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Dissolution Rate Enhancement and Physicochemical Characterization of a Fenofibric Acid–Nicotinamide Eutectic Mixture

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ABSTRACT

Fenofibric acid is a potent lipid-lowering agent that is used clinically in severe hypertriglyceridemia, primary hyperlipidemia, and mixed dyslipidemia. Fenofibric acid is a poorly soluble drug which is classified as a Biopharmaceutical Classification System (BCS) class II. The purpose of the present study was to improve the solubility and dissolution rate of the poorly soluble drug fenofibric acid (FA) by the formation of a simple eutectic mixture with nicotinamide (NIC). A simple eutectic mixture of FA and NIC was prepared using the solvent-drop grinding method. A binary phase diagram of FA and NIC in various molar ratios was constructed by thermal analysis differential scanning calorimetry (DSC). Solid-state characterization was carried out using powder X-ray diffraction (PXRD) analysis, differential scanning calorimetry, Fourier transform-infrared spectroscopy analysis, scanning electron microscopy analysis, and apparent solubility test. The *in vitro* dissolution rate of the simple eutectic mixture in an aqueous medium was determined using a type I USP apparatus. The binary phase diagram demonstrated that FA and NIC form a simple eutectic mixture at a molar ratio of 0.3:0.7. The eutectic mixture melted at an endothermic peak of 112.9°C. The PXRD pattern of the eutectic mixture was representative of each intact component (FA and NIC). SEM microscopic analysis showed that new crystal habits were formed. The solubility and dissolution rate of FA from the eutectic mixture were improved significantly compared to intact FA.

Keywords: Fenofibric acid, Nicotinamide, Eutectic mixture, Solubility, Dissolution rates.

Introduction

Fenofibric acid (FA) is the active metabolite of fenofibrate, which is used clinically to lower blood triglycerides and total cholesterol.[1] FA has a high lipophilicity (log P = 5.24) and is poorly soluble in aqueous media. This compound has been categorized in the Biopharmaceutical Classification System (BCS) as a class II active pharmaceutical ingredient. Its low solubility in water causes dissolution rates to be slow and leads to erratic bioavailability in the systemic circulation.[2] Thus, improving the solubility and dissolution rate of FA is of substantial interest.

Numerous approaches to enhancing FA's solubility and dissolution rates have been widely reported. These strategies include the addition of $MgCO_3$ as an alkalizing agent and carrageenan in formula; formation of a solid dispersion of FA with hyaluronic acid and polyethylenglycol; salt formation using choline bases, diethanolamine, tromethamine, calcium, ethanolamine, and piperazine; formation of a surface solid dispersion using sodium croscarmellose; and self nanoemulsion.[3–7] In recent years, eutectic mixtures have emerged as promising techniques to improve active pharmaceutical ingredients' physicochemical properties.[8,9]

Such mixtures are defined as a combination of two or more solid substances that melt at the lowest temperature of any molar ratio of the components. Eutectic mixtures have been widely applied to enhance the solubility and dissolution rate of poorly soluble drugs, such as irbesartan, meloxicam, and curcumin.[10–12]

The purpose of the present work was to prepare a simple eutectic mixture of FA and nicotinamide (NIC) (Figure 1A and 1B) by using a solvent-dropped grinding (using ethanol as the solvent) in order to improve its solubility and dissolution rate. NIC was selected as the coformer and has been generally recognized as a safe (GRAS) excipient approved by the US Food and Drug Administration (FDA). NIC was also popular as a hydrotropic agent and is widely used to enhance the dissolution rate of poorly soluble drugs.[13–15] A binary phase diagram of FA and NIC was constructed to confirm the formation of the eutectic mixture at a defined molar ratio. The eutectic mixture samples were further characterized regarding their solid-state properties by powder X-Ray Diffraction, differential scanning calorimetry, Fourier Transform infrared spectroscopy, and scanning electron microscopy analysis. Solubility and powder dissolution rates were determined in an aqueous medium, and the dissolved FA concentration was calculated by high-performance liquid chromatography (HPLC).

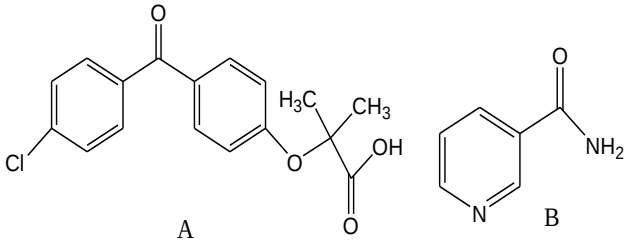

Figure 1: Molecular Structure of (A) fenofibric acid (FA) and (B) nicotinamide (NIC)

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Materials and Methods

Materials

Fenofibric acid (FA) was purchased from BOC Sciences (New York, USA). Nicotinamide was obtained from Sigma Aldrich (USA). Acetonitrile and HPLC-grade ethanol were purchased from Merck (Germany). The water used was double distilled. All other solvents used in this study research were of analytical grade.

