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Formulation of fenofibrate capsules by dropping method using PEG 6000 and PEG 4000 to enhance solubility

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Abstract

The primary aim of the study was to enhance the dissolution rate of fenofibrate, a poorly soluble drug classified under BCS class II. To achieve this, solid dispersions were formulated using the dropping method with polyethylene glycol (PEG) 4000 and PEG 6000 at ratios of 1:1 and 1:2. These formulations were encapsulated and subjected to various evaluations, including solubility tests, assays, FTIR, X-ray diffraction (XRD), differential scanning calorimetry (DSC), and in-vitro dissolution studies. The most effective formulation was then compared to a commercially available product.

The formulation identified as D4, which utilized PEG 6000 at a 1:2 ratio via the dropping method, exhibited the highest solubility at 0.678 ± 0.07 mg/ml, a significant improvement over the pure drug's solubility of 0.018 mg/ml. The assay of D4 showed 98.14 ± 12%, with a practical yield of 95.25 ± 0.17%. In vitro dissolution testing revealed that the solid dispersions released the drug within 60 minutes, while the D4 formulation achieved a release of 99.10 ± 0.18% in just 30 minutes. This performance was notably superior to the pure drug, which had a release rate of 27.38 ± 0.10% in 60 minutes, and comparable to the marketed micronized fenofibrate capsule (Lipicard), which had a release rate of 93.91 ± 0.12% in 30 minutes.

FTIR analysis indicated no interaction between the drug and the excipients, while XRD and DSC studies confirmed that the drug in the solid dispersion was in an amorphous state. The optimized formulations demonstrated stability over time. Thus, employing the dropping method with a minimal carrier ratio of 1:2 significantly improved the drug release profile, making it comparable to the micronized fenofibrate (Lipicard).

Keywords: Solid Dispersion; PEG 6000; PEG 4000; The Dropping Method; Fenofibrate

1. Introduction

Fenofibrate, an anti-hyper lipidemic medication, is characterized by its poor water solubility and a biological half-life of 20 hours. The drug functions by lowering lipid levels through the activation of peroxisome proliferator-activated receptor alpha (PPARα). This activation enhances lipolysis and the elimination of triglyceride-rich particles from the plasma by activating lipoprotein lipase and reducing apoprotein CIII. Additionally, PPARα increases the levels of apoproteins AI and AII, reduces very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) containing apoprotein B, and boosts high-density lipoprotein (HDL) containing apoproteins AI and AII[1].

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Due to its poor water solubility, fenofibrate has dissolution-limited absorption, which can hinder its bioavailability. Improving the solubility of such drugs can significantly enhance their absorption and bioavailability. Solid dispersion techniques are commonly employed to improve the dissolution rates and oral bioavailability of poorly soluble drugs, particularly those classified as BCS class II.

When a solid dispersion is introduced into an aqueous medium, the carrier dissolves, releasing the drug as fine colloidal particles. This increased surface area leads to a higher dissolution rate. Several methods, including fusion, solvent evaporation, spray-drying, melt-evaporation, kneading, physical mixing, and electrospinning, are used to prepare solid dispersions. However, the challenges associated with using organic solvents in these methods have led to the development of the dropping method[2].

For instance, the solvent evaporation method involves dissolving the drug and carrier in an organic solvent, followed by the removal of the solvent. Spray drying and freeze-drying are similar processes where the solvent is removed. However, removing the organic solvent can be problematic due to the viscous, waxy, and amorphous nature of the dispersions. Other issues include residual solvent, further pulverization, sifting, and high recovery costs. In the fusion and melt-evaporation methods, the drug is mixed with carriers (such as semisolids and waxes) by melting, and the mixture is then solidified using ice or other methods. However, developing a dosage form from these dispersions can be challenging due to their soft and tacky nature, poor flowability, and compressibility.

The dropping method offers a solution to these challenges by producing round particles from melted solid dispersions. In this method, the melted drug-carrier mixture is pipetted and dropped onto a plate maintained at or below room temperature, where it solidifies into round particles. The size and shape of these particles depend on the viscosity of the melt and the size of the pipette[3].

