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Preparation of Atorvastatin Calcium-Dipicolinic Acid Multicomponent Solids by Liquid-Assisted Grinding Method to Increase Solubility

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ABSTRACT. Atorvastatin calcium is a cholesterol-lowering drug that is very potent but difficult to dissolve in water, so its bioavailability is low. In this study, atorvastatin calcium-dipicolinic acid multicomponent solids were prepared using the liquid-assisted grinding method to improve the solubility of atorvastatin calcium. Characterization of multicomponent solids was carried out using powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). Solubility test was carried out by shaking method using distilled water media. The results showed that the particles of atorvastatin calcium - dipicolinic acid multicomponent solids had an irregular shape with rough and porous surface topography. The multicomponent solids have a diffractogram with specific peaks of 2θ at 8.8, 9.9, 11.5, 16.7, 19.1, 21.2, 22.4, 23.4, and 27.7°. The DSC thermogram of multicomponent solids showed a sharp endothermic peak at 181.9 °C (ΔH=17.69 J/g), indicating its melting point. The FTIR spectra of atorvastatin calcium-dipicolinic acid multicomponent solids indicated an intermolecular interaction that was thought to be a hydrogen bond between the molecules of atorvastatin calcium and dipicolinic acid. The results of the solubility test showed that the atorvastatin calcium-dipicolinic acid multicomponent solids had a significantly increased solubility ($p<0.05$) compared to the solubility of pure atorvastatin calcium.

Keywords: Atorvastatin calcium, liquid-assisted grinding, multicomponent solids

INTRODUCTION

Atorvastatin calcium is a potent lipid-lowering drug that acts through a competitive inhibitory mechanism against HMG-CoA reductase (Cao et al., 2017; Gaviria-Mendoza et al., 2019). However, based on the Biopharmaceutical Classification System (BCS), atorvastatin calcium is a class II drug compound with high permeability but low solubility (Kwon et al., 2019; Wicaksono et al., 2021). This solubility property causes problems in the formulation process of atorvastatin calcium; namely, the oral bioavailability of the resulting preparation is relatively low. Therefore, research is needed to improve the solubility properties of atorvastatin calcium to overcome bioavailability (Kwon et al., 2019).

One method that is often used to increase the solubility of drugs is the formation of multicomponent solids such as cocrystal and coamorphous solids (Araya-Sibaja et al., 2019; Ferreira et al., 2021; Liu et al., 2021). Cocrystal and coamorphous are multicomponent solids systems composed of two or more components that form a new solids phase through noncovalent interactions, especially hydrogen bond interactions (Berry & Steed, 2017; Liu et al., 2021). Cocrystal and coamorphous solids are generally formed from molecules of drugs and compounds with small molecular weights called coformer. Molecules of drug and coformer in a cocrystal or coamorphous multicomponent solids system form intermolecular interactions so that rearrangements occur, resulting in new network or packing in the solids system. (Haneef & Chadha, 2017). The formation of new network or packing in a multicomponent solids system can cause changes in physicochemical properties, which are different from the physicochemical properties of the constituent materials. The advantage of cocrystal and coamorphous multicomponent solids is that they have new physicochemical properties without changing the drug's pharmacological activity. (Ainurofiq & Choiri, 2020; Fatima et al., 2021). Another advantage of the solids is that the choice of coformer is very diverse, so the opportunity to obtain new solids from a drug is tremendous with the desired new physicochemical properties (Araya-Sibaja et al., 2021; Haneef & Chadha, 2017).

Previous studies have shown that the formation of multicomponent solids of atorvastatin calcium, carried out with maleic acid coformers using the spray drying method, can increase the solubility of atorvastatin calcium in water significantly when compared to its pure solids form (Wicaksono et al., 2021). However, in evaluating lipid-lowering activity, the atorvastatin calcium-maleic acid multicomponent solids did not show increased lipid-lowering activity when compared to the lipid-lowering activity of pure atorvastatin calcium (Wicaksono et al., 2022). This phenomenon is thought to be because atorvastatin calcium in solution forms a charged fraction due to the presence of maleic acid, thereby reducing the permeability of atorvastatin calcium which can inhibit the absorption process and its bioavailability (Sugita et al., 2021). Therefore, it is necessary to develop another multicomponent solids form of atorvastatin calcium using different coformers and methods in the hope that increasing the solubility of atorvastatin calcium can be correlated with increased bioavailability and lipid-lowering activity.

