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Research Paper

Preparation and Characterization of a Eutectic Mixture of Fenofibric Acid and Nicotinic Acid and Evaluatuion of In Vivo Antihyperlipidemic Activity

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Abstract
Fenofibric Acid (FA) is classified under Biopharmaceutical Classification System (BCS) class II due to its poorly soluble in water and high permeability. The present study aimed to prepare the eutectic mixture of FA with nicotinic acid (NA) and characterize its solid state properties and in vitro dissolution rate, along with its in vivo antihyperlipidemic activity. Solvent drop grinding was the method chosen to prepare the eutectic mixture of FA and NA. Solid-state properties were evaluated using thermal analysis Differential Scanning Calorimetry (DSC), crystallographic analysis Powder X-Ray Diffraction (PXRD), FT-IR spectroscopic analysis, and Scanning Electron Microscopy (SEM). To examine in vivo antihyperlipidemic activity, 16 male Swiss-Webster rats were injected with 1% hyperlipidemia-inducing solution, followed by the oral administration of 9.45 mg/kg FA and NA (equivalent to 9.45 mg/kg FA), after which the decrease in cholesterol levels was measured. Two-way ANOVA was used to evaluate the data, followed by Duncan's multiple range test (95% confidence interval). The results proved that FA formed the eutectic mixture with NA at a molar ratio of 6:4. The eutectic mixture of FA-NA had a better solubility and in vitro dissolution rate compared to intact FA, which also led to notably improved antihyperlipidemic activity.

Keywords
Fenofibric Acid, Nicotinic Acid, Eutectic Mixture, Dissolution Rate, Solubility

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1. INTRODUCTION

Approximately 40% of the active pharmaceutical ingredients (APIs) on the market and 90% of the drug compounds at the development stage have low aqueous solubility, which makes it challenging for the pharmaceutical industry to design high-quality solid dosage forms (Kalepu and Nekkanti, 2015). For poorly soluble APIs, the dissolution process in the gastrointestinal fluid becomes a rate-limiting step. Therefore, increasing the dissolution rate could improve the bioavailability and efficacy of the drug, and it is crucial to make efforts to increase drug solubility.

According to the Biopharmaceutical Classification System (BCS), Fenofibric Acid (FA) is classified under BCS class II due to its poor solubility and high permeability. The solubility of FA is 162.5 g/mL and 75% is absorbed in the gastrointestinal tract (Kim et al., 2016). Several methods have been reported to resolve the solubility and dissolution of FA, including salt formation using choline bases, piperazine, calcium, ethanolamine, diethanolamine, and tromethamine (Cink et al., 2013); surface solid dispersion and self-emulsifying nanoemulsion (Windriyati et al., 2019; Suhery et al., 2020).

Several techniques have been reported to increase the in vitro dissolution rate of poorly soluble APIs, such as solid dispersion systems, eutectic mixtures, and inclusion complex formation (Goud et al., 2012; Tommasini et al., 2004). Crystal engineering techniques for the formation of eutectic mixtures of APIs and coformers are a prospective strategy to enhance the physicochemical properties of APIs, including solubility and dissolution rate profile (Bazzo et al., 2020). The advantages of eutectic mixtures include the cost-effectiveness of preparation and ease of scale-up in manufacturing. The eutectic is not considered a new chemical entity or new crystalline form and therefore does not require clinical trials; in addition, in a eutectic mixture, both components are in a very stable crystalline form (Bazzo et al., 2020). A eutectic mixture is a combination of two or more components that normally do not react by intramolecular interaction to form a new crystalline phase; at a certain ratio, the crystallization of the components is prevented, producing a new system with a lower melting point (Hyun

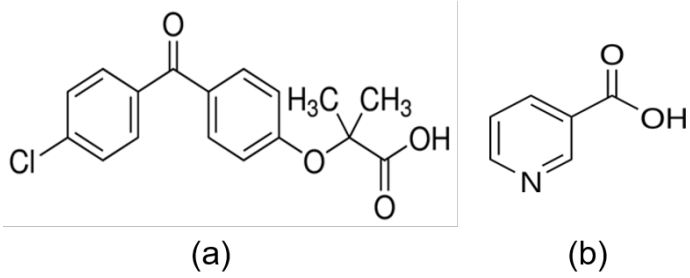

Figure 1. Chemical Structure of (A) Fenofibric Acid ($C_{17}H_{15}ClO_4$) (B) Nicotinic Acid ($C_6H_5NO_2$)

et al., 2019). Eutectic mixtures have been utilized widely to improve the dissolution rate and solubility of poorly soluble APIs such as meloxicam, irbesartan, ketoprofen, curcumin, and quercetin (Narwal et al., 2021; Fernandes et al., 2020; Haneef and Chadha, 2018; Zaini et al., 2015; Zaini et al., 2016).

