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Research Article

Study on Dissolution Rate Enhancement of Fenofibrate through Solid Dispersion with Hydrophilic Carriers and Characterization

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ABSTRACT

Fenofibrate is an antilipidemic drug practically insoluble in water and exhibits an exceedingly slow dissolution rate and poor bioavailability. The present study has emphasized on improving the solubility and dissolution rate of drug .Using various hydrophilic carriers such as PEG6000, HP-BCD, Poloxamer 407 and PVP. Various techniques such as physical mixing, kneading technique, solvent evaporation mixing, and fusion method were used to prepare solid dispersions of fenofibrate. Solid-state characterization of solid dispersions were done by differential scanning calorimetry (DSC) and Fourier-transform infrared (FT-IR) spectrometry. The FTIR spectroscopic studies showed the Compatibility of fenofibrate and absence of well-defined drug polymer interaction. The solid dispersions can be evaluated by *in-vitro* dissolution studies. The solubility and dissolution rate of fenofibrate can be enhanced by the formulations of SDs of fenofibrate can be enhanced by the formulations of SDs of fenofibrate with PEG 4000 at 1:5 ratio. by melting fusion method.

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Introduction

Fenofibrate (isopropyl ester of 2-[4-(4-chloro-benzoyl) phenoxy]-2-methyl propanoic acid is a widely used hypolipidemic drug. [1]

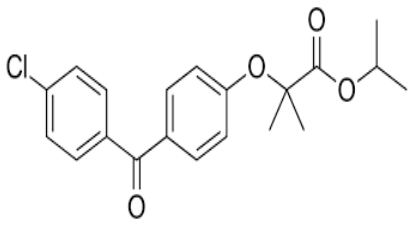


Figure 1: Structure of Fenofibrate

Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma. As fenofibrate dissolves very slightly in water, the present study was undertaken to overcome the limitations existing in available fenofibrate products so as to improve the dissolution profile, absorption characteristics, and bioavailability and to reduce the dose required for administration to attain a desired effect.

To improve the dissolution and bioavailability of poorly water soluble drugs, researchers have employed various techniques such as solubilization, salt formation, Complexation with polymers, changing in physical forms (amorphous) and solid dispersion which is considered one of the most successful strategies to improve the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous. The main advantages of SDs isincreased dissolution rate, enhanced release of drugs, the sustained release of drugs, and improved solubility and the stability.Nowadays, many approaches are used to enhance the solubility and dissolution rate of poorly soluble drugs by the use of pharmaceutical technology.[2]

Solid dispersion technique provides a means of changing particle nature by ineracting with a hydrophillic carrier. As the soluble carrier dissolves; the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. In particular, polymers such as PEGs and PVP have been extensively used as carriers for dispersions due to their low melting point and their hydrophilic environment.

The formulations of solid dispersions result into a reduction in particle size, this leads to an enhanced dissolution rate because an increase in the surface area. When the carrier material dissolves, it has a solubilization effect on the drug. Reduced lattice energy due to the formation of metastable dispersions results in a faster dissolution rate. Carrier used has an enhancing effect on wettability and dispersibility of the drug, thereby markedly improving the dissolution rate.

Here it is reported on a comparative study on effect of different hydrophilic carrier such as PEG6000, HP β-CD, Poloxamer 407and PVP on solubility and dissolution rate of fenofibrate.

Materials and Methods

Materials

Fenofibrate was received as form Alembic Ltd. as gift sample. Poloxamer 407 ,HP β – CD, Poly vinyl pyrrolidone (PVP) were received from Alembic Ltd., Baroda, India, as gift sample from virgo, Goa Poly ethylene glycol (PEG) 6000 from Clariant, Germany, Sodium hydroxide, Hydrochloric acid, Methanol were purchased from RFCL, New Delhi, India, Potassium di-hydrogen phosphate form (Nice Chemicals) ,Sodium Lauryl Sulphate from (Merck Chemicals) were purchased from virgo pharmaceutical Ltd.

