Journal of
Food and Pharmaceutical Sciences

Original Article

Increased Dissolution Rate of Solid Dispersion Fenofibric Acid PEG 6000 and In vivo Study

Deni Anggraini*, Nesa Agistia, Armon Fernando, Amanda Yulia, and Dira Repuja

Sekolah Tinggi Ilmu Farmasi Riau, Pekanbaru, Riau, Indonesia
*Corresponding author: Deni Anggraini | Email: denianggraini@stifar-riau.ac.id

Received: 22 November 2025; Revised: 4 February 2026; Accepted: 8 February 2026; Published: 25 April 2026

Abstract: Fenofibrate acid is a fibrate drug with high permeability but low water solubility, resulting in limited bioavailability. Solid dispersion using hydrophilic carriers is one strategy to increase solubility. The objective of this study was to improve the solubility of fenofibric acid by converting it into a solid dispersion system using PEG 6000 as a carrier. Preparation of solid dispersion systems by the melting method. The fenofibric acid PEG 6000 weight ratios were F1 (1:1), F2 (1:3), and F5 (1:5). Physicochemical characterization of the solid dispersions included DSC, PXRD, FTIR, and SEM tests, as well as dissolution and bioavailability tests with the determination of pharmacokinetic parameters. Characterization results show that fenofibric acid with PEG 6000 as a carrier still exhibits a crystalline phase but with reduced intensity, resulting in increased solubility and dissolution rate. Dissolution test show that solid dispersion F3 (1:5) dissolves faster (78.7%) than pure fenofibric acid (53.2%). after 60 minutes. Pharmacokinetic parameter determination tests showed no significant difference between pure fenofibric acid and solid dispersion. Solid dispersion of fenofibric acid with PEG 6000 as a carrier can improve the physicochemical performance and dissolution rate of fenofibric acid but pharmacokinetic parameters did not differ significantly.

Keywords: fenofibric acid, in vitro dissolution, poorly water-soluble drugs, solubility enhancement

1. INTRODUCTION

The solubility of pharmaceutical active ingredients (API) can affect the bioavailability of these active pharmaceutical ingredients. Poorly soluble drugs have low bioavailability in the human body. Currently, approximately 40% of active pharmaceutical ingredients on the market and 90% of drug compounds in development have poor water solubility [1]. Many methods are available to increase the rate of dissolution, such as salt formation, micronization, and the addition of surfactants. Every method has limitations on its use. Salt crystals are often used, but are limited to ionized compounds. In addition, it does not provide sufficient solubility improvement. Pharmaceutical active ingredients are generally weak acids and bases with low ionization capacity. [2].

Solid dispersion is one method that has been successfully used to increase solubility and dissolution rate. The concept of solid dispersion was introduced in 1961 by Sekiguchi and Obi [3]. In solid dispersion, the drug is dispersed in a water-soluble carrier that is non-reactive in the solid state. The formation of solid dispersions is achieved using water-soluble carriers [4].

Fenofibric acid (FA) is a new generation antihyperlipidemic drug. The physicochemical properties of new drugs need to be developed so that they are more effective, efficient, and have minimal side effects.[5] Based on solubility and permeability classification, FA belongs to the BCS class II group.[6] Therefore, solubility and dissolution rate are the limiting factors of its bioavailability. Improvements in the solubility of fenofibric acid that have been made so far that use of $MgCO_3$ as a catalyst,[7] formation of multicomponent crystals and formation of self nanoemulsion drug delivery system (SNEDDS) [8,9,10].

Efforts to increase the solubility of fenofibric acid have so far been limited to forming multicomponent crystals with various coformers (nicotinic acid, nicotinamide, syringic acid,

proline) [11,12,13,14], but the results in terms of solubility improvement have not been optimal. The formation of fenofibrate acid solid dispersion with PEG 6000 as a carrier have not been reported. Therefore, the formation of fenofibrate acid solid dispersions using PEG 6000 as a carrier and conducting dissolution tests, and determining pharmacokinetic parameters were carried out in this study. The objective of this study was to form fenofibric acid into a solid dispersion with PEG 6000 and to characterize its physicochemical properties, dissolution test, and in vivo study.

