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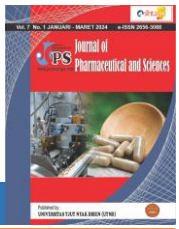

Solid-State Interactions and Eutectic Formation in Gemfibrozil-Nicotinamide Binary Mixtures

Interaksi Padatan dan Pembentukan Eutektik dalam Campuran Biner Gemfibrozil-Nikotinamida

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Abstract

Background: Gemfibrozil is an antihyperlipidemic drug that effectively lowers cholesterol and triglyceride levels in the blood. However, it has limitations, primarily low solubility and compactibility. **Objective:** The objective of this study was to analyze the solid interactions in a binary mixture of gemfibrozil and nicotinamide, which is useful for modifying the physicochemical properties of gemfibrozil through the formation of multicomponent solids. **Methods:** The method employed for solid-state interaction analysis was differential scanning calorimetry (DSC), which involved constructing solid-liquid phase diagrams, accompanied by Fourier transform infrared spectroscopy (FTIR) analysis to identify any hydrogen bonding interactions between the components. **Results:** The results revealed that the gemfibrozil-nicotinamide binary mixture formed a solid-liquid phase diagram characterized by a V-type solid curve. A eutectic mixture was observed at a molar ratio of 8:2, with a eutectic melting point of 59.3 °C. FTIR analysis revealed no hydrogen bonding interactions between gemfibrozil and nicotinamide. **Conclusion:** It was concluded that gemfibrozil in the binary mixture system did not form a solid interaction with nicotinamide but was a eutectic mixture. These findings can be used to design strategies for improving the physicochemical properties of gemfibrozil through the formation of multicomponent solids.

***Keywords*: Gemfibrozil, Nicotinamide, Solid-State Interaction, Binary Phase Diagram, Eutectic**

Abstrak

Latar Belakang: Gemfibrozil merupakan obat antihiperlipidemia yang efektif menurunkan kadar kolesterol dan trigliserida dalam darah. Namun, gemfibrozil mempunyai kendala yaitu sifat kelarutan dan mekanik yang rendah. **Tujuan:** Tujuan penelitian ini adalah menganalisis interaksi padatan pada campuran biner gemfibrozil-nikotinamida yang sangat diperlukan pada penerapan sistem padatan multikomponen untuk peningkatan sifat fisikokimia dari gemfibrozil. **Metode:** Metode yang digunakan untuk analisis interaksi padatan adalah *differential scanning calorimetry* (DSC) melalui penyusunan diagram fase padat-cair dan dilanjutkan dengan analisis Fourier transform infrared spectroscopy (FTIR) untuk mengidentifikasi interaksi ikatan hidrogen antar komponen. **Hasil:** Hasil penelitian menunjukkan bahwa gemfibrozil dengan nikotinamida membentuk diagram fase padat-cair dengan kurva padat tipe-V. Campuran biner gemfibrozil – nikotinamida membentuk campuran eutektik pada perbandingan molar 8:2 dengan titik lebur eutektik pada 59,3 °C. Pengujian dengan FTIR mengindikasikan tidak ada interaksi ikatan hidrogen antara gemfibrozil dengan nikotinamida. **Kesimpulan:** Gemfibrozil dalam sistem campuran biner tidak membentuk interaksi padatan dengan nikotinamida namun merupakan campuran eutektik. Hal ini dapat digunakan untuk merancang strategi pada peningkatan sifat fisikokimia gemfibrozil melalui pembentukan padatan multikomponen.

***Kata Kunci*: Gemfibrozil, Nikotinamida, Interaksi Padatan, Diagram Fase Biner, Eutektik.**

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Introduction

Gemfibrozil (2,2-Dimethyl-5-(2,5-dimethylphenoxy) pentanoic acid) is an antihyperlipidemic drug derived from fibric acid that effectively reduces cholesterol and triglyceride levels in the blood. Gemfibrozil works by binding to the peroxisome proliferator-activated receptor-alpha (PPAR-alpha), thereby activating lipoprotein lipase, an enzyme that accelerates the hydrolysis reaction of triglycerides. Additionally, gemfibrozil is known to increase high-density lipoprotein (HDL), which is the "good" type of cholesterol, and also has milder side effects than other lipid-lowering drugs [1,2]. However, according to the Biopharmaceutical Classification System, gemfibrozil have high permeability, allowing them to easily cross biological membranes, but low solubility in aqueous solutions [3]. The low solubility results in a slow dissolution rate, hence limiting its bioavailability [4]. Additionally, gemfibrozil presents mechanical properties indicative of low compactibility, creating challenges in tablet formulation, such as capping, lamination, and the production of brittle tablets [5]. Consequently, there exists a pressing need for research aimed at improving the solubility and mechanical attributes of gemfibrozil.