Liquid-assisted grinding is a method that is often used to prepare multicomponent solids. The advantage of this method is that the process is simple and fast (Tan et al., 2015; Lohar et al., 2017). In addition, using a small amount of solvent in the liquid-assisted grinding method causes the efficiency of the formation of multicomponent solids to be higher than in the neat grinding method (Lohar et al., 2017).

Based on the description above, research will be carried out to increase the solubility of atorvastatin calcium by forming multicomponent solids using the liquid-assisted grinding method. The multicomponent solids of atorvastatin calcium are formed with the dipicolinic acid coformer considering that the structure of the coformer is very attractive. Dipicolinic acid has two carboxylic acid groups that can rotate freely to change its conformation. Dipicolinic acid is thought to readily become a proton donor and/or acceptor in a noncovalent interaction with other molecules in multicomponent solids systems (Bankiewicz & Wojtulewski, 2019).

EXPERIMENTAL SECTION

Materials

The chemicals used in this study were atorvastatin calcium from PT Dexa Medica (Palembang, Indonesia), dipicolinic acid purchased from Sigma-Aldrich (Saint Louis, USA), and methanol purchased from Merck KGaA (Darmstadt, Germany).

Equipments

The equipment used in this study were analytical balance (Precisa ES 225SM-DR), powder x-Ray diffractometer (Panalytical Xpert Pro), differential scanning calorimeter (Thermo plus EVO DSC 8230), fourier transform infrared spectrophotometer (Bruker FTIR Alpha II), scanning electron microscope (Hitachi TM 3000), UV-VIS spectrophotometer (Thermo Scientific Genesys), and orbital shaker (Thermo scientific).

Methods

Preparation of multicomponent solids

The preparation of multicomponent solids of atorvastatin calcium was carried out with dipicolinic acid coformer using the liquid-assisted grinding method, according to the study of Lohar et al. with a few modifications (Lohar et al., 2017). Atorvastatin calcium and dipicolinic acid were weighed in equimolar ratios, then put into a mortar and mixed using a stamper for 10 minutes. The mixture of the two ingredients was evenly dripped with 5% (w/w) methanol and then ground vigorously with a stamper for 15 minutes. The grinding powder was then sieved using an 80 mesh sieve and stored in a desiccator until testing.

SEM characterization

Characterization was carried out using the Hitachi TM 3000 apparatus. The tub specimens from the SEM apparatus were given double-sided adhesive, and then the sample powder was sprinkled evenly on the adhesive surface. The sample on the adhesive surface was then coated with platinum using an ion sputter for 20 seconds. Microscopic observations with SEM were carried out at a voltage of 15 kV and a current of 12 mA with the appropriate magnification.

PXRD characterization

PXRD testing was carried out using a Philip Xpert Diffractometer with a CuKα1 radiation source (λ = 1.542 A0). The procedure carried out is that the sample powder is flattened using a spatula in the sample chamber of the X-ray diffraction instrument. The test was carried out at an angle range of 2θ 5-50° at a voltage of 40 kV, a current of 30 mA, and a scan speed of 10°/min.

DSC characterization

The DSC test was carried out using a Thermo plus EVO DSC 8230. A sample of about 2 mg was put into an aluminum container with a lid and then sealed tightly with a hydraulic press. The container containing the sample is then inserted into the sample chamber of the DSC equipment, and the equipment is then set at the test temperature range of 30-300 °C. The test was carried out at a heating rate of 10 °C/minute with a dry air flow condition of 50 mL/minute.

FTIR spectroscopy characterization

The FTIR characterization aims to identify functional groups and the presence of intermolecular interactions in multicomponent solids systems. FTIR testing was carried out with the Bruker FTIR Alpha II equipment. The procedure carried out is that a sample of about 5 mg is flattened on a sample board, and then the equipment is run in the wavenumber range of 4000-600 cm^{-1} with a resolution of 4 cm^{-1}.

