

## A New Multi-Component Solid of Atorvastatin Calcium with a Dipicolinic Acid Cofomer for Improving the Water Solubility

Yudi Wicaksono<sup>1\*</sup>, Ari Satia Nugraha<sup>2</sup>, Eka Deddy Irawan<sup>3</sup>, Nadifa Nada<sup>1</sup>, Sofyan Dimas Nurhansyah<sup>1</sup>

<sup>1</sup>*Drug Modification Research Group, Faculty of Pharmacy, University of Jember, Jl. Kalimantan No. 37, Jember 68121, Indonesia*

<sup>2</sup>*Drug Utilisation and Discovery Research Group, Faculty of Pharmacy, University of Jember, Jl. Kalimantan No. 37, Jember 68121, Indonesia*

<sup>3</sup>*Drug Delivery Research Group, Faculty of Pharmacy, University of Jember, Jl. Kalimantan No. 37, Jember 68121, Indonesia*

**Abstract.** Atorvastatin calcium is a potent active pharmaceutical ingredient that reduces blood cholesterol levels. However, oral bioavailability is low because it is difficult to dissolve in water. Therefore, further research to increase the solubility of the drug is needed to improve its bioavailability properties. This research aimed to increase the solubility of atorvastatin calcium through the formation of a multi-component solid. Furthermore, the drug was formed into a multi-component solid with dipicolinic acid as a cofomer using the solvent evaporation-quenching method. A powder X-ray diffractometer (PXRD), Fourier transform infrared (FTIR) spectrometer, differential scanning calorimeter (DSC), and scanning electron microscope (SEM) was used to characterize the solid. Also, the shake-flask method was used to analyze the solubility of the solid in distilled water. The results showed that atorvastatin calcium and dipicolinic acid formed a new multi-component solid of cocrystal type. The solubility of the atorvastatin calcium from the multi-component solid was  $344.31 \pm 37.09$  mg/L, which was a significant increase of about 2.7-fold compared to the pure form.

**Keywords:** Atorvastatin calcium; Dipicolinic acid; Multi-component solid; Solubility properties

### 1. Introduction

The rate of drug absorption in the gastrointestinal tract is determined by solubility. Orally administered drugs must dissolve in the gastrointestinal fluid for a passive diffusion process, the main absorption mechanism, to occur (Pindelska, Sokal, and Kolodziejcki, 2017; Maggi *et al.*, 2015). The bioavailability of the absorbed drug fraction produced the desired pharmacological effect (Williams *et al.*, 2013). Therefore, drugs with low solubility levels have oral bioavailability problems, posing challenges and opportunities for their development (Javeer, Patole, and Amin, 2013; Kawabata *et al.*, 2011).

Atorvastatin calcium is a potent statin drug that reduces blood cholesterol levels. It works by inhibiting the enzyme HMG-CoA reductase in cholesterol biosynthesis (Anwar, Warsi, and Mallick, 2011). According to the biopharmaceutical classification system, it is

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\*Corresponding author's email: [yudi.farmasi@unej.ac.id](mailto:yudi.farmasi@unej.ac.id), Tel.: +62 331 324736; Fax.: +62 331 324736  
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categorized as a Class II drug with high permeability but low solubility. The bioavailability of oral preparations is about 12% due to their low solubility property (Anwar, Warsi, and Mallick, 2011). Therefore, research to increase the solubility of this drug is needed.

