Research Article

Preparation of Eutectic Mixture of Ketoprofen and Nicotinamide for Enhanced Dissolution Rate

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ABSTRACT

To enhance the dissolution rate of ketoprofen, a poorly water-soluble drug, eutectic mixture of ketoprofen with nicotinamide had been prepared by melting technique. The binary phase diagram was constructed to determine the eutectic composition of the binary mixture. The physicochemical properties of this eutectic mixture were investigated by differential thermal analysis (DTA), powder X-ray diffraction (PXRD), scanning electron microscopy, and FT-IR spectroscopy. The *in vitro* dissolution rate was determined by using USP type II dissolution test apparatus. The binary phase diagram revealed that ketoprofen and nicotinamide produced a simple eutectic mixture at molar fraction of 0.6 : 0.4. This result was also supported by the PXRD pattern. The FT-IR spectra and DTA analysis indicated there was no chemical interaction between ketoprofen and nicotinamide in the solid state. The dissolution rate of the eutectic mixture was significantly improved as compared with intact ketoprofen and its physical mixture.

Keywords: eutectic mixture, ketoprofen, nicotinamide, dissolution rate.

INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) effective in treating fever, pain and inflammation. Ketoprofen is a hydrophobic drug with low solubility in water, thus its oral drug absorption is limited by the dissolution rate. This drug is classified as a class II drug according to BCS classification (low solubility and high permeability). Improving the dissolution rate of poorly soluble drug compounds in the water is a key factor to improving the bioavailability. Several previous studies have reported some techniques to improve the dissolution rate of ketoprofen: through formation of inclusion complexes with cyclodextrin; formation of solid amorphous dispersion; and co-grinding with some hydrophilic polymers.[1-3] However, there is no report on the preparation and characterization of a eutectic mixture of ketoprofen and nicotinamide.

The application of eutectic mixture of two solid drugs was firstly reported by Sekiguchi and Obi. Eutectic mixture is a unique combination as this binary mixture has a lower melting point as compared with both of its individual forming components.[4] Recently, several eutectic mixtures of binary system have been reported to increase the rate of dissolution, such as pyrazinamide-isoniazid combination and fenofibrate-aspirin combination.[5,6]

At the eutectic composition, both forming components exhibit a decrease in particle size and are well dispersed. This is one of the factors that contribute to increase the dissolution rate and bioavailability of drug compounds. Nicotinamide is a hydrotropic agent used to improve the solubility of many poorly soluble drug compounds in water such as nifedipine, trimethoprim and nimesulide. Nicotinamide is an excipient which is safe and has low toxicity. The US Food and Drug Administration has classified it as an additional ingredient with GRAS (Generally Recognized As Safe).[7-9]

The aim of this study is to prepare a eutectic mixture between ketoprofen and nicotinamide by melting technique and characterize its solid state properties by constructing its phase diagram using DTA thermal analysis, powder X-ray diffraction (PXRD), scanning electron microscopy, IR spectroscopy and dissolution rate study.

MATERIALS AND METHODS

Ketoprofen was obtained from PT. Bernofarm (Indonesia). Nicotinamide, acetonitrile, methanol, acetic acid (HPLC grade) were purchased from Merck (Germany). Potassium dihydrogen phosphate and sodium hydroxide were purchased from Bratachem (Indonesia).

Binary phase diagram construction

Physical mixture of ketoprofen and nicotinamide was mixed homogenously at various molar ratios from 0.1 : 0.9 to 0.9: 0.1. Approximately 5 mg of each binary mixture was carefully sealed in aluminum DTA sample pans for thermal analysis. DTA thermogram was obtained using Mettler Toledo FP 90 (Switzerland). Temperature of scanning was started from 50 to 200 °C with 10 °C increase per minute. The phase diagram was constructed by plotting the endothermic peak of the binary mixture against the molar ratio. The eutectic composition was furtherly characterized by PXRD, scanning electron microscopy and dissolution rate study.

Preparation of eutectic mixture and physical mixture

The eutectic mixture of ketoprofen and nicotinamide in molar fraction 0.6:0.4 was prepared by melting technique. Nicotinamide and ketoprofen were mixed and

melted in hot plate. The melted mass was cooled and solidified on an ice bath under constant stirring. The mass was pulverized and sifted through 425 µm sieve and stored in a desiccator. The physical mixture in similar molar fraction with eutectic mixture was prepared by homogeneously mixing it in a mortar by simple trituration.