Solubility test

Solubility test was carried out by shaking method using distilled water media. The excess sample powder (about 50 mg) was put into a 100 mL Erlenmeyer, and then 50 mL of distilled water was added. Erlenmeyer was tightly closed with aluminum foil and shaken with an orbital shaker (150 rpm, 37±0.5 °C) for 12 hours. The saturated solution in Erlenmeyer was then filtered with a 0.45 m membrane filter. The concentration of atorvastatin calcium dissolved in the filtrate was then determined using a UV-Vis spectrophotometer. The solubility test was carried out with three repetitions.

Data analysis

Statistical data analysis was conducted to determine the significance of differences in data between samples. Statistical testing was carried out using SPSS 16.0 for windows software. Statistical analysis was performed by independent t-test with a 95% confidence level, where the difference in data was considered significant if the p-value <0.05.

RESULTS AND DISCUSSION

The preparation of multicomponent solids in this study was carried out using the liquid-assisted grinding method, a combination of solid-state grinding and solvent evaporation techniques. The solvent added during grinding can facilitate intermolecular interactions between the constituent components so that the process of transforming the solids' phases into a multicomponent solids system increases (Domingos et al., 2016; Tumanov et al., 2017).

Microscopic

SEM aims to determine solids' particles' shape, size, and surface topography (Boontum et al., 2019). Particle micrographs of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium - dipicolinic acid multicomponent solids are shown in **Figure 1**. Particle micrographs of atorvastatin calcium have rod shape, smooth surface topography, and a 5-30 μm particle length range. Dipicolinic acid has an irregular rod shape, smooth to rough surface topography, and a 20-80 μm particle length range. The atorvastatin calcium - dipicolinic acid multicomponent solids prepared by the liquid-assisted grinding method have irregularly shaped particles and rough and porous surface topography. The results of observations by SEM showed that the atorvastatin calcium-dipicolinic acid multicomponent solids had different micrographs compared to the micrographs of each of its constituent materials. Changes in the micrographs of the prepared multicomponent solids compared to the micrographs of their constituent materials indicated that the multicomponent solids were a new solids-phase form of atorvastatin calcium and dipicolinic acid (Trivedi et al., 2020).

PXRD Diffractogram

PXRD is a method that can be used to analyze solids systems, polymorphisms, and crystal lattice structures of solids materials (Nugrahani et al., 2020). The formation of a new solids phase in a multicomponent solids system is indicated by a diffractogram pattern with different peaks compared to the diffractogram of each starting material (Jia et al., 2021).

In this study, the diffractograms of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid are shown in **Figure 2**. The PXRD diffractogram of atorvastatin calcium showed diffraction peaks of 2θ at 19.4, 10.2, 11.8, 17.0, 19.4, 21.6, 23.7, and 43.9°, while the dipicolinic acid diffractogram showed 2θ diffraction peaks at 10.9, 16.9, 19.4, 24.4, 27.9, and 37.1°. The atorvastatin calcium-dipicolinic acid multicomponent solids showed a diffractogram with 2θ peaks at 8.8, 9.9, 11.5, 16.7, 19.1, 21.2, 22.4, 23.4, and 27.7°. The diffractogram of atorvastatin calcium-dipicolinic acid multicomponent solids produced by the liquid-assisted grinding method has 2θ diffraction peaks different from the 2θ diffraction peaks of the diffractogram of the starting material. The results of the diffractogram analysis have indicated that atorvastatin calcium and dipicolinic acid in the solids system are not a physical mixture but have interacted to form a new solids phase, a multicomponent crystalline solids system (Nugrahani et al., 2020).

