Preparation and Characterization of a Novel Cocrystal of Atorvastatin Calcium with Succinic Acid Coformer

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Abstract: *Preparation and characterization of a novel cocrystal of atorvastatin calcium with succinic acid coformer were successfully performed. This research aims to modify the crystalline form of atorvastatin calcium through cocrystallization with succinic acid coformer. The cocrystal was prepared by a solvent evaporation method and characterized by Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM). The atorvastatin calcium-succinic acid cocrystal has new crystalline peaks at 2θ of 12.9, 18.2 and 26.7° indicating the formation of a new crystalline phase. The cocrystal showed the melting point at 205.7 °C with an enthalpy of fusion 30.2 J/g which is different from the initial components. The FTIR spectra of cocrystal showed the shifting of absorption peaks of groups of initial components indicating of formation of atorvastatin calcium-succinic acid cocrystal through acid–amide intermolecular hydrogen bond interactions. The solubility and dissolution test showed that the cocrystal has solubility and dissolution rate significantly higher than the solubility and dissolution rate of pure atorvastatin calcium.*

Keywords: *novel cocrystal; atorvastatin calcium; crystalline phase; solubility; dissolution rate*

■ INTRODUCTION

Atorvastatin calcium is one of the drug members of the statin group used to lower cholesterol levels in the blood. It is considered one of the most effective synthetic agents for lowering low-density lipoprotein cholesterol, triglycerides and total cholesterol [1-2]. The highly effective cholesterol-lowering effect of atorvastatin calcium makes it one of the most common cholesterol-lowering drugs used worldwide [2-3].

Patent protection for atorvastatin calcium has expired in 2011, so the research to modify the physicochemical properties of atorvastatin calcium is an exciting opportunity in the field of pharmaceutical research. The most common ways to modify the atorvastatin calcium is by the formation of new polymorphs, solvates and crystalline forms [4-5].The formation of a new form from atorvastatin calcium is known to improve the solubility [6], dissolution rate [7] and stability [8].

Cocrystallization is an alternative strategy for the formation of a new crystalline form of drugs. It is carried out by crystallizing together the drug with a coformer agent in the same crystal lattice [9]. The intermolecular interactions between the drug and the coformer in the new crystal lattice form different packing arrangements that trigger a change in physicochemical properties [10]. It is a potential method to improve the physicochemical properties of a drug in solubility [11-13], dissolution rate

[14], stability [15-16], bioavailability [17], compressibility and hygroscopicity [18].

In the present work, we investigated the formation of a novel cocrystal of atorvastatin calcium using succinic acid coformer. Succinic acid is a member of the generally regarded as safe compounds, so it is often used as coformer for cocrystallization of drugs [19-21]. The co-crystal was prepared via solvent evaporation method using methanol. The characterization was performed by Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transforms Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM). The solubility test of cocrystal was performed in distilled water and dissolution behavior of cocrystal was evaluated by dissolution test in phosphate buffer pH 6.8.

■ EXPERIMENTAL SECTION

Materials

Atorvastatin calcium in trihydrate form (purity ≥ 99.5%) was kindly donated by PT Dexa Medica (Indonesia). Succinic acid (purity ≥ 99.5%), disodium hydrogen phosphate dihydrate (purity ≥ 99.5%) and sodium dihydrogen phosphate monohydrate (purity ≥ 99.0%) were purchased from Merck (Darmstadt, Germany). Methanol (purity ≥ 99.8%) was purchased from Smart Lab Indonesia (Tangerang, Indonesia).

Instrumentation

The instruments for preparation of cocrystal were analytical balance (Precisa ES 225SM-DR) and a magnetic stirrer (Scilogex MS7-H550-Pro). The instruments for the characterization of cocrystal included powder X-ray diffractometer (Philip Xpert), differential scanning calorimeter (Rigaku DSC 8230), Fourier Transform Infrared Spectrophotometer (Alpha Bruker), Scanning Electron Microscope (Hitachi TM 3000), sputter coater ion (Hitachi E-1045), orbital incubator (Stuart S1600), USP dissolution test apparatus II (Logan UDT-804) and UV-Vis spectrophotometer (Hitachi U-2900).