Powder X-ray diffraction analysis

X-ray diffractogram of the samples were investigated on X-ray diffractometer (PAN Analytical, The Netherlands). Samples were irradiated with monochromatized CuKα and analyzed between 2-theta 10 to 40° at a step size of 0.02°. The generator voltage and current were 40 kV and 30 mA, respectively.

Scanning electron microscope analysis

Samples were mounted on a double faced adhesive tape and sputtered with thin gold palladium layer by sputter coater unit. Crystal properties were observed with a scanning electron microscope (JEOL model JSM-6360LA, Tokyo, Japan).

Infrared fourier transform spectroscopy

The spectra of the samples were obtained using an FT-IR spectrometer (Perkin Elmer 1600, Germany). About 2-3 mg of the sample was mixed with dry potassium bromide and then scanned from 4000 – 400 cm^{-1}.

Dissolution rate study

The dissolution rate was evaluated using USP type II dissolution test apparatus (Hanson SR08 plus). The samples equivalent to 50 mg ketoprofen were placed in the dissolution vessel containing 900 mL phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C and stirred at 100 rpm. Samples were collected at the indicated periods up to 60 minutes and replaced with a fresh dissolution medium. Concentration of dissolved ketoprofen was determined by high performance liquid chromatography apparatus (HPLC) (Shimadzu, Japan). The HPLC system consisted of a 4.6 x 250 mm Shim-Pack C-18 ODS (Shimadzu, Japan). Acetonitrile and acetic acid 1% (75 : 25) were used as mobile phase. Ketoprofen was detected by UV at wavelength of 260 nm. The retention time (t_R) of ketoprofen was 4.27 min.

RESULTS AND DISCUSSION

Figure. 1 shows thermogram DTA overlay of physical mixture of various molar ratios of ketoprofen and nicotinamide. The binary mixture containing 0.5 – 0.1molar fraction of ketoprofen showed two endothermic peaks (Fig. 1 f-j). A single endothermic peak of the binary mixture was obtained at molar fraction 0.6:0.4 (Fig.1e). In molar fraction of ketoprofen at 0.7 to 0.9, two more endothermic peaks were observed. These data indicated formation of simple eutectic mixture between ketoprofen and nicotinamide at molar fraction 0.6 : 0.4. This mixture gave a eutectic point of 78.2 °C. This melting point was lower than the melting point of ketoprofen (97.6 °C) and nicotinamide (133.6 °C).

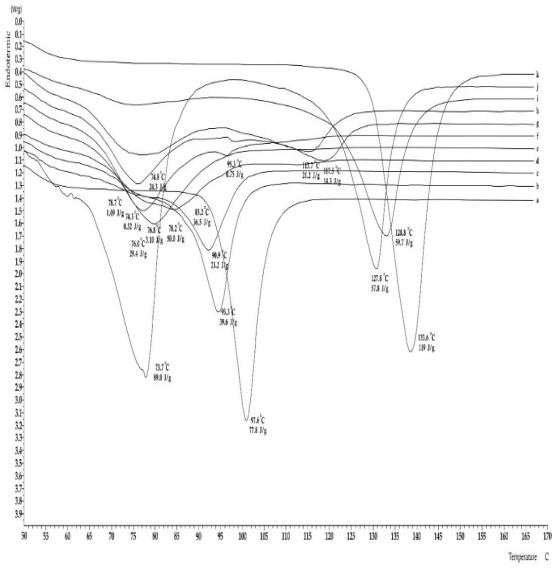

Figure 1: DTA Thermogram overlay for screening of eutectic composition. Key: molar fraction ratio of ketoprofen to nicotinamide was a) 1:0, b) 0.9 : 0.1, c) 0.8 : 0.2, d) 0.7 : 0.3, e) 0.6 : 0.4, f) 0.5 : 0.5, g) 0.4 : 0.6, h) 0.3 : 0.7, i) 0.2 : 0.8, j) 0.1 : 0.9, k) 0: 1.

The binary phase diagram (Fig. 2) of ketoprofen and nicotinamide was constructed on the basis of endothermic peak of DTA results. Binary phase diagram demonstrated formation of simple eutectic mixture at molar fraction ratio (0.6 : 0.4) of ketoprofen and nicotinamide.