This method does not require organic solvents, pulverization, sifting, or compressibility adjustments. However, it is limited to thermostable drugs, and physical instability of the solid dispersions can be a challenge. Polyethylene glycol (PEG) is commonly used in the dropping method due to its melting point below 65°C, which is beneficial for manufacturing solid dispersions. PEGs also have the advantage of solubilizing some compounds and improving their wettability.

In the present study, solid dispersions of fenofibrate were prepared using the dropping method with PEG 4000 and PEG 6000 as carriers in ratios of 1:1 and 1:2. The resulting particles were encapsulated and evaluated for their physicochemical properties and dissolution behavior. The optimized formulation was compared with solid dispersions prepared by the physical mixture and kneading methods[4,5].

2. 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.

2.1. Preparation of Solid Dispersion by Dropping Method (DM)[6,7,8]

Solid dispersions of fenofibrate were prepared using PEG 4000 and PEG 6000 at ratios of 1:1 and 1:2. The process began by melting the necessary amount of PEG in a China dish on a hot plate. Once the carrier was melted, the drug was incorporated into the mixture. This drug-carrier blend was then pipetted and dropped onto a stainless steel plate, allowing it to solidify into particles.

Figure 1 Solid Dispersion by Dropping Method- Particles of Formulation

The solidified particles were filled into size 0 hard gelatin capsules for further investigation. The formulations of the solid dispersions (DMs) are detailed in Table 1. The optimized formulation was compared with those prepared using the physical mixture and kneading methods with PEG 6000 at a 1:2 ratio, also encapsulated.

To prepare the physical mixture, the drug and carrier were blended at a 1:2 ratio and passed through a sieve (#60). For the kneading method, the drug and carrier in the same ratio were mixed using a glass mortar and pestle. Methanol was gradually added, and the mixture was triturated vigorously until a damp, granular mass formed. This mixture was then dried in a hot air oven at 45°C to produce dry granules. Finally, the granules were sieved through sieve #60, retaining the appropriate size for encapsulation.

Table 1 Formulations of Dropping Method of Fenofibrate

Formulationcode	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

2.2. Characterization of Solid Dispersion[9,10]

- **Assay:** Accurately weighed samples of the solid dispersions, each equivalent to 50 mg of fenofibrate, were transferred to a 100 ml volumetric flask. To this, 20 ml of methanol was added, and the mixture was shaken for 20 minutes to ensure the drug was completely dissolved. The solution was then diluted to 100 ml with 0.05 M sodium lauryl sulfate (SLS) in distilled water. After filtering the dispersions, a 1 ml aliquot of the solution was taken and further diluted to 10 ml with 0.05 M SLS in distilled water. The absorbance of these solutions was measured at 287 nm using a UV-double beam spectrophotometer, with 0.05 M SLS in distilled water serving as the blank.
- **Solubility Studies:** An excess amount of pure fenofibrate and the prepared solid dispersions were placed in screw-capped bottles containing distilled water. These bottles were then shaken mechanically in an orbital shaker bath at room temperature for 24 hours. After this period, the samples were filtered using 0.45 µm Whatman filter paper, appropriately diluted, and analyzed using a UV-double beam spectrophotometer at 287 nm.
- **Percentage Practical Yield[11,12]:** The prepared soliddispersions were weighed accurately, and it was taken as a practical yield. Then the practical percentage yield was calculated by using the formula as follows:

$$\% \text{ of practical yield} = \text{practical yield} \times 100 / \text{theoretical yield}$$