The multi-component solid is one technique used to improve the solubility of poorly soluble drugs (Zaini *et al.*, 2020; Chadha, Sharma, and Haneef, 2017; Haneef and Chadha, 2017). Cocrystal is a type of multi-component solid that has gained attention for improving the solubility properties of poorly soluble drugs. Furthermore, the multi-component cocrystal is formed through noncovalent intermolecular interactions between drug molecules and coformers to produce a single-phase material with a new crystal lattice structure. Generally, the drugs that form cocrystals have new physical properties that differ significantly from the starting materials (Shaikh *et al.*, 2018). The solubility of the multi-component cocrystal can be improved by lowering the lattice energy and/or increasing the solvent affinity (Thakuria *et al.*, 2013). Also, the presence of a diverse coformer in the multi-component solid increases the possibility of obtaining drug solids with better physical solubility properties (Douroumis, Ross, and Nokhodchi, 2017; Gao *et al.*, 2012; Tilborg *et al.*, 2010). In addition, ketoprofen-nicotinamide, atorvastatin calcium-succinic acid, and aripiprazole-succinic acid are examples of multi-component cocrystals shown to increase solubility (Butreddy *et al.*, 2021; Wicaksono *et al.*, 2019; Wicaksono *et al.*, 2018).

The research aimed to improve the water solubility properties of atorvastatin calcium through the formation of a multi-component solid. Dipicolinic acid was used as a coformer due to its solubility in water. The molecules have two donors and five acceptors of hydrogen bonds, making it easy to form intermolecular interactions with other molecules (Hiendrawan *et al.*, 2016). In addition, the dipicolinic acid coformer is inert. Hence it has no toxic effects. The atorvastatin calcium-dipicolinic acid multi-component solid was prepared using the solvent evaporation-quenching method. A powder X-ray diffractometer (PXRD), Fourier transform infrared (FTIR) Spectrometer, differential scanning calorimeter (DSC), and scanning electron microscope (SEM) were used to characterize the solid. The shake-flask method was used to analyze the solubility of the samples in distilled water.

## 2. Methods

### 2.1. Materials

Atorvastatin calcium (>98.0%) was provided by PT Dexa Medica (Palembang, Indonesia). Dipicolinic acid (>98.5%), methanol (>99.8%), and distilled water were purchased from Sigma-Aldrich (Saint Louis, USA), PT Smart Lab (Tangerang, Indonesia) and CV Makmur Sejati (Jember, Indonesia) respectively.

### 2.2. Preparation of Multi-component Solid

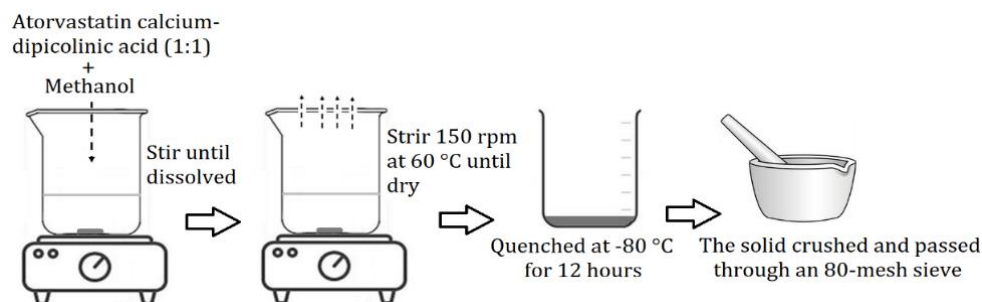
The solvent evaporation-quenching method was used to prepare the atorvastatin calcium-dipicolinic acid multi-component solid. The preparation of the solid was carried out in a methanol solution with a molar ratio of atorvastatin calcium-dipicolinic acid (1:1). The solution was evaporated on a hotplate at 60 °C and stirred at 150 rpm until a dry solid was obtained. Then the resulting solid was quenched at -80 °C for 12 hours, crushed with the mortar, and passed through an 80-mesh sieve. The solid powder was stored in a desiccator until it was tested for solid-state and solubility properties. The scheme for the preparation of multi-component solids is shown in Figure 1.

### 2.3. Characterization

#### 2.3.1. PXRD

PXRD was a method used to analyze the phase types of solid materials. Furthermore, the analysis was conducted using a Philip Xpert diffractometer and a CuK $\alpha$ 1 radiation

source. The diffractogram was determined by filling the sample holder cavity of the X-ray diffractometer with sample powder and flattening it with a spatula. Also, the X-ray diffractometer was set at a voltage of 40 kV, a current of 30 mA, and a scan speed of  $2\theta = 10^\circ/\text{minute}$  with a range of  $2\theta$  at  $5\text{-}50^\circ$ .