2. MATERIALS AND METHODS

Material used in the preparation of solid disperses; fenofibric acid (BOC Sciences USA), PEG 6000 (Tokyo Chemical Industries Japan), Ethanol 96% pro analyzer (Merck Germany). Materials used in pharmacokinetic testing: male rabbits (Oryctolagus cuniculus), heparin, plasma, internal standard 4′-chloro-5-fluoro-2-hydroxybenzophenone (CFHB) (Tokyo Chemical Industries Japan), HCl (Merck), ethyl acetate (Merck), acetonitrile (Merck)

2.1. Preparation of Formula

2.1.1. FA PEG 6000 Solid Dispersion

FA and PEG 6000 were weighed in ratios of F1 (1:1), F2 (1:3), and F3 (1:5). Each formula was made into a 10 g solid dispersion powder. PEG 6000 was melted on a hot plate at a temperature of ± 65 °C, then FA was added and stirred until homogeneous. After mixing, cool quickly using ice and leave for 1 hour. Grind the solid dispersion and sieve it using a 425 μm sieve. Store in a desiccator for further testing.

2.1.2. FA PEG 6000 Physic Mixture

The physical mixture is made by physically homogenizing FA and PEG 6000 in a mortar with a spatula for 10 minutes.

2.2. Physical and Chemical Characterization of Solid Dispersions

2.2.1. Thermal Analysis

Thermal analysis using DSC (Shiamdzu® DSC-60 Plus, Japan)The DSC instrument was set at a temperature of 30˚-300˚C with a heat flow of 10˚C/minute. Analysis was performed on FA, PEG 6000, and FA-PEG 6000 solid dispersion.

2.2.2. PXRD Analysis

Using an X-ray diffractometer (PANalitycal® MPD PW3040/60), the sample was placed on a sample holder and analyzed at an angle of 2θ in the range of 5˚-35˚. The analysis was conducted at room temperature using a Cu target metal, Kα filter, 45kV voltage, and 40 mA current. Determine the diffractogram pattern to evaluate changes in crystallinity. This analysis was conducted on FA, PEG 6000, and FA-PEG 6000 solid dispersion.

2.2.3. SEM Analysis

The samples analyzed at several magnifications using a SEM. A comparative analysis of the particle shapes in each sample was performed. This test was conducted on FA, PVP K-30, FA-PEG 6000 solid dispersion, and physical mixtures.

2.2.4. FTIR Analysis

Infrared spectroscopy analysis was performed using an IR spectrophotometer Shimadzu® IR Spirit-A224`58. The absorption of the analyzed samples was recorded at wavelengths of 4000-600 nm-1. The spectra were analyzed for FA, PEG 6000,and FA-PEG 6000 solid dispersion.

2.3. Dissolution Test

Dissolution testing was conducted using a type 1 dissolution apparatus (SR8-Plus Hanson Research, USA), at 50 RPM and 37°C, in 900 mL of distilled water. Dissolution test for 60 minutes.

The sample absorbance is analyzed with a spectrophotometer at the maximum wavelength. The experiment was conducted triplo on FA samples and FA-PEG 6000 solid dispersions.

2.4. In Vivo Study

2.4.1. Pharmacokinetic Study of Fenofibric Acid in Rabbit

Animal testing has been approved by the Riau University Faculty of Medicine Ethics Committee No. 068/UNI.9.5.1.1.8/UEPKK/2025. The research design used a two-period randomized crossover method. The test was conducted on three male New Zealand white rabbits, aged three months and weighing 2-3.5 kg. Two groups of experimental animals, namely the solid dispersion group and the pure fenofibrate acid group. Each group consisted of six rabbits calculated based on Federer's formula. The animals were acclimatized and fasted for 12 hours before administration of the drug. Each group of animals was given 4.9 mg/kg of fenofibric acid orally and a solid dispersion equivalent to 4.9 mg/kg. The oral dosage form for the FA sample is a suspension, while the FA PVP K-30 solid dispersion sample is a solution dosage form. Volume of drug administration according to Thomson's law from a 1% concentration drug solution. Blood was collected from the marginal vein of the rabbit's ear at a volume of 1 mL. At 0 hours (before drug administration) and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, and 72 hours. Add 100 µL of heparin to the blood sample, centrifuge at 2000 RPM for 8 minutes. The supernatant was stored at −20°C for analysis.