Method

Linear plot of fenofibrate

A series of standard solutions of fenofibrate (5-30 ppm) were prepared from a stock solution of 50 ppm. using methanol as cosolvent 0.5% SLS medium as solvent system. The linear ploat was obtained by reading corresponding absorbance values at 291nm. Using Shimadzu 1800 UV-Vis spectrophotometer.

Saturation studies [3-6]

The phase or saturation solubility study was conducted using a water bath shaker (Remi Instrument Division, Mumbai) for 48 h at 37±0.1ºC. An indication of the process of transfer of drugs from pure water to the aqueous solutions of the hydrophilic carrier was obtained from the values of Gibbs free energy change.

$$\Delta G_{tr}^{0} = -2.303\ RT \log S_0/S_s$$

Where So/Ss = the ratio of molar solubility of drug in aqueous solutions of carriers to that of the pure water.

Drug dissolution studies

Dissolution studies of fenofibrate (API), It's SDs, and PMs were performed by using the (USP) dissolution test apparatus type-2 at rotation speed of 50 rpm in 900 mL distilled water containing 0.5% w/v of SLS, as dissolution medium at 37±0.5ºC . The SDs or PMs Equivalent to 90 mg of the fenofibrate was weighed using a digital balance (Sartorius) Germany and added into the dissolution medium. At the specified times 10, 20, 30, 45 & 60 minutes 5 mL samples were withdrawn by using syringe filter (0.45µm) (Sepyrane, Mumbai) and then assayed for the fenofibrate, content by measuring the absorbance at 290 nm using the UV-Visible spectrophotometer. Fresh medium

(5 mL), which was maintained at 37°C, was replaced to maintain sink condition

Preparation of Solid dispersions by fusion method

The SDs of fenofibrate, with PEG 6000 and Poloxamer 407 (hydrophilic polymers) containing three different weight ratios of drug and polymer (1:1, 1:3 and 1:5) were prepared by melting or fusion method[8-10] . In melting method, a required amount of drug and hydrophilic polymers were melted in a beaker on a heating mantle. The mixture was suddenly cooled using an ice bath dryed mixture was then powdered and sieved through a 60-mesh sieve, and stored in a screw-cap vial at room temperature until further use. Various formulation parameters for the preparation of SDs were summarized in for fenofibrate.

The physical mixtures (PMs) having the same weight ratio as SDs were prepared by thoroughly mixing the required amount of drug and PEGs or Poloxamer 407 in a mortar. The resulting mixtures were sieved through a 60 mesh sieve. The mixtures were stored in a screw-cap vial at room temperature until further study use.

Preparation of Solid Dispersions by kneading technique [11-12]

Inclusion complexes of drug with HPβ-CD were prepared by kneading technique in the weight ratios of 1:1, 1:3 and 1:5. Solid dispersion by kneading was prepared by mixing of drug and HPβ-CD, and then kneading with 1:9 mixture of ethanol-water to obtain a mass with a pasty consistency, which was dried in a tray dryer at 45 to 50 ^{0}c, anhydrous calcium chloride in desiccators sieved through 40 mesh sieve

The physical mixtures (PM) with HPβ-CD were prepared by sieved through 40 mesh sieve mixing of drug and HPβ-CD using mortar and pestle by simple trituration for 15 to 20 minutes and passing through 40 mesh sieve.

Differential Scanning Colorimetry

The thermal behavior of the SDs were studied using a differential scanning calorimeter (DSC 4000, Perkin Elmer, USA). A sample of 5 mg was kept in an Al pan and sealed. The isothermal study process was kept at 40°C/m and a flow rate of 25 ml/m at a temperature range of (5- 300°C) in an atmosphere of nitrogen as a purge gas.