DSC Thermogram

DSC characterization produces a thermogram that can provide information about the thermal properties and solids phase transformation of the sample due to interactions between components in the sample (Satapathy et al., 2021; Thorat et al., 2021; Wicaksono et al., 2020). DSC thermograms of solids of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid are shown in **Figure 3**. The thermogram of atorvastatin calcium showed a sharp endothermic peak at 155.0 °C (ΔH = 69.04 J/g), whereas dipicolinic acid showed one sharp endothermic peak at 260.0 °C (ΔH = 496.76 J/g). The sharp endothermic peak on the thermogram indicates the melting point of atorvastatin calcium and dipicolinic acid, which agrees with the data stated in the literature (Chadha et al., 2012; Hiendrawan et al., 2016). Meanwhile, atorvastatin calcium-dipicolinic acid produced a thermogram with a sharp endothermic peak at 181.9 °C with an enthalpy value (ΔH) of 17.69 J/g.

In solids with a crystalline structure, the DSC thermogram shows the presence of sharp endothermic peaks indicating the melting point, while the PXRD diffractogram shows the presence of diffraction peaks (Budiman & Aulifa, 2022). The DSC thermogram of atorvastatin calcium-dipicolinic acid showed a sharp endothermic peak at 181.9 °C with

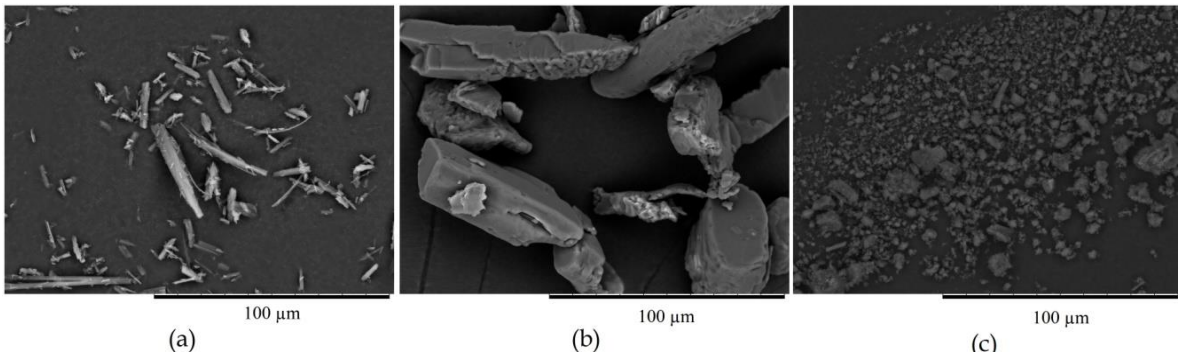

Figure 1. SEM micrographs of constituent materials and prepared multicomponent solids, (**a**) atorvastatin calcium, (**b**) dipicolinic acid, and (**c**) atorvastatin calcium - dipicolinic acid multicomponent solids (15 kV, 12 mA, 1000x)

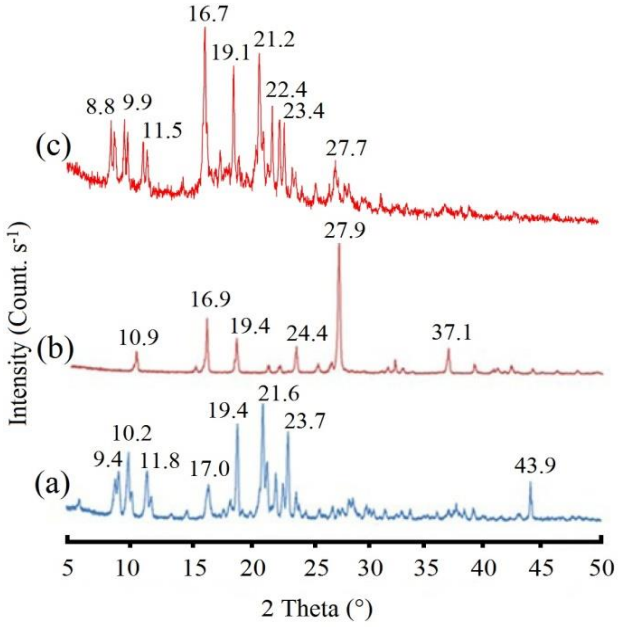

Figure 2. Diffractogram of constituent materials and prepared multicomponent solids, (**a**) atorvastatin calcium, (**b**) dipicolinic acid, and (**c**) atorvastatin calcium - dipicolinic acid multicomponent solids

