RJC

RASĀYAN *J. Chem.*
Vol. 18 | No. 4 |2006-2011| October-December | 2025
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

INCREASED DISSOLUTION RATE AND SOLUBILITY OF FENOFIBRIC ACID-MANNITOL SOLID DISPERSION PREPARED BY THE HOT MELT METHOD

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ABSTRACT

Fenofibrate acid is a new drug for the treatment of hyperlipidemia with low solubility. The very low solubility of the active pharmaceutical ingredient in water results in low bioavailability of the active pharmaceutical ingredient. Solid dispersion technology is a technique that can be used to increase solubility. In this study, the preparation of fenofibrate acid mannitol solid dispersion was carried out using the melting method. The objective of this study is to evaluate the ability of the solid dispersion system of fenofibrate acid and mannitol to enhance dissolution rate. Three formulations were prepared: F1 (fenofibrate acid to mannitol ratio 1:1), F2 (1:3), and F3 (1:5). The solid dispersion system was characterized using FTIR, DSC, X-ray diffraction, and SEM. The physical mixture and solid dispersion were characterized for dissolution. The results showed that the solid dispersion of fenofibric acid was crystalline with a decrease in the physical properties of the melting point. There was no chemical interaction between fenofibric acid and mannitol, and the crystal morphology of the solid dispersion of fenofibric acid was different from that of the original compound. The dissolution rate increased with increasing mannitol concentrations. F3 showed the highest dissolution rate among all formulas. The dissolution rate of solid dispersion F3 was 91.53% after one hour, while that of pure fenofibric acid was 53.20%. Statistical analysis showed a significant difference ($P<0.05$) in dissolution efficiency among all formulas.

Keywords: Solid Dispersion, Fenofibric Acid, Dissolution Rate, Mannitol, Solubility.

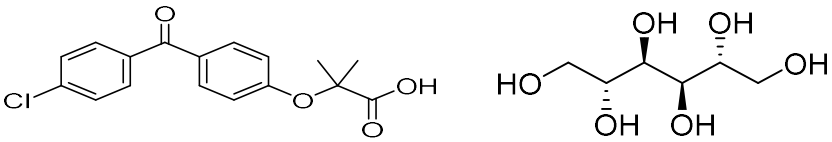
RASĀYAN *J. Chem.*, Vol. 18, No.4, 2025

INTRODUCTION

The physical properties (solubility) of active pharmaceutical ingredients must be taken into account during drug development. Many drugs have pharmacological potential but fail to become drugs due to solubility issues. The dissolution rate of active pharmaceutical ingredients is largely determined by their solubility. Almost 40% of new active pharmaceutical ingredients are insoluble in water, and the dissolution rate is low when the solid dosage form is compact, so this is a limitation.[1] Water-insoluble drugs take longer to dissolve in gastrointestinal fluids, which can delay drug absorption into systemic circulation.[2] There are numerous techniques to improve solubility, such as reducing particle size, forming complex compounds, forming salts, microencapsulation, and forming solid dispersions using hydrophilic polymers.[3] Solid dispersion techniques have been used to increase the dissolution and absorption rates of drugs. Solid dispersions are produced using melting, dissolution, or solvent-melting methods.[4] Solid dispersions utilize hydrophilic matrices and hydrophobic drugs, with insoluble drugs combined with hydrophilic excipients[5], thereby increasing the solubility of water-insoluble drugs.[6,7] Mannitol (MN) is a sugar alcohol, widely used in pharmaceutical formulations and food products.[8] Mannitol is soluble in water at 216 mg/mL and has a melting point of 168 ºC.[9] Mannitol is highly soluble in water and safe for use as a pharmaceutical excipient, making it a suitable polymer for use in the manufacture of fenofibrate acid solid dispersions.[10] The attempt to combine hydrotropic compounds has a significant synergistic effect in increasing solubility.[11] Fenofibric acid (FA) is a new drug for anti-hyperlipidemia treatment.[12] The active form of fenofibric acid is more effective due to a better absorption rate than fenofibrate, because the solubility of fenofibric acid is poor in water; efforts need to be made to increase solubility.[13] Development of new drugs is crucial to ensure that active pharmaceutical ingredients are more effective, efficient, and have fewer side effects. Efforts to date related to increasing the solubility of fenofibric acid have involved the formation of multicomponent crystals and the formation of eutectic mixtures.[14,15]

http://doi.org/10.31788/RJC.2025.1849425

Ongoing research continues to obtain an effective drug. The objective of this study was to improve the solubility of fenofibric acid using a solid dispersion system that has not been reported in previous studies.



(A) (B)

Fig.-1: Molecule structure of Fenofibric acid (A), mannitol (B)

EXPERIMENTAL

Materials

This study used fenofibric acid (BOC Sciences, New York, USA) and mannitol (Bratachem). The solvent used in this study was an analytical grade solvent.

