ATLANTIS PRESS

Advances in Health Sciences Research, volume 26

2nd Bakti Tunas Husada-Health Science International Conference (BTH-HSIC 2019)

Cocrystallization of Mefenamin Acid and Ascorbic Acid by the Solvent Evaporation Method

Indra*, Physca Fathiyatul Azhariyah, Ratih Aryani
Department of Pharmacy
Sekolah TInggi Ilmu Kesehatan Bakti Tunas Husada
Tasikmalaya, Indonesia
*indraf04@stikes-bth.ac.id

Abstract*—Objectives: The purpose of this study was to determine the physicochemical properties of mefenamic acid after going through the process cocrystallization using solvent evaporation method and characterization. Method: cocrystallization process is made with 3 ratio (mefenamic acid:ascorbic acid) that is 1:1, 1:2 and 2:1. Physicochemical characteristic of the modified crystal form of aspirin was investigated by polarizing microscopy, X-Ray Powder Diffraction, FT-IR spectrophotometer, Differential Scanning Calorimetry, and thermogravimetric analysis Results and Discussion: Cocrystallization process is made with 3 ratio (mefenamic acid:ascorbic acid) that is 1:1, 1:2 and 2:1. Polarizing microscope analysis showed the same crystal habit with mefenamic acid standard. Analysis melting point by DSC showed 230,3ºC (mefenamic acid standard), 229,4ºC (1:1), 228,2ºC (1:2) and 232,5ºC (2:1). The infrared spectrum showed wavelength shift in all samples but not significant. Diffractogram pattern showed new peaks in all samples. Based on the characterization shows that cocrystal formed. The solubility test of the samples 1:1, 1:2 and 2:1 showed increases in solubility compared to mefenamic acid standard. Conclusion: The new crystalline phase has been formed from mefenamic acid and ascorbic acid which has higher solubility than its pure material.

Keywords: mefenamic acid, ascorbic acid, cocrystallization

I. INTRODUCTION

Generally, pharmaceutical preparations contain medicinal ingredients and excipients. The combination of two or more active ingredients and also with excipients can cause physical and chemical transformations and interactions of solids [1]. Such interactions can cause changes in the physicochemical properties of drug ingredients such as stability [2], [3], solubility [4], dissolution rate profile [5], degree of crystallinity and hygroscopicity [6].

In order to improve the bioavailability and dissolution rate of drugs, cocrystallization method has been proposed intensively. In principle, cocrystallization is the interaction between drugs and coformers excipient. Cocrystal is a crystal structure consisting of at least two components, where components are a possible atom, ion or molecule [7]. This crystallization technique is a possible modification of physicochemical properties of active pharmaceutical ingredients (API) leading to intrinsically stable drug molecular activity [8].

Mefenamic acid (MA) is a nonsteroidal anti-inflammatory drug (NSAID) group. MA is a derivative of anthranilic acid (phenomic). This drug has analgesic and antipyretic activity and also has a small anti-inflammatory effect. Mefenamic acid has a small solubility in water (0.0041 g / 100 mL) at 25ºC and 0.008 g / 100 mL at 37ºC at pH 7.1. MA belongs to Biopharmaceutical Classification System class II with low solubility and high permeability [9].

The purpose of the present work was to prepare cocrystal of mefenamic acid using ascorbic acid as coformer and evaluate it for physicochemical characterization and dissolution rate study.

II. MATERIAL AND METHOD

A. Material

Mefenamic acid (MA) and ascorbic acid (AA) was purchased from PT. Indofarma. Methanol and tetrahydrofuran was obtained from Merck Chemical (Germany).

B. Procedure

Several standard mefenamic acid and ascorbic acid are weighed in each molar ratio i.e. 1: 1, 1: 2 and 2: 1, then put into the beaker glass. Then it is dissolved in a mixed solvent (tetrahydrofuran and methanol) until it disappears completely. The solution is evaporated at room temperature. Characterization of solid phase is carried out at the resulting precipitate.

C. Analysis by polarization microscopy

Characterization performed on mefenamic acid and ascorbic acid raw materials, crystal MA:AA 1:1, 1:2, and 2:1. The sample used was only a spatter tip and then observed on a polarizing microscope at 200x magnification.

D. Analysis by DSC

About 10-20 mg of powder sample is placed in an alumina container on the DSC instrument. Thermal analysis carried out in a temperature range of 30-250 °C with a heating rate of 20 ° C per minute and with nitrogen gas flow.

E. Analysis by FTIR

The powder was measured by an infrared spectrophotometer using a KBr tablet. The absorption spectrum was recorded at wavenumbers from 400-4000 cm^{-1}.

F. Analysis by PXRD

This test is carried out on mefenamic acid and ascorbic acid raw material and crystal samples (MA: AA). Recorded at an angle of 2θ (5-45°) using a radiation X-Ray diffractometer with Cu as an anode material and graphite monochromator, operated at a voltage of 40 kV, current of 30 mA.