**Figure 1** Scheme for preparation of multi-component solids

### 2.3.2. DSC

Generally, the DSC test was used to determine the solid-liquid or solid-solid transformation temperature of the sample. The Thermo plus EVO DSC 8230 equipment was used, and about 2 mg of the powder sample was placed into an aluminum container and tightly closed with a press device. Then the sample was placed into the DSC, which was set to run at a temperature range of  $30\text{-}300^\circ\text{C}$ . The heating rate of DSC was  $10^\circ\text{C}/\text{minute}$  under dry nitrogen gas flow conditions at  $50\text{ mL}/\text{minute}$ .

### 2.3.3. FTIR

The FTIR testing was used to identify the functional groups and intermolecular interactions of molecules in the solids. About 5 mg of the sample powder was placed on the equipment's board (Alpha Bruker), and then the instrument was run at the wavenumber range of  $4000\text{-}600\text{ cm}^{-1}$ .

### 2.3.4. SEM

The SEM analysis aims to obtain the microscopic properties, including surface topography and particle size of a sample. About 2 mg of the sample was placed on a stub specimen that had been given adhesive and then coated with platinum for 20 seconds using the Hitachi E-1045 ion sputter. Then the sample was inserted into the SEM base holder, and the voltage and current were set at 15 kV and 12 mA, respectively. The observation of the shape, size, and topography of the sample particles was carried out using the appropriate magnification.

## *2.4. Solubility Testing*

The shaking method was used to determine the water solubility of the atorvastatin calcium from a multi-component solid. Furthermore, the excess sample was placed into a 250 mL Erlenmeyer flask, and then 50 mL of distilled water was added to produce a saturated solution. The flask was closed tightly with aluminum foil and placed horizontally on the orbital shaker. Shaking was done for 12 hours at  $37 \pm 0.5^\circ\text{C}$  and 150 rpm. The supernatant was filtered through a  $0.45\ \mu\text{m}$  cellulose nitrate filter membrane, and the atorvastatin calcium content in the solution was determined using a UV-Vis spectrophotometer.

## **3. Results and Discussion**

### *3.1. The Multi-component Solid*

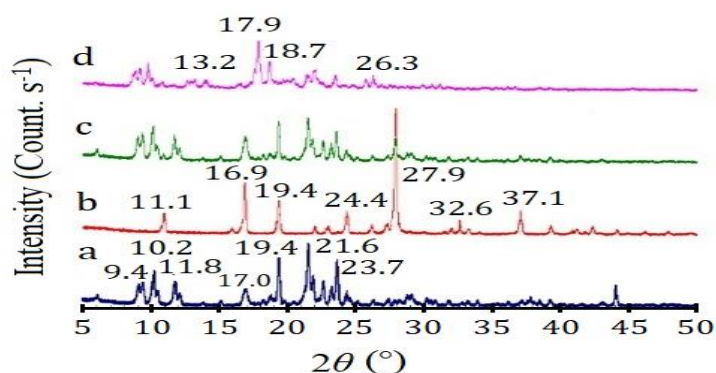
The solvent evaporation-quenching method was used to prepare an atorvastatin calcium-dipicolinic acid multi-component solid. Methanol was used as the solvent because

it easily dissolves atorvastatin calcium and dipicolinic acid. The drug and coformer used in the preparation of the multi-component solid were 0.968 and 0.135 g, respectively, while the total solvent was 15 mL. Also, the time required for the solvent evaporation process was 60 minutes. The solids were quenched in a deep freezer at  $-80\text{ }^{\circ}\text{C}$  for 12 hours, then crushed with a mortar and passed through an 80-mesh sieve.

