Journal of Pharmaceutical Research Science &Technology

journal homepage: https://ijpp.edwiserinternational.com

Original Article

Evaluation of Co-Crystals of Selected Drugs for Enhancement of Pharmaceutical Characteristics

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ARTICLE INFO

Received 01 December 2025
Revised 24 January 2026
Available Online 31 January 2026

Keywords:
Solubility enhancement
Solid-state modification
Dissolution improvement
Pharmaceutical co-crystals
Drug–coformer interactions

ABSTRACT

Fenofibrate, a BCS class II drug, exhibits poor aqueous solubility, which limits its dissolution rate and oral bioavailability. The present study aimed to improve the physicochemical, dissolution, and pharmacological properties of fenofibrate through co-crystallization with a Generally Recognized as Safe (GRAS) co-former. Fenofibrate–benzoic acid co-crystals were prepared using the solvent drop grinding method in different stoichiometric ratios. Among the evaluated formulations, the 1:1 drug–co-former ratio produced stable and well-defined co-crystals. The formation of co-crystals was confirmed using Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FT-IR), and Powder X-ray Diffraction (PXRD), which demonstrated the emergence of a new crystalline phase with altered thermal and structural properties. In-vitro dissolution studies revealed a significant enhancement in drug release from the optimized co-crystals, with approximately 89.83% cumulative drug release within 30 minutes, compared to 39.57% from pure fenofibrate and 61.91% from the marketed formulation. Dissolution kinetics followed a first-order release model. In-vivo antihyperlipidemic evaluation using a Triton X-100–induced hyperlipidemic rat model demonstrated that fenofibrate co-crystals significantly reduced serum total cholesterol, triglycerides, and low-density lipoprotein levels while increasing high-density lipoprotein levels when compared to the pure drug. Accelerated stability studies conducted at 40°C/75% RH for six months indicated improved stability of the co-crystals (73% drug content retained) compared to the pure drug (61%), with both formulations following first-order degradation kinetics. Overall, the study confirms that co-crystallization with benzoic acid is an effective and promising strategy to enhance the dissolution, stability, and antihyperlipidemic efficacy of fenofibrate, thereby offering potential for improved oral drug delivery and therapeutic performance.

Introduction

A significant proportion of newly developed chemical entities exhibit poor aqueous solubility, leading to low and variable bioavailability. Nearly 40–60% of marketed drugs and up to 70% of new chemical entities are reported to be poorly water soluble, posing serious challenges during formulation development. Traditional approaches such as salt formation, particle size reduction, solid dispersions, and inclusion complexes

have been employed to address these limitations; however, each approach has inherent drawbacks related to stability, scalability, or applicability [1].

Pharmaceutical co-crystals are crystalline materials composed of an API and one or more neutral co-formers in a definite stoichiometric ratio, bonded through non-covalent interactions such as hydrogen bonding, π–π stacking, and van der Waals forces. Unlike salts, both components remain in a neutral solid state under ambient conditions. Co-crystallization enables modification of physicochemical properties such as solubility, dissolution rate, melting point, hygroscopicity, and stability without altering the chemical structure or pharmacological activity of the API.

The design of pharmaceutical co-crystals relies on supramolecular synthon concepts, particularly interactions between carboxylic acids, amides, alcohols, and nitrogen-containing functional groups. The availability of a wide range of GRAS-listed co-formers further enhances the applicability of this approach in pharmaceutical development [2].

The present research aims to evaluate co-crystals of selected poorly soluble drug(s) with suitable co-formers to enhance pharmaceutical characteristics such as solubility, dissolution, and stability, thereby improving overall drug performance [3].

Materials and Methods

Materials

The selected API(s) with poor aqueous solubility were obtained from authenticated sources. Co-formers such as nicotinamide, succinic acid, citric acid, urea, glycine, saccharin, glutamic acid, and ascorbic acid were selected based on functional group compatibility, aqueous solubility, melting point, and GRAS status. All solvents and reagents used were of analytical grade.