Procedure

Preparation of atorvastatin calcium-succinic acid cocrystal

The 1:1 molar ratio of atorvastatin calcium and acid was dissolved with methanol in a beaker glass. The resulting solution allowed to slowly evaporating at an ambient temperature. The resulted crystal was crushed in a pestle to reduce the particle size and then sifted through a sieve no. 80 mesh (ASTM no. 80).

Powder X-ray diffraction

PXRD patterns were collected at room temperature using a Philip Xpert diffractometer system. The radiation source is Cu-Kαλ = 1.54060 Å. The voltage and current were respectively maintained at 45 kV and 40 mA. The data were collected by a continuous scan over an angle range from 5–50° in 2θ.

Differential scanning calorimetry

Thermal behavior of the samples was analyzed using differential scanning calorimeter (Rigaku DSC 8230). The pre-useinstrument was calibrated for the accuracy of temperature and heat flow with indium. The samples of 2–3 mg were accurately weighed in hermetic aluminum pan and scanned at the temperature range 50–250 °C with a heating rate of 10 °C/min. The experiments were performed on the atmosphere of dry nitrogen gas (flow rate 50 mL/min).

Fourier transform infrared spectroscopy

The FTIR spectra of samples were obtained by Fourier transform infrared spectrophotometer (Alpha Bruker). Measurements were recorded over a range 4000–500 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). Approximately 10 mg of sample was placed on a specimen stub previously given a two-sided adhesive and then coated with platinum for 10 sec by sputter coater ion (Hitachi E-1045). The samples were inserted into the sample chamber holder base on the microscope and observed at 15 kV and 500x magnification value.

Solubility test

The samples were tested for solubility in distilled water by the shake-flask method. An excess of the sample was placed in a 250 mL Erlenmeyer flask and added distilled water. Erlenmeyer flask was continuously shaken

using an incubator orbital (Stuart S1600) at 150 rpm and 37 ± 0.5 °C for 12 h. The amount of dissolved atorvastatin calcium was determined by UV-Vis spectrophotometer (Hitachi U-2900) at λ 300 nm. Testing was conducted with three repetitions.

Dissolution test

The dissolution test was performed with the paddle method using a USP dissolution test apparatus II (Logan UDT-804).The sample equivalent to 50 mg of atorvastatin calcium was added to 900 mL of phosphate buffer pH 6.8 medium then stirred at 100 rpm and 37 ± 0.5 °C. Approximately 5 mL of dissolution medium was withdrawn every 15 min for 60 min. New dissolution medium with the same amount was added after each withdrawal of sample. The concentrations of atorvastatin calcium in solution were determined by UV-Vis spectrophotometer at λ 300 nm. Dissolution test of each sample was performed in triplicate.

Statistical analysis

The average values of results were analyzed by using the software of one-way analysis of variance (ANOVA) of SPSS version 16.0 for windows. The mean value is considered to have a significant difference at $p \leq 0.05$.

■ RESULTS AND DISCUSSION

Powder X-Ray Diffraction

The PXRD technique is the primary tool for the study and characterization of crystalline materials. By using PXRD, crystalline phases of material can be distinguished by its unique diffraction pattern which is a fingerprint of crystal structures. These phases may represent different materials or different crystalline form of related materials [22]. The overlay of PXRD patterns of atorvastatin calcium, succinic acid, and atorvastatin calcium-succinic acid cocrystal is shown in Fig. 1.

The PXRD pattern of atorvastatin calcium exhibited characteristic peaks at 2θ of 9.2, 10.0, 11.6, 19.2, 21.3 and 23.5°. The PXRD pattern showed that the atorvastatin calcium sample is the crystalline form I of atorvastatin calcium, in agreement with the literature [23]. The PXRD pattern of succinic acid showed characteristic peaks at 2θ of 20.1, 26.3, 38.6 and 42.1°, also in agreement with the literature [19]. The PXRD pattern of atorvastatin calcium-succinic acid cocrystal showed the difference with the PXRD pattern of the initial components. The PXRD pattern of cocrystal has new crystalline peaks at 2θ values of 12.9° and 18.2°, and 26.7°. It indicated that atorvastatin calcium-succinic acid cocrystal has a different crystal lattice arrangement with the crystal lattice of atorvastatin calcium and succinic acid. Atorvastatin calcium-succinic acid cocrystal has a crystalline phase different from the initial components. It showed that atorvastatin calcium and succinic acid formed a new crystalline form with crystal lattice arranged by atorvastatin calcium and succinic acid [24-25].