Solid Dispersion Preparation

Solid dispersion was prepared by melting method, MN was melted at 168 ºC on a hot plate and then FA was added, dried at room temperature, crushed homogeneously, sieved with mesh 40 and stored in a desiccator for evaluation The mixture of FA and MN was made in 3 ratios of 1:1, 1:3, and 1;5 (FA-MN1, FA-MN2, FA-MN3).

Preparation of Physical Mixtures

The physical mixture was produced by combining FA and MN in a mortar and then stirring. It was then stored in a desiccator. The mixture of FA and MN was made in 3 ratios of 1:1, 1:3, and 1 5.

Evaluation of FA-MN Solid Dispersion

Fourier Transforms Infrared Analysis

FTIR analysis was performed to examine the compatibility of drugs and polymers by studying the functional group spectra that appeared in the FA-MN, pure FA, and MN solid disperse systems. Testing was conducted at wave numbers of 600-4000 cm^{-1}. The analysis results were displayed in the form of spectra and spectrum overlays using OriginPro 8.5 2015.

Differential Scanning Calorimetric Analysis

Thermal analysis was performed using a DSC device (Shimadzu DSC-60 plus, Japan). Samples (FA, MN, and FA-MN solid disperse) of 5-7 mg were placed in 10 µL containers. The samples were heated and measured in a temperature range from 30 to 250 ºC, with a heating rate of 10ºC per minute. Nitrogen was used as a purge gas with a flow rate of 20 mL/min. The analysis results were displayed in the form of thermograms and thermogram overlays of each sample using Origin Pro 8.5 2015.

Powder X-Ray (PXRD) Analysis

X-ray diffraction analysis used the PXRD (Panalytical PW (Netherlands). The analysis was carried out at 2θ angles in a temperature range of 5 to 35 °C. Diffractogram patterns were analyzed to evaluate changes in the degree of crystallinity. Tests were conducted on FA, MN, and FA-MN solid dispersions. The analysis results were displayed in the form of diffractograms and diffractogram overlays of each sample using OriginPro 8.5 2015.

Scanning Electron Microscope (SEM) Analysis

Identification of morphology and crystal habit was performed using a scanning electron microscope (HITACHI FLEXSEM 1000, Japan). The test was carried out by comparing the morphology and habit of the drug substance FA, MN, and solid dispersion FA-MN.

Solubility Test

The solubility testing used an orbital shaker (Heidolf Plug, Germany). An excess amount of FA-MN solid dispersion was weighed equivalent to 25 mg FA, then dissolved in 100 mL of distilled water. It was then stirred for 24 hours at room temperature. The amount dissolved was determined using UV spectroscopy. Solubility testing was performed on FA, FA-MN solid dispersion, and physical mixtures. The test was repeated three times.

Dissolution Test of FA-MN Solid Disperse and FA in Distilled Water Medium

Dissolution testing was performed using a type II dissolution apparatus, 900 mL of Aquadest medium, at a speed of 50 RPM for 60 minutes. The FA-MN solid dispersion equivalent to 50 mg of FA was weighed. The sample was placed in the dissolution apparatus containing 900 mL of Aquadest medium. Five mL of the sample solution from the dissolution test was taken at 5, 10, 15, 30, 45, and 60 minutes. The absorbance of the solution was measured at the maximum wavelength. The amount of FA dissolved at each time point is calculated using the calibration curve.

Data Analysis

The effect of MN weight fraction on FA dissolution rate in solid dispersed systems was evaluated using two-way analysis of variance (ANOVA).

RESULTS AND DISCUSSION

The development of pharmaceutical active ingredients is often hampered by solubility issues. Solubility issues often cause pharmacologically active pharmaceutical ingredients to fail as drugs. In recent years, there have been many reports of drug candidates with poor solubility characteristics.[16] Physically modifying drug ingredients using solid dispersion techniques is one of the most effective strategies for overcoming solubility and dissolution issues.[17] In this study, efforts were made to increase the solubility of fenofibric acid using a solid dispersion technique with mannitol as a carrier. The solid dispersion system was characterized using FTIR, DSC, PXRD, SEM, solubility testing, and dissolution testing.

FTIR Analysis

Infrared spectra were analyzed for the solid disperse system, physical mixture, fenofibric acid, and mannitol. The absorption at certain wavelengths illustrates the presence of a specific functional group. The IR spectrum (Fig.-2) of FA showed (C=O ketone) group at wave number 1645 cm^{-1}, C-O ether at 1235 cm-1, C=C aromatic at 1593 cm^{-1}, and C=O carboxylate at 1703 cm^{-1}. The IR spectrum of MN showed (O-H) groups at wave numbers 3389 cm^{-1}, 3279 cm^{-1}, 3232 cm^{-1}, (CH aromatic) 2900 cm^{-1}, and (CH2) 2935 cm^{-1}. The solid dispersion showed the presence of fenofibric acid functional groups. There was a peak shift, but it was still within the range of FA and MN functional groups. The FTIR spectrum of the FA-MN solid dispersion showed the same peaks as those appearing in the FA and MN spectra, indicating that FA and MN are compatible and no chemical interaction occurs.