One promising approach to improving physicochemical properties of active pharmaceutical ingredients is through the formation of multicomponent solids [6]. This method requires the combination of active pharmaceutical ingredients with excipients, commonly referred to as coformers. The interactions between the active pharmaceutical ingredient and coformers can yield various solid forms (e.g., cocrystals or eutectics), which are dictated by the nature of the intermolecular interactions [7]. Cocrystals are formed when active pharmaceutical ingredients and coformers engage through noncovalent interactions such as hydrogen bonding, van der Waals forces, and π–π stacking, whereas eutectics arise when the constituent components, despite lacking intermolecular interactions, exhibit miscibility under specific conditions of temperature and molar ratio, leading to a lower melting point than that of the individual components [7,8]. The formation of cocrystals and eutectic systems has been associated with enhanced solubility, improved dissolution rate, greater stability, and superior mechanical properties compared to the original active pharmaceutical ingredient [8-10]. Therefore, the modification of active pharmaceutical ingredients through the formation of multicomponent solids represents a viable strategy for improving their physicochemical characteristics.

In the present study, the solid-state interactions between gemfibrozil and coformers in a binary solid system were analyzed. This analysis utilized differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), which serve to elucidate solid-state interactions based on discernible changes in melting points and shifts in the absorption peaks of functional groups [7]. Nicotinamide was selected as the coformer due to its prevalent application in multicomponent solid systems, attributed to its high water solubility and classification as a generally recognized as safe (GRAS) compound, indicating its safety for human consumption [11]. In addition, nicotinamide is able to form non-covalent interactions with various functional groups of drug molecules such as alcohols, carboxylic acids, amides, and ester groups [12]. The objective of this investigation was to delineate the solid-state interactions present within the gemfibrozil-nicotinamide binary system. The novelty of this study is that the examination of solid-state interactions in the gemfibrozil-nicotinamide mixtures is carried out for the first time, which may make a significant contribution to the development of gemfibrozil multicomponent solids. The molecular structures of gemfibrozil and nicotinamide are shown in Figure 1.

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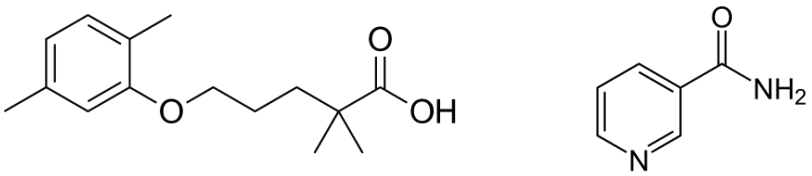

(a) (b)

Figure 1. Molecular structures of (a) gemfibrozil and (b) nicotinamide

Experimental Section

Materials and Apparatus

The materials used include gemfibrozil (Zhejiang Excel Pharmaceutical Co. Ltd., China), nicotinamide (Jubilan Ingrevia Ltd., India), and isopropyl alcohol (PT. Smart Lab, Indonesia). The main equipment used was a Powder X-Ray Diffractometer (Panalytical Xpert Pro), a Differential Scanning Calorimeter (Thermo Plus EVO), and a Fourier Transform Infra-Red Spectrophotometer (ThermoScientific Nicolet iS10).

Methods

Preparation of Gemfibrozil-Nicotinamide Binary Mixtures

Binary mixtures of gemfibrozil and nicotinamide were prepared with molar ratios of gemfibrozil/nicotinamide of 2:8, 4:6, 5:5, 6:4, and 8:2. Gemfibrozil and nicotinamide powders were sieved using an 80 mesh sieve to obtain powders with the same particle size range (<200 μm). The powdered materials for each binary mixture were weighed according to the ratio (total weight 1 gram) and then carefully mixed in a porcelain mortar using a pestle for about 5 minutes at room temperature to obtain a homogeneous mixture. Each gemfibrozil-nicotinamide binary mixture was subsequently tested using DSC [13,14].

