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Original Research Article

Solubility Enhancement Solid Dispersion Fenofibric Acid HPMC and Their Physicochemical Characterization

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ABSTRACT

Fenofibric acid is a water-soluble antihyperlipidemia drug, and the solubility of fenofibric acid is 162.5 µg/mL.[1] Solid dispersion systems are aimed to improve the solubility of poorly soluble active pharmaceutical ingredients. This study aimed to formulate and characterization fenofibric acid-hydroxypropyl methylcellulose (HPMC) solid dispersion. The solid dispersion of fenofibric acid was prepared using the solvent evaporation method. The ratios of fenofibric acid and HPMC were F1 (1:1), F2 (1:3) and F3 (1:5). The formulated products were subjected to various physicochemical characterisation using X-ray diffractograms, DSC thermograms, SEM and FTIR, including particle size distribution and solubility test. The physicochemical characterisation showed the specific characteristics of the solid dispersions. X-ray diffractograms, DSC thermograms and SEM photographs indicated that fenofibric acid was amorphous and trapped in the HPMC matrix. FTIR test results show no new functional groups indicating no chemical interaction between the active pharmaceutical ingredients and the matrix. SEM results show that the solid dispersion system was morphologically different from pure fenofibric acid and the physical mixture. The solubility of fenofibrate acid was 42.33 µg/mL while the solubility of solid dispersion F3 ratio 1:3 was 113.25 µg/mL. The solubility of fenofibrate acid solid dispersion with HPMC 1:3 ratio is 2.68 times greater than that of pure fenofibrate acid.

***Keywords*:** Solid dispersion, Fenofibric acid, Hydroxypropyl methylcellulose, Solubility, Physicochemical characterization.

Introduction

Fenofibric acid (FA) is an antihyperlipidemic drug which is the active metabolite of fenofibrate. After oral administration, fenofibrate is hydrolyzed by esterases into the active metabolite fenofibric acid. [2]Fenofibric acid is more effective than fenofibrate because of its better absorption in the gastrointestinal tract.[3] FA is a new drug for hyperlipidemia treatment and may replace fenofibrate as the main antihyperlipidemic drug in the future, but with a low water solubility problem, although it has high tissue permeability and hence classified into class II biopharmaceuticals according to the biopharmaceutical classification system (BCS).[4] The drug is easily soluble in 250 mL of water at pH 1-7.5.[5]

New drugs need to be developed to produce active pharmaceutical ingredients (APIs) that are more effective, efficient, safe and with fewer side effects. [6] The solubility character of active pharmaceutical ingredients needs to be considered and controlled because most failures of new drug development are due to poor solubility in water. The low water solubility of drugs leads to low absorption. As such efforts are needed to increase drug solubility, one of which is the use of solid dispersion technique.

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Efforts that have been made to improve the solubility of fenofibrate acid currently include crystal engineering with various cofomers such as nicotinic acid, nicotinamide, theobromine, and siringic acid. [7,8,9,10] The results obtained from these studies generally increased the solubility of fenofibrate acid by only 1 time from the pure compound. Efforts to increase fenofibrate acid by solid dispersion method using hydrophilic polymers have never been reported and are the novelty of this study.

Solid dispersion is a technique widely used to overcome drug bioavailability problems and was first introduced by Sekiguchi and Obi in 1961. Drugs prepared by solid dispersion technique increase the wettability of drug powders. This mechanism results in increased interaction of the active ingredient with the solid dispersion carrier and reduces agglomeration during storage. In addition, the drug will be released under saturated conditions resulting in faster absorption.[11]

Hydroxypropyl methylcellulose (HPMC) is a synthetic polymer widely used in pharmaceutical excipients and as a food additive. As a pharmaceutical additive, HPMC is used for slow-release tablet formulas and to improve solubility. HPMC is relatively safe, biocompatible and biodegradable.[12]In this study, we evaluated the physicochemical properties and solubility properties of fenofibric acid solid dispersions using HPMC polymers.

Materials and Methods

Materials

Fenofibric acid was obtained from BOC Sciences (USA), and HPMC from TCI (Tokyo, Japan). Ethanol 96% pro analyzer (Merck Germany), Dicloromethane (Merck Germany)

Preparation of Solid Dispersion FA-HPMC by Solvent Method

The solid dispersion of FA-HPMC was made with 3 variations of formula 1, 2, and 3 with the ratio of FA to HPMC being 1:1, 1:3, and 1:5, respectively (Table 1). In the solvent evaporation method, FA was dissolved in ethanol, and HPMC was dissolved in a solvent mixture of ethanol and dichloromethane (1:1). HPMC solution was added to the

FA solution slowly while stirring. The solution mixture was evaporated and dried in a vacuum oven at 40º - 50º C. The resulting solid was crushed and sieved with mesh 60 and stored in a desiccator.[11]

Preparation of Physical Mixture FA-HPMC.
Each ingredient in the different formulas as weighed according to the determined composition. Each ingredient was pulverized by grinding separately, then mixed and homogenized with a mortar and pestle lightly for 10 minutes, and stored in a desiccator.