FT-IR Studies

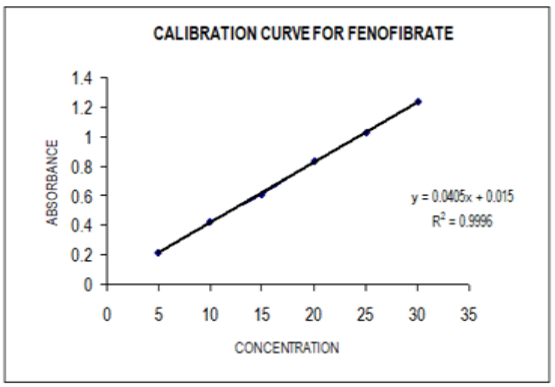
An interaction study was conducted by FT-IR anlysis (Shimadzu, Japan, FTIR-8400S). The spectra were obtained for the drug carriers and drug carrier mixture

(SDs) Samples were made using KBr discs and scanning from 450-4000 cm^{-1}

RESULTS

Linear plot

The linear plot was obtained with coefficient more than 0.999



Phase solubility studies

In case of fenofibrate, the poloxamer 407 and HP β-CD showed the highest solubilizing power, with a more than seven-fold increase of drug intrinsic solubility in the presence of 1% carrier. For PEGs there is a fourfold increase in solubility. An indication of the process of transfer of drugs from pure water to the aqueous solutions of carriers was obtained from the values of Gibbs free energy change.

Negative Gibbs free energy values indicate favorable conditions. ΔG_{tr}^{0} values were all negative for carriers at various concentrations, indicating the spontaneous nature of drug's solubilisation, and it decreased with an increase in its concentration, demonstrating that the reaction became more favorable as the concentration of carrier increased.

Dissolution profile of fenofibrate

The % drug dissolved for the SDs are showed in figure.

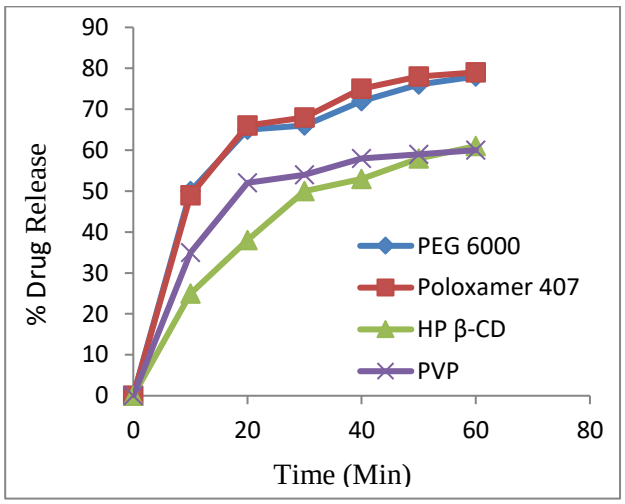


Figure 2: Dissolution profile of fenofibrate

Drug content

The percentage drug content in all the SDs was found to be between 95-98 %.

Dissolution study

Pure fenofibrate showed 28.63 % dissolution in 60 min.. Dissolution rate was found to be highest i.e., more than 90 % in case of solid dispersions of drug with PEG 4000 at the ratio of 1:5. This was considered that the hydrophobic molecule of fenofibrate preferably interacted with PEG 4000. Hence drug molecular dispersion was slightly higher in this system .

The fenofibrate solid dispersions of PEGs and Poloxamer prepared by melting or fusion technique showed better dissolution rate compared to that of Cyclodextrins prepared by kneading technique.

The enhancement of dissolution caused by the hydrophilic carriers was found to be in the order of PEGs >Poloxamer >Cyclodextrins.

Fourier Transform Infrared Spectroscopy

IR spectrum of pure fenofibrate revealed the presence of a peak at 3100 cm-1 indicating the presence of an aromatic C-H bond. Peak at 2914 cm^{-1} indicates the presence of C-H bond. Presence of peak at 1730 cm^{-1} indicates the presence of carbonyl group (C=O), Peaks in the range of 1100-1000 cm^{-1} confirms C-O stretching. IR spectra in the range of 900-600 cm^{-1} indicate presence of aromatic rings. Peak at 769 cm^{-1} is due to aromatic C-Cl stretching.

O-H stretching at 3432 cm^{-1} for PEGs and C=O stretching at 1730 cm^{-1} for drug in the solid dispersions have not undergone any change and individual peak characteristics are retained indicating the absence of interaction between the drug and the carrier.

The IR spectrum for Inclusion complexes of drug with HP-β-CD reveals the presence of a broad peak at 3422 cm^{-1}, indicative of O-H functional group. Peak at 3027 cm^{-1} indicates stretching vibration for C-H group. Retention of individual peak characteristic in the inclusion complexes by drug with HP-β-CD indicates the absence of significant interaction between the drug and the carrier.