- **Characterization of Fenofibrate Capsules: Weight Variation Test:** 20 capsules wererandomly selected, their weight and average weightwas determined. The test requirements are met ifnone of the individual weights is less than 90% ormore than 110% of the average [13].
- **Content Uniformity:** 10 capsules are selected andare 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 75to 125% [13].
- ***In-vitro* Drug Release Studies[13,14]:** The in-vitro drug release of fenofibrate capsules was assessed using a USP dissolution apparatus II (Paddle type) (Electrolab TDL-08L). The test was conducted in 900 ml of 0.05 M SLS in distilled water maintained at 37 ± 0.5 °C. A winder was utilized to hold the capsules in the dissolution basket. The paddle rotation speed was set to 75 rpm. Samples of 5 ml were withdrawn at intervals of 5, 10, 15, 20, 30, 45, and 60 minutes, with the same volume of fresh media added each time to maintain constant volume. The absorbance of these samples was measured at 287 nm using a UV spectrophotometer (Chemito 2600 double beam spectrophotometer). The dissolution profiles of the optimized formulation were compared with those of the pure drug, physical mixture formulation (PM), kneading method formulation (KM), and the marketed micronized fenofibrate capsules (Lipicard).

2.3. Drug-Excipient Compatibility Studies[15,16]

- **Fourier Transformed Infrared Spectroscopy (FTIR):** The spectrum analysis of the pure drug and its physical mixture with various excipients used in the preparation of solid dispersions was conducted using FTIR. The FTIR spectra were recorded by creating potassium bromide (KBr) disks with a Shimadzu FTIR spectrophotometer (model 8400S, Kyoto, Japan). The KBr disks were prepared by blending a small amount of the sample with potassium bromide and then compacting the mixture in a hydrostatic press under vacuum at a pressure of 6-8 tons.
  The resulting disk was placed in a suitable holder in the IR spectrophotometer, and the IR spectrum was recorded over a range of 4000 cm-1 to 500 cm-1 with a scan time of 12 minutes. The spectra were then analyzed for any spectral changes, focusing on the presence of characteristic peaks corresponding to specific functional groups in the compounds.
- **Differential Scanning Calorimetry (DSC)[17]:** The physical properties of the drug, polymer, and optimized formulations were examined using Differential Scanning Calorimetry (DSC). The DSC analysis was carried out with a Shimadzu DSC-60 differential scanning calorimeter. Calibration of the instrument was done using an indium standard. Samples weighing 3-5 mg were placed in closed hermetic sample pans with pinholes. Thermograms were recorded by heating the samples at a constant rate of 10 °C per minute, with a dry nitrogen gas purge at a flow rate of 50 ml per minute. The samples were heated from 0 °C to 350 °C. Observations included the melting point, heat of fusion, the disappearance of the sharp crystalline peak of the drug, and the appearance of any new peaks. [15].
- **X-Ray Diffraction Analysis (XRD)[18]:** 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 (□=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[19,20]:** 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].

3. Results and discussion

Solid dispersions of fenofibrate were prepared using the dropping method as detailed in Table 1. These solid dispersions were assessed for their assay, solubility, and percentage yield. Assay values ranged from 92.71 ± 0.19% to 95.42 ± 0.14%, with some decrease likely due to losses when the drug is melted and pipetted onto a plate to form round particles. The solubility of the formulations ranged from 0.552 ± 0.11 mg/ml for formulation D1 to 0.678 ± 0.07 mg/ml for formulation D4, with solubility increasing as the carrier ratio increased. All formulations showed significantly enhanced solubility compared to the pure drug, which had a solubility of 0.018 mg/ml, as shown in Table 2. The percentage yield of the formulations varied from 89.16 ± 0.11% to 95.25 ± 0.02%, with decreases in yield attributed to procedural losses during 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 encapsulated in size 2 capsules and evaluated for weight variation and content uniformity. The weight variation tests for formulations D1 to D4 fell within the acceptable range of 90% to 110% of the average weight. The content uniformity, assessed by the assay of ten capsules, also met the official limits.

In-vitro dissolution studies of the fenofibrate solid dispersions encapsulated in capsules were performed using the USP dissolution apparatus II (paddle type). The D4 formulation exhibited the highest drug release, achieving 99.10 ± 1.42% in 30 minutes, compared to the pure drug in a capsule, which showed 27.38 ± 1.42% in 60 minutes. Formulation D2 released 87.04 ± 1.41%, and D1 released 60.3 ± 1.39% in 60 minutes. An increased carrier ratio resulted in faster drug

release, with D3 releasing 79.59 ± 1.43% in 60 minutes. PEG 6000 formulations released the drug faster compared to PEG 4000 formulations.

