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Original Article

MICRONIZED EUTECTIC MIXTURE OF FENOFIBRIC ACID-SACCHARIN FORMATION FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT

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ABSTRACT

Objective: This study aims to increase the solubility and dissolution rate of fenofibric acid by forming a micronized eutectic mixture of fenofibric acid-saccharin with spray drying technique.

Methods: Suspension of the eutectic mixture was prepared in ethanol: distilled water (3:1) followed by a spray drying method to obtain the microparticles. Microparticles characterization was performed by particle size analysis (PSA), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), FT-IR spectroscopy, and scanning electron microscopy (SEM). Solubility test was carried out in CO_2-free distilled water, meanwhile the dissolution rate study was conducted in phosphate buffer solution at pH 6.8.

Results: The results showed the mean of the samples' particle size was 72.29±7.33 µm. Compared to the intact fenofibric acid, the micronized eutectic mixture sample has a decreased melting point, fusion enthalpy, and crystallinity without any wavenumber shifted in the FT-IR spectra. The solubility of micronized eutectic mixture was 2.2 times higher than intact fenofibric acid, while the amount of micronized eutectic mixture dissolved at 60 min was 11.7 times higher.

Conclusion: It can be concluded that the spray-dried micronized eutectic mixture of fenofibric acid-saccharin was having the ability to enhance the dissolution of fenofibric acid.

Keywords: Dissolution enhancement, Eutectic mixture, Fenofibric acid, Microparticles, Saccharin, Spray drying

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INTRODUCTION

Fenofibric acid is the active metabolite of fenofibrate which is used as an antihyperlipidemia by activating PPARα receptors to modify fatty acid and lipid metabolism to reduce levels of Low-Density Lipoprotein Cholesterol (LDL-C), total cholesterol, triglycerides, apolipoprotein B and increase levels of High-Density Lipoprotein Cholesterol (HDL-C) [1]. The development of fenofibric acid in dosage form is still constrained by its solubility properties. Based on the Biopharmaceutical Classification System (BCS), fenofibric acid belongs to BCS class II with low solubility and high permeability [2]. Low solubility drugs often correlated to low dissolution rate and bioavailability [2, 3]. Fenofibric acid solubility in water, approximately 2.9 mg/ml, is the main cause of its low gastrointestinal absorption rate due to limited amount of drug that is ready to be absorbed [4].

Various approaches can be applied to increase drug solubility, such as particle size reduction, crystal modification, particle amorphization, and wettability alteration [5]. One of the factors that affect the solubility of a drug is particle size. Microparticles formation is one of the most potential approach to increase the bioavailability of lipophilic drugs by reducing the particle size [6]. Microparticles increase drug bioavailability by increasing the total surface area of drug particles [7]. There are several methods used to reduce the particle size into micrometer scale, for example, by using a planetary ball mill method, high-pressure homogenization, and precipitation method [8]. The drying method can be carried out by several techniques, such as freeze drying and spray drying [9]. Spray drying is a particle size reduction technique that is fast, easy to operate, and has a higher success rate [10].

Umar, et. al has conducted research on the formation of a eutectic mixture of fenofibric acid and saccharin by a liquid-assisted grinding technique to increase the dissolution rate of fenofibric acid. In that study, saccharin was chosen as a coformer to increase the dissolution rate of drugs that are poorly soluble in water [12]. Saccharin has good co-former criteria since it is soluble in water and has been widely used in the formation of multicomponent crystals [11]. The X-ray diffractogram exhibited no new diffraction pattern, but only a decrease in peak intensity that indicated the formation of a eutectic mixture. The eutectic mixture formation was supported by the thermal properties of 1:1 molar ratio eutectic mixture of fenofibric acid-saccharin that melted at 171.9 °C meanwhile, the intact fenofibric acid and saccharin were melted at higher temperature, 185.36 °C and 229.63 °C respectively. This study showed an increase in the solubility of fenofibric acid 1.8 times higher than intact fenofibric acid [12]. In this research, the spray-dried eutectic mixture of fenofibric acid-saccharin microparticles is expected to enhance the solubility and dissolution rate of fenofibric acid.