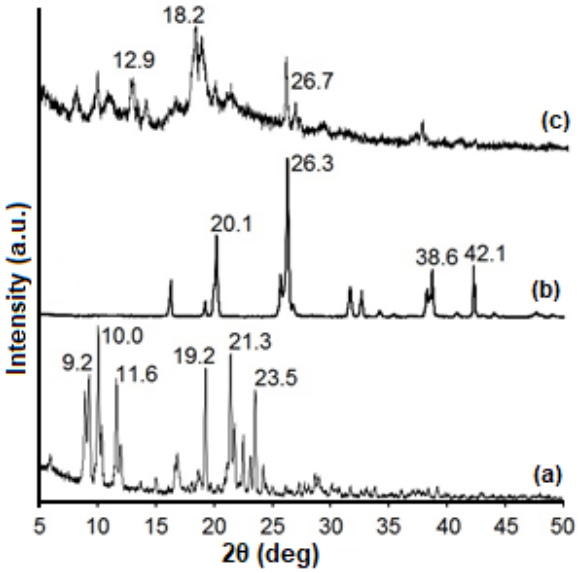

Fig 1. PXRD patterns of (a) atorvastatin calcium, (b) succinic acid and (c) atorvastatin calcium-succinic acid cocrystal

The diffraction peaks on the PXRD pattern of atorvastatin calcium-succinic acid cocrystal showed a weaker intensity than the intensity of the initial components. This indicates that the atorvastatin calcium-succinic acid cocrystal has lower crystallinity campared to the initial component [14]. The decrease of crystallinity is thought to be due to succinic acid in the cocrystal decreasing the ordering of crystal lattice of cocrystal. The lower ordered crystal lattice causes decreasing of crystallinity of cocrystal compared to the crystallinity of initial components [26].

Differential Scanning Calorimetry

DSC is the most commonly used thermal analysis method, especially since its implementation is relatively quick and easy. This technique is a powerful tool for the detection of new crystalline formation of materials and also for stability studies of crystalline materials as a function of temperature [22]. The cocrystal has a different melting point from initial materials which was suspected due to the influence of differences in the crystal lattice and packing arrangement [18,26]. Fig. 2 shows an overlay of the DSC thermogram of atorvastatin calcium, succinic acid, and atorvastatin calcium-succinic acid cocrystal.

The DSC thermogram of atorvastatin calcium showed a broad peak at 108.5 °C which depicts water loss and a sharp endothermic peak at 159.4 °C with an enthalpy of fusion value (ΔH_f) 35.9 J/g related to its melting point [27]. The DSC thermogram of succinic acid has a melting endothermic peak at 188.5 °C with an enthalpy of fusion value (ΔH_f) 328.6 J/g, in agreement with the literature [28]. The atorvastatin calcium-succinic acid cocrystal showed a melting at 205.7 °C with an enthalpy of fusion value (ΔH_f) 30.2 J/g. The broad endothermic peak at 160.1 °C in the DSC thermogram of cocrystal suspected as the melting point of atorvastatin calcium which is not formed cocrystal with succinic acid. The atorvastatin calcium-succinic acid cocrystal exhibited a melting point higher than the melting point of the initial components. This result indicated that the crystalline form of atorvastatin calcium-succinic acid cocrystal has higher stability compared to the initial components [29].

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy is a spectroscopic technique often used to analyze the interaction between molecules in the crystal lattice that accompanies the formation of new crystalline solids. In the FTIR spectra of cocrystals, the formation of a new crystalline phase is characterized by the shifts of the absorption peaks from the functional groups of the initial components which interacting in the hydrogen bond [10,30]. The FTIR spectra of atorvastatin calcium, succinic acid, and atorvastatin calcium-succinic acid cocrystal are presented in Fig. 3.