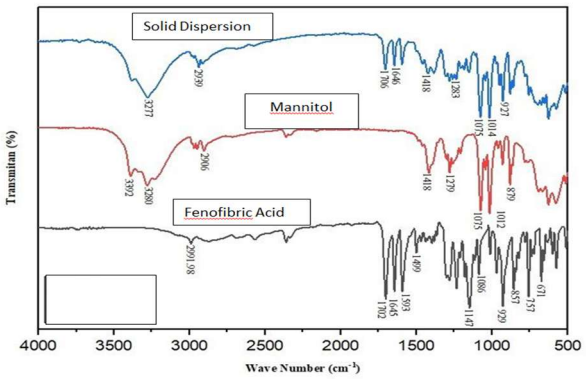


Fig.-2: IR Spectra of FA, MN, and Solid Dispersion FA-MN

DSC Analysis

DSC thermograms of FA, MN, and FA-MN solid disperse are shown in Fig.-3. FA and MN were crystalline compounds with endotherm points of 185.88°C and 168.31°C, respectively; they represent the melting point of each substance according to the literature. The thermogram of the FA solid dispersion with mannitol carrier did not show the same endotherm peak as pure FA. A possible explanation is that FA was dissolved in the carrier structure (MN), forming a solid solution in the carrier. The FA-MN solid disperse endotherm peak appeared with lower intensity (167.14 °C) but was still in crystalline form, characterized by a sharp endotherm peak.

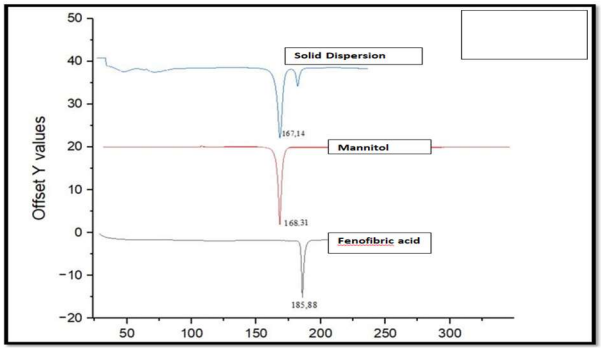


Fig.-3: Overlay Thermogram of FA, MN, and Solid Dispersion FA-MN

Powder X-ray Analysis

X-ray diffractogram of FA, MN, and FA-MN solid disperse is illustrated in Fig.-4. The X-ray diffraction spectra of FA-MN solid dispersion were compared with those of pure FA and its carrier (MN). The FA diffractogram showed sharp peaks at 2 theta angles of 18.72, 19.43, 21.73, 23.24, and 30.42, while the mannitol diffractogram showed sharp peaks at 18.70, 20.36, 21.05, 23.36, and 29.43. The FA-MN solid dispersion remained a crystalline solid, but the intensity decreased. No new diffraction peaks were observed, and a new crystalline phase was formed. The results of PXRD analysis in conjunction with thermal analysis showed a decrease in the lattice energy of the FA-MN solid dispersion system, which resulted in an increase in FA solubility. As solid dispersions with lower melting points have lower crystal lattice energies, they do not require considerable energy to disrupt the crystal lattice.[18]

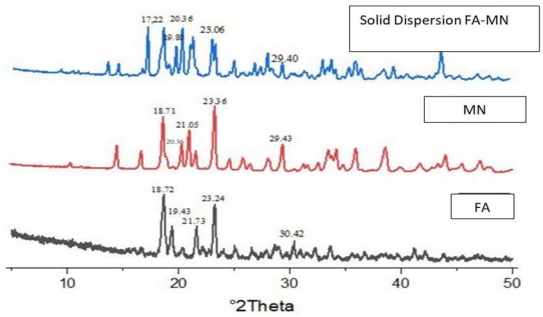


Fig.-4: Overlay Difractogram of FA, MN, and Solid Dispersion FA-MN

SEM Study

Micrographs of FA, MN, and FA-MN solid dispersion using SEM are shown in Fig.-5. The result of the SEM test showed that the crystal habit of pure FA was in the form of irregular cubic agglomerates with sharp edges. The MN habit resembled large chunks, while the solid dispersion of FA-MN could no longer be distinguished from the morphology of its components, as FA had already dispersed into MN.