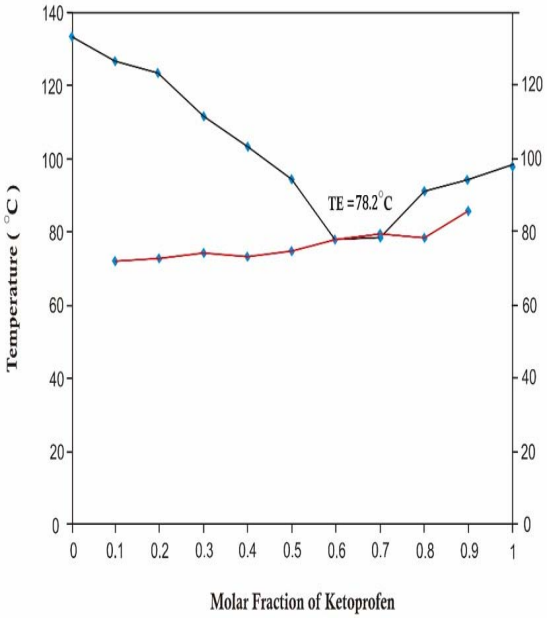

Figure 2: Binary phase diagram of simple eutectic mixture of ketoprofen and nicotinamide

The eutectic composition of ketoprofen and nicotinamide at 0.6:0.4 molar fraction was furtherly characterized by PXRD, scanning electron microscopy, FT-IR spectroscopy

and dissolution rate study. Powder X-ray diffractometry is a reliable technique to characterize solid state interaction between two solid components whether the changes of crystalline state are occurred. Figure 3 shows PXRD pattern of ketoprofen, nicotinamide, their physical mixture and eutectic mixture. Both ketoprofen and nicotinamide are crystalline solids, as demonstrated by sharp and intense diffraction peaks (Fig.3 a-b). Crystalline ketoprofen showed specific diffraction peaks at 2θ = 13.09; 14.40; 17.27; 18.34; 20.02; 22.80 and 23.84. While nicotinamide exhibited diffraction peaks at 2θ = 14.68; 22.13; 23.24; 25.75; and 27.23. PXRD patterns of the physical mixture and eutectic mixture (Fig.3 c-d) are the superimposition of diffraction peaks of ketoprofen and nicotinamide. There is no new diffraction peak, thereby the formation of solid solution and cocrystal in solid state is ruled out.[10]

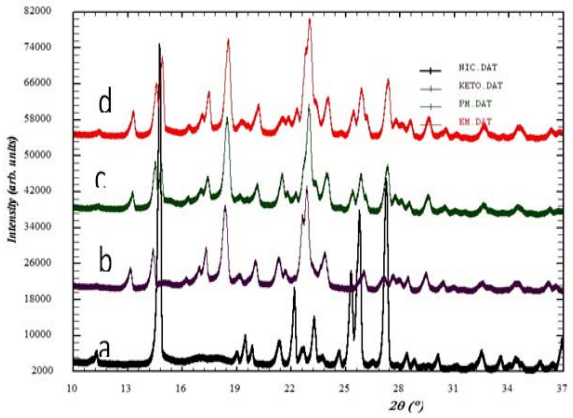

Figure 3: Powder X-ray diffractogram of a) intact ketoprofen, b) nicotinamide, c) physical mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction) and d) eutectic mixture ketoprofen and nicotinamide (0.6:0.4 molar fraction).

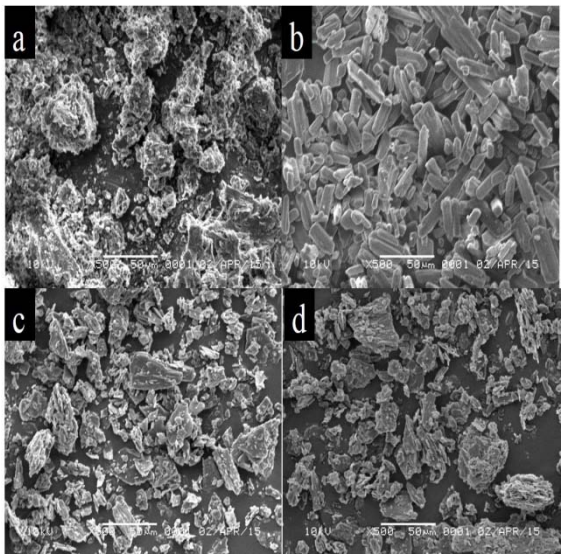

Figure 4: SEM Microphotograph of a) intact ketoprofen, b) nicotinamide, c) physical mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction) and d) eutectic mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction).