### 3.2. PXRD Diffractogram

The PXRD characterization was conducted to analyze the solid-state phase of the atorvastatin calcium-dipicolinic acid multi-component solid. Although the diffractogram of crystalline solids is characterized by the presence of sharp diffraction peaks, that of amorphous solids is characterized by the absence of diffraction peaks. The formation of new crystalline solids from the starting material mixture was indicated by a diffractogram with new diffraction peaks different from each starting material (Karagianni, Malamatar, and Kachrimanis, 2018).

Figure 2 shows the diffractograms of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid multi-component solid. The diffractogram of atorvastatin calcium has diffraction peaks of  $2\theta$  at  $9.4$ ;  $10.2$ ;  $11.8$ ;  $17.0$ ;  $19.4$ ;  $21.6$ ; and  $23.7^{\circ}$ , while the dipicolinic acid has diffraction peaks of  $2\theta$  at  $11.1$ ;  $16.9$ ;  $19.4$ ;  $24.4$ ;  $27.9$ ;  $32.6$ ; and  $37.1^{\circ}$ . Also, the physical mixture of atorvastatin calcium and dipicolinic acid powder showed a diffractogram with diffraction peaks of  $2\theta$ , which are a combination or overlay of the respective diffraction peaks. However, the atorvastatin calcium and dipicolinic acid multi-component solid showed the new diffraction peaks of  $2\theta$  at  $13.2$ ;  $17.9$ ;  $18.7$ ;  $23.5$ ; and  $26.3^{\circ}$ , in contrast to the individual peaks.



**Figure 2** Diffractogram of (a) atorvastatin calcium, (b) dipicolinic acid, (c) physical mixture of atorvastatin calcium and dipicolinic acid, and (d) atorvastatin calcium - dipicolinic acid multi-component solid

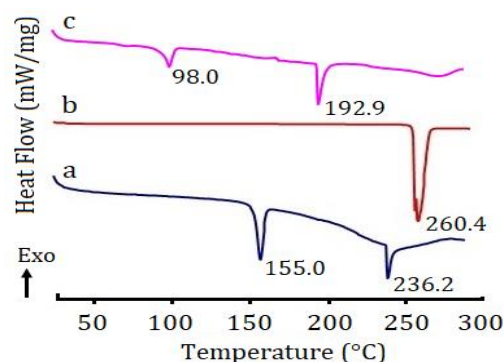
The results of PXRD characterization showed that the solid-state of atorvastatin calcium-dipicolinic acid multi-component solid has a diffractogram different from each starting material, indicating the formation of a solid with a new crystalline phase. Also, the dipicolinic acid molecules acted as a coformer in the atorvastatin calcium-dipicolinic acid multi-component solid, forming a new crystal lattice with the atorvastatin calcium molecules (Karagianni, Malamatar, and Kachrimanis, 2018). This lattice has different energy from the starting material, resulting in new physicochemical properties (Thakuria *et al.*, 2013).

### 3.3. DSC Thermogram

DSC characterization was used to observe the solid-state phase transformation of the sample due to heating (Wicaksono *et al.*, 2020). The melting point data, enthalpy of fusion, and phase transformation profile were obtained from this characterization (Pindelska,

Sokal, and Kolodziejski, 2017; Karagianni *et al.*, 2018; Qiao *et al.*, 2011). Figure 3 showed the DSC thermograms of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid multicomponent solid. The atorvastatin calcium DSC thermogram showed two sharp endothermic peaks at 155.0 °C ( $\Delta H = 69.04$  J/g) and 236.2 °C ( $\Delta H = 23.56$  J/g), indicating the melting point and decomposition temperature, respectively (Shete *et al.*, 2010). In addition, the dipicolinic acid DSC thermogram showed one sharp endothermic peak at 260.4 °C ( $\Delta H = 496.76$  J/g), indicating the melting point and no decomposition up to 300 °C which is in line with the literature (Hiendrawan *et al.*, 2016).