The FTIR spectra of the atorvastatin calcium showed characteristic absorption peaks at 3672 cm^{-1} due to free O-H stretching (belongs to the trihydrate functionality), 3364 cm^{-1} due to free N-H stretching, 3056 cm^{-1} due to O-H stretching, 2971 cm^{-1} due to C-H stretching, at 1651 cm^{-1} due to C=O stretching and 1216 cm^{-1} due to C-N stretching. The characteristic peaks of succinic acid occurred at 2931 cm^{-1} due to –O-H group (stretching-vibrations), 1690 cm^{-1} due to –C=O group, at 1419 cm^{-1} due to C-O-H (in-plane bending) and 1309 cm^{-1} due to C-O stretching vibration. The

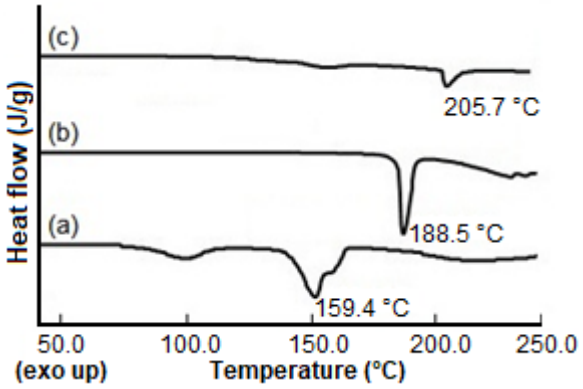

Fig 2. DSC thermograms of (a) atorvastatin calcium, (b) succinic acid and (c) atorvastatin calcium-succinic acid cocrystal

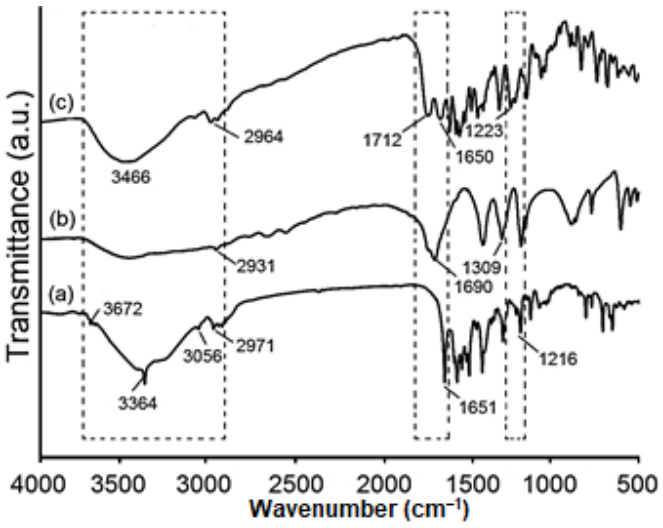

Fig 3. The FTIR spectra of (a) atorvastatin calcium, (b) succinic acid and (c) atorvastatin calcium-succinic acid cocrystal

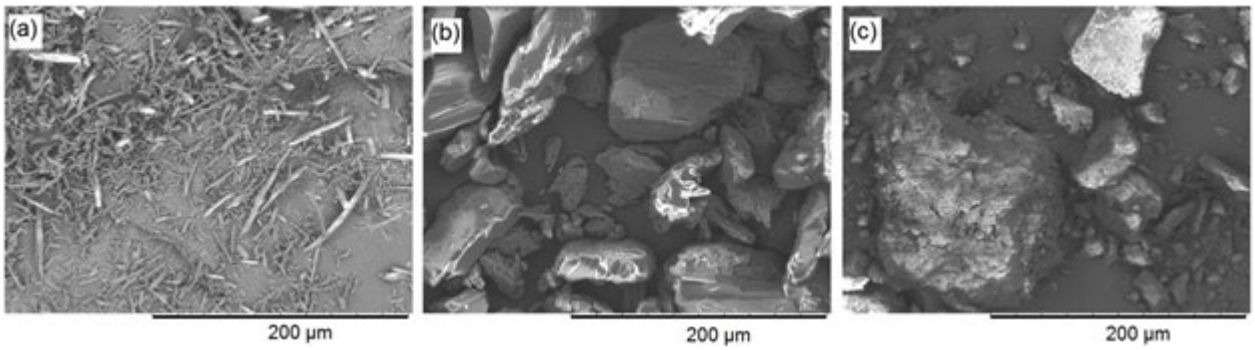

Fig 4. SEM images of (a) atorvastatin calcium, (b) succinic acid and (c) atorvastatin calcium-succinic acid cocrystal

atorvastatin calcium and succinic acid exhibited the FTIR spectra in correspondence with the literature [28,31].