Preparation of Co-Crystals

Solvent Evaporation Method

The API and co-former were dissolved separately in a common solvent in a suitable molar ratio. The solutions were mixed and allowed to evaporate slowly at room temperature. The obtained solid was dried under vacuum at 30 °C for 48 h [4].

Grinding Methods

- **Neat Grinding:** Drug and co-former were ground together in a mortar and pestle for a specified duration.
- **Liquid-Assisted Grinding:** A few drops of solvent were added during grinding to accelerate co-crystal formation.

Slurry Method

The API and co-former were suspended in a minimal quantity of solvent and stirred at room temperature for several hours. The solvent was decanted and the solid was dried.

Characterization of Co-Crystals

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectra were recorded to identify shifts in characteristic functional group frequencies, indicating hydrogen-bond formation between the drug and co-former [5-8].

Powder X-Ray Diffraction (PXRD)

PXRD analysis was performed to confirm the formation of a new crystalline phase by comparing diffraction patterns of the co-crystals with those of pure components.

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded to study thermal behavior and melting point changes, confirming co-crystal formation.

Scanning Electron Microscopy (SEM)

SEM was used to study surface morphology and particle shape of the prepared co-crystals.

Evaluation of Pharmaceutical Characteristics

Saturation Solubility Studies

Saturation solubility was determined using the shake-flask method in water and buffer media. Co-crystals exhibited significantly higher solubility compared with the pure drug [8-11].

In-Vitro Dissolution Studies

Dissolution studies were conducted using USP type II apparatus in phosphate buffer (pH 7.4). Co-crystals showed faster and more complete drug release.

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https://doi.org/10.31531/jprst.1000201

pH-Solubility Relationship

Solubility was evaluated across different pH conditions to assess the effect of co-crystallization on pH-dependent solubility behavior [12-15].

Stability Studies

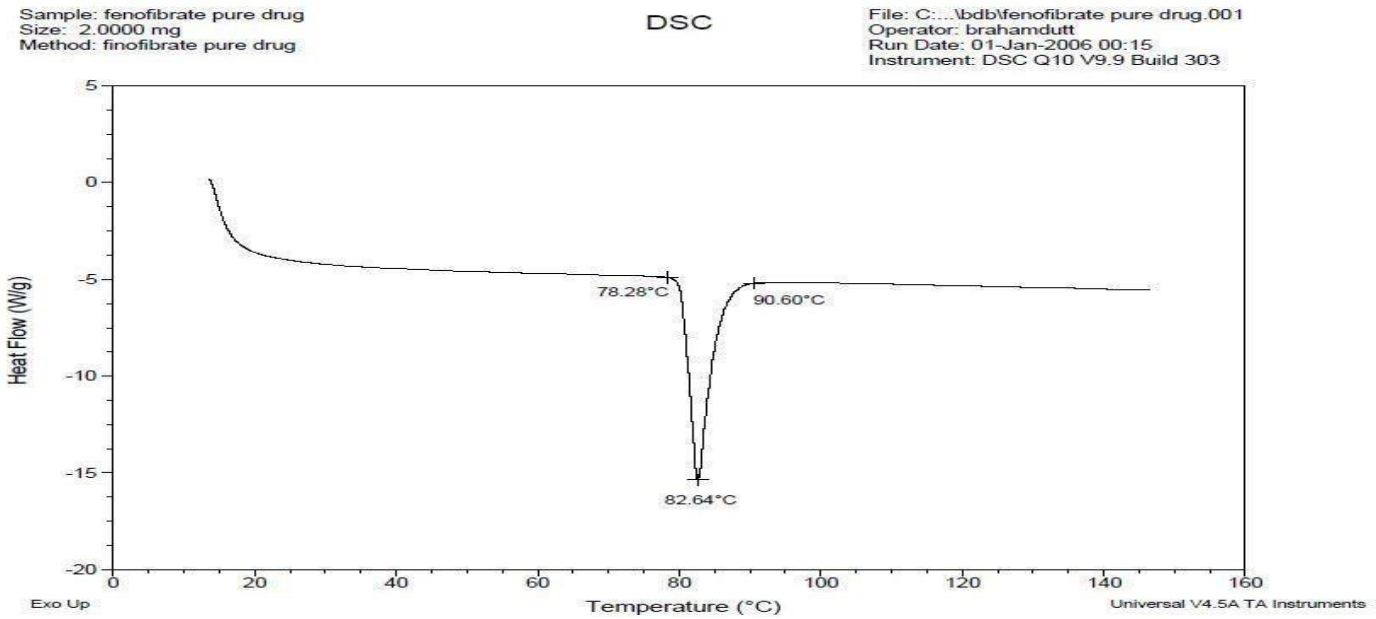
Accelerated stability studies were carried out at 40 °C ± 2 °C / 75% ± 5% RH for six months as per ICH guidelines. Co-crystals demonstrated improved physical and chemical stability [15-20].