2.4.2. Preparation of Plasma Sample

Plasma sample (200 µL) was added to 50 µL of CFHB internal standard solution (250 µg/mL) and 1 mL of 1 N HCl and mixed for 30 seconds in a vortex mixer. Three mL of ethyl acetate was added. The mixture was vortexed for 5 minutes and centrifuged for 15 minutes. Separate the supernatant, evaporate to dryness at 40°C. Dissolve the dry residue in 100 µL of mobile phase, and inject 60 µL into the HPLC apparatus. Determine the area under the curve, calculate the concentration of fenofibric acid in the blood sample, and determine the pharmacokinetic parameters (AUC, Cmax, Tmax, and t½ values). The chromatographic conditions for testing are mobile phase acetonitrile phosphate buffer (75:25), C18 column (4.6x150 mm), flow rate 1 ml/minute, wavelength 298 nm.

2.5. Data Analysis and Statistic

Pharmacokinetic parameters (AUC, Tmax, Cmax, and elimination t1/2) were calculated using the PKSolver Ms.Excel application and analyzed statistically using the t-test. Solubility and dissolution test data were presented descriptively in tables and graphs.

3. RESULTS AND DISCUSSION

This study prepared a solid dispersion of fenofibric acid using PEG 6000. Solid dispersions are drug dispersions in a solid matrix, where the matrix consists of small molecules or polymers. Solid dispersions can be eutectic mixtures, crystalline/glass solutions, and amorphous/crystalline suspensions.[15] In solid dispersions, the drug is molecularly dispersed in a hydrophilic carrier. This method is very promising for the development of drugs that have poor solubility in water [16].

3.1. Thermal Analysis

DSC analysis is a method used to analyze the behavior of solids when subjected to heat flow [17]. This method can be used to characterize the thermodynamic properties of the solid phase. The DSC thermogram overlay (Figure 1) shows a peak at 185.75°C, which is the melting point of fenofibric acid. PEG 6000 shows a peak at 56.63°C, which is the melting point of PEG 6000. A decrease in the melting point occurs in the FA PEG solid dispersion system (53.92°C). The shift of the melting point to a lower point and the decrease in enthalpy value will reduce the intermolecular bond energy, which ultimately reduces the crystal lattice energy [18].

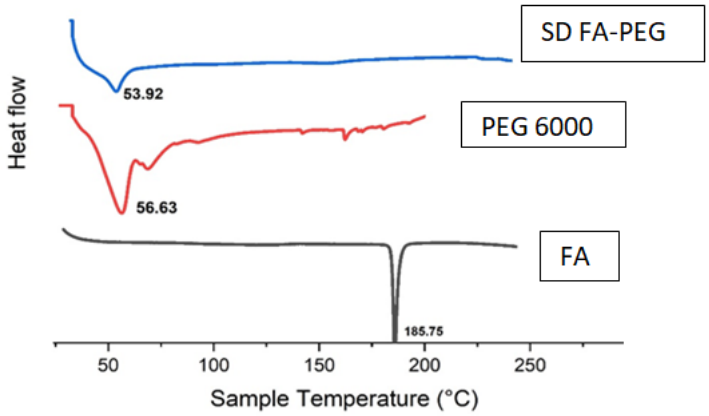

Figure 1. Overlay Thermogram DSC

3.2. PXRD Analysis

PXRD analysis to examine the crystallinity of a substance, which can be analyzed based on the diffraction pattern formed. The X-ray diffraction patterns for fenofibric acid, PEG 6000, and solid dispersion FA-PEG can be seen in Figure 2. The fenofibric acid diffraction pattern at an angle of 2 theta shows diffraction peaks at 18.65, 19.41, 21.60, and 23.28. The characteristic diffraction of PEG 6000 at 2 theta are 19.17; 23.33; and the solid dispersion diffraction pattern shows a superimposed diffraction peak pattern between the diffraction peaks of fenofibric acid and PEG 6000, but with decreased intensity. The overlay diffraction pattern shows no new diffraction peaks, crystalline solids characterized by sharp peaks, but a decrease in crystallinity compared to pure fenofibric acid. This data correlates with the decrease in melting point in the DSC test [19].