The FTIR spectra of atorvastatin calcium-succinic acid cocrystal showed the shifting of absorption peaks compared to the FTIR spectra of the initial components. The absorption peaks of atorvastatin calcium-succinic acid cocrystal were showed the shifting of atorvastatin calcium groups at N-H stretching from 3364 to 3466 cm^{-1}, C-N stretching from 1216 to 1223 cm^{-1} and C=O stretching from 1651 to 1712 cm^{-1}. The absorption peaks of succinic acid were showed shifting from 1690 to 1712 cm^{-1} and 2931 to 2964 cm^{-1}. The shifting of absorption peaks of FTIR spectra of atorvastatin calcium-succinic acid cocrystal indicated appearance intermolecular hydrogen bond interactions between functional groups of atorvastatin calcium and succinic acid [28,32]. Based on the shift of the absorption peaks indicated the formation of atorvastatin calcium-succinic acid cocrystal through intermolecular hydrogen bond interactions as acid-amide heterosynthon. In addition to the FTIR spectra, the absorption peak of free O-H stretching was notfound in the FTIR spectra of atorvastatin calcium-succinic acid cocrystal. It indicated that the atorvastatin calcium-succinic acid cocrystal was an anhydrous crystalline form. Overall, the results of characterization by powder X-ray diffraction, differential scanning calorimetry, and Fourier transform infrared spectroscopy have indicated the formation of a novel cocrystal of atorvastatin calcium-succinic acid cocrystal.

Scanning Electron Microscopy

The SEM images of atorvastatin calcium, succinic acid, and atorvastatin calcium-succinic acid cocrystal are shown in Fig. 4. The atorvastatin calcium was showed rod-shaped particles with the size of length approximately about 30–100 µm, while the succinic acid was showed semi-spherical particles with the average sizes ranging from 20–100 µm. These results are in correspondence with previous literature [28,33].

The particles of atorvastatin calcium-succinic acid cocrystal were flaky structures with an irregular shape which the average sizes were ranging from 10 µm to several hundred microns. The particles of atorvastatin calcium-succinic acid cocrystal were demonstrated the difference in the morphology and size with the atorvastatin calcium and succinic acid as initial components. The change of the morphology can be caused by the interaction between atorvastatin calcium and succinic acid molecules, which results in the modification of the crystal faces of initial components and hence the crystal morphology [14]. The alteration of morphological characteristics was indicated by the formation of a new crystalline form of atorvastatin calcium-succinic acid cocrystal [10].

Solubility

The solubility of pure atorvastatin calcium and atorvastatin calcium-succinic acid cocrystal in distilled water was 170.86 ± 0.06 and 198.18 ± 0.79 mg/L, respectively. Atorvastatin calcium-succinic acid cocrystal showed a significant increase in solubility ($p < 0.05$) compared to pure atorvastatin calcium. Increasing solubility of cocrystal is often associated with the decrease of the ordered crystal lattice. The decrease of the

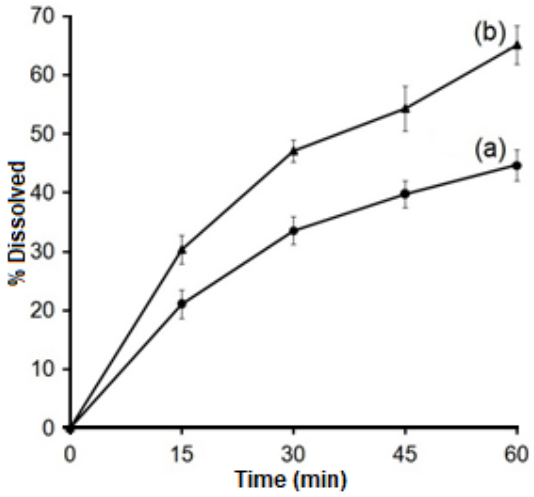

Fig 5. The dissolution profile in phosphate buffer pH 6.8 of (a) atorvastatin calcium and (b) atorvastatin calcium-succinic acid cocrystal (data are expressed as mean ± SD, $n = 3$)

ordered crystal lattice of cocrystal causes the reduction of packing efficiency in the crystal lattice, which is significantly increased aqueous solubility [26].