Experimental studies using animals are needed to evaluate drug effects in living tissues. In this study, a eutectic mixture of FA (Figure 1) with the coformer nicotinic acid (NA; Figure 1) was prepared by solvent drop grinding. Solid-state properties were then characterized by thermal analysis DSC, PXRD, FT-IR spectroscopy, and microscopic analysis SEM.

A two-phase diagram of FA and NA was built to corroborate the formation of eutectic mixtures at specific mole ratios. NA, which is known as a Generally Recognized as Safe (GRAS) excipient approved by the Food and Drug Administration (FDA), was selected as a coformer. NA has also been used extensively to resolve the dissolution rate of poorly soluble drugs (Ghosh et al., 2021; Sanphui et al., 2015). The antihyperlipidemic activity of the eutectic mixture of FA and NA was evaluated in vivo using the enzymatic method.

2. EXPERIMENTAL SECTION

2.1 Materials

FA was acquired from BOC Sciences (New York, USA), NA was acquired from Sigma Aldrich (USA), and acetonitrile and ethanol (HPLC grade) were acquired from Merck (Germany). Double-distilled water was used for the cholesterol oxidase-peroxidase aminoantipyrin (CHOD-PAP) reagent. All additional chemicals were of analytical grade.

2.2 Methods

2.2.1 Formation of the Two-Phase Diagram

The binary system of FA and NA was mixed and ground in a mortar and pestle with a few drops of ethanol at various molar ratios ranging from 0.1:0.9 to 0.9:0.1 (solvent drop grinding technique). The mixtures were placed in vials and dried in a desiccator. DSC apparatus was used to identify the endothermic peaks in each mixture and obtain a DSC thermogram (Shimadzu DSC-60 Plus, Japan). Ten degrees per minute were added to the scanning temperature, increasing it from 30 to 250 °C. Plotting the eutectic mixture's endothermic peak against the molar ratio allowed for the construction of the phase diagram.

2.2.2 Differential Scanning Calorimetry Analysis

In a covered aluminum pan, 5–7 mg of a sample eutectic mixture was placed. Using DSC (Shimadzu DSC-60 Plus, Japan) with a temperature range of 30 to 250°C and a heating rate of 10°C per minute, a thermal examination of the samples was performed.

2.2.3 Powder X-Ray Diffraction Analysis

Using a PANalytical PW 30/40 X-ray diffractometer (the Netherlands), PXRD analysis was performed under the following measurement conditions: K filter, Cu metal, 40 mA current, and 40 kV voltage. Analysis was done between 2 theta 10 and 40 degrees. Origin Lab software was used to process the diffractograms.

2.2.4 Fourier-Transform Infrared Spectroscopy Analysis

FTIR spectroscopy (Thermo Scientific, USA) was used to analyze the intermolecular reactions in intact FA and NA and the eutectic FA-NA mixture. Pellets were formed by compressing the mixture of samples in a ratio of 1:100. The absorption was recorded at wave numbers between 4000 and 400 cm^{-1}

2.2.5 Scanning Electron Microscopy Analysis

Microscopic examination of the eutectic mixture was performed using an SEM instrument (HITACHI type Flexsem 1000, Japan) under the following measurement conditions: 10 kV voltage and 12 mA. A thin gold-palladium layer was sprayed onto the samples before placing them in the sample container.

2.2.6 Characterization of Eutectic Mixtures Using a Polarizing Microscope

NA powder was placed on a slide and covered, then heated until it melted and allowed to recrystallize. FA powder was placed on the edge of the cover glass. The system was heated until all of the FA melted, and the melt moved and came into contact with the surface of the NA crystals. Under a polarizing microscope with 200x magnification, the development of new crystals in the contact zone between the coformer solids and the fused FA was observed and recorded with a digital camera.

