COCRYSTAL OF ATORVASTATIN CALCIUM – MALONIC ACID

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INTRODUCTION

Cocrystal is a relatively new solid form of active pharmaceutical ingredient that offers an alternative platform in improving physicochemical properties of active pharmaceutical ingredients [Padrela et al., 2009; Mashhadi et al., 2004]. Cocrystal is defined as a stoichiometric multi-component system connected by non-covalent interactions where all the components neutral and solid under ambient conditions [Thakuria et al., 2013]. Cocrystal can be constructed through interaction hydrogen bonding, pi-stacking, and van der Waals forces [Mashhadi et al., 2004]. A pharmaceutical cocrystal is composed of an API and an appropriate coformer as carboxylic acids and amides [Qiao et al., 2011]. Cocrystallization of active pharmaceutical ingredient is an opportunity for enhancement of important physiochemical properties of an active pharmaceutical ingredient without changing its molecular structure [Maeno et al., 2014].

Atorvastatin Calcium (AC), ([(R-(R*,R*)]-2-(4-fluorophenyl)-beta, delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid), calcium salt (2:1) trihydrate ($[C_{33}H_{34}FN_2O_5]_2Ca.3H_2O$), is considered as one of the most effective of synthetic lipid lowering agent [Shete et al., 2010]. The drug is orally used to reduce of total cholesterol, low density lipoprotein and triglycerides [Anwar et al., 2011]. There are 42 crystalline structures of AC [Shayanfar et al., 2013]. However, chance to create AC into another crystal structure to improving physicochemical properties of AC is still fully open [Chadha et al., 2012].

In the present study, we explored cocrystallization of AC by solvent evaporation method**.** This study aimed to confirm whether AC was able to form cocrystal with malonic acid (MA) as coformer. AC-MA cocrystal was prepared by solvent evaporation method by using methanol as solvent. Characterization of cocrystal was done by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), fourier transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM).

EXPERIMENTAL SECTION

Materials

AC was kindly donated by PT Dexa Medica (Indonesia). MA and methanol were purchased from Merck (Germany) and Smart Lab (Indonesia), respectively.

Instrumentation

The instruments used were X-ray diffractometer (PANalytical X'Pert-Pro), differential scanning calorimeter (Rigaku Thermo Plus EVO II), FT-IR spectrometer (ALPHA Bruker), Scanning Electron Microscope (Hitachi Tabletop Microscope TM 3000), and ion sputter coater (Hitachi E-1045).

Procedure

Cocrystallization by Solvent Evaporation Method

AC and MA at (1:1) mole ratio was dissolved in methanol with stirring. The resulting solution allowed to slowly evaporating at an ambient temperature. The resulted cocrystal was crushed and characterized by PXRD, DSC, FTIR, and SEM.

Powder x-ray diffraction

Powder X-ray diffraction patterns of samples were collected at room temperature using an X'Pert PRO diffractometer system with Cu Kα radiation (1.54060 Å). The voltage and current were set at 40 kV and 30 mA, respectively. Sample was placed in an aluminium sample holder and flatted. The data were collected by a continuous scan over an angle range from $5\text{-}50^0$ in 2θ at a step size of 0.017^0 and scanning speed of 10^0/min.

Differential Scanning Calorimetry

DSC analysis of sample was performed with a DSC which was calibrated for temperature and heat flow accuracy using indium. The samples of 2-3 mg were accurately weighed in hermetic aluminium pans and scanned over the range of 30-250 ^{0}C at a heating rate of 10 ^{0}C/min.

Fourier Transform Infrared Spectroscopy

IR spectra of cocrystal were obtained by an FT-IR spectrometer (ALPHA Bruker). Measurements were recorded over a range 4000–400 cm^{-1} at a resolution of 4 cm^{-1}.

Scanning Electron Microscopy

The morphology and shape of samples were characterized using scanning electron microscope (Hitachi Tabletop Microscope TM 3000) at 15 kV

accelerating voltage. All samples were coated with a thin layer of platinum using an ion sputter coater (Hitachi E-1045) before SEM analyses.