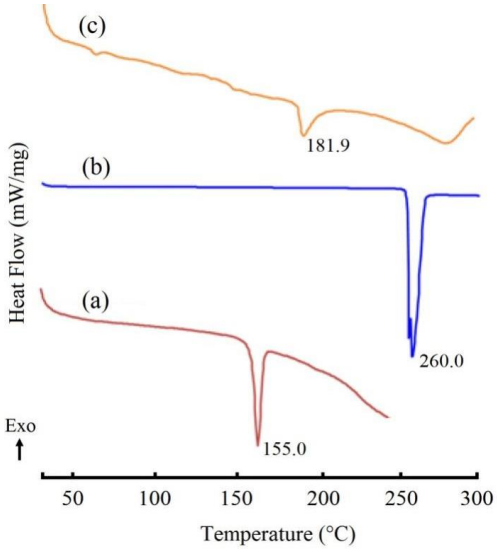

Figure 3. Thermogram of constituent materials and prepared multicomponent solids, (**a**) atorvastatin calcium, (**b**) dipicolinic acid, and (**c**) atorvastatin calcium - dipicolinic acid multicomponent solids

an enthalpy (ΔH) value of 17.69 J/g, and the PXRD diffractogram showed diffraction peaks. Thus it can be concluded that the solids of atorvastatin calcium-dipicolinic acid are a multicomponent crystalline solid with a melting point of 181.9 °C (Li et al., 2022).

The molecules of atorvastatin calcium and dipicolinic acid in the multicomponent solids form intermolecular interactions that produce a new solids phase. The multicomponent solids atorvastatin calcium-dipicolinic acid has a different molecular arrangement than the individual solids of its constituent materials (Satapathy et al., 2021). Different molecular arrangements cause changes in the pattern of molecular arrangement in the solids system and produce new crystal packing with different crystal lattice energies (Volodin et al., 2020; Kilinkissa et al., 2020; Ejarque et al., 2021). The crystal lattice energy of crystalline solids is known to correlate with the melting point of solids whereas the melting point of multicomponent solids is generally between the melting points of its constituent components (Qiao et al., 2011; Salahinejad et al., 2013; Gamidi et al., 2018).

FTIR Spectra

FTIR spectroscopy is a common technique for analyzing functional groups and intermolecular interactions in multicomponent solids (Salim et al., 2021). The presence of intermolecular interactions between constituent components in multicomponent solids is indicated by changes in the intensity and shift of absorption peaks in the FTIR spectra of multicomponent solids compared to absorption peaks of constituent materials (Hermanto et al., 2020; Satapathy et al., 2021). The FTIR spectra of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium - dipicolinic acid are shown in Figure 4.

The FTIR spectra of atorvastatin calcium showed specific absorption peaks at 3364 cm^{-1} (free N-H stretching), 2973 cm^{-1} (O-H stretching), 1650 cm^{-1} (C=O stretching), and 1216 cm^{-1} (C-N stretching). Dipicolinic acid has a broad absorption peak at wave number 3254-2363 cm^{-1} (O-H stretching) and a sharp absorption peak at 1692 cm^{-1} (C=O stretching). The FTIR spectra of both materials showed the same specific absorption peaks as mentioned in the literature (Wicaksono et al., 2021; Hiendrawan et al., 2016). The FTIR spectra of atorvastatin calcium - dipicolinic acid multicomponent solids showed a change in the intensity and shift of the absorption peak in the functional groups of atorvastatin calcium and dipicolinic acid. The absorption peaks that experienced changes in intensity and shift were the absorption peaks of the proton donor and acceptor groups of hydrogen bonds in the molecules of atorvastatin calcium and dipicolinic acid. Based on the results of the FTIR analysis it has been indicated that the atorvastatin calcium and dipicolinic acid molecules in the solids have formed intermolecular interactions, especially hydrogen bonds (Yaseen et al., 2017; Vemuri & Lankalapalli, 2021).