The scanning electron microphotographs of pure ketoprofen, pure nicotinamide, physical mixture and eutectic mixture are shown in Fig. 4. Intact ketoprofen consists of a mixture of some large agglomerate particles with irregular shape. Nicotinamide, on the other hand, exhibits long rod shapes. In the physical mixture we can still distinguish between ketoprofen and nicotinamide. The eutectic mixture demonstrates irregular shaped matrices with the fine particles of the drug embedded in it. Therefore the reduced particle size, increased surface area and better contact between the nicotinamide and ketoprofen might be the reasons for the increased dissolution rate of eutectic mixture.

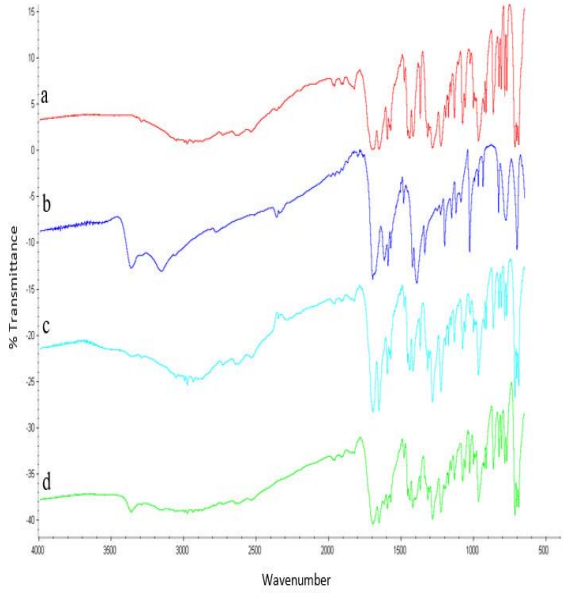

Figure 5: FT-IR spectra of a) intact ketoprofen, b) nicotinamide, c) physical mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction) and d) eutectic mixture ketoprofen and nicotinamide (0.6:0.4 molar fraction).

FT-IR spectroscopy analysis was performed for the intact drugs, physical mixture and eutectic mixture to investigate any signs of interaction represented by a change in the position or disappearance of any characteristic stretching vibrations of the compound. Figure 5(a-d) shows the FT-IR spectra of intact ketoprofen, nicotinamide, its physical mixture and eutectic mixture, respectively. Ketoprofen exhibits two carbonyl absorption bands, at 1696 cm^{-1} and1652 cm^{-1}. These are due to carboxyl-carbonyl stretching and ketonic-carbonyl stretching, respectively.[11] There is no significant change in the spectra of its physical mixture and eutectic mixture. The results indicate that most of transmittance peaks of the mixtures are the superimposition of ketoprofen and nicotinamide peaks. This suggests the absence of chemical interaction in solid state between ketoprofen and nicotinamide. This finding is also supported by the results of PXRD analysis.

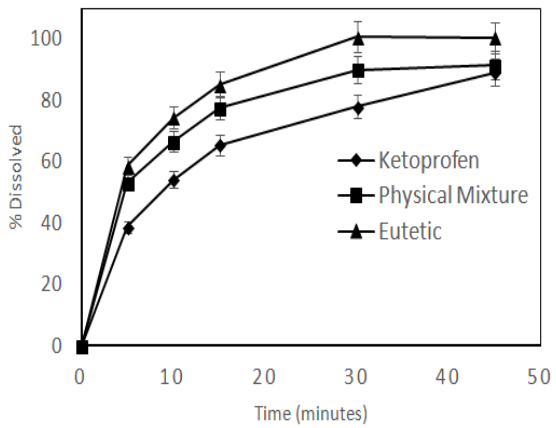

Figure 6: In vitro dissolution profile of intact ketoprofen, physical mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction) and eutectic mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction).