The IR spectra of drug with poloxamer 407 reveal presence of broad peak at 3451 cm^{-1} indicating presence of O-H bond stretch . Peak at 2877 cm^{-1} indicates C-H bond. Peak at 1729 cm-1 indicates carbonyl functional group. Peak in the range 1100-1000 cm^{-1} confirms C-O stretching. Spectrum in the ranges of 900-600 cm^{-1} indicates the aromatic ring present in the drug. No significant shifting of peak characteristic indicates no significant interaction.

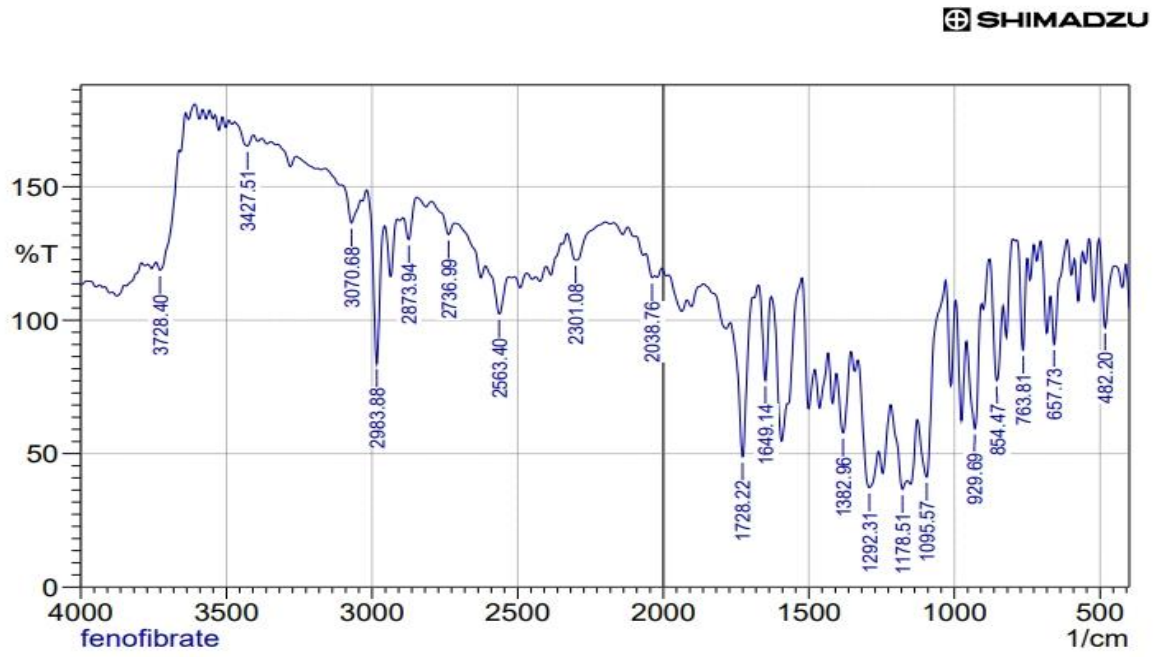


Figure 3: FTIR Spectra of Fenofibrate

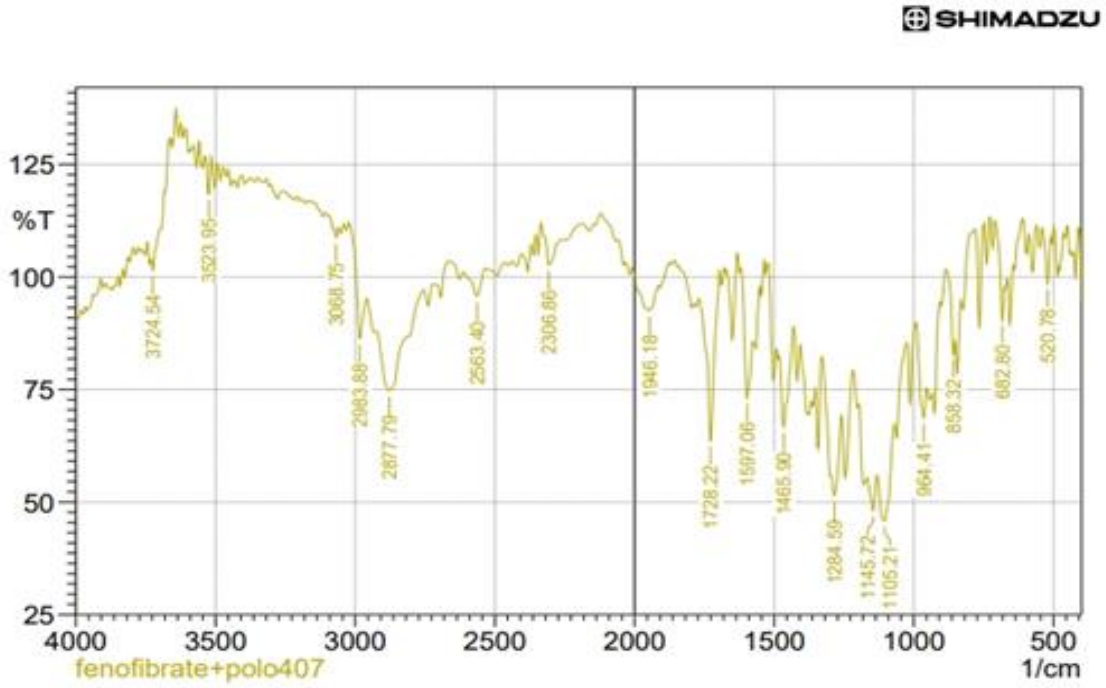


Figure 4: FTIR Spectra of Fenofibrate with Poloxamer 407