G. Solubility measurement

Mefenamic acid and the sample were weighed as much as 50 mg in 10 mL of water and then put into vials. Then stir using a magnetic stirrer until the solution is saturated at room temperature. The filtrate was then measured for absorption at a wavelength of 296 nm.

III. RESULTS AND DISCUSSION

The habit crystal of an API is one of the important parameters in the manufacture of pharmaceutical preparations that can affect its mechanical properties and affect the performance of the final dosage form [10]. From Figure 1 with polarized microscope the crystal habit of MA:AA has different crystal habit compared to pure components.

FTIR spectroscopy is excellent technique for characterizing and studying cocrystallization and solvate/hydrate formation [13]. The IR spectrum (Figure 2) of MA showed peak at 3310, 3013 cm^{-1} (corresponding to N-H and O-H respectively) and 1653 cm^{-1} (C=O, ketone group vibration). The FT-IR spectra of all sample crystal MA:AA after cocrystallization showed no distinct shift. This results suggesting that MA and AA there is no physical interaction accour such as hydrogen bonding

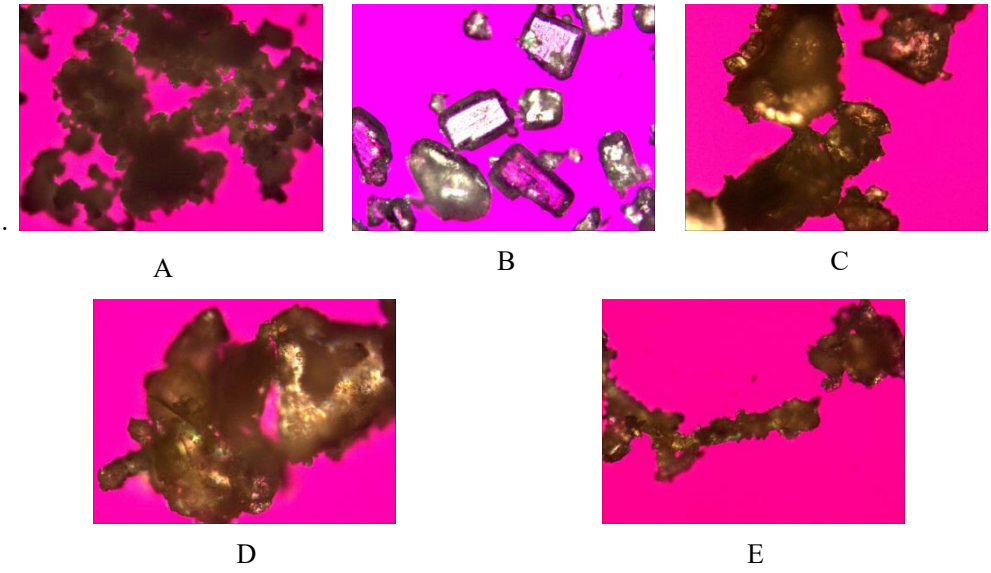

Figure 1: PLM image of (A) MA, (B) AA, (C) 1:1, (D) 1:2, (E) 2:1

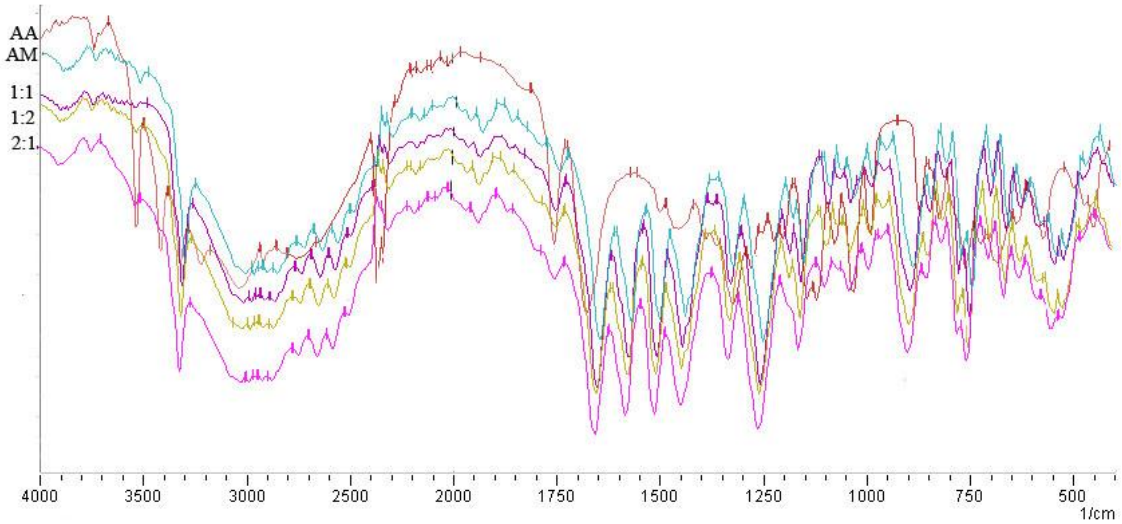

Figure 2: FTIR spectrum

One method for determining crystal properties is by thermal analysis using DSC. This thermal instrument analyzes the change in enthalpy and melting temperature of a crystal [11]. Changes in the melting point can be related to changes in the geometry and crystallinity of the sample during preparation [12]. The results of thermal analysis using DSC are carried out with temperatures starting from 30-250° C. Based on the DSC thermogram (Figure 3), the melting point obtained in each sample is almost the same as mefenamic acid (untreated). The mefenamic acid showed a melting point of 230.3°C, ascorbic acid 196.4°C, sample 1:1 229.4°C, sample 1:2 228.2°C and in sample 2:1 232.5°C.