DSC Testing

DSC testing was conducted to obtain thermodynamic data from gemfibrozil, nicotinamide, and gemfibrozil-nicotinamide binary mixtures. Approximately 2.0 mg of each binary mixture sample was weighed using an analytical balance (Precisa ES 225SM-DR). Weighing was performed in aluminum containers equipped with lids. The powder samples in the aluminum containers were then sealed tightly using a press. The DSC equipment used has been calibrated using an indium standard. DSC testing (Thermo Plus EVO) was conducted in a temperature range of 25–250 °C at a heating rate of 10 °C/minute under dry air flow conditions.

Solid-Liquid Phase Diagram

The solid-liquid phase diagram was constructed based on thermodynamic data from DSC testing. The temperatures of the endothermic peaks on the DSC thermogram of each gemfibrozil-nicotinamide binary mixture were plotted against the molar fraction of gemfibrozil. The plotted results consisted of a solid curve at low temperatures indicating the eutectic melting point and a liquid curve at higher temperatures indicating the melting temperature of the excess material. From the solid-liquid phase diagram, information about the phase area of the binary mixture, the eutectic composition, and the eutectic temperature of the gemfibrozil-nicotinamide binary system can be obtained [15].

FTIR Testing

FTIR analysis is a reliable method for characterizing intermolecular interactions between components in multicomponent solids. FTIR test samples were prepared by mixing gemfibrozil and nicotinamide in a 1:1 molar ratio, followed by isopropanol addition until all the solids were dissolved. The solvent was then evaporated at room temperature to produce a dry solid. The solids were finely ground using a mortar and analyzed by FTIR. FTIR testing is performed at a resolution of 4 cm^{-1} over the wavenumber range of 4000–400 cm^{-1} [13].

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Results and Discussion

DSC Testing

DSC is a highly effective analytical method for determining solid-state interactions between solid materials in multicomponent systems. DSC thermograms can reveal the thermal behavior of each material according to its interaction characteristics with other materials in a multicomponent mixture [16]. The results of the DSC thermogram are shown in Figure 2, while the thermodynamic data for gemfibrozil and nicotinamide are presented in Table 1. The DSC thermogram of gemfibrozil showed a sharp endothermic peak at 60.2 °C with a melting enthalpy (ΔH) of 90.18 J/g. This endothermic peak indicated the melting point of gemfibrozil, as mentioned in previous studies [17]. Nicotinamide had a DSC thermogram with a sharp endothermic peak at 129.6 °C with a melting enthalpy (ΔH) of 167.40 J/g. The DSC test results for nicotinamide were consistent with previous studies [18].

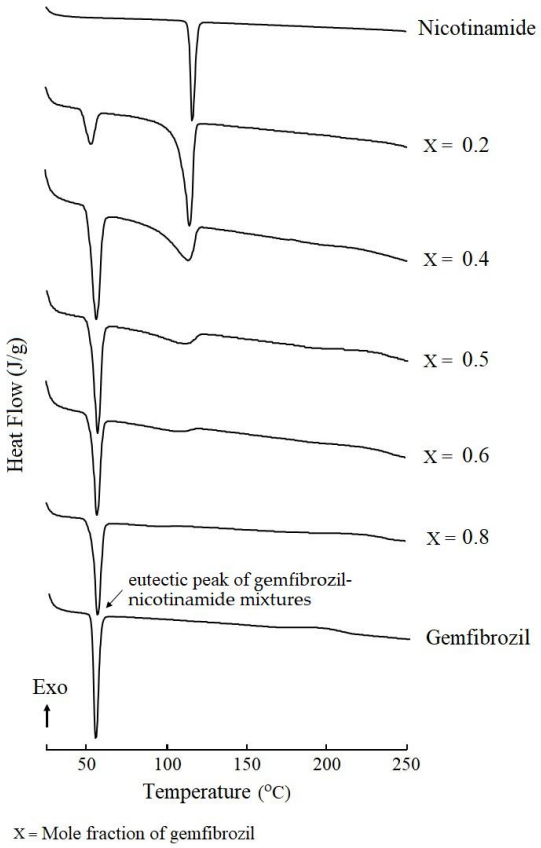

Figure 2. DSC thermogram of gemfibrozil, nicotinamide, and gemfibrozil-nicotinamide mixtures

Table 1. Thermodynamic data of pure gemfibrozil and nicotinamide

Compounds	Melting point (°C)		Melting enthalpy/ΔH (J/g)		References
	Result	Report	Result	Report	
Gemfibrozil	60.2	60.9	90.18	72.24	[17]
Nicotinamide	129.6	129.9	167.40	208.6	[18]

The sharp endothermic peak corresponded to the melting of solid to liquid, which represented the melting points of gemfibrozil and nicotinamide, respectively. In the DSC thermograms of gemfibrozil and nicotinamide, only one endothermic peak was observed for each, indicating that both substances were pure and did not undergo decomposition within the temperature range of 30–250 °C [19].