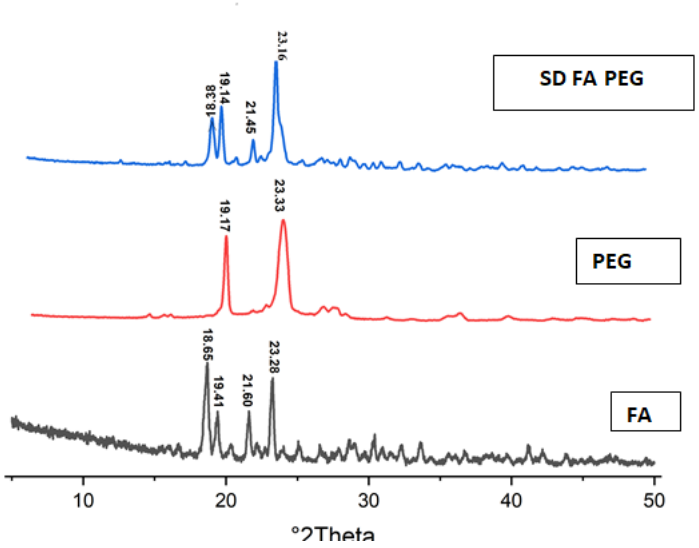

Figure 2. Overlay Diffractogram

3.3. *SEM Analysis*

Analysis of particle shape obtained SEM (Figure 3) shows the morphology of FA, PEG 6000, and solid disperse. The morphology of FA is irregular cubic agglomerates with sharp edges. The morphology of PEG 6000 is lumps that are larger than FA. The morphology of the solid dispersion

powder shows a different morphology from FA and PEG 6000, indicating that a physical change has occurred in the solid dispersion system [20].

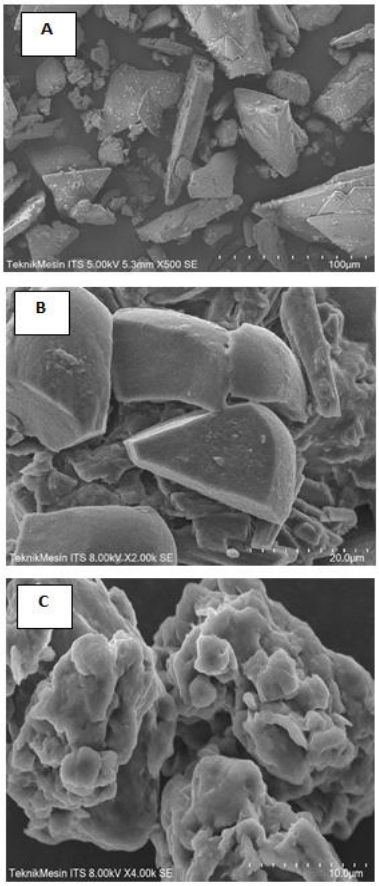

Figure 3. Scanning electron micrographs of (A) Fenofibric Acid (B) PEG 6000 (C) Solid Dispersion

3.4. FTIR Analysis

FTIR spectroscopy analysis to observe the spectrum formed from the solid dispersion powder between FA and PEG 6000 compared to the spectrum of pure FA. The IR spectrum in Figure 4 shows that the wave numbers in the fingerprint region produced from the solid dispersion powder with FA are not significantly different. The solid dispersion powder does not show any interaction between FA and PEG 6000 due to the similarity in the fingerprint region at wave numbers of 4000 - 500 cm^{-1}.

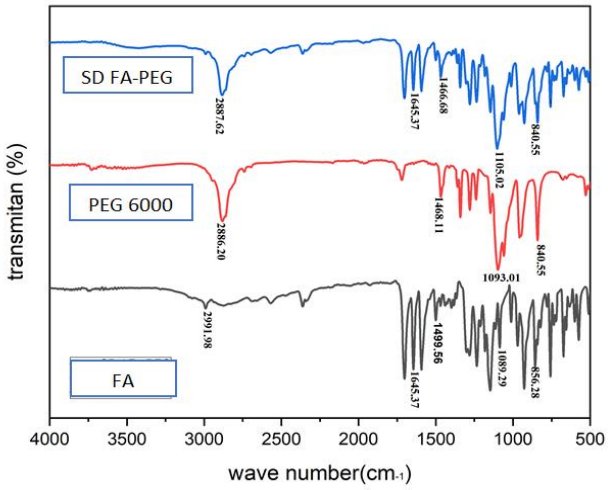

Figure 4. Spectrum of FA, PEG 6000 and Solid Dispersion FA-PEG

3.5. Dissolution Study

The dissolution study was conducted using a CO_2-free distilled water dissolution medium at a temperature of 37 °C. The dissolution rate profiles of FA and solid dispersions (F1, F2, F3) shown in Figure 5. Based on the results of the study, it can be concluded that PEG 6000 can increase the dissolution rate of FA. FA dissolved at 60 minutes was 53.2%, while solid dispersions F1, F2, and F3 dissolved at 57.05%, 60.54%, and 78.76%, respectively. The dissolution rate of the solid dispersion system increased in line with the increase in the PEG 6000 ratio in the formulation.