RESULTS AND DISCUSSION

Powder X-ray Diffraction

PXRD pattern of a crystalline sample has been in use for fingerprint characterization of crystalline materials. Every crystalline material has unique characteristics in PXRD pattern [Niazi, 2007]. The PXRD patterns of AC, MA and ACMA cocrystal are shown in Figure 1. PXRD patterns of AC exhibited characteristic peaks at 2ϑ values of 10.0°, 11.6°, 19.3° and 21.4°, while MA has characteristic peaks at 2ϑ values of 18.8°, 23.7°, 23.8° and 25.2°. ACMA cocrystal has unique crystalline peaks of PXRD pattern at 2ϑ values of 13.2°, 18.1° and 26.1°. PXRD pattern of ACMA is different from the individual pattern of AC and MA. It indicates formation of new crystalline phase of ACMA cocrystal.

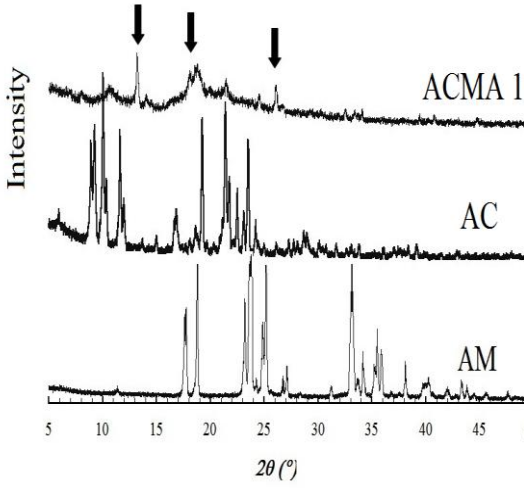

Figure 1. PXRD pattern of AC, MA and ACMA cocrystal

Differential Scanning Calorimetry

DSC measurements were taken to investigate thermal properties of ACMA cocrystal. The thermal properties are important to study physicochemical properties of drugs. Formation of cocrystal was evidenced by the appearance of a single endothermic peak attributed to melting of cocrystal phase [Patel et al., 2012]. Figure 2 shows DSC curves of AC, MA and ACMA cocrystal. AC and MA have endothermic peak at 159.4 °C and 135.6 °C, respectively. DSC curve of ACMA showed different melting point (endothermic peak) with AC and MA, which was observed at 204.1 °C. It means that the cocrystal has higher melting point than melting point of individual components.

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy is an important spectroscopic technique in determining the structure conformation of cocrystal. It can distinguish cocrystal from salts when a carboxylic acid is taking part in hydrogen bond formation [Aakeroy et al., 2007].

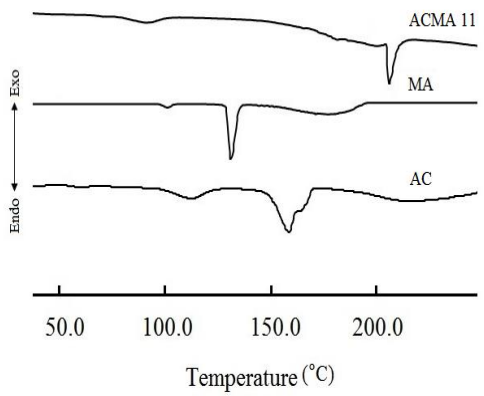

Figure 2.DSC curves of AC, MA and ACMA cocrystal

FTIR spectra of AC, MA, and ACMA cocrystal are shown in Figure 3. FTIR spectra of AC has characteristic absorption peaks at 3373 cm^{-1} indicating free O-H stretching, aromatic N-H stretching at 3363 cm^{-1}, C=O stretching at 1649 cm^{-1} and C-N stretching at 1216 cm^{-1}. FTIR spectra of MA show O-H stretching at 3400-2400 cm^{-1} and C=O stretching of carboxylic acid at 1700 cm^{-1}. The shifting of peaks was observed in FTIR spectra of ACMA. The FTIR spectra of ACMA shift in N-H stretching frequency from 3363 cm^{-1} to 3382 cm^{-1} and C-N stretching from 1216 cm^{-1} to 1222 cm^{-1}. Absorption peaks of C=O stretching was not shifted but decreased in sharpness. The shift can correspond to the N-H and C-N group of AC which is interacting via H-bonding with MA.