The thermodynamic data of the binary mixture of gemfibrozil and nicotinamide are shown in Table 2. Binary mixtures of gemfibrozil and nicotinamide with molar ratios of 2:8, 4:6, 5:5, and 6:4 exhibited thermograms with two endothermic peaks, while the binary mixture with a molar ratio of gemfibrozil to nicotinamide of 8:2 showed only one endothermic peak. The first endothermic peak of the binary mixture was

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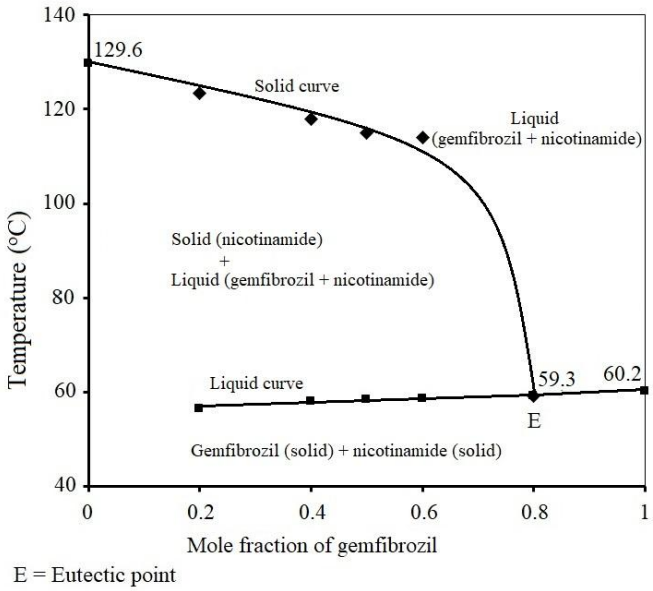
a sharp peak occurring at a lower temperature than the melting points of gemfibrozil and nicotinamide. This lower-temperature endothermic peak indicated the eutectic melting point of the gemfibrozil-nicotinamide binary mixture [16]. The second endothermic peak was a broad peak at a higher temperature than the eutectic melting point, depending on the mixture composition. This second endothermic peak represented the melting temperature of the excess component at the eutectic ratio of each binary mixture [20]. The gemfibrozil and nicotinamide binary mixture with a molar ratio of 8:2 in its thermogram has only one sharp endothermic peak at 59.3 °C, which was lower than the melting points of gemfibrozil and nicotinamide. These results indicated that gemfibrozil and nicotinamide formed an eutectic mixture with a molar ratio of 8:2 and a melting point of 59.3 °C [16].

Table 2. Thermodynamic data of gemfibrozil-nicotinamide

Mole fraction of gemfibrozil (X)	Peak 1		Peak 2
	Temperature (°C)	Melting enthalpy/ΔH (J / g)	Temperature (°C)
0.0	-	-	129.6
0.2	56.6	26.65	123.5
0.4	58.1	51.31	117.9
0.5	58.4	49.98	115.0
0.6	58.6	63.07	114.1
0.8	59.3	81.39	-
1.0	-	-	60.2

Solid-Liquid Phase Diagram

The results of the solid-liquid phase diagram of the gemfibrozil-nicotinamide binary mixture are shown in Figure 3. The solid-liquid phase diagram is the result of mapping the gemfibrozil composition against temperature. The phase diagram showed the phase regions of various compositions of the gemfibrozil-nicotinamide binary mixture, as well as the solid-liquid curves as a function of temperature. The temperature below the solid curve indicated the solid region of the gemfibrozil-nicotinamide mixture, which was immiscible. Meanwhile, temperatures above the liquid curve represented the liquid region of the gemfibrozil-nicotinamide mixtures, which was completely miscible. At temperatures between the solid and liquid curves lay the area where equilibrium occured between the solid phase of gemfibrozil and the liquid phase of the gemfibrozil and nicotinamide mixtures [21].