Methods

Construction of binary phase diagram

A binary mixture of FA and NIC in various molar ratios of 0.1: 0.9 to 0.9: 0.1 were combined and ground in a mortar and pestle with the addition of a few drops of ethanol (solvent-dropped grinding technique). The binary mixture was stored in a vial and dried in a desiccator. The endothermic peaks of each mixture were determined using a DSC apparatus. A DSC thermogram was obtained using a differential scanning calorimeter (Shimadzu DSC-60 Plus, Japan). Scanning temperatures ranged from 30 to 200°C at a rate of 10°C per minute. A phase diagram was constructed by plotting the endothermic peak of the eutectic mixture versus the molar ratio.

Differential scanning calorimetry (DSC) analysis

Thermal analysis of the samples was performed using differential scanning calorimetry (Shimadzu DSC-60 Plus, Japan). A sample eutectic mixture of 5–7 mg was placed in a closed aluminum pan. The DSC apparatus was programmed over a temperature range of 30 to 220°C with a heating rate of 10°C per minute.

Powder X-ray diffraction analysis

Powder X-ray diffraction analysis of the samples was carried out at room temperature using a PANalytical PW 30/40 X-ray diffractometer (the Netherlands). The measurement conditions were as follows: metal Cu, Kα filter, voltage 40 kV, current 40 mA, and the analysis was performed in the range 2 theta 10–40°.

Fourier transform-infrared spectroscopy

Intermolecular reactions were analyzed using FT-IR spectroscopy (Thermo scientific, USA). The sample was mixed with KBr at a ratio of 1:100, and this mixture was compressed to form pellets. Sample absorptions were recorded at 4000–600 cm^{-1} wavenumbers. Analyses were performed for intact FA, NIC, and the FA–NIC eutectic mixture.

Scanning electron microscopy

Microscopic analysis of eutectic mixtures was carried out using an SEM apparatus (HITACHI type S-3400N, Japan). Samples were placed in the sample holder, and all samples were sprayed with a thin gold–palladium film. The measurement conditions were 10 kV and 12 mA.

Solubility

Solubilities were determined for the FA–NIC eutectic mixture, and intact FA. The saturated solubility in CO_2-free distilled water was evaluated at room temperature using an orbital shaker. An excess amount of sample was added to 100 ml media, and samples were stirred on an orbital shaker for 5 days and then filtered through a 0.45-µm PTFE filter. FA concentrations were determined using an HPLC SHIMADZU (Japan) equipped with a DAD UV-Vis detector. The HPLC system used XRS C18 4.6 × 150 pursuit columns. A mixture of acetonitrile and water adjusted to pH 3 (70:30) was used as the mobile phase. The FA retention time was 6.187 min, and all experiments were carried out in triplicate.

In vitro dissolution rate profile

Dissolution rate profiles were determined by using a USP type 1 dissolution apparatus (SR8-Plus Hanson Research, USA) at 100 rpm and 37 ± 0.5°C. The dissolution medium was 900 mL distilled water containing 0.1% w/v Tween 80. Aliquots were withdrawn after 5, 10, 15, 30, 45, and 60 minutes. Each solution was filtered with a 0.45-µm PTFE filter. The analysis was performed using a SHIMADZU (Japan) HPLC equipped with a DAD UV-Vis detector. The HPLC system consisted of XRS C18 4.6 × 150 pursuit columns. A mixture of acetonitrile and water adjusted to pH 3 (70:30) was used as the mobile phase.

Statistical Analysis

The data from the experiment were presented as mean ± SEM. Statistical analysis was evaluated by using independent *t*-test with 95% confidence interval.