The dissolution test results showed a significant difference in the rate of solid dispersion compared to pure fenofibric acid. The mechanisms is dissolution and increased drug moisture in a microenvironment rich in hydrophilic carriers formed on the surface of the drug crystals after the drug dissolves [21,22]. In the PEG 6000 solid dispersion system, the crystallinity of fenofibrate acid decreases. The IR spectrum shows no interaction between FA and PEG 6000.

The solid properties of pharmaceutical active ingredients (APIs)—including crystal form, particle size, and amorphous content—significantly influence the in vitro dissolution rate, which will determine in vivo pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to peak concentration (Tmax), and area under the curve (AUC). This relationship is formally modeled through In Vitro-In Vivo Correlation (IVIVC), where the dissolution profile serves as a surrogate for drug absorption in the gastrointestinal tract [23].

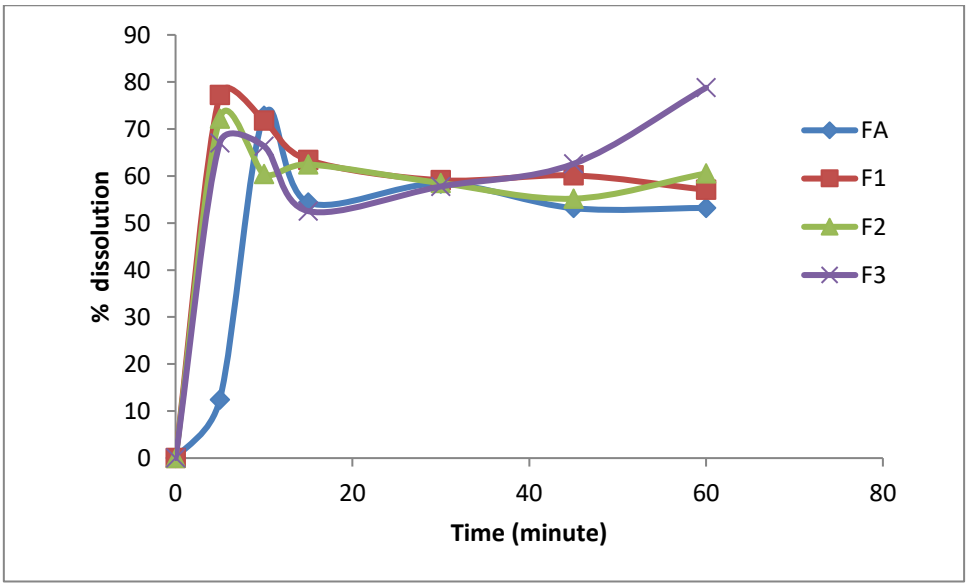

Figure 5. Dissolution Profile of FA and Solid Dispersion

3.6. In Vivo Pharmacokinetic Study

Determination of pharmacokinetic parameters (AUC, Tmax, Cmax, and elimination T1/2) of fenofibric acid in rabbit blood using high-performance liquid chromatography. All pharmacokinetic parameters are listed in Table 1. The pharmacokinetic parameters (AUC and C_{max} of fenofibric acid different significantly ($p<0.05$) compared to its solid dispersion system, this indicates that the plasma profile produced by fenofibric acid was higher than that of the solid dispersion. The differences in initial solubility observed in the in vitro test were not reflected in the in vivo test. This is because fenofibric acid is absorbed with the help of an active transport mechanism transporter. Although in limited quantities, it is mostly soluble [24, 25].

Theoretically, the in vivo profile directly corresponds to the in vitro dissolution profile. In this study, fenofibric acid, a class II biopharmaceutical drug substance, did not show this, which may be due to fenofibric acid having complex absorption properties where each process is significantly influenced by physiological factors throughout the gastrointestinal tract [26].

Table 1. Pharmacokinetic parameters (n=6)

Pharmacokinetic Parameters	C_{max} (μg/mL)±SD	T_{max} (hours)	AUC(0-72)±SD	$T_{1/2}$ (hours)
Fenofibric acid	678.68±0.02	8	6613.66±0.09	13
Solid dispersion FA PEG	720.68±0.07	8	4271.48±0.04	15

C_{max} and AUC value analyzed with independent t-test with 95% confidence interval, n= 6, different significantly at $p < 0.05$.