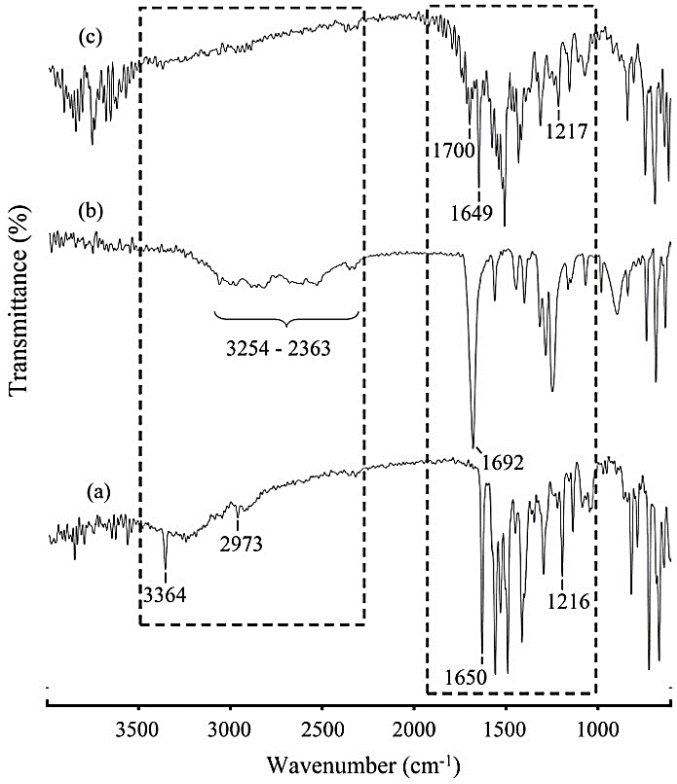

Figure 4. FTIR spectra of constituent materials and prepared multicomponent solids, (**a**) atorvastatin calcium, (**b**) dipicolinic acid, and (**c**) atorvastatin calcium - dipicolinic acid multicomponent solids

Solubility

Solubility is one of the critical properties of the drugs that determine the absorption process, bioavailability, and therapeutic effect (Fink et al., 2019). Atorvastatin calcium is a drug that is poorly soluble in water, presumably because atorvastatin calcium forms a stable crystal packing so that it is difficult to be hydrated by water molecules (Ozaki et al., 2014; Kwon et al., 2019; Dey et al., 2021). In forming multicomponent crystalline solids, intermolecular interactions between components can change the crystal packing arrangement, increasing solubility (Sopyan & Gozali, 2019). The test results have shown that pure atorvastatin calcium and atorvastatin calcium - dipicolinic acid multicomponent solids in distilled water have a solubility of 137.83±13.41 and 226.33±21.68 mg/L, respectively. The result of the solubility test showed that the formation of multicomponent solids of atorvastatin calcium - dipicolinic acid could significantly increase the solubility ($p<0.05$) compared to the solubility of pure atorvastatin calcium. The increase in solubility of atorvastatin calcium in multicomponent solids is thought to be due to the intermolecular interaction of hydrogen bonds between molecules of atorvastatin calcium and dipicolinic acid, resulting in a new solids phase with a different crystal packing than pure atorvastatin calcium (Guo et al., 2018). The presence of molecules of dipicolinic acid in multicomponent solids changes the crystal packing arrangement so that it is thought to reduce the crystal lattice energy. The decrease in crystal lattice energy causes the multicomponent solids to be easily hydrated, which leads to increased solubility (Wicaksono et al., 2021; Docherty et al., 2015; Bergström & Larsson, 2018; Ozaki et al., 2014).

CONCLUSIONS

Atorvastatin calcium and dipicolinic acid can form crystalline multicomponent solids with the liquid-assisted grinding method. The atorvastatin calcium-dipicolinic acid multicomponent solids showed significantly higher solubility ($p<0.05$) than pure atorvastatin calcium. Therefore, the formation of multicomponent solids of atorvastatin calcium-dipicolinic acid using the liquid-assisted grinding method can be used to overcome the solubility and bioavailability of atorvastatin calcium.

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