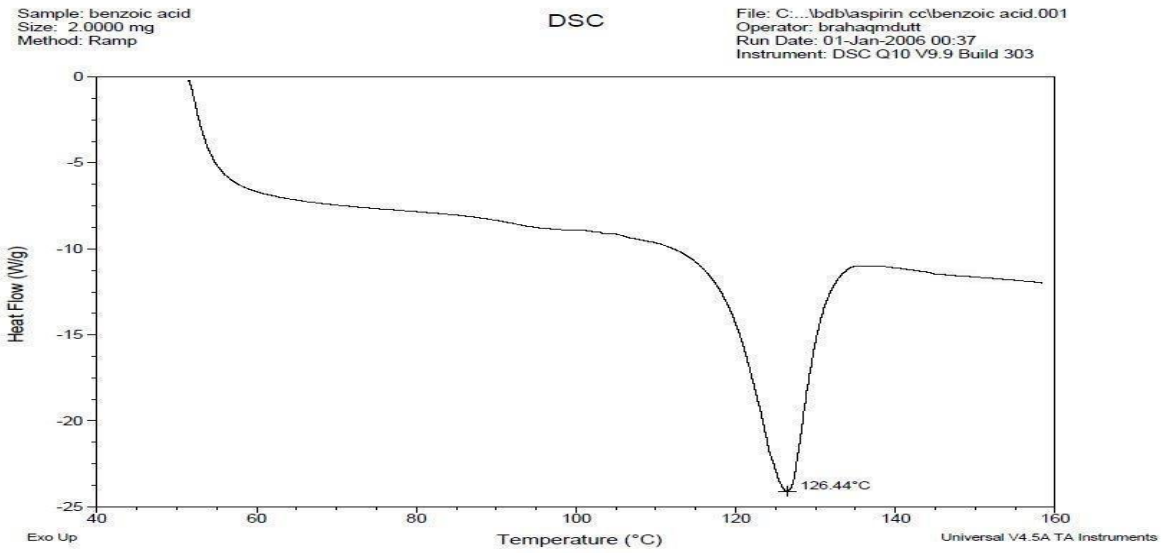
Results and Discussion

Formation and Optimization of Fenofibrate Co-crystals

Fenofibrate co-crystals were prepared using benzoic acid as a co-former by the solvent drop grinding method in different stoichiometric ratios (1:1, 1:2, and 2:1). Preliminary screening using Differential Scanning Calorimetry (DSC) revealed that the 1:1 drug–co-former ratio produced a distinct and single endothermic peak, indicating the formation of a stable and well-defined co-crystalline phase. In contrast, the 1:2 and 2:1 ratios exhibited additional endothermic peaks corresponding to the parent drug and co-former, suggesting incomplete co-crystallization.

These findings indicate that equimolar interaction between fenofibrate and benzoic acid is optimal for co-crystal formation, likely due to favorable hydrogen bonding interactions predicted by ΔpKa analysis.