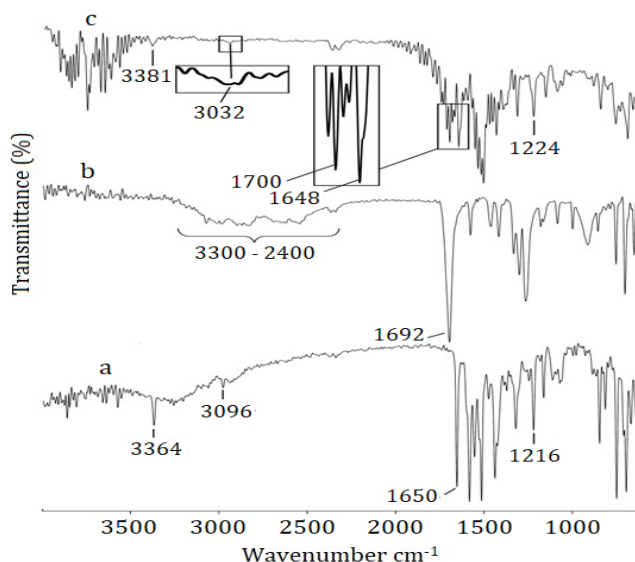
The DSC thermogram of atorvastatin calcium and dipicolinic acid multi-component solid showed two sharp endothermic peaks at 98.0 °C ( $\Delta H = 26.62$  J/g) and 192.9 °C ( $\Delta H = 35.21$  J/g). The sharp endothermic peak at 98.0 °C indicated the melting point of the solid, while the peak at 192.9 °C depicted the decomposition temperature. Therefore, the results of DSC characterization showed that the solid has a thermogram profile that differs from the starting material in terms of melting point and decomposition temperatures. The changes in the thermogram profile indicated the presence of intermolecular interactions in the multi-component solid between molecules of the drug and the coformer. Also, the multi-component solid of atorvastatin calcium and dipicolinic acid showed a lower melting point and enthalpy of melting than the individual material. The decrease in melting point and enthalpy of melting indicated lower lattice energy, making it easy to convert the solid into liquid when heated (Thakuria *et al.*, 2013; Qiao *et al.*, 2011).



**Figure 3** DSC thermogram of (a) atorvastatin calcium, (b) dipicolinic acid, and (c) atorvastatin calcium - dipicolinic acid multi-component solid

### 3.4. FTIR Spectra

The FTIR characterization aimed to analyze the functional groups in atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid multi-component solids. In addition, the FTIR spectra were used to analyze the presence of intermolecular interactions between the drug and the coformer in the multi-component solids (Bekbayeva *et al.*, 2022; Karagianni, Malamataris, and Kachrimanis, 2018; Pindelska Sokal, and Kolodziejski, 2017). Figure 4 showed the FTIR spectra of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid multicomponent solid. The drug showed FTIR spectra with specific absorption peaks at 3364  $\text{cm}^{-1}$  (NH-free stretching), 3096  $\text{cm}^{-1}$  (OH- stretching), 1650  $\text{cm}^{-1}$  (C=O stretching), and 1216  $\text{cm}^{-1}$  (CN stretching), indicating suitability as stated in the literature (Wicaksono *et al.*, 2019). According to the literature, the FTIR spectrum of the coformer showed a wide and strong absorption peak at 3300-2400  $\text{cm}^{-1}$  (OH stretching of the carboxylic acid group) and 1692  $\text{cm}^{-1}$  (C=O stretching of carboxylic the acid group), respectively (Hiendrawan *et al.*, 2016).