Characterization of FA-HPMC Solid Dispersion
DSC Analysis
Thermal analysis was performed on FA, HPMC and FA-HPMC solid dispersions using a DSC instrument (Shimadzu DSC60 Japan). Nitrogen as a cleaning gas was supplied at a flow rate of 20 mL/minute. A sample (FA, HPMC and FA-HPMC solid dispersion) of 3-5 mg was placed on an aluminium pan and heated to a temperature of 30-250°C and a heat flow rate of 10°C/min. The results of the analysis are displayed in the form of thermograms and overlay the thermograms of each sample using OriginPro 8.5 2015.

X-Ray Analysis
X-ray diffraction patterns were obtained using a PXRD Panalytical PW (The Netherlands). The analysis was performed at 2θ angles and a temperature range of 5-35°. The diffractometer was set up as follows: Cu target metal, Kα filter, 45 kV voltage, and 40 mA current. Diffractogram patterns were analyzed to evaluate changes in the degree of crystallinity. Tests were conducted on FA, HPMC, and FA-HPMC solid dispersions. The results of the analysis are displayed in the form of diffractogram and overlay diffractogram of each sample using OriginPro 8.5 2015.

Scanning Electron Microscope (SEM) Analysis
Identification of morphology and habit using Scanning Electron Microscope (HITACHI FLEXSEM 1000, Japan). The test was carried out by comparing the morphology and habit of the drug substance FA with HPMC and solid dispersion FA-HPMC.

Fourier Transform-Infrared Spectroscopic Analysis
Compatibility analysis between drug and carrier using a Fourier transform infrared spectrophotometer (Shimadzu IRSpirit) was evaluated. The spectra were obtained by measuring the absorption at wave numbers 4000 - 400 cm^{-1}. IR spectrum analysis was performed on FA, HPMC and FA-HPMC solid dispersion. The results of the analysis are displayed in the form of spectrum and overlay spectrum the of each sample using OriginPro 8.5 2015.

Particle Size Distribution
Particle size distribution of the solid dispersion system was carried out with a calibrated ocular micrometre. Samples were dispersed in liquid paraffin, and placed under a microscope (Zeiss 700, Germany) to observe their shapes and photographs of the shapes of the particles at a certain magnification were taken. The particle sizes were measured and 500 particles were counted. From the data, the average particle size was calculated. [13]

Solubility Test
FA-HPMC solid dispersion was weighed in excess (equivalent to 25 mg FA) and dissolved in 100 mL distilled water. The solution was shaken for 24 hours using an orbital shaker (Heidolf Plug Germany) at room temperature to reach solubility equilibrium. The amount of FA dissolved was analyzed using UV spectroscopy. The test was performed on FA, FA-HPMC solid dispersion and physical mixture. Each test was performed triplicate.

Analysis method
test results of thermal analysis, x-ray diffraction, functional groups were analyzed descriptively using the OrginPro 8.5 2015 application. SEM test data was analyzed descriptively by comparing the morphology and habit of FA, HPMC and FA-HPMC solid dispersion. Solubility test results were analyzed with one-way anova

Results and Discussion

Fenofibric acid is a new antihyperlipidemia drug. The molecular structure of phenofibric acid (Figure 1) is in the form of an ester form, which is the active form of Fenofibrate. Fenofibrate is metabolized into the active form of fenofibric acid. [2]Fenofibric acid poor solubility in water but better absorption than fenofibrate, [3] so the solubility of fenofibric acid needs to be improved
Solid dispersions can be used to increase the .solubility of drugs. This technique is a two-component system of drug and polymer. In this system, the interaction of the drug with the polymer determines the quality of the solid dispersion in improving drug solubility. With this technique, hydrophobic drugs will be dispersed in hydrophilic polymers, resulting in increased surface area which leads to increased solubility. [14]
In this study, three solid dispersion formulas were made with 3 FA HPMC ratios namely F1 (1;1), F2 (1:3) and F3 (1;5). FA and HPMC were dissolved in ethanol solvent and a mixture of ethanol: dichloromethane (1;1) respectively. The two phases were mixed and the solvent was evaporated with a vacuum oven. The physical mixture of FA-HPMC was mixed and homogenized in a mortar for 10 minutes.
The purpose of the thermal analysis was to evaluate the interaction between two materials in the solid state. DSC analysis also provides information about changes in the thermal properties of a solid shown by the appearance of endotherm peaks caused by melting, phase transition, recrystallization, and dehydration. [15] Thermal analysis test results showed that the solid dispersion endotherm peak decreased compared to the FA endotherm peak. The endotherm peaks of FA and HPMC occur at 185ºC and 46.9ºC respectively which are the melting points of both materials. The DSC thermogram of the solid dispersion in Figure 2 shows the shifting of 2 endothermic peaks at lower points (85.56ºC and 170.59ºC). DSC *thermogram of* FA-HPMC solid dispersion in Figure 2 shows a sharp shift of the FA endothermic peak indicating the interaction between the drug molecules with the polymer in the solid state. Enthalpy is the amount of energy required to fuse a solid by decreasing the degree of crystallinity. [16] The decrease in melting point and the shift in the endothermic peak of FA-HPMC solid dispersion also shows a decrease in enthalpy of fusion as shown in Table 2.
X-ray diffraction analysis using PXRD is a reliable method to analyze the interaction of solids. This method can be used to analyze the crystallinity of solid materials. Solid dispersions will generally change from crystalline to amorphous form. [17]X-ray diffraction analysis (Figure 3) shows that the FA diffraction peaks are in the crystalline phase, which is characterized by sharp and distinctive peaks, but HPMC does not show any distinctive and sharp peaks, which is characteristic of the amorphous phase.