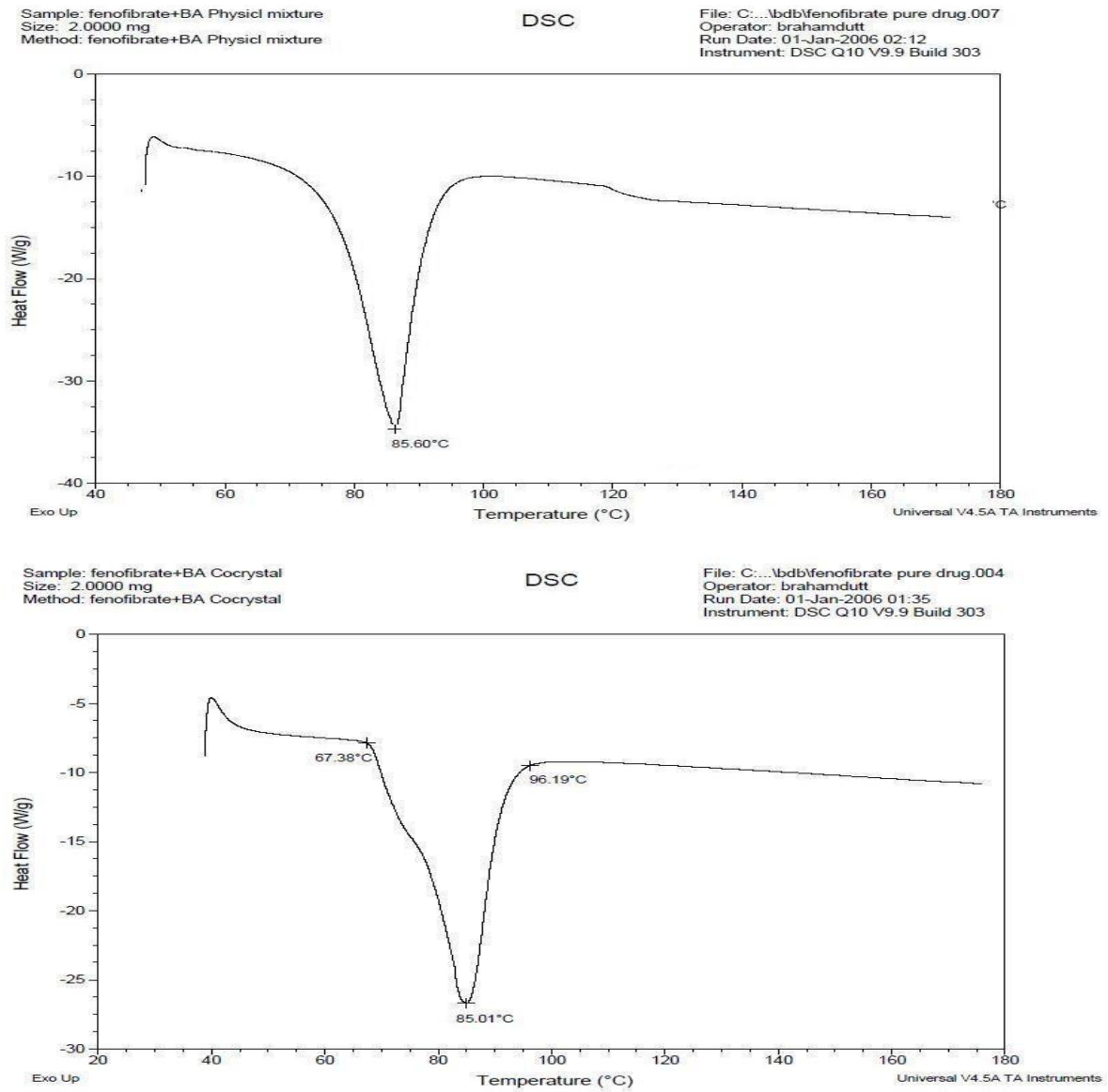


Figure 1: DSC thermograms of (A) fenofibrate, (B) benzoic acid, (C) physical mixture, and (D) fenofibrate–benzoic acid (1:1) co-crystals.

Solid-State Characterization

FT-IR Spectroscopy

FT-IR spectra of fenofibrate co-crystals showed noticeable shifts and changes in characteristic functional group frequencies compared to the pure drug and physical mixture. The disappearance of the hydroxyl stretching vibration of benzoic acid and the shifting of fenofibrate halogen-related peaks confirmed intermolecular hydrogen bonding between the drug and co-former. These spectral changes clearly indicated the formation of a new solid phase rather than a simple physical mixture.