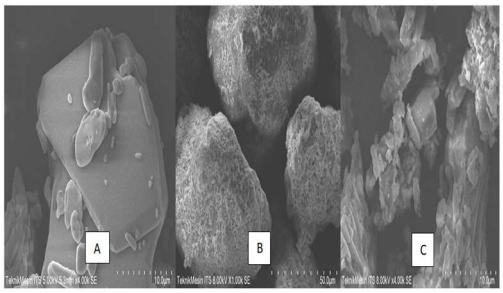


Fig.-5: SEM Image of (A) FA, (B) MN, (C) Solid Dispersion, 4000 Magnification

Solubility Study

Solubility testing in water was conducted using an orbital shaker for 24 hours at room temperature. The result showed that variations in the ratio of FA to MN carrier affected drug solubility (Table-1). Increased

FA solubility was observed in solid disperse formulations and physical mixtures. Among all formulations, the solid dispersion showed a significant increase. The results also showed that the FA-MN3 solid dispersion at a 1:3 ratio had a solubility that was 1.7 times higher than that of pure FA. Physical mixtures also showed increased solubility, as mannitol is a hydrophilic solid dispersion carrier.[17] The solubility of FA-MN solid dispersion increased compared to FA because of the decrease in crystallinity, which reduced the crystal lattice energy. In order to dissolve, the crystal lattice must be disrupted, and with the decrease in crystallinity, high energy is not required to disrupt the crystal lattice. Thermal analysis test results showed that the solid dispersion powder had a lower melting point than the original compound, resulting in a decrease in lattice energy and an increase in solubility.[18]

Table-1: Composition of FA Solid Dispersions and Physical Mixture with Carriers and their Solubility

Formula	Solubility(µg/mL)	Increased(time)
FA	43.32 ± 0.03	-
Solid dispersion FA-MN 1:1	42.62 ± 0.09	1.08 time
Solid dispersion FA-MN 1:3	46.07 ± 0.07	1.3 time
Solid dispersion FA-MN 1:5	56.07 ± 0.03	1.7 time
Physic Mixture 1:1	45.87 ± 0.03	1.0 time
Physic Mixture 1:3	50.83 ± 0.07	1.1 time
Physic Mixture 1:5	72.04 ± 0.09	1.3 time

The in vitro release profiles of the solid dispersion and pure FA are shown in Fig.-6 and Table-2. The F3 solid dispersion with an FA and MN ratio of 1:5 was a formula with the highest dissolution rate, higher than pure FA and other solid dispersion formulas. The percentage of FA dissolved within 60 minutes from FA, FA-MN1, FA-MN2, and FA-MN3 was 53.2, 61.32, 81.33, and 91.53%, respectively. The dissolution test data and solubility test data indicate that the effect of dissolution increases the dissolution rate. The formation of water structures due to the influence of carrier mannitol, such as the formation of D-mannitol, causes an increase in the solubility and dissolution of fenofibric acid:o-mannitol. This will strengthen the hydrogen bonds between molecules in water, causing the solvent to become more hydrophilic and thus favoring the dissolution of the carrier.[19] The results of this study have proven that the solid dispersion technique of fenofibric acid using mannitol as a carrier contributes to increasing the dissolution rate and solubility of fenofibric acid itself, thereby enhancing the efficacy of fenofibric acid as an antihyperlipidemic drug. This is because increased solubility can reduce the dosage, thereby reducing the side effects of the drug.[20] The results of this study can be further developed so that the solid dispersion system of fenofibrate acid can be commercialized as a more effective and efficient drug in the community.

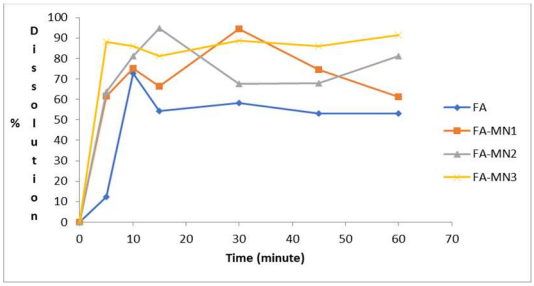


Fig.-6: Dissolution Profile of FA and Solid Dispersion in Aquadest at 37.8 ºC, 150 rpm (n/3)

CONCLUSION

This study it can be concluded that solid dispersion technology using mannitol as a carrier can be used to increase the solubility and dissolution rate of fenofibric acid. Characterization of the solid state indicates that the solid dispersion of fenofibric acid with mannitol remains in a crystalline solid form but exhibits a reduced degree of crystallinity.

ACKNOWLEDGMENTS

The authors are grateful for the financial support from the DRTPM of the Ministry of Higher Education, Science, and Technology, Republic of Indonesia, contract number 022/LL17/DT.05.00/PL/2025

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest in this study.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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