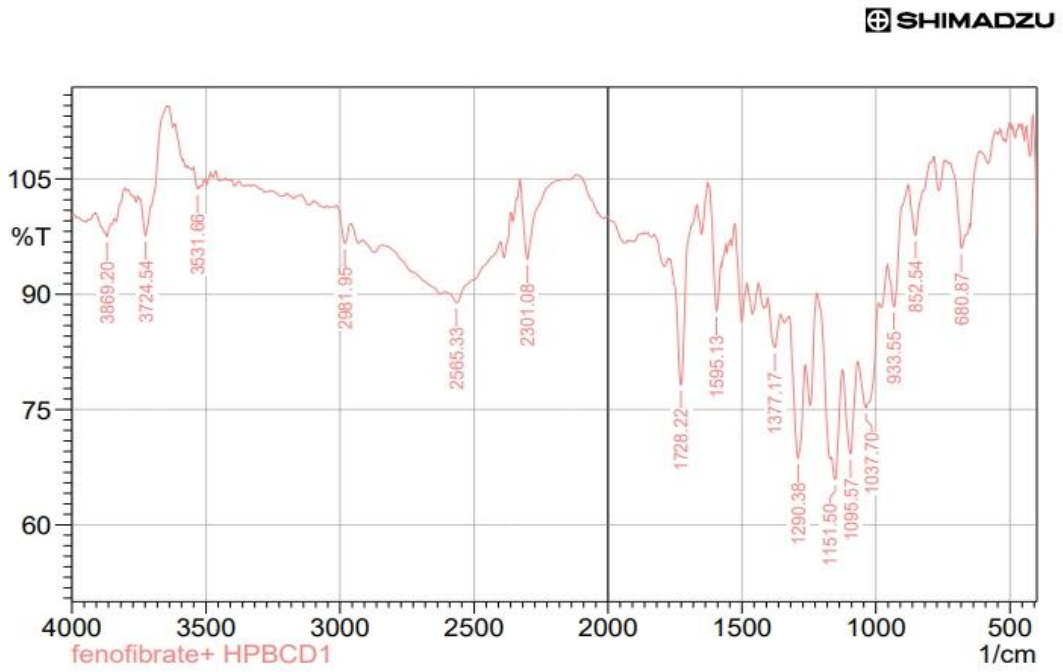


Figure 5: FTIR Spectra of Fenofibrate with HPβ-CD

ii) Differential scanning calorimetry

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The DSC thermo gram of fenofibrate is shown under the figures (F-F). A single endothermic peak corresponding to its melting point was observed at 82.21^0C .No peak for the drug was observed in the DSC curve indicating conversion of crystalline form of drug into amorphous form in the SD and homogenous distribution of drug in the formulation. Similar result was observed for SD formulation with PEG 4000 showing endothermic peaks at 60.450C without any significant peak for the drug.