The dissolution rate profiles of intact ketoprofen, the physical mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction) and the eutectic mixture (0.6:0.4 molar fraction) are illustrated in Figure 6. Intact ketoprofen demonstrated a poor dissolution rate in phosphate buffer (pH 7.4). The amount of dissolved ketoprofen from the intact and physical mixture at 30 minutes were 77.94 ± 0.91 % and 89.95 ± 0.77 % respectively, whereas dissolved ketoprofen from eutectic mixture reached 100.65 ± 0.89 %. This indicated that eutectic mixture of ketoprofen and nicotinamide (0.6:0.4 molar fraction) exhibited better dissolution rate profile than intact ketoprofen and the physical mixture. The physical mixture exhibited a slight improvement in the dissolution rate properties compared to intact ketoprofen. This result was attributed to a local solubilization effect produced by nicotinamide in the diffusion layer surrounding the particle of ketoprofen immediately. The increase in dissolution rate of ketoprofen from eutectic mixture with nicotinamide might be caused by alteration of thermodynamic properties such as high free energy, greater molecular mobility and weaker intermolecular interaction. In addition, other factors also contributed to the improvement of dissolution rate of ketoprofen, such as particle size reduction, decreased in crystallinity index and formation of water soluble complexes on the basis of π electron donor – acceptor mechanism.[4,8,12]

CONCLUSION

Finally, based on above explanations, it is concluded that formation of eutectic mixture between ketoprofen and nicotinamide in molar fraction of 0.6:0.4 significantly enhance the dissolution rate of ketoprofen compared to intact ketoprofen and its physical mixture. FT-IR spectra and PXRD pattern indicate there is no chemical interaction between ketoprofen and nicotinamide in solid state.

REFERENCES

1. Lu WL, Zhang Q, Zheng L, Wang H, Li RY, Zhang LF, Shen WB, Tu XD. Antipyretic, analgesic and anti-inflammatory activities of ketoprofen-β-cyclodextrin inclusion complexes in animals. Biol. Pharm. Bull. 27(10), 2004, 1515-1520.
2. Salman, Ardiansyah, Nasrul E, Rivai H, Ben ES, Zaini E. Physicochemical characterization of amorphous solid dispersion of ketoprofen –polyvinylpyrrolidone K-30. Int. J. Pharm. Pharm. Sci. 7(2), 2015, 209-212.
3. Mura P, Moyano JR, Gonzalez-Rogriquez ML, Rabasco-Alvarez AM, Cirri M, Maestrelli F. Characterization and dissolution properties of ketoprofen in binary and ternary solid dispersion with polyethylene glycol and surfactants. Drug Dev. Ind. Pharm. 31, 2005, 425-434.
4. Sekiguchi K and Obi N., Studies on absorption of eutectic mixture I. a comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man, Chem. Pharm. Bull. 9, 1961, 866-872.
5. Górniak A, Wojakowska A, Karolewicz B, Pluta J. Phase diagram and dissolution studies of the fenofibrate–acetylsalicylic acid system. J. Therm. Anal. Calorim, 104(3), 2010, 1195-1200.
6. Cherukuvada S, & Nangia A. Fast dissolving eutectic compositions of two anti-tubercular drugs. Cryst.Eng. Comm, 14(7), 2012, 2579-2588.
7. Suzuki H, Sunada H. (1998). Mechanistic studies on hydrotropic solubilization of nifedipine in nicotinamide solution. Chem. Pharm. Bull., 46(1), 125-130.
8. Zaini E, Halim A, Soewandhi SN, Setyawan D. Peningkatan Laju Pelarutan Trimetoprim Melalui Metode Ko-Kristalisasi Dengan Nikotinamida. Jurnal Farmasi Indonesia. 5(4), 2011, 205-212.
9. Agrawal S, Pancholi SS, Jain NK, Agrawal, GP. Hydrotropic solubilization of nimesulide for parenteral administration. Int. J. Pharm. 274(1), 2004, 149-155.
10. Zaini E, Sumirtapura YC, Soewandhi SN, Halim A. Identification of physical interaction between trimethoprim and sulfamethoxazole by contact method Kofler and crystallization reaction. Indonesian J. Pharm, 21(1), 2010, 32-39.
11. Liversidge GG, Ketoprofen In Analytical Profile of Drug Substances. Florey K, Ed. Academic press, New York, 10, 1981, 443-471.
12. Goud NR, Suresh K, Sanphui P, Nangia A. Fast dissolving eutectic compositions of curcumin. Int. J. Pharm. 439(1), 2012, 63-72.

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