MATERIALS AND METHODS

Materials

Fenofibric acid (BOC Sciences, New York, USA), saccharin (Sigma Aldrich, USA), ethanol (analytical grade) (Merck, Germany), acetonitrile (liquid chromatography grade) (Merck, Germany), phosphate buffer solution at pH 6.8 (Merck, Germany).

Methods

Micronized fenofibric acid-saccharin eutectic mixture formation

The eutectic mixture of fenofibric acid and saccharin was prepared by the liquid-assisted grinding (LAG) method at a ratio of 1:1 mole according to previous study [12]. The formation of microparticles begins with spray drying process parameters optimization using BUCHI Mini spray dryer B-290 (BUCHI, Switzerland). The selected condition used to form micronized eutectic mixture were 110 °C and 60 °C for the inlet and outlet temperatures; flow rate was at 35 L/hour, with 0.7 mm nozzle diameter. The eutectic mixture suspension was prepared in three solvents: distilled water, distilled water: ethanol (1:1), and distilled water-ethanol (1:3) by dispersing 1 g of eutectic mixture powder in 200 ml solvent. The dried samples were collected, weighed, and stored in a sealed vessel in a desiccator until further analysis.

Solid state characterization

The particle size of microparticles and eutectic mixture of fenofibric

acid-saccharin were measured by dynamic scattering method at 25 °C by PSA Horiba SZ-10 (Horiba Ltd., Kyoto, Japan). The thermal properties of eutectic mixture of fenofibric acid-saccharin, micronized particle, and intact fenofibric acid were analyzed with DSC (Shimadzu DSC-60 Plus, Japan) for the temperature range of 30-250 °C with heat rate of 10 °C/min. X-ray diffraction analysis (PANanalytical MPD PW3040/60 type X'Pert Pro, Netherlands) was carried out to determine the crystallinity using Cu Kα radiation, with an operating voltage of 40 kV and a current of 40 mA, in the range of 2 theta 10–40^0. To determine the chemical groups in each sample, analysis with FT-IR spectroscopy (Shimadzu IRTracer-100 AH, Japan) were carried out by preparing the sample in the KBr plate and analyzed at wave number range of 4000-500 cm^{-1}. The morphological structure of the powders were captured with SEM apparatus (JEOL type JSM-6360LA, Japan) at at 10 kV voltage and 12 mA current. The birefringences of micoparticles, eutectic mixture of fenofibric acid-saccharin and intact fenofibric acid were observed with Zeiss Axioscope 5 polarizing microscope (Zeiss, Jena, Germany).

Solubility test

Solubility test was carried out in CO_2-free distilled water by sonication. An excess amount of samples and 100 ml solvent were put into 100 ml Erlenmeyer flask followed by sonication for 30 min. The solution was filtered using 0.45 µm Whatmann paper to remove the excessive particle before the measurement. The amount of fenofibric acid was quantified using HPLC (Shimadzu LC-20D, Japan) with acetonitrile: water (70:30) pH 3, as the mobile phases combined with a 287 nm UV detector.

Dissolution test

The dissolution profile was studied for the eutectic mixture, the microparticles, and the intact fenofibric acid. The dissolution test was carried out using an apparatus 1 dissolution tester (SR8 Plus Dissolution Test Station Hanson Virtual Instrument, USA) in a phosphate buffer medium of pH 6.8 at a temperature of 37 °C±0.5 °C and 50 rpm [12]. Each sample was weighed for and put into a capsule. The dissolution solution was sampled at 5; 10; 15; 30; 45; and 60 min as much as 5 ml then filtered using a 0.45 m pore filter (Whatman filter paper) and then analyzed by HPLC under appropriate analytical conditions.

RESULTS

One of the most important parameters in the spray-dried microparticles forming process is the solvent used to make the solution or suspension. The solvent choice would directly affected the inlet spray drying temperature and particle morphology [19, 20]. The solvent used is the key to obtain a stable eutectic mixture and the desired particle size profile. Based on the optimization results in table 1, the formulas for the eutectic suspension mixture that were successfully carried out were formulas A1 and A3. In formula A1, microparticles were produced with a yield value of 9%, this is due to the high solubility of the mixture in ethanol solvent and the inlet temperature used was not able to dry the particles completely so that many products are attached to the drying chamber and cannot separate themselves into the cyclone. The low percentage yield is due to the loss of particles on the walls of the drying chamber at a relatively constant amount and fine particles (<2 µm) usually enter the exhaust air due to an ineffective separation process [13]. Formula A3 was not successful because of the inability of the eutectic mixture to dissolve in the solvent used due to low solubility in water. This was also the reason the optimization was not performed in solvent combinations that contain more than 50% water. From 3 formulas that were optimized, the A2 formula was the most optimal parameter to form the microparticles of the eutectic mixture because it produced the highest yield.