Results and Discussion

Thermal analysis using differential scanning calorimetry (DSC) is a rapid and simple analytical method to determine the properties of crystals when a material is heated. This approach can be used to characterize the thermodynamic properties of the solid phase and screen for intermolecular interactions between two solids.[16] A binary phase diagram was constructed using DSC thermal analysis. The endothermic peaks for FA, NIC, and an FA–NIC binary mixture in various molar ratios were determined using a DSC apparatus (Fig. 2). The binary phase diagram of a simple FA–NIC eutectic mixture is depicted in Figure 3. FA showed a sharp endothermic peak at 185.3°C, indicating its melting point, and NIC had a single endothermic peak at 130.9°C, also attributed to its melting temperature. The binary mixture diagram exhibited a V-shaped form that demonstrated the formation of a simple FA–NIC eutectic mixture. Figure 3 provides a binary phase diagram of FA and NIC at constant pressures. When FA and NIC were mixed at various molar ratios, the melting points of the binary mixture decreased gradually to the lowest melting point (112.9°C) at a 0.3: 0.7 molar ratio of FA–NIC (eutectic temperature of the binary mixture). Plotting of the melting temperature against the molar ratio of FA–NIC ($T_{FA} - T_E - T_{NIC}$) generated a liquidus curve. Above this curve, FA and NIC were in a liquidus phase and dissolved each other. The lowest melting point (T_E) on the curve was defined as the eutectic temperature.[17]

PXRD analysis was conducted to verify the formation of the FA–NIC eutectic mixture at a 0.3:0.7 molar ratio. The PXRD patterns of FA, NIC, and the FA–NIC eutectic mixture are shown in Figure 4. The PXRD pattern of FA showed the presence of an active pharmaceutical ingredient with high crystallinity and a sharp diffraction peak at 2Θ; 15.82, 18.44, 19.37, 23.08, 30.24, and 33.46. The NIC diffraction peaks appeared at 2Θ = 15.11, 19.59, 22.37, 26.09, and 27.45. Meanwhile, the diffractogram of the FA–NIC binary mixture represented a superimposition of the peaks of intact components without any new diffraction patterns. The simple eutectic mixture did not produce a new crystalline form but, rather, a mixture of its intact components, which were displayed in the PXRD pattern of the FA–NIC eutectic mixture, in which the diffraction peaks of each component (FA and NIC) still appeared on the PXRD pattern. The difference was only in the intensity of each diffraction peak due to their preferred orientation caused by recrystallization from a melted sample and particle size reduction.[18]

FT-IR spectroscopic analysis is a reliable method used to determine the solid-state interactions of active pharmaceutical ingredients and excipients. The formation of multicomponent crystals is indicated by a significant difference in functional group vibrations in comparison to the intact component based on supramolecular hetero- and homosynthons.[19] The results of FT-IR spectra are provided in Figure 5. The FT-IR spectra of the FA-NIC eutectic mixture showed no shift in the position of the wavenumbers from the various functional groups present. No shift in the position of the characteristic peaks is observed, with no widening of the peaks, and no missing peaks or new peaks appearing in the IR spectrum. Hence, no chemical interactions were formed between FA and NIC.

SEM analysis was used to determine the samples' crystalline habits and morphology.[20] The SEM results demonstrated interactions between FA and NIC that could affect each component's crystal morphology. Microphotographs of the samples are depicted in Figure 6, showing that new crystal habits were formed that were different from those of standard crystals. The crystal habit of intact FA showed agglomerates of cubic-like crystals. NIC exhibited long, rod-shaped

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crystals, whereas the crystal habit of the FA–NIC eutectic mixture appeared to form aggregates. FA–NIC eutectic mixture microphotographs demonstrated that the mixture formed a new crystal habit that was different from the intact components.

The solubility and dissolution rate are crucial parameters in the preformulation stage for developing oral solid dosage forms. Drug solubility and dissolution rate can predict the absorption of active pharmaceutical ingredients in the gastrointestinal tract.[21] Poorly soluble drugs (BCS Classes II and IV) often exhibit low, and improving solid-state properties through the formation of a eutectic mixture with excipients has recently been shown to be a promising strategy. The solubility test results and dissolution rate profile of intact FA and the FA–NIC eutectic mixture are displayed in Table 1 and Figure 7, respectively. The solubility of FA from its eutectic mixture was significantly (1.94-fold) better than intact FA. The dissolution rate of FA was also remarkably faster in the eutectic mixture compared to intact FA. In 5 minutes of testing, the FA-NIC eutectic mixture dissolved approximately 21.28%, whereas intact FA only dissolved 13.15%. Within 60 minutes, the FA–NIC eutectic mixture had dissolved by approximately 35.8%, whereas in the same amount of time, the intact FA had dissolved by approximately 31.45%.

