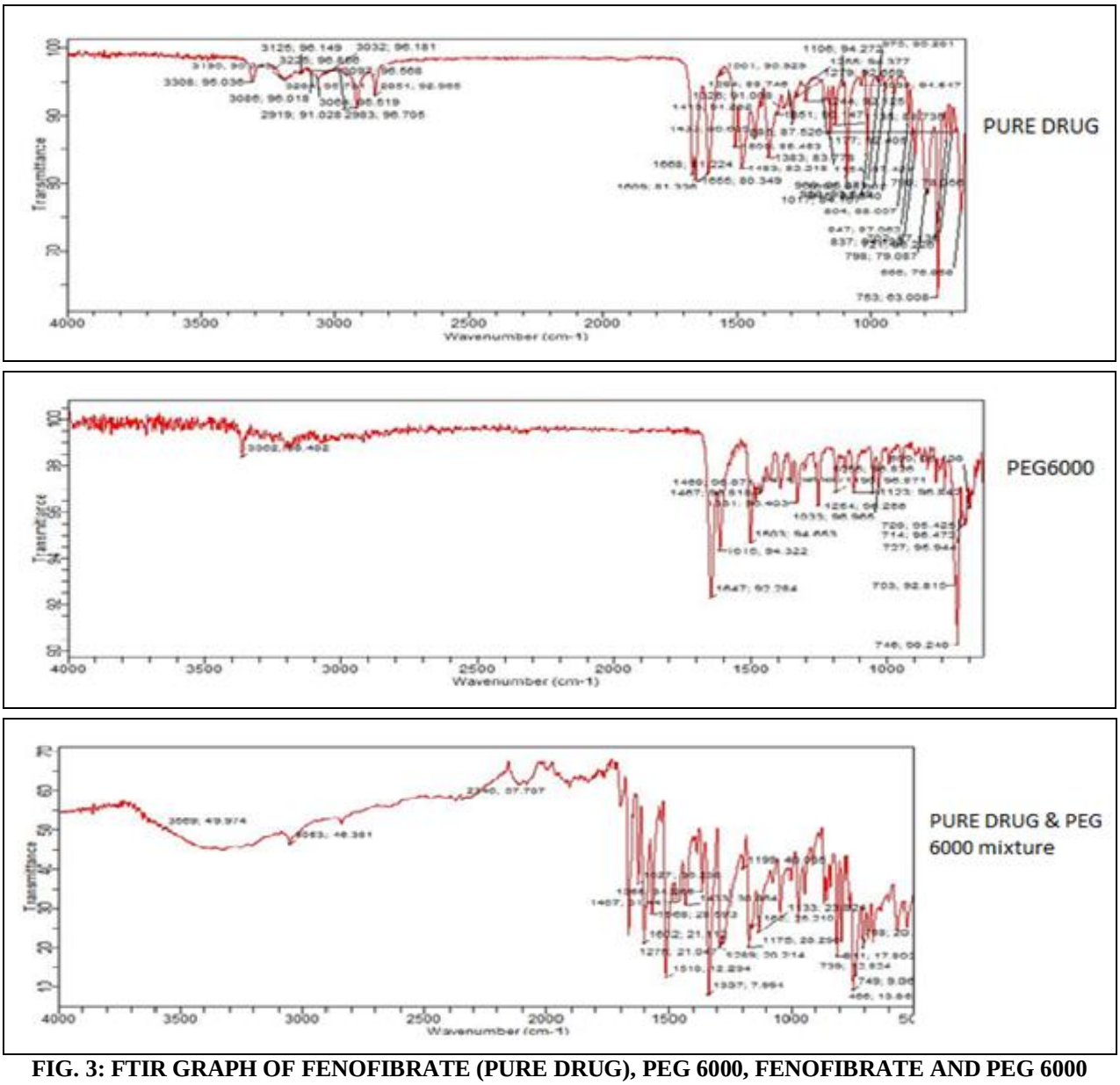

FIG. 3: FTIR GRAPH OF FENOFIBRATE (PURE DRUG), PEG 6000, FENOFIBRATE AND PEG 6000

Drug-excipient compatibility was studied by FTIR spectral analysis. In IR spectra of pure drug, the peaks (3064.84, NH stretching; 3159.18, CH stretching; 1615, C=O stretching; 1595.02, CN stretching; 1483, C=C stretching) were observed which were also present in the mixture of pure drug with PEG 6000, indicating there was no interaction **Fig. 3**. Solid dispersions were characterized by DSC studies. The thermograms of the pure drug showed a sharp endothermic peak at 64.7 ºC, and formulation D4, 62.6 ºC, this slight change in peak could be due to solubilization of drug in the carrier during formulation [15] **Fig. 4**.