Table 1: FT-IR spectral interpretation of fenofibrate co-crystals.

Functional Group	Fenofibrate (cm^{-1})	Benzoic Acid (cm^{-1})	Co-crystals (cm^{-1})	Interpretation
O–H stretch	–	2500–3300	Absent	Hydrogen bond formation
C=O stretch	1648	1684	1702	Shift confirms interaction
Halogen stretch	761	–	764	Participation in bonding

Powder X-Ray Diffraction (PXRD)

PXRD patterns of the optimized co-crystals displayed new diffraction peaks along with the disappearance of several characteristic peaks of fenofibrate and benzoic acid. This confirmed the formation of a distinct crystalline lattice. The sharp and intense peaks observed in the co-crystal diffractogram indicate enhanced crystallinity, which is essential for improved physicochemical stability.

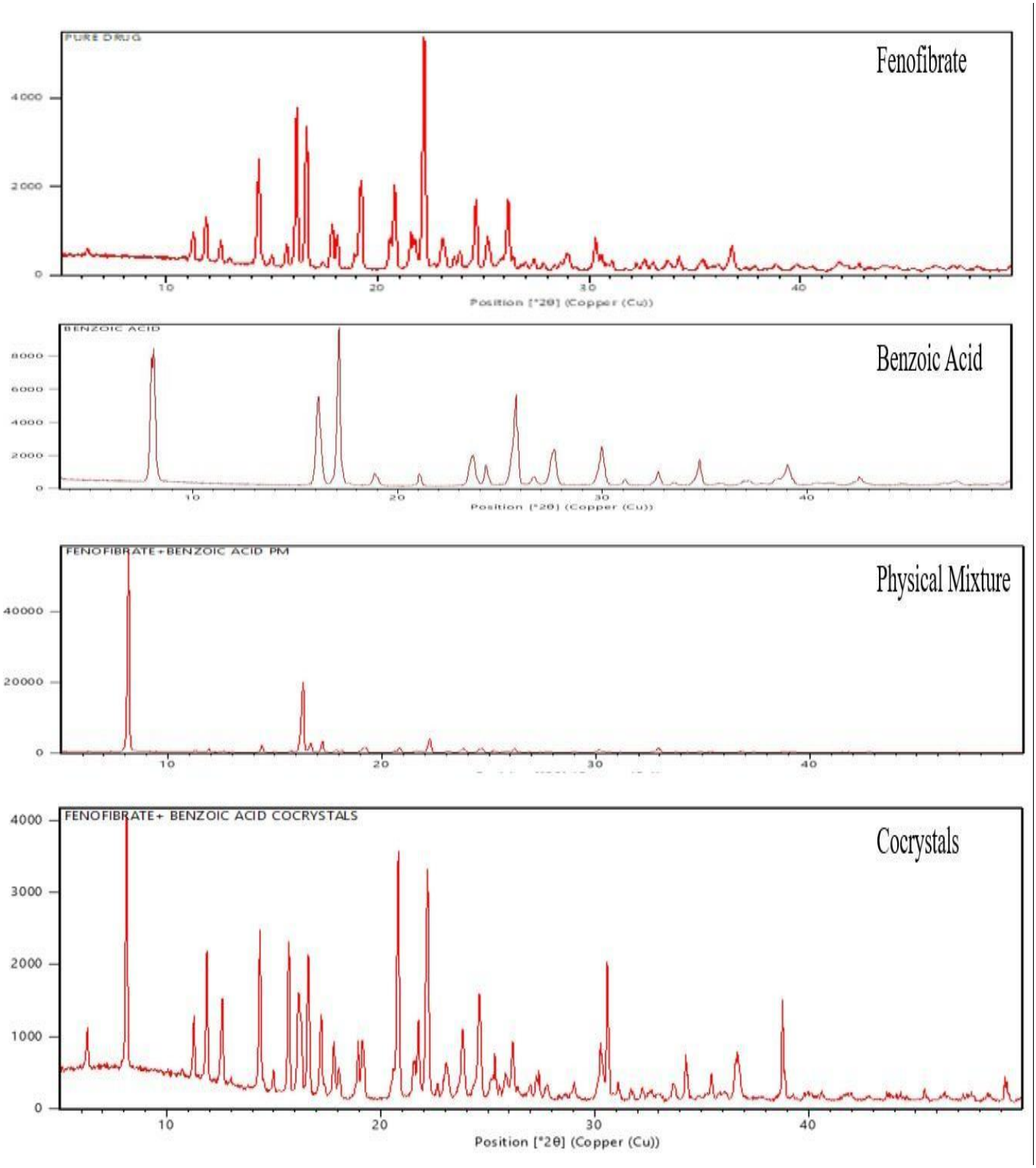


Figure 2: PXRD patterns of fenofibrate, benzoic acid, physical mixture, and optimized co-crystals.

Differential Scanning Calorimetry (DSC)