4. CONCLUSION

The solid dispersion system of fenofibric acid with PEG 6000 can increase the dissolution rate of fenofibric acid but does not affect its pharmacokinetic parameters. The solid dispersion of FA PEG 6000 with a ratio of 1:5 is the best solid dispersion, dissolving 78.7% after 60 minutes, while pure FA only dissolves 53.2%.

Funding: Directorate of Research, Technology, and Community Service (DRTPM)
Acknowledgments: The authors are grateful for the financial support from the DRTPM of the Ministry of Higher Education, Science, and Technology of the Republic of Indonesia (contract number 022/LL17/DT.05.00/PL/2025
Conflicts of interest: The authors declare no conflict of interest.

References

1. S. Kalepu, & V. Nekkanti, " Insoluble drug delivery strategies: Review of recent advances and business prospects". *Acta Pharmaceutica Sinica* B, 5(5), 442–453, 2015. https://doi.org/10.1016/j.apsb.2015.07.003
2. N.Thakral, N. K., Behme, R. J., Aburub, A., Peterson, J. A., Woods, A., Diseroad, B. A., Suryanarayanan, R., & Stephenson, G. A. "Salt Disproportionation in the Solid-State : role of solubility and counter-ion volatility Salt Disproportionation in the Solid-State" : role of solubility and counter-ion volatility. 2016 https://doi.org/10.1021/acs.molpharmaceut.6b00745
3. K. Sekiguchi, & N. Obi, " Studies on absorption of eutectic mixture. I.A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man." *Chem Pharm Bull* ; 9: 866-72.1961
4. W.I. N.L., Chiou, & S. Riegelmant "Pharmaceutical sciences Pharmaceutical Applications of Solid" 60(9), 1281–1302. 1971
5. Jalan, P., Bahan, P., Obat, B., & Negara, T. L. *BERITA NEGARA*. 1656, 1–40.2013
6. Y.Tsume, D.M., Mudie, P. Langguth, G.E Amidon, & G.L. Amidon, "The Biopharmaceutics Classification System" : Subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. *European Journal of Pharmaceutical Sciences*, 57(1), 152–163. 2014 https://doi.org/10.1016/j.ejps.2014.01.009
7. K.S. Kim, J.H. Kim, S.G. Jin, D.W Kim, D. W.,D. S., Kim, J. O., Yong, C. S., Cho, K. H., Li, D. X., Woo, J. S., & Choi, H. G. Effect of magnesium carbonate on the solubility, dissolution and oral bioavailability of fenofibric acid powder as an alkalising solubilizer. *Archives of Pharmacal Research*, 39(4), 531–538. 2016 https://doi.org/10.1007/s12272-015-0701-9
8. W.N. Suhery, Y.C. Sumirtapura, J.S. Pamudji, & D. Mudhakir, " Development and characterization of self-nanoemulsifying drug delivery system (Snedds) formulation for enhancing dissolution of fenofibric acid". *Journal of Research in Pharmacy*, 24(5), 738–747. 2020 https://doi.org/10.35333/jrp.2020.227
9. D. Anggraini, G. Novita, & I. Wulandari, Improved Solubility Novel Multicomponent Crystals of Fenofibric Acid-Acetylsalisylic Acid. *Medical Sains : Jurnal Ilmiah Kefarmasian*, 10(1), 89–98. 2025 https://doi.org/10.37874/ms.v10i1.1690
10. D. Anggraini, F. Firmansyah, G. Novita, & R.A. Audia, " Improving the Solubility of Fenofibric Acid via Multicomponent Crystal Formation with Theobromine Coformer. *Tropical Journal of Natural Product Research*, 8(4), 6901–6905. 2024. https://doi.org/10.26538/tjnpr/v8i4.21
11. D. Anggraini, H. Salsabila, S.Umar, Y.Aldi, & E. Zaini, Preparation and Characterization of a Eutectic Mixture of Fenofibric Acid and Nicotinic Acid and Evaluatuion of In Vivo Antihyperlipidemic Activity. Science and Technology Indonesia, 7(4), 514–521. 2022 https://doi.org/10.26554/sti.2022.7.4.514-521