2.2.7 Stability Test

The stability of the eutectic mixture was tested by placing samples at 40°C in 75% and 90% relative humidity for 2 weeks in a climatic chamber. After storage, the samples were evaluated by PXRD analysis.

2.2.8 Solubility Test

Solubility tests were performed on the intact FA and the FA-NA eutectic mixture. Saturation solubility in CO_2-free distilled water was investigated at room temperature using an ultrasonicator. An excess amount of the samples was added to 100 ml of medium, stirred for an hour, filtered through a 0.45-m

PTFE filter, and quantified using HPLC (Shimadzu, Japan) with a DAD UV-Vis detector. The HPLC system consists of Pursuit XRS C18 4.6×150 columns. The mobile phase was a 70:30 combination of acetonitrile and pH 3 water. FA had a retention period of 6.187 minutes. The trials were performed in triplicate.

2.2.9 In-vitro Dissolution Rate Profile

Using a USP type 1 dissolution apparatus (SR8-Plus Hanson Research, USA) at 100 rpm and 37 ± 0.5°C, dissolution rate profiles were determined. As a dissolution medium, 900 mL of distilled water containing 0.1% w/v Tween 80 was utilized. After 5, 10, 15, 30, 45, and 60 minutes, the aliquots were collected. Each solution underwent a 0.45-m PTFE filtering process. With a DAD UV-Vis detector, HPLC (Shimadzu, Japan) was used for the analysis. The HPLC system consists of Pursuit XRS C18 4.6×150 columns. The mobile phase was a 70:30 combination of acetonitrile and pH 3 water.

2.2.10 In Vivo Evaluation of Antihyperlipidemic Activity

2.2.10.1 Animal Preparation

Sixteen 3-month-old male Wistar rats weighing 250–300 g were housed at room temperature for 10 days to acclimate under typical environmental conditions. The experimental protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Andalas No. 61/UN.16.2/KEP-FK/2020.

2.2.10.2 Antihyperlipidemic Activity Evaluation

The antihyperlipidemic activity was evaluated by the cholesterol oxidase method. . Previously, all experimental animals were induced via the oral administration of inducing solution consisting of cholesterol, propylthiouracil, and peanut oil, which are known to induce rat cholesterol, at 1% body weight (Vogel et al., 1997). The animals were divided into three treatment groups receiving intact FA, the physical FA-NA mixture, and the eutectic FA-NA mixture and one control animal group receiving 1% Na CMC. All substances were administered orally via gavage at a dosage of 9.45 mg/kg body weight.

2.2.10.3 Determination of Serum Cholesterol Levels

Serum cholesterol levels were determined on day 15 post-treatment. Blood samples were drawn through a vein in the eye and then put into a clot/gel activator tube and centrifuged at 3000 rpm for 15 minutes. The serum was transferred to a microtube with a micropipette, and a CHOD-PAP reagent was added. Cholesterol levels were determined using a photometer.

2.2.11 Statistical Analysis

The independent t-test, two-way ANOVA, and Duncan's multiple range test were used for the statistical analysis, and the data were reported as mean (SD) and 95% confidence interval for significance level. SPSS version 25 was used for all calculations.

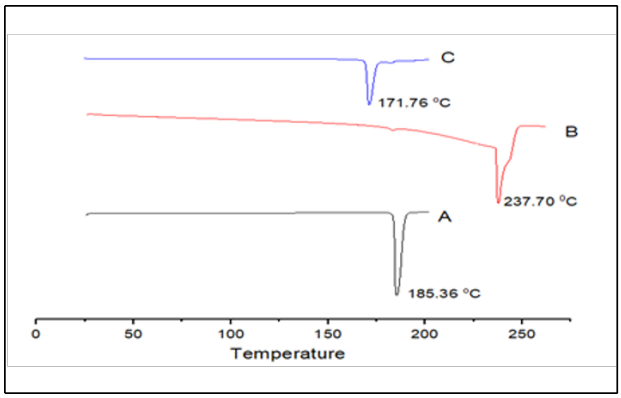

Figure 2. DSC Thermogram of (A) FA, (B) NA, and (C) FA-NA Eutectic Mixture

3. RESULT AND DISCUSSION

The thermodynamic properties of FA, NA, and the eutectic mixture of FA and NA were analyzed by DSC to study solid-state interactions, multicomponent crystal formation, and endothermic and exothermic phenomena such as polymorphic transformation, melting, decomposition, and recrystallization. DSC thermograms show different endothermic peaks for each component if a new crystalline phase is formed (Zaini et al., 2010).