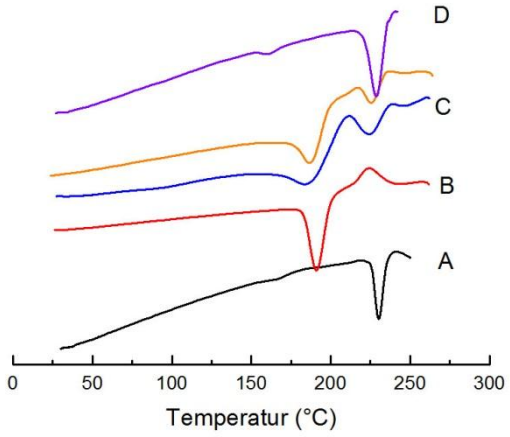

Figure 3. DSC thermograms of (A) MA, (B) AA, (C) 1:1, (D) 1:2, (D) 2:1

Diffractogram analysis is carried out to identify a cocrystal form by comparing the location and intensity of the lines on the diffractogram against the lines in known samples. the solid phase of ascorbic acid shows a high degree of crystallinity characterized by distinctive interference peaks in the powder X-Ray diffraction pattern image (Figure 4). Mefenamic acid has a typical interference at 2 theta = 6.3; 13.8; 21.4; 26.2 while ascorbic acid at 2 theta = 10.6; 17.5; 28.1.

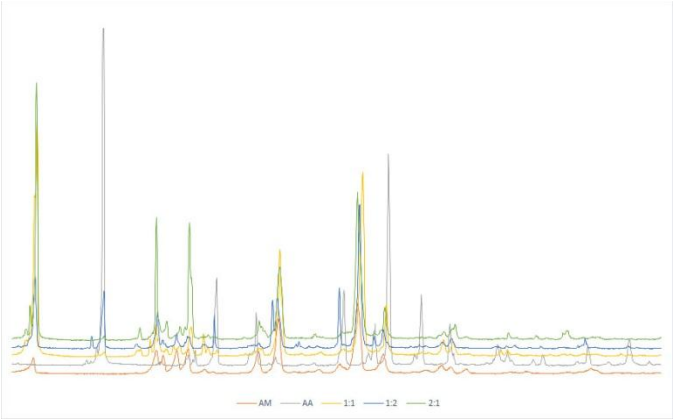

Figure 4: X-Ray Diffraction pattern

Powder X-Ray diffractogram resulting from the interaction between mefenamic acid and ascorbic acid has the same diffraction pattern with mefenamic acid and ascorbic acid without treatment, only differing in the peak interference intensity which shows different degrees of crystallinity. this indicates that there is no physical interaction (cocrystal), but a conglomeration of the two crystalline phases in a solid state or often referred to as a simple eutectic mixture.

Basically the dissolution rate is measured from the amount of active substance dissolved in a certain time into a liquid medium whose volume is known at a relatively constant temperature. The purpose of the dissolution test is to find out how much standard mefenamic acid or contained in the sample dissolved in a certain condition and time.