Table 1: Optimization data for the formation of a eutectic mixture suspension

Formulation	Solvent		Melting point	Yield (%)	Particle size (µm)
	Aquadest	Ethanol			
A1	-	100%	170.38 °C	9%	1.2
A2	25%	75%	170.81 °C	50%	1.5
A3	50%	50%	-	-	-

The DSC thermogram showed a lower melting point of the microparticles of the eutectic mixture to 170.81 °C compared to the eutectic mixture and intact fenofibric acid, which were 172.24 °C and 185.36 °C, respectively. The decrease in melting point indicates a weakening of the lattice energy between the crystals in the microparticles of the eutectic mixture so as to increase the solubility and dissolution rate of fenofibric acid. DSC thermal analysis was also used to confirm the formation of a eutectic mixture by considering the eutectic point. An eutectic mixture exhibited an endothermic peak with a lower temperature compared to each compound melting point [12]. The thermogram shown that the eutectic mixture melting point is 172.24 °C, which is clearly lower than fenofibric acid (185.36 °C) and saccharin (229.63 °C).

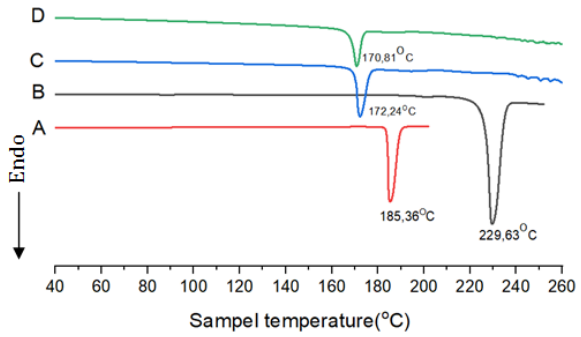

Fig. 1: Differential scanning calorimetry thermogram of (A) fenofibric acid, (B) shaccarin (C) eutectic mixture of fenofibric acid-shaccarin (1:1 molar ratio) (D) eutectic mixture microparticles of fenofibric acid-shaccarin

X-Ray diffraction analysis is very important to know the solid state of the sample. The fenofibric acid diffractogram shows a distinctive and sharp interference peak with a high degree of crystallinity at a diffraction angle of 15.08°; 18.44°; 19.28°; 23.08°; and 30.44°. Similarly, with saccharin showing a sharp peak interference at the diffraction angle value of 2θ, which is 9.49°; 19.08°; 21.46°; and 27.35°. The sharp reflection of the peaks of fenofibric acid and saccharin confirmed the crystallinity of the starting material. The eutectic mixture showed indifferent peak interference from that in fenofibric acid or saccharin indicating no interaction between fenofibric acid and saccharin. In the microparticle diffractogram of the eutectic mixture, the intensity decreases compared to that of the eutectic mixture and its initial constituents. No new peaks were found in the microparticles of the eutectic mixture, so it can be concluded that the mixture was still in the form of eutectic. This decrease in intensity is thought to occur due to a change in crystal habit, which can indicate a change in the size of the crystal [14]. A decrease in the intensity of the diffraction pattern also indicates a change in crystallinity; this will affect the drug dissolution rate to be faster [15].

FTIR analysis is used to identify the chemical group in the eutectic mixture by analyzing the molecular interactions at the specific wave number that appears in the spectrum [16]. Different compounds will produce a different infrared spectrum. The comparison of the FTIR spectra of the eutectic mixture microparticles with their constituent compounds can be seen in the Figure 3. A small shift is seen in the microparticle spectrum of the eutectic mixture, but this shift does not indicate the formation of a new crystalline phase or new bonds between the initial compounds. The analysis showed the absence of a strong intermolecular interaction between the fenofibric acid and the specified saccharin and the phase separation of the eutectic component in the solid state.