DSC can be used to confirm the purity of the solid phase. When the melting point is lower than that of either of the components, DSC can identify the eutectic properties of multicomponent systems (Dalal et al., 2017). DSC thermograms of FA, NA, and the eutectic mixture of FA and NA in a 1:1 molar ratio are shown in Figure 2. FA and NA exhibited a single endothermic peak at 185.36°C enthalpy (ΔH=-578.42 mJ/g) and 237.70°C enthalpy (ΔH=-179.44 J/g), respectively, which correspond to the melting point of these two compounds, while the eutectic mixture of FA and NA showed an endothermic peak at 171.76°C enthalpy (ΔH=-322.89°C), indicating a melting point of 171.76°C. The FA-NA mixture had a lower melting point than both the drug and the coformer, which supports the idea that a eutectic FA-NA mixture was formed. The melting point of the crystalline phase, which denotes intermolecular bonds in the crystal structure and lattice energy, affects the solubility and rate of dissolution of crystalline solids in water (Dwichandra Putra et al., 2016; Putra et al., 2018).

Nine variations of the molar ratio of FA and NA were designed to clarify the eutectic point and then analyzed with a two-phase diagram. The eutectic point is the lowest point of the nine variations of the mixture, and the eutectic point of FA-NA was at a molar ratio of 6:4 (Figure 4). The binary mixture diagram (3) showed a V shape that demonstrated how a eutectic mixture of FA with NA was formed. The melting point of the binary mixture rapidly fell if FA and NA were mixed in different molar ratios, with the lowest melting point (171.76 oC) occurring at an FA-NA molar ratio of 6:4 (eutectic temperature of the binary mixture; Figure 4). On a two-phase

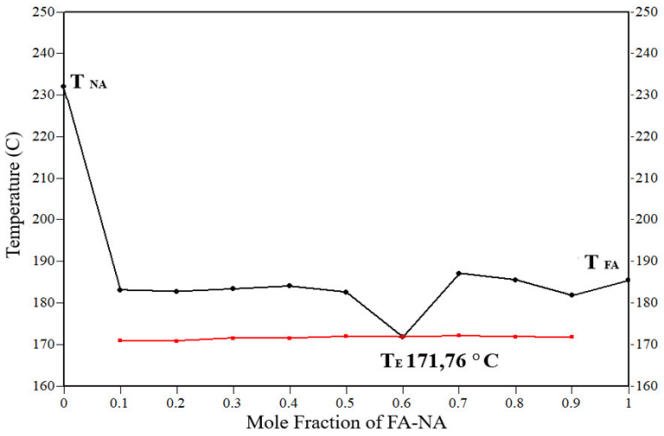

Figure 3. Two-phase Diagram of the FA and NA

diagram, this temperature is also referred to as the temperature of solidus.

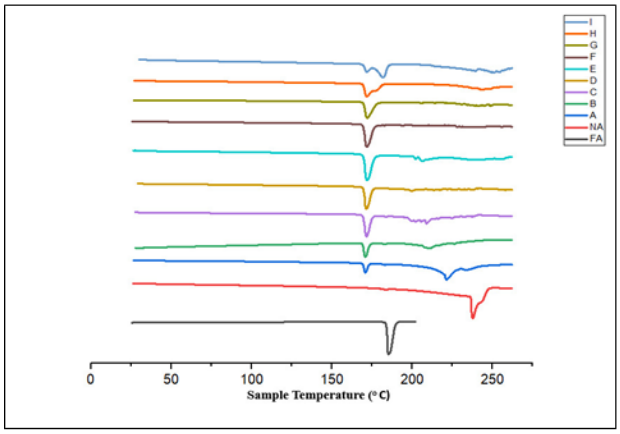

Figure 4. DSC Thermogram Overlay of FA, NA, and Molar Fraction Ratio of FA to NA, (A) 0.1:0.9, (B) 0.2:0.8, (C) 0.3:0.7, (D) 0.4:0.6, (E) 0.5:0.5, (F) 0.6:0.4, (G) 0.7:0.3, (H) 0.8:0.2, (I) 0.9:0.1.