In case of inclusion complex formulations with HP β-CD, there was presence of less intense endothermic peaks at 81.110C , indicating presence of crystalline form of the drug in the formulations.

The DSC thermo gram of SDs of drug with poloxamer 407, showed an endothermic peak at 50.630C, which corresponds to the MP of Poloxamer 407. Absence of any peak for drug in the thermo gram shows the conversion of drug into amorphous form in formulations.

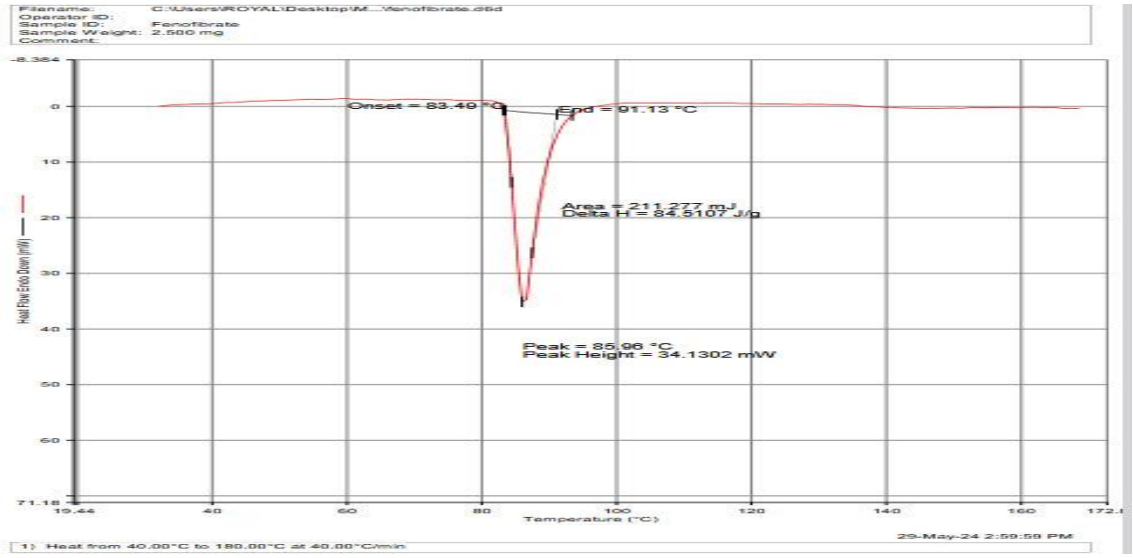


Figure 6: DSC thermogram of fenofibrate

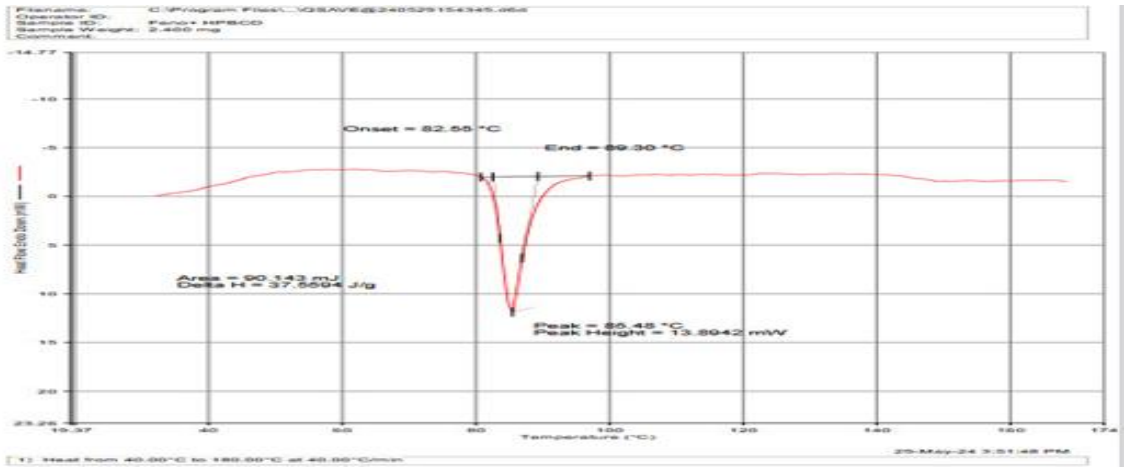


Figure 6: DSC thermogram of fenofibrate SD with Poloxamer 407 (1:5 w/w)

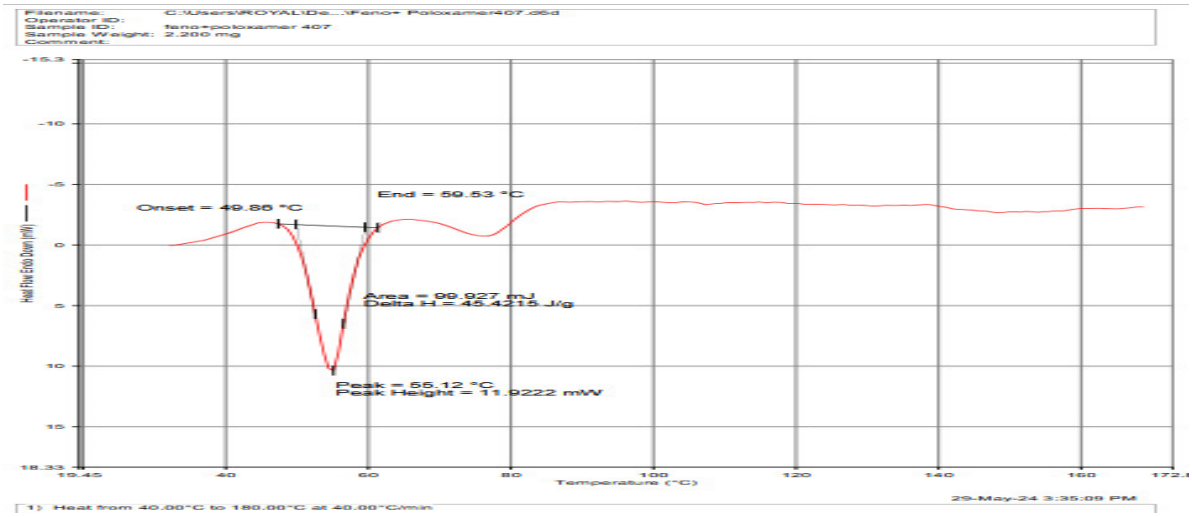


Figure 7: DSC thermogram of fenofibrate SD with HP β-CD(1:5w/w)