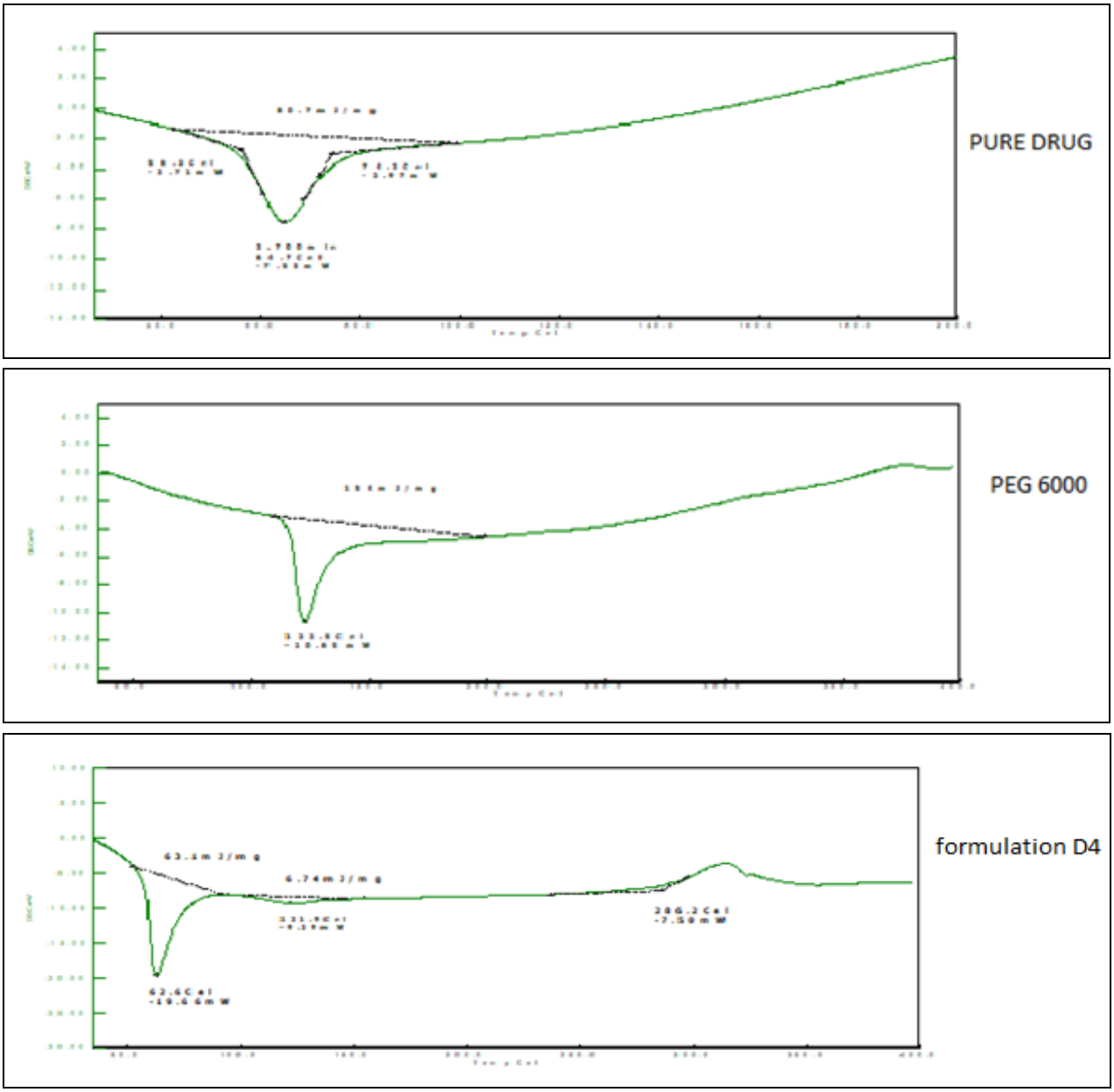

FIG. 4: DSC GRAPH OF PURE DRUG (FENOFIBRATE), PEG 6000, FORMULATION D4

The optimised formulation was characterized for crystallinity by XRD. Sharp peaks seen in the pure drug were not observed in formulation D4. The intensity of peaks and the number of peaks also decreased, indicating the amorphous nature of sample **Fig. 5** [15]. The optimized formulation D4 was stored at 40 ºC ± 2ºC, 75% ± 5% RH, for three months and studied for its stability by evaluating weight variation, content uniformity and dissolution study at a sampling interval of every month. The weight variation and content uniformity were found to be within official limits. There was no significant change in the percentage release of the drug. Hence, the formulation was stable.

CONCLUSION: To enhance the solubility of fenofibrate (BCS class II), solid dispersions were prepared by dropping method. Formulation D4, (PEG, 1:2 ratio) showed good enhanced solubility of 0.678 mg/ml, 99.10 ± 1.42% release in 30 min in 0.05 M SLS in distilled water. When compared to pure drug (fenofibrate) 0.018 mg/ml; 27.38 ± 1.42% in 60 min. The drug release by D4 formulation was similar to marketed Lipicard containing micronized fenofibrate. Drug-excipient compatibility studies showed there was no interaction between the drug and carrier. XRD characterization indicates crystalline to amorphous.

In conclusion, it can be stated that the objective of the study has been achieved. Solid dispersion technique was successful in improving the dissolution rate of fenofibrate. The hydrophilic carriers like PEG 6000 were successful in improving the dissolution rate of fenofibrate by dropping method.

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CONFLICT OF INTEREST: Nil

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