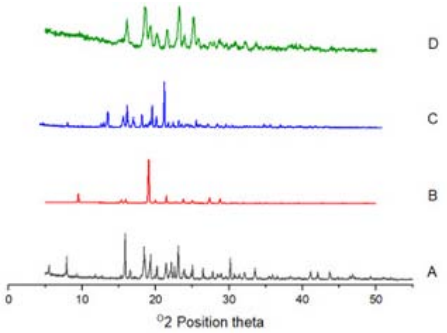

Fig. 2: X-ray diffractogram of fenofibric acid (A), saccharin (B), eutectic mixture (C), eutectic mixture microparticles (D)

To observe the surface morphology of the sample, SEM characterization was carried out. Based on the results of microphotography, it can be seen that fenofibric acid has a crystalline surface morphology, while the saccharin coformers are partially rod-shaped crystals. In the eutectic mixture of fenofibric acid-saccharin, the surface morphology looks like an aggregate consisting of large lump-shaped particles that still show the crystalline form of fenofibric acid and saccharin, while the microparticles of the eutectic mixture also have a shape that is not much different from the shape of the eutectic mixture, only that it has a smaller size.

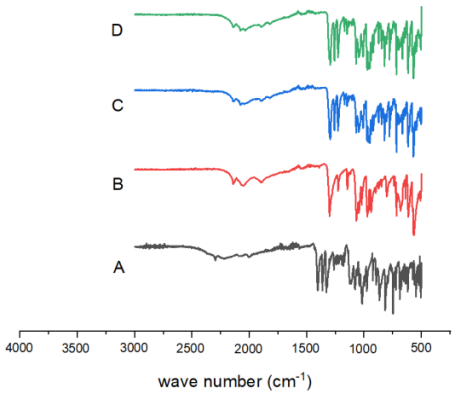

Fig. 3: FTIR spectra of fenofibric acid (A), saccharin (B), eutectic mixture (C), eutectic mixture microparticles (D)

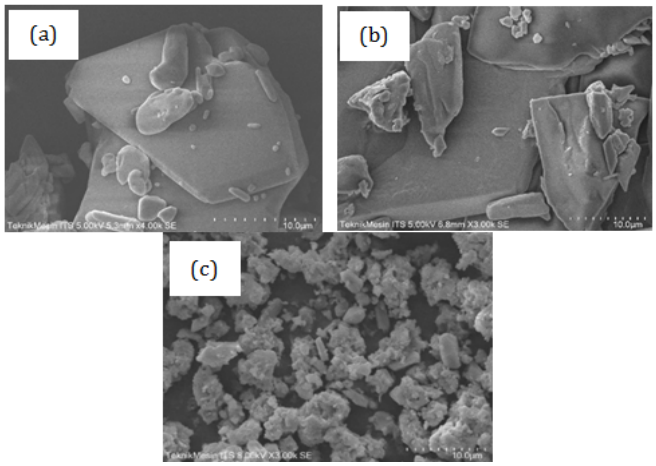

Fig. 4: SEM morphology fenofibric acid (a), saccharin (b) and eutectic mixture microparticles (c)

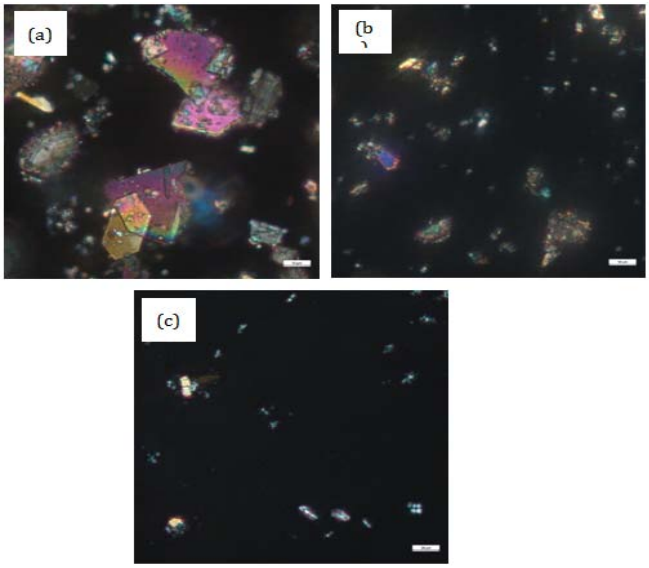

Fig. 5: Polarized microscopic image of fenofibric acid (a), eutectic mixture (b) and eutectic mixture microparticles (c)