12. D. Anggraini, S. Umar, H. Arifin, & E. Zaini, E. Dissolution rate enhancement and physicochemical characterization of a fenofibric acid–nicotinamide eutectic mixture. Tropical Journal of Natural Product Research, 5(9), 1614–1618. 2021 https://doi.org/10.26538/tjnpr/v5i9.14
13. E. Zaini, F. Wahyuni, H. Salsabila, D. Anggraini, Y. Yuliandra, & H. Lucida, Eutectic Mixture of Fenofibric Acid and Syringic Acid: Improvement of Dissolution Rate and Its Antihyperlipidemic Activity. ChemistrySelect, 8(20). 2023 https://doi.org/10.1002/slct.202300044
14. D. Anggraini, & E. Zaini, Multicomponent crystals of fenofibric acid-L-proline with enhanced dissolution rate and antihyperlipidemic activity. Journal of Research in Pharmacy, 28(4), 974–981. 2024 https://doi.org/10.29228/jrp.780
15. Y. Huang, & W.G. Dai, "Fundamental aspects of solid dispersion technology for poorly soluble drugs". *Acta Pharmaceutica Sinica B*, 4(1), 18–25. 2014 https://doi.org/10.1016/j.apsb.2013.11.001
16. S. Baghel, H.Cathcart, & N.J.O Reilly, "Polymeric Amorphous Solid Dispersions" : A Review of Amorphization , Crystallization , Stabilization , Solid-State Characterization , and Aqueous Solubilization of Biopharmaceutical Classi fi cation System Class II Drugs. *Journal of Pharmaceutical Sciences*. 2016 https://doi.org/10.1016/j.xphs.2015.10.008
17. Yamashita, H., Hirakura, Y., Yuda, M., Teramura, T., & Terada, K. "Detection of Cocrystal Formation Based on Binary Phase Diagrams Using Thermal Analysis. 1(26). 2012. https://doi.org/10.1007/s11095-012-0850-1
18. K. Chaturvedi, H.S. Shah, K. Nahar, R. Dave, & K.R Morris, "Contribution of Crystal Lattice Energy on the Dissolution Behavior of Eutectic Solid Dispersions" 2020 https://doi.org/10.1021/acsomega.9b03886
19. L. Grinding, "Screening for Pharmaceutical Cocrystal Hydrates via Neat and Liquid-Assisted Grinding". 4(3), 347–354. 2007
20. E.R., Fischer, B.T. Hansen, V. Nair, F.H.Hoyt, L. Cindi, & D.W Dorward, "Scanning Electron Microscopy". 4(5), 1–91. 2025 https://doi.org/10.1002/cpz1.1034.Scanning
21. Y. Huang, & W.G Dai, " Fundamental aspects of solid dispersion technology for poorly soluble drugs" . *Acta Pharmaceutica Sinica B*, 4(1), 18–25. 2014 https://doi.org/10.1016/j.apsb.2013.11.001
22. Justen, A., Schaldach, G., & Thommes, M. Insights into the Mechanism of Enhanced Dissolution in Solid Crystalline Formulations. Pharmaceutic. 16. 510, 2024.
23. Kim, T. H., Shin, S., Jeong, S., Lee, J. B., & Shin, B. S. (2019). Physiologically relevant in vitro-in vivo correlation (Ivivc) approach for sildenafil with site-dependent dissolution. Pharmaceutics, 11(6). https://doi.org/10.3390/pharmaceutics11060251
24. T.T Do, S. Van, M., Mols, R., Annaert, P., Martens, J., Van Humbeeck, J., Vermant, J., Augustijns, P., & Van Den Mooter, G. "The conflict between in vitro release studies in human biorelevant media and the in vivo exposure in rats of the lipophilic compound fenofibrate" . *International Journal of Pharmaceutics,* 414(1–2), 118–124 .2011 https://doi.org/10.1016/j.ijpharm.2011.05.009
25. Hildebrandt, J., Bauerschlag, D. O., Fricker, G., Girreser, U., Kellers, F., Maass, N., Clement, B., & Fl, I. (2025). In Vivo. https://doi.org/10.1021/acsptsci.4c00596
26. Dunne, A., Devane, J., & O'Hara, T. (1999). The Relationship between In vitro Drug Dissolution and In vivo Absorption. Journal of the Royal Statistical Society. Series D (The Statistician), 48(1), 125–133. 1999. http://www.jstor.org/stable/2680901

© 2026 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).