The study only tested 1:1 and 1:2 ratios due to the limitations of capsule sizes suitable for human use, with size 0 being the maximum optimal size. Given the drug dose of 200 mg, the total weight of 600 mg could be achieved with a 1:2 ratio. The optimized D4 formulation was compared with a 1:2 PEG 6000 ratio in both the physical mixture (PM, 67.24 ± 1.88% in 60 minutes) and the kneading method (KM, 72.15 ± 1.75% in 60 minutes). The dropping method showed a faster drug release, with D4 having a similar release profile to the marketed Lipicard capsule (93.91 ± 0.22% in 30 minutes), which contains micronized fenofibrate.

The enhanced dissolution rate of the solid dispersions is attributed to several factors, including the reduction of crystalline size, the solubilization effect of the carrier, the prevention of drug crystallite aggregation, improved wettability, and dispersibility of the drug from the dispersion, as well as the dissolution of the drug in the hydrophilic carrier and conversion of the drug to an amorphous state. Pure fenofibrate, due to its hydrophobic nature and poor solubility, tends to form aggregates and float on the surface, reducing the effective surface area and thus decreasing dissolution. As the concentration of PEG 6000 increased, the release of fenofibrate from the solid dispersion via the dropping method also increased due to the greater availability of the carrier for coating.

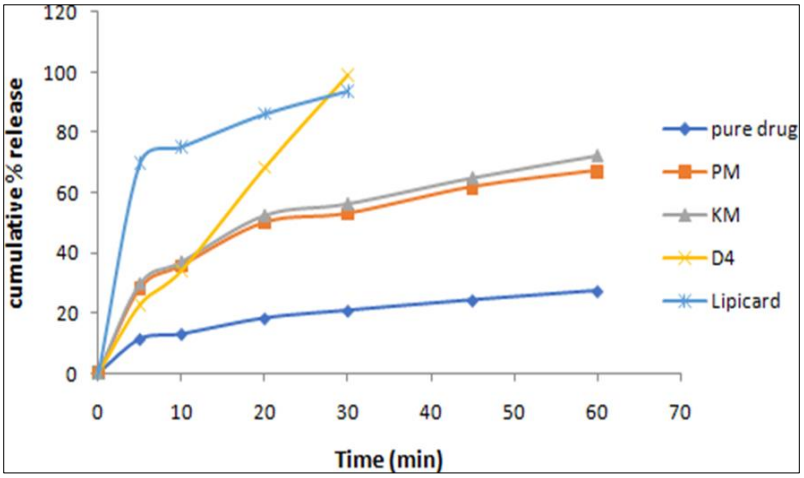

Figure 2 Percentage Release Profiles of Fenofibrate Solid Dispersions comparison of Release Profiles of D4, Physical Mixture (Pm), Kneading Method (Km), Pure Drug and Marketed (Lipicard)