The results of the solid-state characterization with DSC were confirmed by the PXRD analysis. PXRD analysis is an important tool for assessing the crystallinity degree and the formation of new crystalline phases. Each crystalline phase can be identified by its own diffraction pattern in the solid crystalline phase. The diffractogram of FA, NA, and the eutectic mixture of FA and NA are presented in Figure 5. The diffractogram of FA showed that the solid drug had sharp diffraction and high crystallinity, which peaked at 2θ equal to 15.82, 18.44, 19.32, 23.08, 25, 26.4, 30.24, and 33.46. Distinctive diffraction peaks of NA were seen at 2θ equal to 15.33, 20.24, 21.2, 24.6, 25.91, 26.8, and 27.8. A simple eutectic mixture of FA and NA did not form new crystals but a mixture of its intact components. The XRD pattern of the FA-NA eutectic mixture still showed each component's diffraction peaks (FA and NA) but with a decrease in intensity due to the recrystallization of the melted sample and reduction in particle size (Erizal et al., 2008).

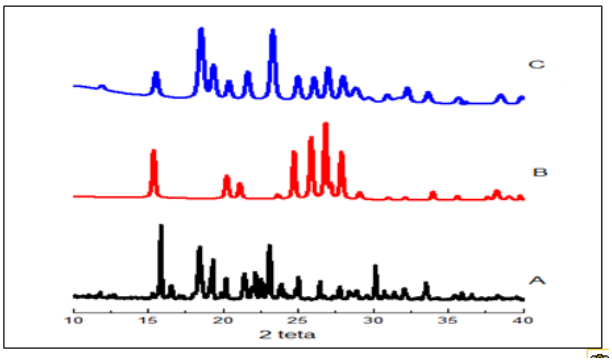

Figure 5. XRD Overlay of (A) FA, (B) NA, and (C) Eutectic Mixture FA-NA

The solubility enhancement observed in the eutectic mixture was due to reduced crystallinity resulting in the attenuation of the crystal lattice energy. The energy of the crystal lattice affects the free energy of dissolution. The eutectic mixture melts at a lower temperature than the parent compound, resulting in lattice energy depletion and solubility improvement (Chadha et al., 2017). In addition, smaller particle sizes and increased wettability in the eutectic mixture also lead to improved solubility, which in turn affects the dissolution rate (Sekiguchi and Obi, 1961).

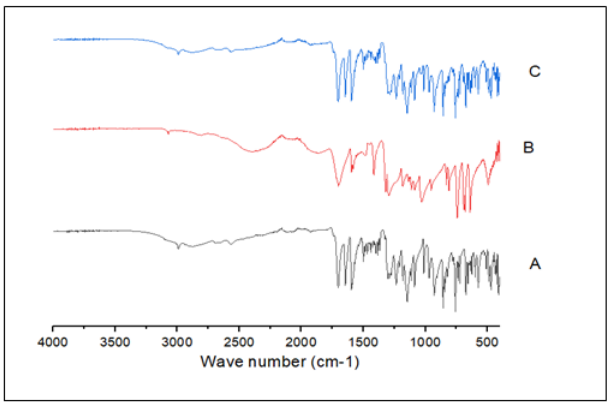

Figure 6. FT-IR Spectra of (A) FA, (B) NA, and (C) Eutectic Mixture FA-NA

FTIR spectroscopic analyzes were performed for FA, NA, and the eutectic mixture of FA and NA to investigate signs of interactions represented by positional changes or disappearances of the stretching vibrations characteristic of the compound. Figure 6 displays the findings of the FTIR analysis. A broad peak at wave number 2991 cm^{-1} (O-H strain) in the FTIR spectra of intact FA indicated the existence of a carboxylic acid