E = Eutectic point

Figure 3. Solid-liquid phase diagram of a gemfibrozil-nicotinamide binary mixtures

Based on the solid-liquid phase diagram, it appeared that the binary mixture of gemfibrozil and nicotinamide formed a eutectic mixture at a molar ratio of gemfibrozil to nicotinamide of 8:2. The binary mixture became miscible above the eutectic point, which at temperatures below the eutectic point (59.3 °C), it

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formed a crystalline microstructure solid with a melting point lower than the melting point of gemfibrozil (129.6 °C) and nicotinamide (60.2 °C) [22]. The formation of a eutectic mixture was also observed in saquinavir (m.p. 153.5 °C) and piperine (m.p. 129.4 °C) with a molar ratio of 6:4, which melted at a lower temperature than the pure components, specifically at 122.6 °C [23]. Similarly, the mixture of pyrazinamide (m.p. 189.5 °C) and acetylsalicylic acid (m.p. 140.8 °C) formed a eutectic mixture at a molar ratio of pyrazinamide to acetylsalicylic acid of 1:2, with an eutectic point of 114.2 °C [8].

In an eutectic mixture, the components existed in a miscible liquid phase, but in the solid phase, they showed immiscibility. The eutectic mixture indicated that in the liquid phase, the non-bonded interactions between dissimilar molecules (gemfibrozil and nicotinamide) were stronger than the interactions between similar molecules (gemfibrozil-gemfibrozil or nicotinamide-nicotinamide) [21]. Based on the phase diagram, the solid curve exhibited a V-type pattern, indicating that the gemfibrozil-nicotinamide mixture formed a eutectic solid rather than a cocrystal [15,16].

FTIR Testing

The intermolecular interaction between gemfibrozil and nicotinamide in the gemfibrozil-nicotinamide solid was analyzed using FTIR testing. The FTIR spectra of gemfibrozil, nicotinamide, and gemfibrozil-nicotinamide (1:1) are shown in Figure 4. Gemfibrozil exhibited spectra with absorption peaks at 2917 cm^{-1} (-OH) and 1704 cm^{-1} (-C=O), which were in agreement with the literature [24]. The FTIR spectrum of nicotinamide showed absorption peaks at 3365 cm^{-1} and 3148 cm^{-1} (-NH2), 1673 cm^{-1} (-C=O), and 1392 cm^{-1} (-CN), as mentioned in the literature [18].

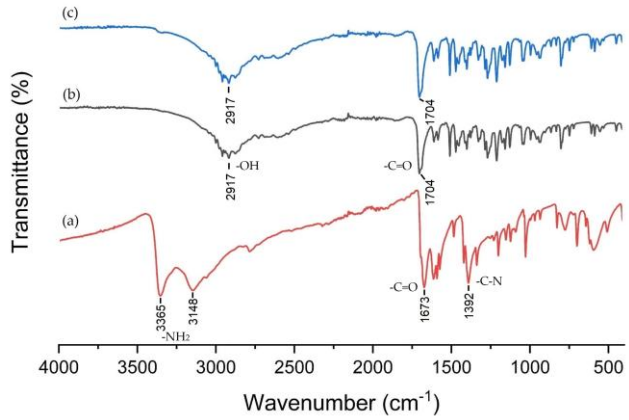

Figure 4. FTIR spectra of (a) nicotinamide, (b) gemfibrozil, and (c) gemfibrozil-nicotinamide (1:1)

In the FTIR spectra of gemfibrozil–nicotinamide (1:1), the hydrogen bond donor/acceptor groups of gemfibrozil showed absorption peaks that no shift, remaining at 2917 cm^{-1} (-OH) and 1704 cm^{-1} (-C=O), compared to the individual spectra of gemfibrozil. The spectra suggested no hydrogen bonding interactions were present between gemfibrozil and nicotinamide in the gemfibrozil-nicotinamide solid [16]. In eutectic solids, the constituent components retained their respective molecular structures, and no strong intermolecular interactions were observed between them [8]. These findings were consistent with the DSC data and the solid–liquid phase diagram, which indicated that gemfibrozil and nicotinamide formed a eutectic mixture—i.e., a system in which the solid phases were immiscible (lacking solid-state interactions), while in the liquid phase, intermolecular interactions occurred, resulting in a fully miscible liquid phase [21].

Conclusions

The gemfibrozil-nicotinamide system formed a eutectic mixture (8:2 molar ratio) with no evidence of hydrogen bonding interactions. This suggested potential for enhancement of the physicochemical properties of gemfibrozil via eutectic formation rather than cocrystallization. These findings can be used to design strategies to improve the physicochemical properties of gemfibrozil, such as solubility and mechanical properties, through the formation of multicomponent solids.

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Conflict of Interest

The authors declare no conflict of interest involving any individual or organisation in conducting this research and writing this article. The authors also affirm that all materials were prepared with full responsibility and awareness.

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