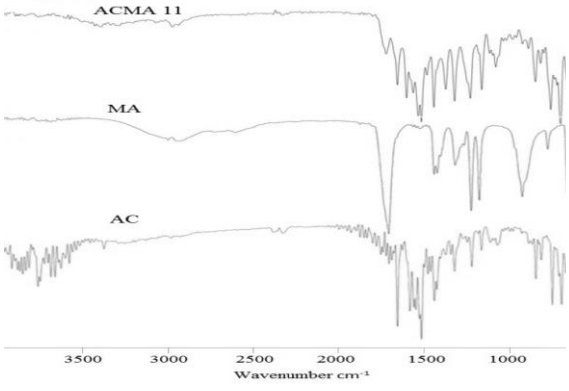

Figure 3.FTIR spectra of AC, MA and ACMA cocrystal

Scanning Electron Microscopy

Morphology and size have a great influence on physical properties of cocrystal [Padrela et al., 2014]. SEM images of AC, MA and ACMA cocrystal are presented in Figure 4. The SEM analysis revealed that morphology of ACMA cocrystal are different from that of individual components. AC shows needle-shaped particles with size of length approximately about 30-100 µm, while MA has round-shaped particles with a size of approximately 500 µm. ACMA cocrystal has multi-shaped particles with rough surfaces.

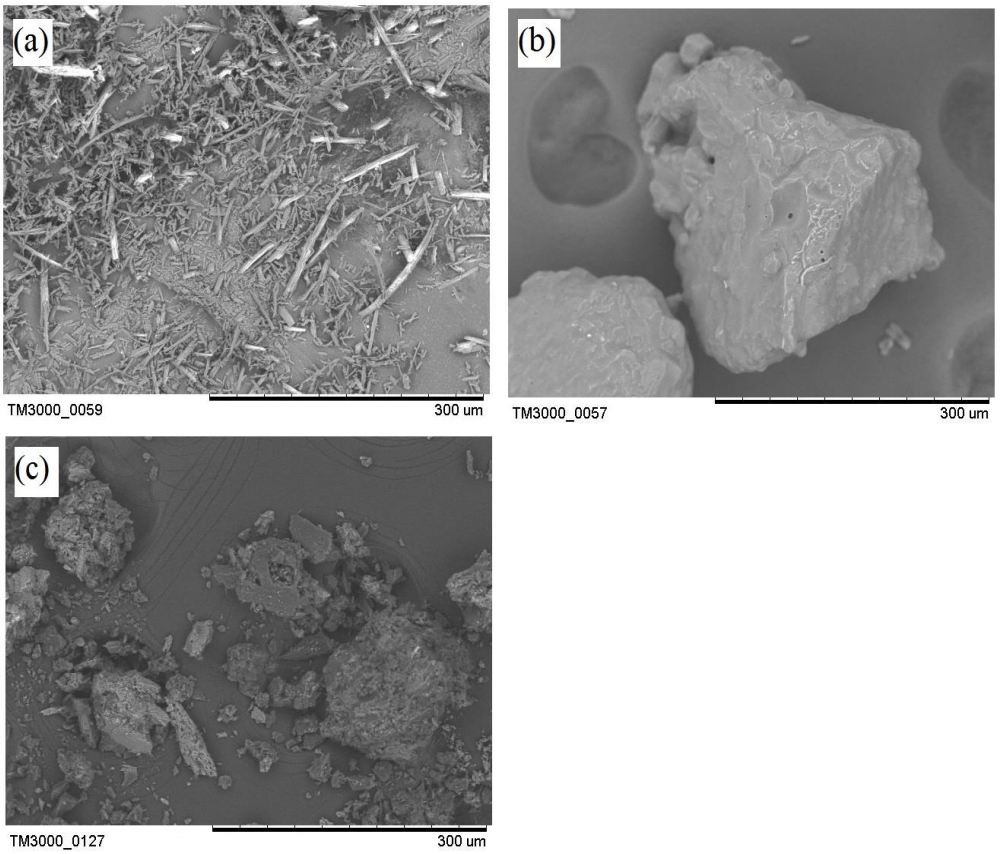

Figure 4.SEM images of (a) AC (b) MA and (c) ACMA cocrystal (15kV, 500x)

CONCLUSION

AC and MA at (1:1) molar ratio form cocrystal by slow solvent evaporation method. The PXRD characterization has showed difference of diffraction patterns of ACMA cocrystal with the constituent component. DSC scanning of ACMA cocrystal has a melting point which higher than the melting point of the individual component. FTIR spectra displayed shifting of the absorption band which indicates interaction of functional group of AC and MA. ACMA cocrystal has multi-shaped particles with rough surfaces.

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