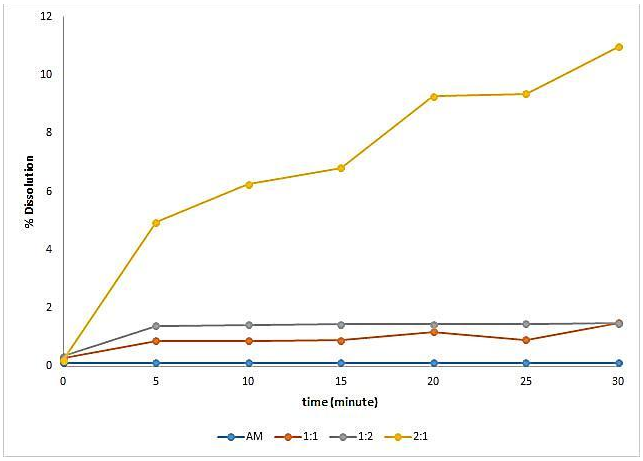

Figure 5: Dissolution rate profile

The test is carried out on all samples for 30 minutes (Figure. 5) percent dissolved for 30 minutes for mefenamic acid, MA: AA ratio of 1: 1; 1: 2; and 2: 1, respectively 0.13%, 1.5%, 1.48% 10.96%. From these data it can be seen that all samples with a ratio of 1: 1, 1: 2 and 2: 1 can increase the dissolution rate compared to standard mefenamic acid. From this data it can be seen that all crystals resulting from the solvent evaporation increase the dissolution rate compared to standard mefenamic acid.

IV. CONCLUSION

The co-crystallization method between mefenamic acid and ascorbic acid produces a simple eutectic mixture. The rate of dissolution of mefenamic acid from co-crystallization with ascorbic acid can significantly increase compared to single mefenamic acid.

REFERENCES

[1] Y. Chandramouli, R. Gandhimathi, B. R. yasmeen, A. Vikram, B. Mahitha, and S. M. Imroz, "REVIEW ON COCRYSTAL AS AN APPROACH WITH NEWER IMPLICATIONS IN PHARMACEUTICAL FIELD," vol. 2, no. 2, p. 10, 2012.

[2] Z.-Z. Wang, J.-M. Chen, and T.-B. Lu, "Enhancing the Hygroscopic Stability of S -Oxiracetam via Pharmaceutical Cocrystals," Cryst. Growth Des., vol. 12, no. 9, pp. 4562–4566, Sep. 2012.

[3] I. Sarcevica, L. Orola, M. V. Veidis, A. Podjava, and S. Belyakov, "Crystal and Molecular Structure and Stability of Isoniazid Cocrystals with Selected Carboxylic Acids," Cryst. Growth Des., vol. 13, no. 3, pp. 1082–1090, Mar. 2013.

[4] I. Indra, F. M. Janah, and R. Aryani, "Enhancing the Solubility of Ketoconazole via Pharmaceutical Cocrystal," J. Phys. Conf. Ser., vol. 1179, p. 012134, Jul. 2019.

[5] H. N. Imtihani, A. Nuniek W, D. Setyawan, and E. Hendradi, "Improvement of Dissolution Properties Through Acyclovir - Succinic Acid Cocrystal Using Solvent Evaporation Technique," Int. J. Drug Deliv. Technol., vol. 7, no. 04, Dec. 2017.

[6] S. Datta and D. J. W. Grant, "Crystal structures of drugs: advances in determination, prediction and engineering," Nat. Rev. Drug Discov., vol. 3, no. 1, pp. 42–57, Jan. 2004.

[7] I. Sathisaran and S. Dalvi, "Engineering Cocrystals of Poorly Water-Soluble Drugs to Enhance Dissolution in Aqueous Medium," Pharmaceutics, vol. 10, no. 3, p. 108, Jul. 2018.

[8] N. Takata, K. Shiraki, R. Takano, Y. Hayashi, and K. Terada, "Cocrystal Screening of Stanolone and Mestanolone Using Slurry Crystallization," Cryst. Growth Des., vol. 8, no. 8, pp. 3032–3037, Aug. 2008.

[9] M. Dixit, P. Kulkarni, and R. Vaghela, "Effect of Different Crystallization Techniques on the Dissolution Behavior of Ketoprofen," Trop. J. Pharm. Res., vol. 12, no. 3, pp. 317–322, Jun. 2013.

[10] S. Hiendrawan, B. Veriansyah, E. Widjojokusumo, S. N. Soewandhi, S. Wikarsa, and R. R. Tjandrawinata, "Physicochemical and mechanical properties of paracetamol cocrystal with 5-nitroisophthalic acid," Int. J. Pharm., vol. 497, no. 1–2, pp. 106–113, Jan. 2016.

[11] indra Indra, A. Fauzi, and R. Aryani, "Karakterisasi dan Uji Disolusi Aspirin Hasil Rekristalisasi Penguapan Pelarut," vol. 06, no. 02, p. 7, 2019.

[12] A. N. Winantari, D. Setyawan, S. Siswodihardjo, and S. N. Soewandhi, "COCRYSTALLIZATION ACYCLOVIR-SUCCINIC ACID USING SOLVENT EVAPORATION METHODS," Asian J. Pharm. Clin. Res., vol. 10, no. 6, p. 91, Jun. 2017.

[13] R. Chadha, P. Arora, R. Kaur, A. Saini, M. Singla, and D. Jain, "Characterization of solvatomorphs of methotrexate using thermoanalytical and other techniques," Acta Pharm., vol. 59, no. 3, Jan. 2009.