DSC analysis showed that fenofibrate co-crystals exhibited a new melting endotherm at a temperature lower than that of pure fenofibrate, indicating altered thermal behavior due to co-crystal formation. The absence of melting peaks corresponding to individual components further confirmed the formation of a homogeneous co-crystalline phase.

In-Vitro Dissolution Studies

In-vitro dissolution studies revealed a substantial improvement in the dissolution rate of fenofibrate from the co-crystal formulation compared to the pure drug, physical mixture, and marketed formulation. The optimized co-crystals released approximately **89.83%** of the drug within 30 minutes, whereas the pure drug showed only **39.57%** release during the same period.

This enhancement in dissolution can be attributed to modified crystal packing, reduced lattice energy, and improved wettability of the co-crystals.

Table 2: Percent cumulative drug release of fenofibrate formulations (n = 3).

Time (min)	Pure Drug (%)	Co-crystals (%)	Marketed Formulation (%)
5	13.21 ± 2.16	35.34 ± 1.79	17.95 ± 0.86
10	22.83 ± 1.82	57.65 ± 1.91	34.51 ± 1.29
15	32.33 ± 1.64	72.36 ± 2.11	45.21 ± 2.82
20	37.34 ± 2.13	84.17 ± 1.71	54.09 ± 2.61
30	39.57 ± 1.73	89.83 ± 0.54	61.91 ± 1.27