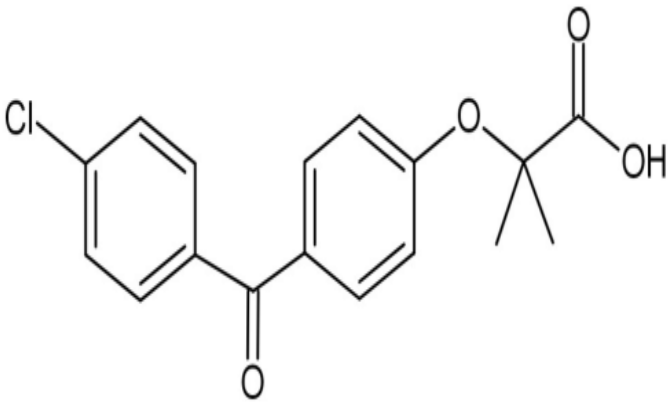

Figure 1: Structure of fenofibric acid

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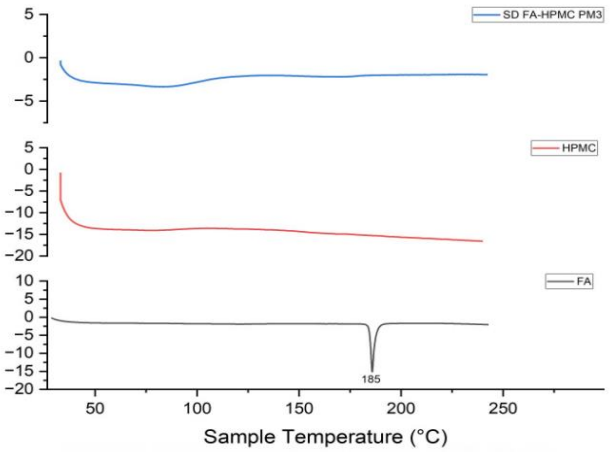

Figure 2: A Thermogram showing FA, HPMC and solid dispersion of FA-HPMC curves

The diffraction pattern of FA-HPMC solid dispersion shows a different pattern from the active substance and polymer, there is a decrease in several specific peaks in the diffractogram which indicates that the FA-HPMC solid dispersion has decreased the level of crystallinity. [17]
FTIR analysis was used to support the XRD and DSC test results and also to determine the intermolecular interactions between the solid material and the polymer. [18] The absorption at certain wavelengths in the IR spectrum illustrates the presence of specific functional groups. The IR spectrum of fenofibric acid shows bands at wave numbers 1593 cm^{-1} (C=C aromatic), 1703 cm^{-1} (C=O), 757 cm^{-1} (C-Cl), 2995 cm^{-1} (OH-carboxylate). The IR spectrum of HPMC showed bands at wave numbers 3420.85 cm^{-1} (OH), 2901.93 cm^{-1} (CH aliphatic), 1049.27 cm^{-1} (C-O-C aliphatic ether).The FT-IR spectra (Figure 4) showed the same functional groups of FA-HPMC solid dispersion as the functional groups of FA and HPMC. There was a shift in the wave number but still within the range of the same functional group.