Polarizing microscopy analysis is used to observe samples microscopically. In addition to observing the crystal shape of the sample, a polarizing microscope is also used to see the crystallinity of the sample. Crystalline solids will give a different color when

compared to amorphous solids, which tend not to give color because of their inability to refract light caused by the low degree of crystallinity [17]. It can be seen that the results of microparticles of the eutectic mixture give various colors, which prove that the eutectic mixture is still in the crystalline phase.

The solubility of fenofibric acid in the microparticles of the eutectic mixture of fenofibric acid-saccharin has a higher solubility compared to pure fenofibric acid, which is increased by 2.2 times. This is due to the reduction in particle size through the spray drying method through the formation of smaller droplet sizes. Particle size reduction in the micrometer range affects the solubility of a drug. By reducing the particle size, the total surface area will be increased when compared to the previous particle size. This increase in total surface area can increase the solubility of the drug particles [18].

Table 2: Solubility test result of fenofibric acid, eutectic mixture of fenofibric acid-saccharin, and micronized eutectic mixture of fenofibric acid-saccharin

Sample	Soluble fenofibric acid content±SD (mg/100 ml)
Fenofibric acid	0.5882±0.01
Eutectic mixture	1.223±0.02
Eutectic mixture microparticles	1.292±0.03
n=3	

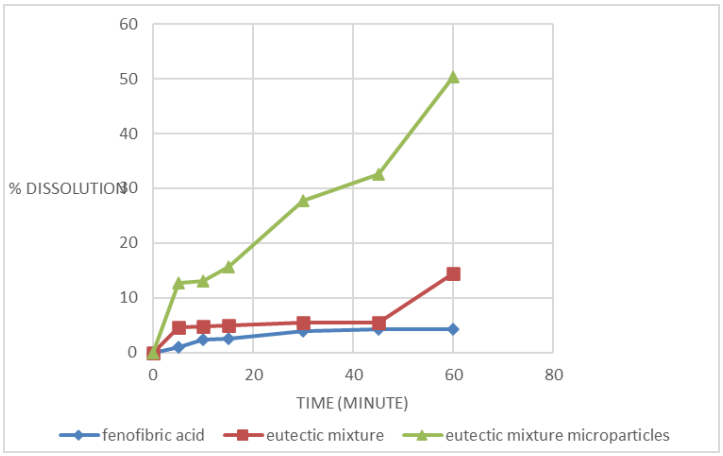

Fig. 6: Dissolution profile of fenofibric acid in phosphate buffer medium at pH 6.8

The dissolution profile is shown in fig. 6. After 60 minutes, the amount of fenofibric acid dissolved for intact fenofibric acid, the eutectic mixture and microparticles of the eutectic mixture were 4.29%, 14.43% and 50.40%. The dissolved amont of fenofibric acid is 11.7 times higher compared to intact fenofibric acid and 3.5 times higher compared to the eutectic mixture. fenofibric acid-saccharin.

Micronization is one of many ways to enhance the solubility as well as the dissolution of a solid active pharmaceutical ingredients [10]. In this research, a simple eutectic mixture of fenofibric acid that previously proven to increase solubility by 1.8-fold [12] was slightly enhanced for its micronized particles. But an excessive enhancement was presented by the micronized dissolution profile which is 11.7 times higher than the intact fenofibric acid at 60 min. This finding can be explained by the Noyes-Whitney equation, that dissolution is directly affected by the particle size where the smaller particle would show higher dissolution rate due to the greater amount of total surface area available to contact with the dissolution medium This increase in dissolution is supported by characterization data, such as a decrease in melting point, a decrease in the peak intensity of X-ray diffraction results, a reduction in particle size and solubility test data showing an increase in solubility.

CONCLUSION

The formation of microparticles of the fenofibric acid-saccharin eutectic mixture by the spray drying method was successfully carried out and exhibited an increase in the solubility and dissolution rate of fenofibric acid.

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AUTHORS CONTRIBUTIONS

Each authors contributed equally in the research and article preparation.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interest

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