**Figure 4** FTIR spectra of (a) atorvastatin calcium, (b) dipicolinic acid, and (c) atorvastatin calcium-dipicolinic acid multi-component solid

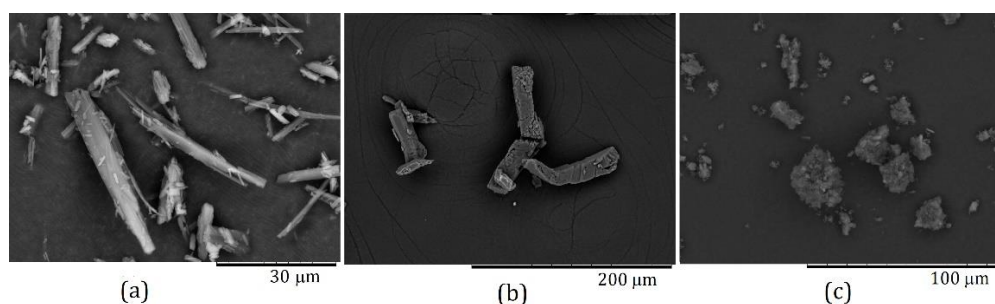
The FTIR spectra of atorvastatin calcium-dipicolinic acid multi-component solid showed absorption peaks that were the combination of the components. However, the absorption peaks changed in intensity and wave number. The FTIR spectra showed that the absorption peaks of atorvastatin calcium in the multi-component solids shifted, with free NH stretching from 3364 to 3381  $\text{cm}^{-1}$ , OH from 3096 to 3032  $\text{cm}^{-1}$ , C=O from 1650 to 1700  $\text{cm}^{-1}$ , and CN from 1216 to 1224  $\text{cm}^{-1}$ . Meanwhile, the absorption peaks of dipicolinic acid in the multi-component solid spectra changed, with a decrease in the intensity of the O-H absorption peak of the carboxylic acid group and a shift in the C=O stretching from 1692 to 1648  $\text{cm}^{-1}$ . According to the FTIR analysis, the solid spectra showed shifts in the absorption peaks of the acceptor and donor groups of hydrogen bonds of atorvastatin calcium and dipicolinic acid molecules. This indicated the presence of intermolecular hydrogen bonds between molecules of the drug and coformer in the solid (Karagianni, Malamatari, and Kachrimanis, 2018).

The PXRD analysis showed that atorvastatin calcium-dipicolinic acid formed a new crystalline solid with a different diffraction pattern and crystal lattice from the starting materials. Furthermore, the DSC analysis results showed that the component's solid state has a new single solid phase with different thermal properties (melting point and enthalpy of fusion) from the starting material. The FTIR analysis showed that intermolecular hydrogen bonds were formed between the acceptor and donor groups of hydrogen bonds of atorvastatin calcium and dipicolinic acid molecules. According to the analysis of the PXRD diffractogram, DSC thermogram, and FTIR spectra, the solid-state of the atorvastatin calcium-dipicolinic acid is a new multi-component cocrystal (Karagianni, Malamatari, and Kachrimanis, 2018; Pindelska Sokal, and Kolodziejcki, 2017; Qiao *et al.*, 2011).

### 3.5. Morphology

The SEM examination aimed to analyze microscopic properties, including the sample's surface topography and particle size (Sukeksi *et al.*, 2021; Ali *et al.*, 2020; Qiao *et al.*, 2011). Figure 5 shows the micrographs of atorvastatin calcium, dipicolinic acid, and atorvastatin calcium-dipicolinic acid multi-component solid. The atorvastatin calcium powder particles were rod-shaped, with lengths ranging from 30-100  $\mu\text{m}$ . Also, the surface topography of drug particles showed surface properties, as stated by the literature (Wicaksono *et al.*, 2019). The dipicolinic acid particles were shaped as a plate light measuring 20-200  $\mu\text{m}$  in

length and a flat surface, as stated in the literature (Hiendrawan *et al.*, 2016). In addition, the preparation of atorvastatin calcium-dipicolinic acid multi-component solid produced irregularly shaped particles with a diameter of 15-40  $\mu\text{m}$  and a rough surface. The multi-component solid showed microscopic differences with each starting material because the morphological identity of these materials was not observed in the atorvastatin calcium-dipicolinic acid multi-component solid. Therefore, it can be concluded that the drug and coformer formed a new multi-component solid system with new physical characteristics and solid-state properties.