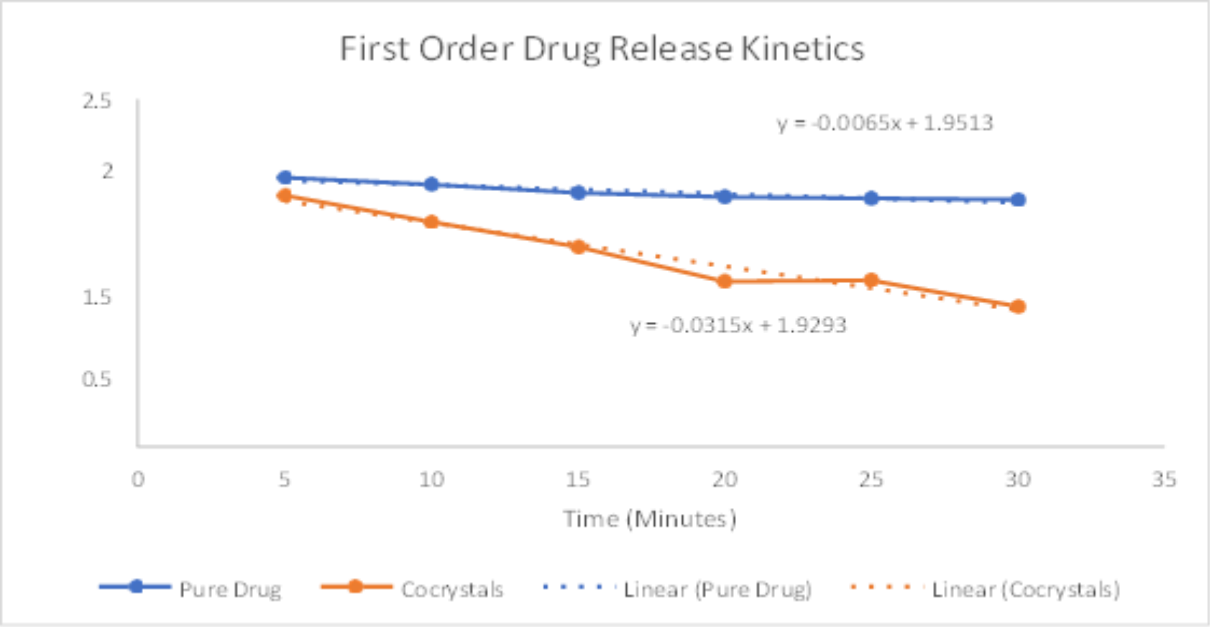


Figure 3: Comparative dissolution profiles of pure drug, co-crystals, and marketed formulation.

Kinetic analysis revealed that drug release followed **first-order kinetics**, indicating concentration-dependent drug release behavior.

In-Vivo Antihyperlipidemic Activity

In-vivo antihyperlipidemic evaluation using a Triton X-100–induced hyperlipidemic rat model demonstrated that fenofibrate co-crystals significantly reduced serum lipid levels compared to the pure drug. The optimized co-crystal formulation (50 mg/kg) showed a pronounced decrease in total cholesterol, triglycerides, and LDL levels, along with an increase in HDL levels.

The enhanced pharmacological response can be directly correlated with the improved dissolution and absorption characteristics of the co-crystals.

Table 3: Serum lipidemic data.

Groups	Dose	TC	TG	HDL	LDL	VLDL
I	Control (Triton X100- 300 mg/kg)	173.05±3.89	169.48±4.46	29.47±4.53	109.33±2.89	28.86±3.49
II	Cocrystal s (25 mg/kg)	159.67±4.85 **	122.31±3.82 **	27.80±0.59 ns	102.10±2.31 **	26.73±1.41 ns
III	Cocrystal s (50 mg/kg)	89.23±3.72* *	81.37±3.35* *	38.12±1.13 **	45.97±2.09* *	15.83±0.98 **
IV	fenofibrat e (50 mg/kg)	108.2±2.55* *	98.55±2.03* *	33.21±1.98 ns	58.31±3.61* *	20.76±2.39 **

Statistical analysis using ANOVA confirmed that the observed lipid-lowering effects were statistically significant ($p < 0.05$) when compared to the control and pure drug groups.

Stability Studies

Accelerated stability studies conducted at **40°C ± 2°C / 75% ± 5% RH** for six months showed that fenofibrate co-crystals retained approximately **73%** of drug content, whereas the pure drug retained only **61%**. HPLC analysis confirmed improved stability and slower degradation kinetics in co-crystals.

Both pure drug and co-crystals followed **first-order degradation kinetics**, but the co-crystals exhibited a lower degradation rate constant, indicating enhanced stability.

Table 4: Stability comparison of fenofibrate and co-crystals.

Formulation	Drug Content after 6 months (%)	Degradation Kinetics
Pure drug	~61	First order
Co-crystals	~73	First order