3.1. FTIR Profile of Pure Drug, PEG 6000, D4 Formulation

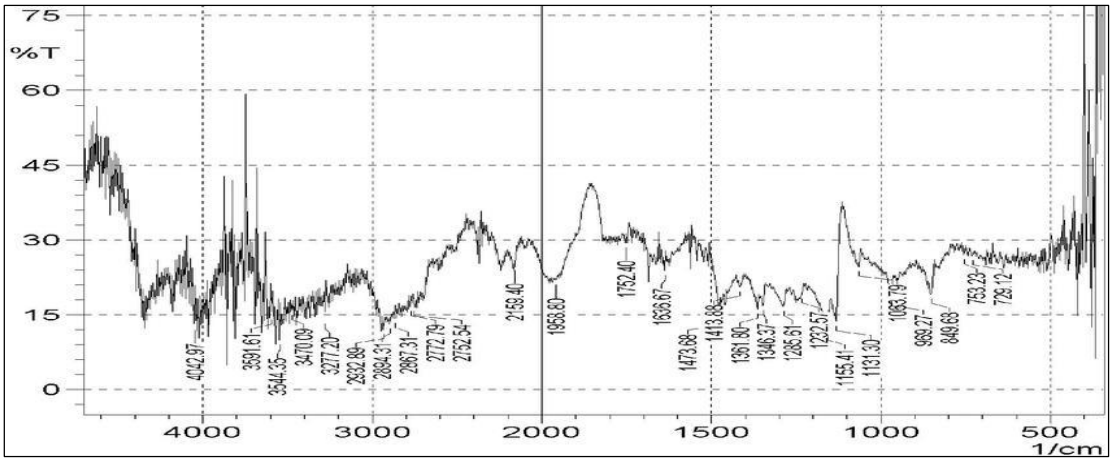

Figure 3 FTIR Graph of Fenofibrate (Pure Drug)

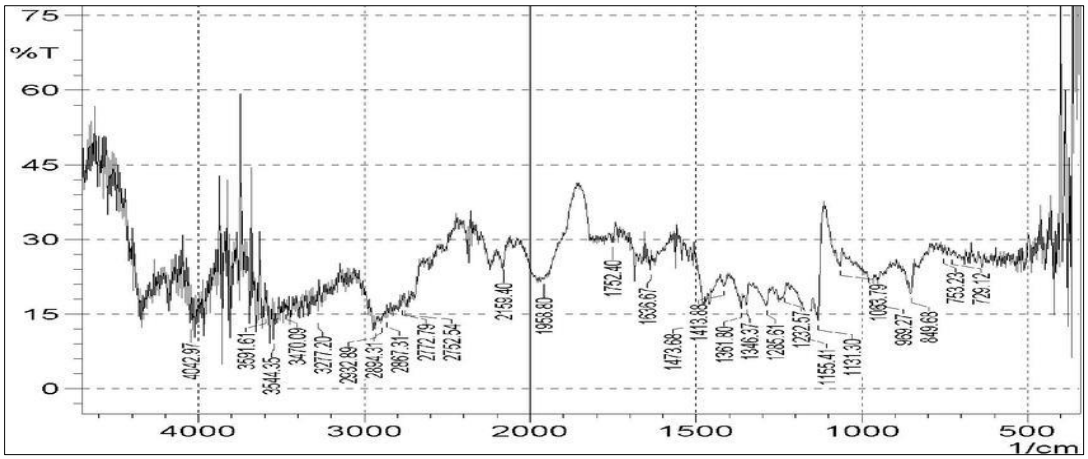

Figure 4 FTIR Graph of PEG 6000

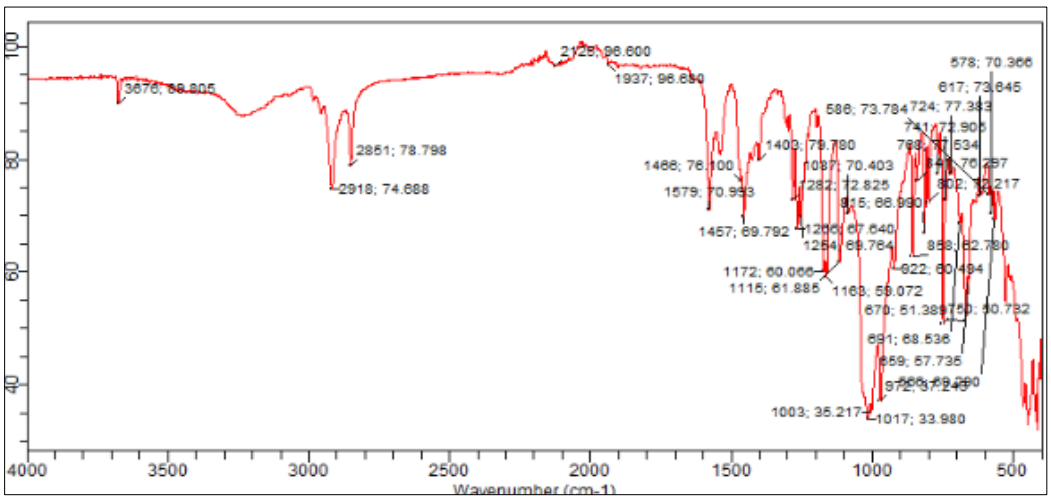

Figure 5 FTIR Graph of Fenofibrate (Pure Drug), Peg 6000, Fenofibrate and Peg 6000