**Figure 5** Micrographs of a) atorvastatin calcium, (b) dipicolinic acid, and (c) atorvastatin calcium-dipicolinic acid multi-component solid

### 3.6. Solubility

Solubility is a parameter that directly affects the bioavailability and pharmacological effect of an active pharmaceutical ingredient. However, atorvastatin calcium is an active pharmaceutical ingredient with low solubility. Therefore, developing the solubility properties of the drug is necessary to prevent the problem of low bioavailability and lack of pharmacological response when formulated into pharmaceutical preparations (Anwar, Warsi, and Mallick, 2011). Table 1 shows the solubility test of pure atorvastatin calcium and atorvastatin calcium-dipicolinic acid multi-component solid.

The test showed that the solubility of atorvastatin calcium was  $127.63 \pm 7.52$  mg/L. This result indicated that 31.91 mg of atorvastatin calcium would dissolve in 250 water media. Conversely, atorvastatin calcium is formulated into tablets with doses of 40 and 80 mg. Therefore, atorvastatin calcium is categorized as a Class II drug in the biopharmaceutical classification system, indicating low solubility, and often has bioavailability when formulated into pharmaceutical preparations (Pobudkowska *et al.*, 2015). The solubility of the drug in the multi-component solid was  $344.31 \pm 37.09$  mg/L, which was significantly higher than the pure form ( $p < 0.05$ ). Therefore, the formation of atorvastatin calcium-dipicolinic acid multi-component solid can be used to solve the solubility problem of the drug.

**Table 1** The solubility of pure atorvastatin calcium and atorvastatin calcium - dipicolinic acid multi-component solid in distilled water

Replication	Solubility (mg/L)	
	Atorvastatin calcium	Atorvastatin calcium-dipicolinic acid multi-component solid
1	121.46	385.51
2	136.01	333.82
3	125.43	313.59
Mean $\pm$ SD	$127.63 \pm 7.52$	$344.31 \pm 37.09$

The solubility of a crystalline solid is influenced by the lattice energies of the crystal (Elder, Holm, and Diego, 2013). Generally, crystalline solids with lower lattice energies are more soluble because the constituent molecules are bound in a lattice with weaker energies

(Kuleshova *et al.*, 2013; Thakuria *et al.*, 2013). The PXRD test showed that the atorvastatin calcium-dipicolinic acid multi-component cocrystal had a different diffractogram pattern from each constituent component. Also, the FTIR analysis results showed that the multi-component solid formation resulted in a new crystalline structure through intermolecular hydrogen bonds (Khadka *et al.*, 2014). Therefore, atorvastatin calcium-dipicolinic acid multi-component solid has a higher solubility than the pure form of the drug due to the decrease in lattice energies of the crystal. This phenomenon caused the molecules of the drug and cofomer to interact more easily with solvent molecules during the dissolution process (Kuleshova *et al.*, 2013; Thakuria *et al.*, 2013).

#### 4. Conclusions

The solvent evaporation-quenching method was used to convert atorvastatin calcium to a new multi-component solid with a dipicolinic acid cofomer. Furthermore, the PXRD, DSC, FTIR, and SEM analyses indicated that the solid state of atorvastatin calcium-dipicolinic acid was a multi-component cocrystal. The solubility testing of the multi-component solid in distilled water showed a significant improvement of about 2.7-fold in atorvastatin calcium solubility compared to the pure form. Therefore, the formation of the multi-component solid can be used to solve the atorvastatin calcium bioavailability problem due to its low solubility. Atorvastatin calcium-dipicolinic acid multi-component solid still needs to be further tested for its *in vivo* bioavailability so that the multi-component solid can be formulated into pharmaceutical preparations with better performance.

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