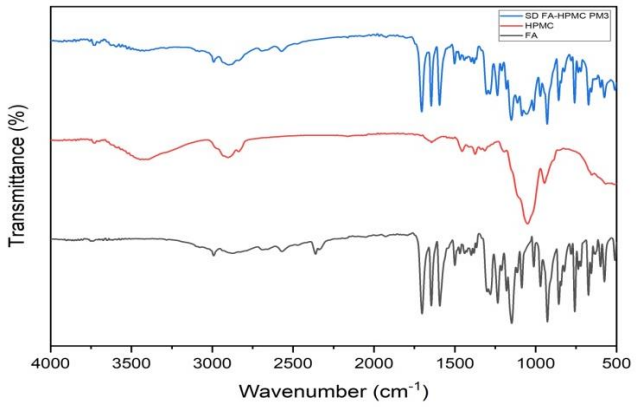

Figure 4: FT-IR spectrum FA, HPMC and solid dispersion FA-HPMC

Table 1: Composition of FA solid dispersion with HPMC

Formulation	1	2	3
FA	5 g	2.5g	1.67g
HPMC	5 g	7.5g	8.3g

Table 2: Melting point and enthalpy of FA, HPMC and FA-HPMC solid dispersions

Description	FA	HPMC	FA-HPMC solid dispersion
Peak Endotherm	185.84 ºC	46.91 ºC	85.5 ºC, 170.59 ºC
Enthalpi	66.3 (J/g)	351.1 (J/g)	39 (J/g), 6.03 (J/g)

FA : Fenofibric acid
HPMC : Hydroxyprpyl Methyl Cellulose

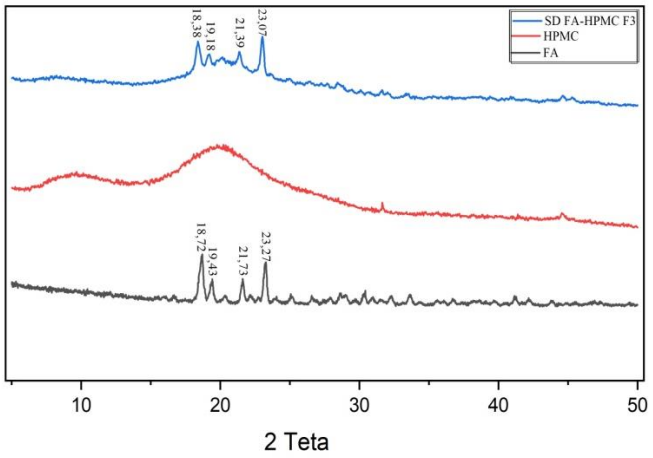

Figure 3: Diffractogram of FA, HPMC and solid dispersion FA-HPMC

SEM analysis was used to study particle morphology and crystal habit (Figure 5). The SEM photographs at 500 times magnification showed FA in the form of cubic crystal agglomerates, and HPMC in the form of irregular lumps. SEM photographs of the solid dispersion showed that FA was homogeneously dispersed in the HPMC carrier and was difficult to distinguish compared to the morphology of the physical mixture. This is because the physical mixture was made by simple mixing without any treatment that could damage the shape of each ingredient.
Also, the particle size distribution was determined by plotting the size range and the percentage frequency of particles in that size range on a normal distribution curve. The distribution curve shows a normal distribution curve indicating a uniformly distributed particle size. In general, figure 6 shows that FA is in the smaller particle size range (0-10 µm) more than the solid dispersed powder. Solid dispersions have larger particle sizes than pure FA.
The solubility test result is presented in Table 3. The solubility of FA-HPMC solid dispersion F3 was 2.68 times greater than the solubility of pure FA and the physical mixture. Solid dispersion F3 ratio 1: 3 is the solid dispersion with the highest solubility (113.25 µg/mL) while the solubility of pure fenofibric acid (42.33 µg/mL). The results of the solubility test were statistically analyzed by one-way anova test with $p>0.05$. This indicates that there is a significant difference in the solubility level of each sample. The increase in solubility of fenofibric acid in F3 may be due to a change from crystalline to amorphous, a result supported by X-ray diffraction and DSC analysis. In this study, the solubility of FA-HPMC solid dispersion increased due to a decrease in lattice energy, where the free energy of dissolution depends on lattice energy and dissolution requires disruption of the crystal lattice. A solid dispersion with a lower melting point indicates a lower crystal lattice energy, so it does not require considerable energy to disrupt the crystal lattice. [19]

Table 3: Data of Solubility Test

Material	Mean solubility (µg/mL)	Increase (times)
FA	42.33 ± 0.03	-
Solid dispersion F1	56.62 ± 0.16	1.34
Solid dispersion F2	88.53 ± 0.15	2.09
Solid dispersion F3	113.25 ± 0.23	2.68
Physical mixture	45.66 ± 0.06	1.08

Analyzed with one-way ANOVA with 95% confidence interval, p > 0.05

Conclusion

The solid dispersion system of fenofibric acid with HPMC polymer can transform the crystalline solid into an amorphous solid. The findings from this study revealed that the FA-HPMC (1:5) solid dispersion formula exhibited the best solid dispersion with a solubility of 1.46 times greater than pure fenofibric acid. Solid dispersion techniques are potentially used to improve the solubility of fenofibric acid and the absorption of insoluble active pharmaceutical ingredients.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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