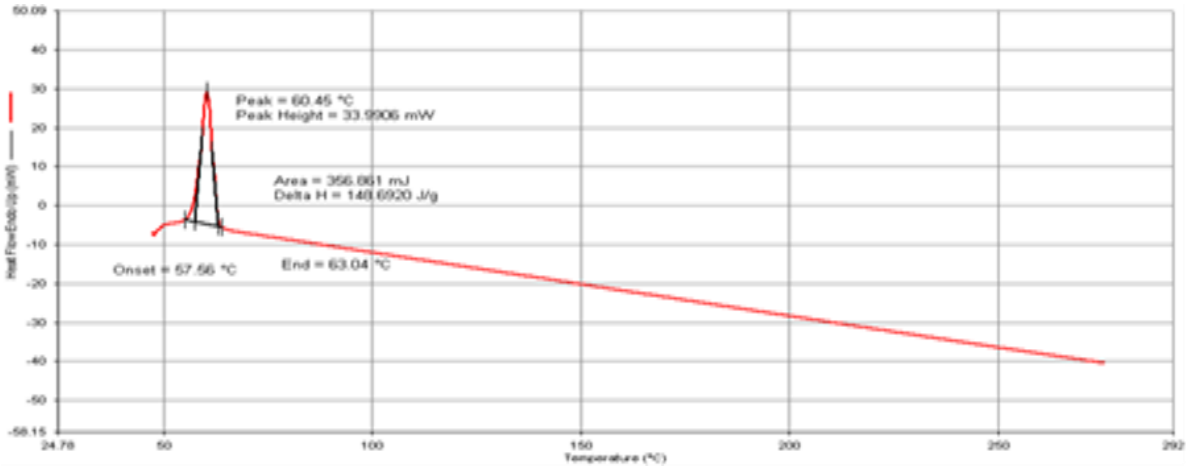


Figure 8: DSC thermogram of fenofibrate SD with PEG 6000 (1:3w/w)

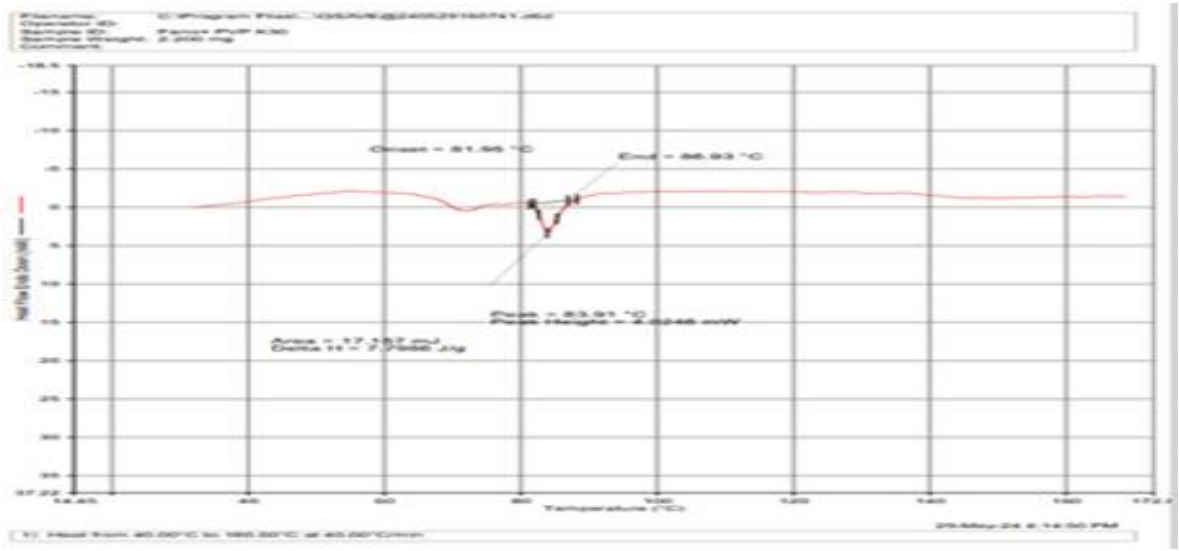


Figure 9: DSC thermogram of fenofibrate SD with PVP (1:5w/w)

Conclusion

All the formulations of solid dispersions were successfully prepared and evaluated for solubility and dissolution rate. Highest solubilizing power of PEGs towards fenofibrate was shown by phase-solubility and dissolution studies. The solubilisation effect of PEGs may be contributed due to reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug from its SD.

From FTIR spectroscopy and DSC studies, it was concluded that there was no well-defined chemical interactions between fenofibrate and PEGs in SDs. The DSC study revealed no significant interaction between fenofibrate and PEGs and there was change in crystallinity of pure fenofibrate to amorphous state in their solid dispersions. It can be concluded that the SD formulation of

fenofibrate with PEGs provides a promising way to enhance its solubility and dissolution rate.

The results indicated that hydrophilic carriers used in the formulation of solid dispersions enhanced dissolution of drugs. In case of fenofibrate, PEG 6000 can be a better polymer as a carrier for solid dispersions.

Acknowledgment

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Conflict of interest

The authors declare no conflict of interest.

Author contribution

Anjan Kumar Mahapatra designed the study and planned the work with its aim and objectives, reviewed the manuscript, and edited the manuscript. Madhusmita Lenka performed the work, collected data, and wrote the manuscript.

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