group in the dimer structure. Alkenes and ketones' functional groups were shown by the peaks at 1708 cm^{-1} (C=O strain) and 1647 cm^{-1} (C-C=C symmetrical strain), respectively. The aromatic ring could be seen in the peaks at 1593 cm^{-1} and 1498 cm^{-1} (C-C=C symmetrical strain), while vibrations at 759 cm^{-1} and 671 cm^{-1} revealed the presence of alkyl halide (C-Cl) groups. Strong and distinct bands could be seen in the FT-IR spectrum of NA at 1707 cm^{-1}, which corresponded to the C=O functional group, 3106 cm^{-1} (O-H), and 1675 cm^{-1} (C-C and C=N).

The FA-NA FT-IR spectrum (Figure 7C) is a combined transmittance peak of FA and NA; this spectrum is a superimposition between FA and NA but tends to be similar to the FTIR spectrum of FA because the eutectic composition of FA-NA has a higher FA fraction so that FA is more dominant. There was a slight shift in the wave number in the O-H bond strain at FA 2994 cm^{-1}, NA 3106 cm^{-1}, and the eutectic mixture FA-NA 2882 cm^{-1}. In the IR spectrum, there was no alteration in peak location or broadening, and neither new peaks nor missing peaks appeared, suggesting that FA and NA did not interact chemically. Some studies suggest that a slight shift in wave number indicates the presence of weak hydrogen bonds (Bazzo et al., 2020). A slight wave number shift was detected by FTIR analysis, although it was still within a functional group's range, indicating that the chemical interaction between FA and NA was ruled out.

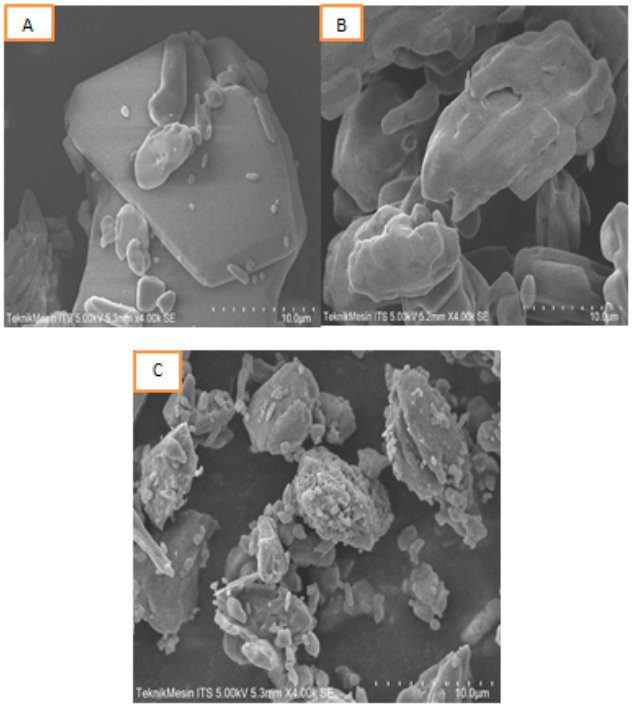

Figure 7. SEM of (A) FA; (B) NA ; and (C) Eutectic Mixture of FA-NA (All Images at 4000 x Magnification)

SEM analysis is used to observe and characterize samples based on their surface morphology, structure, and chemical composition (Pereira-da Silva and Ferri, 2017). SEM data (Figure 7) showed that a novel crystal habit developed that was distinct from the pure crystal habit. FA showed agglomerates of cubic-like crystals and nicotinic acid formed irregular crystals, while the habit of solid FA-NA resembled rod crystals, a novel crystal habit that was distinct from the pure crystal habit; this is because the interaction between FA and NA affected the crystal morphology of each substance.

Polarizing microscope analysis of the eutectic mixture of FA and NA showed recrystallization of fused FA in side A, an intermediate zone in side B, and recrystallized fused NA in side C (Figure 8). Both components exhibited a distinctive crystal habit. After being left for about 1 hour, a new needle-shaped crystal habit began to form in zone C. Differences in crystal habit and thermal behavior indicate solid interactions between the two components FA and NA (Davis et al., 2004).