Several mechanisms are involved in improving the solubility and dissolution rate of FA from a eutectic mixture. The first one involves decreasing the melting point of a binary mixture, causing a weak lattice energy in the crystal structure of the solid substances and, thus, facilitating intermolecular interaction breakdown in the crystal lattice.[22,23] This phenomenon increases poorly soluble drugs' solubilities. Another approach involves the use of hydrophilic excipients, such as nicotinamide to enhance mixture wettability by a local solubilization effect. Nicotinamide has also been used as a hydrotropic agent to improve the solubility and dissolution rate for some poorly soluble drugs, such as efavirenz, ketoprofen, felodipine, and nimesulide.[13–15,24]

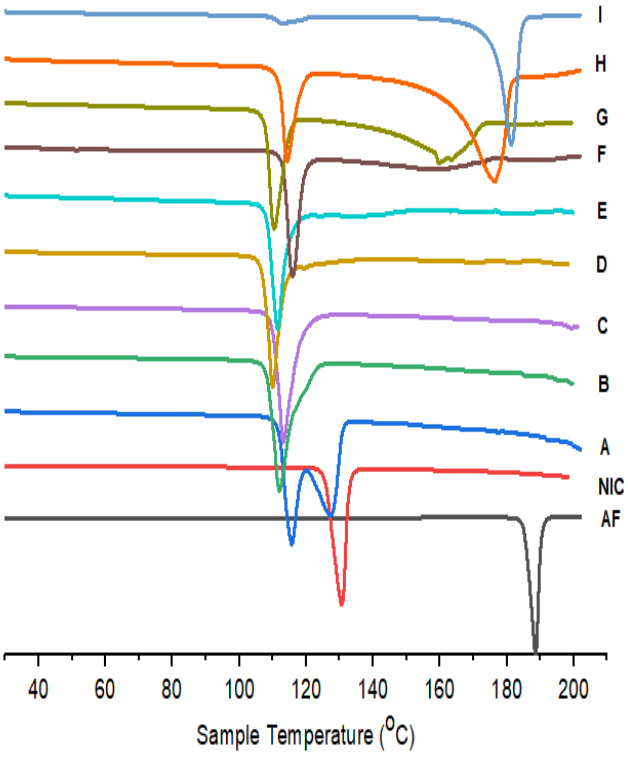

Figure 2: DSC thermogram of FA, NIC, and molar fraction ratio of FA to NIC A) 0.1:0.9, B) 0.2:0.8, C) 0.3:0.7, D) 0.4:0.6, E) 0.5:0.5, F) 0.6:0.4, G) 0.7:0.3, H) 0.8:0.2, I) 0.9:0.1.

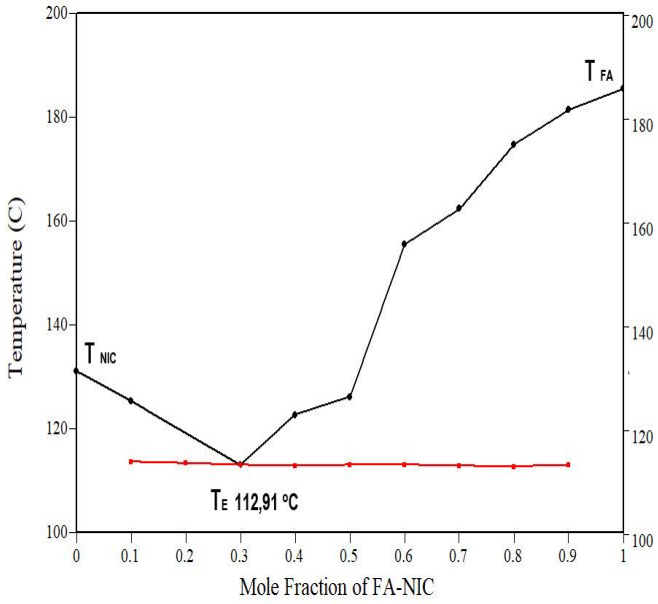

Figure 3: Two-phase diagram of the binary mixture of fenofibric acid-nicotinamide