Drug-excipient compatibility was assessed through FTIR spectral analysis. In the IR spectra of the pure drug, the characteristic peaks were observed at 3064.84 cm-1 (NH stretching), 3159.18 cm-1 (CH stretching), 1615 cm-1 (C=O stretching), 1595.02 cm-1 (CN stretching), and 1483 cm-1 (C=C stretching). These peaks were also present in the mixture of the pure drug with PEG 6000, indicating no interaction between the drug and the excipient. Solid dispersions were further characterized using DSC studies. The thermogram of the pure drug exhibited a sharp endothermic peak at 46.7 ºC. In comparison, formulation D4 displayed a peak at 56.2 ºC. This slight shift in the peak could be attributed to the solubilization of the drug within the carrier during the formulation process.15.

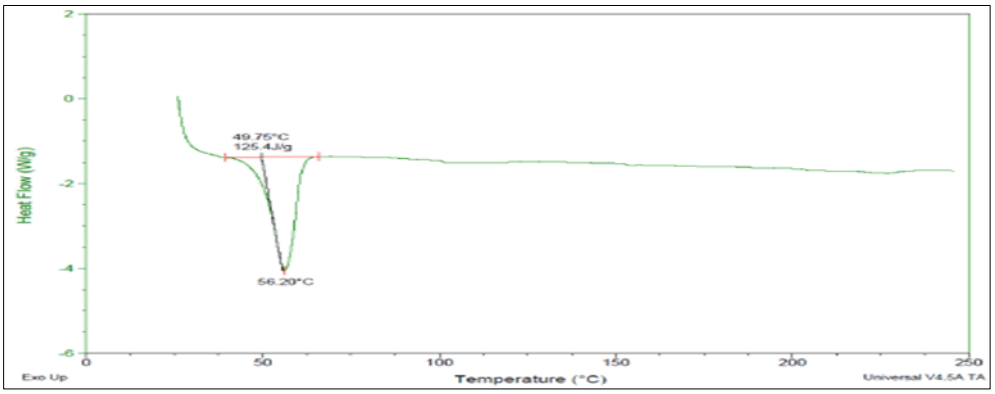

Figure 6 DSC Graph of Pure Drug (Fenofibrate), PEG-6000, Formulation D4

The optimized formulation was characterized for crystallinity using XRD. The sharp peaks present in the pure drug were absent in formulation D4. Additionally, the intensity and number of peaks were reduced, indicating the amorphous nature of the drug in the formulation.

The optimized formulation D4 was tested for stability by storing it at 40 ºC ± 2 ºC and 75% ± 5% RH for three months. Stability was assessed by evaluating weight variation, content uniformity, and dissolution studies at monthly intervals. The weight variation and content uniformity remained within official limits throughout the testing period. There was no significant change in the drug release percentage, indicating that the formulation remained stable.

4. Conclusion

Solid dispersions were prepared using the dropping method to enhance fenofibrate's solubility (a BCS class II drug). Formulation D4, utilizing PEG 6000 in a 1:2 ratio, demonstrated significantly improved solubility of 0.678 mg/ml and achieved a 99.10 ± 1.42% release in 30 minutes in 0.05 M SLS in distilled water. This is a substantial improvement compared to the pure drug, which had a solubility of 0.018 mg/ml and a release of 27.38 ± 1.42% in 60 minutes. The drug release from the D4 formulation was comparable to that of the marketed product Lipicard, which contains micronized fenofibrate.

Drug-excipient compatibility studies indicated no interaction between fenofibrate and the carrier. XRD characterization revealed a transformation from crystalline to amorphous form. Thus, the objective of the study was successfully met. The solid dispersion technique effectively improved the dissolution rate of fenofibrate. Hydrophilic carriers like PEG 6000 were particularly effective in enhancing the dissolution rate of fenofibrate when using the dropping method.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declared no conflict of interest.

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