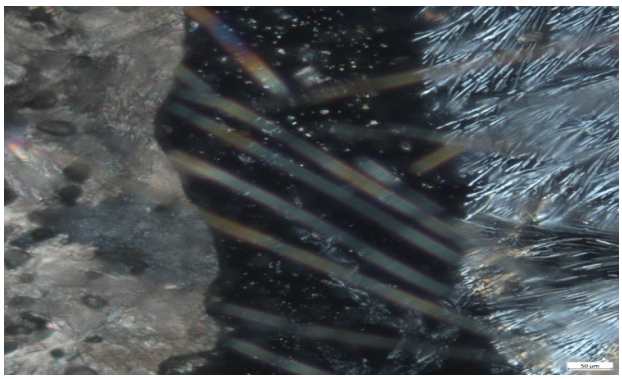

Figure 8. Polarizing Microphoto (A) FA, (B) Contact Zone Between FA-NA, and (C) NA

The results of the FA-NA stability test under high humidity are shown in Figure 9, which revealed that the eutectic mixture of FA and NA was unable to maintain stability at 75% and 90% relative humidity. Analysis of the stability test results using PXRD was used to examine the stability of the eutectic FA-NA mixture. The stability test results showed the same diffractogram pattern, which indicates that the crystal structure did not change, but the intensity did. There was a change in the intensity of several peaks, indicating a change in the degree of crystallinity. The low intensity was most likely due to the rearrangement or low regularity of the crystal lattice due to thermodynamic activity (Ainurofiq et al., 2018). From these characterizations, we could determine suitable storage conditions for this mixture.

The results of the solubility test of FA and the eutectic mixture of FA-NA are presented in Table 1. They indicated that the solubility of the eutectic FA-NA mixture was significantly higher (1.23-fold) than that of intact FA. FA dissolved more rapidly in the eutectic mixture than in the intact form. In contrast to intact FA, which only dissolved by 15.22% throughout the 10-minute test period, the FA-NA eutectic mixture dissolved by about 20.62%. The FA-NA eutectic mixture and

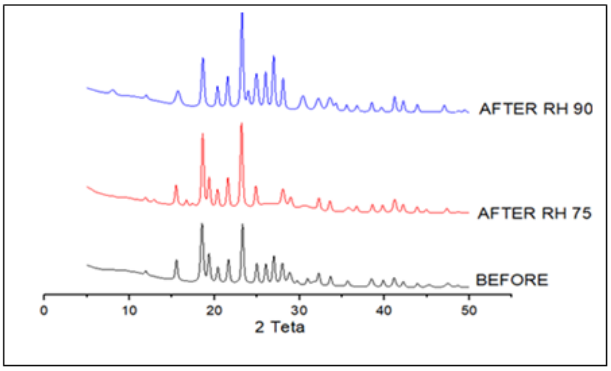

Figure 9. PXRD of Eutectic Mixture of FA-NA Before and After 2 weeks at 75% and 90% RH

intact FA both dissolved by approximately 32.33% and 31.45%, respectively, in 60 minutes (Figure 10).

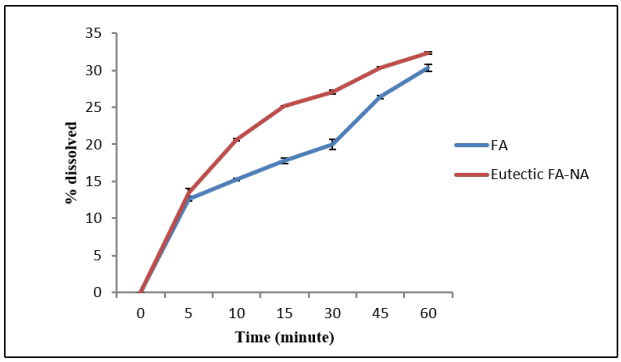

Figure 10. Dissolution Profile of FA and FA-NA Eutectic Mixture (n=3)

Table 1. Solubility of Fenofibric Acid (FA) and Eutectic Mixture of Fenofibric Acid-acid Nicotinic (FA-NA). Analysed with Independent t-test with 95% Confidence Interval, n=6 P <0.05.