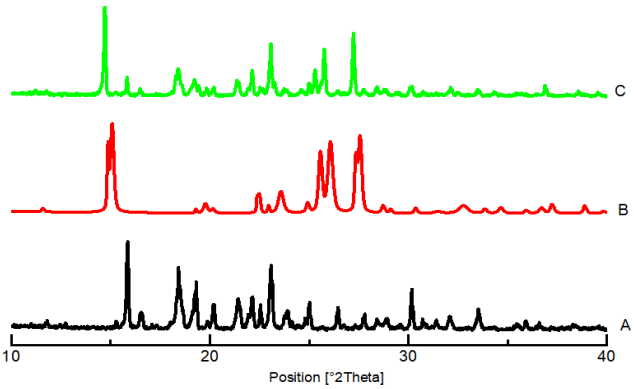

Figure 4: PXRD pattern of (A) FA, (B) NIC and (C) eutectic mixture of FA-NIC

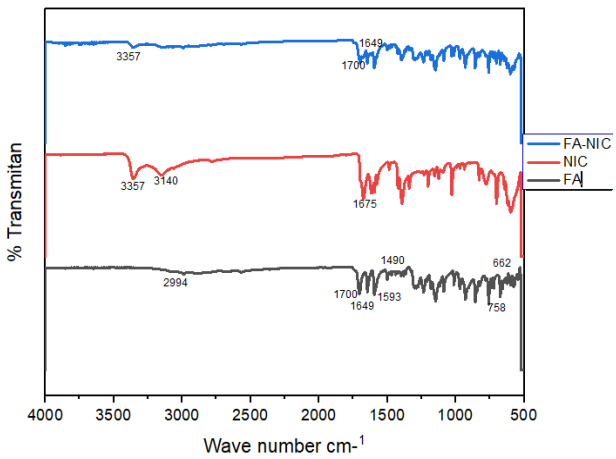

Figure 5: FT-IR spectra of FA, NIC and eutectic mixture of FA-NIC

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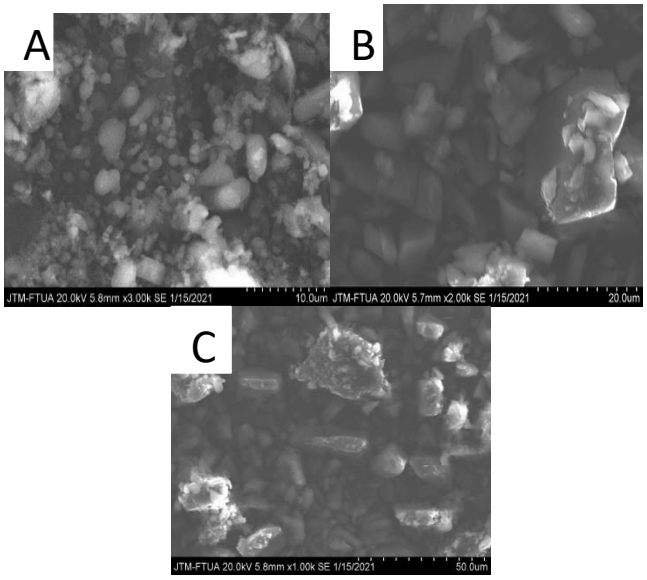

Figure 6: Scanning electron microphotographs of (A) fenofibric acid; (B) nicotinamide; and (C) eutectic mixture of fenofibric acid-nicotinamide (2000 x magnification).

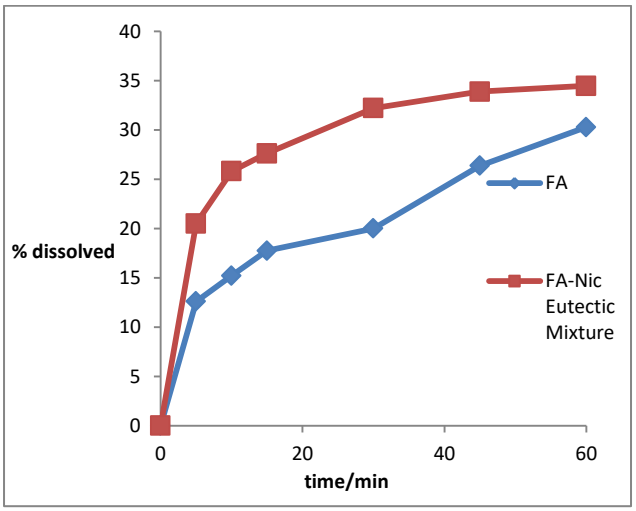

Figure 7: Dissolution rate profile of FA and eutectic mixture of FA-NIC

Table 1: Solubility of fenofibric acid (FA) and eutectic mixture of fenofibric acid- Nicotinamide (FA-NIC)

Compound	Solubility (µg/mL)	± SEM	Increased solubility
FA	31.8	0.4173	-
FA-NIC	61.52	0.3555	1.94 -fold

Analysed with independent *t*- test with 95 confidence interval, n = 6, $P < 0.05$.

Conclusion

A novel, simple eutectic mixture of fenofibric acid and nicotinamide was successfully prepared using the solvent-drop grinding method. This mixture showed a significantly higher solubility and dissolution rate than intact fenofibric acid.

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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