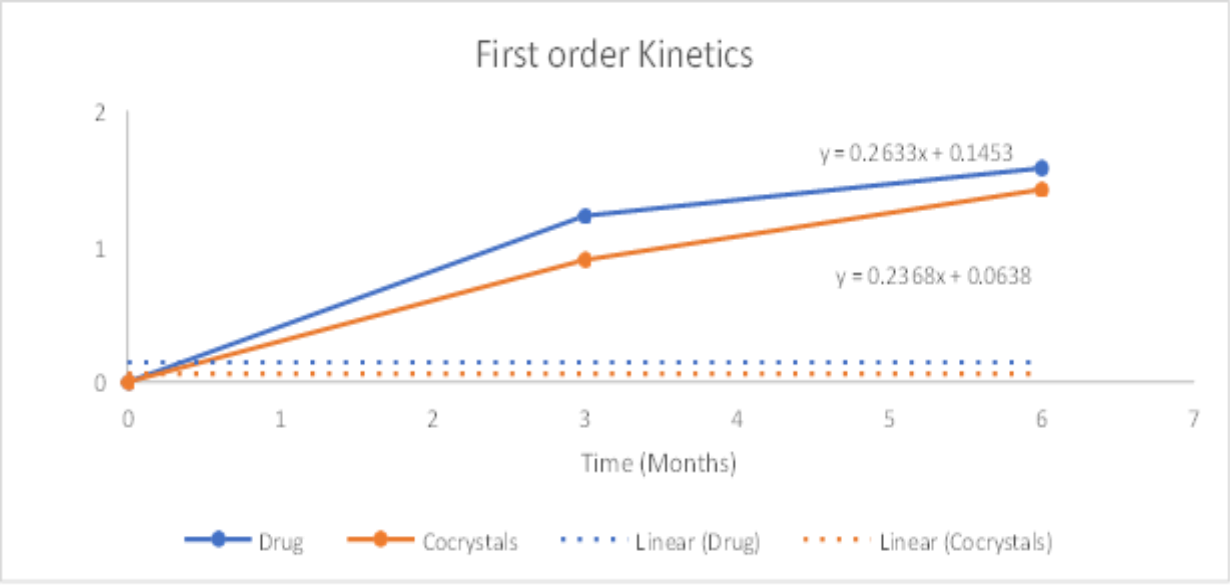


Figure 4: First-order degradation kinetics of fenofibrate and co-crystals.

Conclusion

The present investigation successfully demonstrated the potential of co-crystallization as an effective solid-state modification strategy to overcome the limitations associated with the poor aqueous solubility of fenofibrate, a BCS class II drug. Fenofibrate–benzoic acid co-crystals were successfully developed using the solvent drop grinding technique, with the equimolar (1:1) ratio producing stable and well-defined co-crystals.

Comprehensive solid-state characterization using DSC, FT-IR, and PXRD confirmed the formation of a new crystalline phase resulting from intermolecular interactions between fenofibrate and benzoic acid. The optimized co-crystal formulation exhibited a significantly enhanced dissolution profile, achieving approximately 89.83% drug release within 30 minutes, which was markedly higher than that of the pure drug and the marketed formulation. Dissolution kinetics followed a first-order release model, indicating concentration-dependent drug release behavior.

Furthermore, in-vivo antihyperlipidemic evaluation in a Triton X-100–induced hyperlipidemic rat model demonstrated superior lipid-lowering efficacy of the co-crystals, evidenced by significant reductions in serum total cholesterol, triglycerides, and LDL levels, along with an increase in HDL levels. Accelerated stability studies further revealed improved stability of the co-crystal formulation, with higher drug content retention compared to the pure drug over a six-month period under stress conditions.

Overall, the findings confirm that co-crystallization with benzoic acid significantly enhances the dissolution, stability, and therapeutic performance of fenofibrate, highlighting its potential as a promising approach for improving oral drug delivery of poorly water-soluble drugs.

Future Prospects

Although the present study provides strong evidence supporting the advantages of fenofibrate co-crystals, further investigations are warranted to facilitate their translation into a clinically viable dosage form. Future research should focus on:

- **Scale-up and manufacturing feasibility**, including evaluation of industrially applicable co-crystallization techniques and batch-to-batch reproducibility.
- **Comprehensive toxicological and safety assessments** to establish the long-term safety of the co-crystal formulation.
- **Pharmacokinetic and bioavailability studies** in higher animal models and humans to confirm enhanced systemic absorption.
- **Development of solid oral dosage forms**, such as tablets or capsules, incorporating co-crystals and evaluation of their in-vitro–in-vivo correlation (IVIVC).
- **Exploration of alternative GRAS co-formers** to further optimize physicochemical and biopharmaceutical properties.
- **Regulatory evaluation**, focusing on compliance with pharmaceutical guidelines for co-crystal-based drug products.

With continued research and development, fenofibrate co-crystals hold strong potential for clinical and commercial application, offering an efficient and cost-effective strategy to improve the performance of poorly soluble therapeutic agents.

Funding

The project did not received any funding from private or government sources.

Conflict of Interest

None declared.

Author Contributions

All the authors contributed to the study.

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