Compound	Solubility (μg/mL)	± SEM	Increased solubility
FA	18.53	0.1909	-
FA-NA	22.87	0.4529	1.23-fold

Orally administered solid drug compounds undergo a dissolution process in gastrointestinal fluid and then penetrate through the lipid membrane before reaching systemic circulation. A sufficient number of drug molecules must be present at the target action site in order for a pharmacological activity to occur rapidly and effectively. One of the most important physicochemical properties that influence how soon drug molecules are dissolved and absorbed in the gastrointestinal tract is the solubility (Dressman et al., 2007). This study demonstrated that the eutectic mixture of FA and NA had solubility much superior to that of the intact FA (Table 1).

The increasing solubility of FA and NA in the eutectic mixture is a result of a decrease in the melting point, which causes weak lattice energy in the solid phases so as to break the intermolecular interactions in the crystal lattice (Chaturvedi et al., 2020; Haneef et al., 2021; Zaini et al., 2017). Moreover, the introduction of hydrophilic excipients such as NA, which improve the mixture's wettability, also contributes to the increase in solubility and dissolving rate. NA has been used in combination with several other drugs for the purpose of increasing solubility, including hydrochlorothiazide, modafinil, and norfloxacin (Ferreira et al., 2020; Sanphui et al., 2015; Zaini et al., 2010).

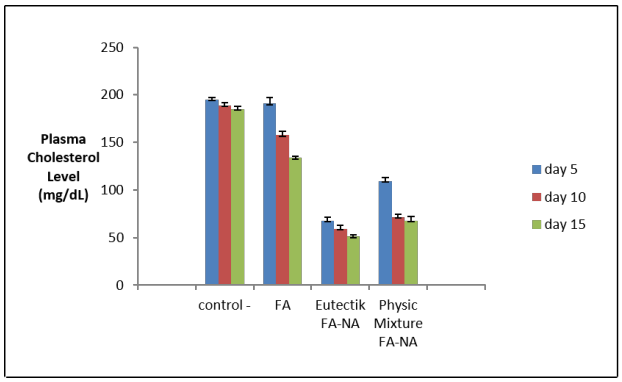

Figure 11. Comparative Plasma Cholesterol Level Between Groups p<0.05 as Compare with Control Group (analyzed with Duncan's MRT Following Two-way ANOVA 95% Confidence Interval n=16).

The CHOD/PAP method, one of the most used methods to assess antihyperlipidemic activity, was utilized in this study to evaluate antihyperlipidemic activity in rats. Hyperlipidemia in rats was induced orally by an inducting solution consisting of cholesterol, propylthiouracil, and peanut oil, which are known to induce hyperlipidemia in rats (Vogel et al., 1997). The plasma cholesterol level of all experimental animals after being induced with the inducing solution was 216.89 mg/dL. Plasma cholesterol levels were also determined after 5, 10, and 15 days of drug administration. The plasma cholesterol level of the experimental animals was calculated by comparing their plasma cholesterol levels before and after drug administration. The in vivo evaluation of antihyperlipidemic activity (Figure 11) in this study showed that the eutectic mixture of FA and NA was more effective in lowering cholesterol compared to intact FA and the physical FA-NA mixture. Determination plasma cholesterol level began to be seen from day 5 after drug administration until day 15. Comparison of the plasma cholesterol level between groups revealed that the eutectic FA-NA mixture exhibited the strongest antihyperlipidemic effect, significantly better than that of intact FA and the FA-NA physical mixture.

Low solubility and a slow rate of dissolution restrict BCS II drug absorption, including FA, in the gastrointestinal tract. The poor solubility of this drug may result in incomplete absorption

even though the membrane permeability is good (Amidon et al., 1995). The formation of a eutectic FA-NA mixture can overcome this limitation. This study shows an increase in solubility that simultaneously enhances the antihyperlipidemic effect in experimental animals

4. CONCLUSION

The present study revealed that the eutectic mixture of FA and NA exhibited a eutectic point at 171.76°C at a molar ratio of 6:4. The results of the study indicated that the preparation of a eutectic mixture of FA with NA as the coformer significantly improved FA solubility. The eutectic mixture also enhanced the antihyperlipidemic effect of FA as compared to its physical mixture with NA and intact FA.

5. ACKNOWLEDGMENT

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