Dissolution Behavior

Dissolution is a process of the phase transformation from the solid phase to the liquid phase of solids in a solvent. It kinetics is determined by the thermodynamic equilibrium between the strength of the molecular bond in crystal packing of solid with the interaction energies of the solid to solvent. Cocrystal has the ability to increase the dissolution rate by reducing the energy of the crystal lattice or changing the solvent affinity [34]. The dissolution profile of atorvastatin calcium and atorvastatin calcium-succinicacid cocrystal in phosphate buffer pH 6.8 is presented in Fig. 5. The atorvastatin calcium-succinic acid cocrystal has a dissolution rate significantly higher than atorvastatin calcium ($p < 0.05$) atall time interval. The atorvastatin calcium dissolved only 33.6 ± 2.3% within 30 min; however, the atorvastatin calcium-succinic acid cocrystal has achieved dissolution of 47.1 ± 1.9% during the same period. At the end of the dissolution test, the percentage of drug release during the dissolution of atorvastatin calcium-succinic acid cocrystal increased approximately 1.5 fold compared to pure atorvastatin calcium.

■ CONCLUSION

Atorvastatin calcium-succinic acid cocrystal as a new form of atorvastatin calcium was successfully formed by solvent evaporation method. The results of characterization have indicated the formation of the new crystalline phase of atorvastatin calcium-succinic acid cocrystal. The cocrystal showed solubility and dissolution rate significantly higher than the initial components. Furthermore, this work provides insights into the improvement of physicochemical properties of the drug via the formation of cocrystal.

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■ REFERENCES

[1] Kadu, P.J., Kushare, S.S., Thacker, D.D., and Gattani, S.G., 2011, Enhancement of oral bioavailability of atorvastatin calcium by self-emulsifying drug delivery systems (SEDDS), *Pharm. Dev. Technol.*, 16 (1), 65–74.

[2] Gao, J., Guo, Y.H., Wang, Y.P., Wang, X.J., and Xiang, W.S., 2011, A novel and efficient route for the preparation of atorvastatin, *Chin. Chem. Lett.*, 22 (10), 1159–1162.

[3] Skorda, D., and Kontoyannis, C.G., 2008, Identification and quantitative determination of atorvastatin calcium polymorph in tablets using FT-Raman spectroscopy, *Talanta*, 74 (4), 1066–1070.

[4] An, S.G., Sohn, Y.T., 2009, Crystal forms of atorvastatin, *Arch. Pharmacal. Res.*, 32 (6), 933–936.

[5] Shayanfar, A., Ghavimi, H., Hamishekar, H., and Jouyban, A., 2013, Coamorphous atorvastatin calcium to improve its physicochemical and pharmacokinetic properties, *J. Pharm. Pharm. Sci.*, 16 (4), 577–587.

[6] Chadha, R., Kuhad, A., Arora, P., and Kishor, S., 2012, Characterisation and evaluation of

pharmaceutical solvates of atorvastatin calcium by thermoanalytical and spectroscopic studies, *Chem. Cent. J.*, 6 (1), 114.

[7] Kim, J.S., Kim, M.S., Park, H.J., Jin, S.J., Lee, S., and Hwang, S.J., 2008, Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using spray-drying and SAS process, *Int. J. Pharm.*, 359 (1-2), 211–219.

[8] Rao V.P.R., Somannavar, Y.S., Kumar N.S., Reddy, S.B., Islam, A., and Babu B.H., 2011, Preparation of stable new polymorphic form of atorvastatin calcium, *Pharm. Lett.*, 3 (5), 48–53.

[9] Wicaksono, Y., Setyawan, D., and Siswandono, 2017, Formation of ketoprofen-malonic acid cocrystal by solvent evaporation method, *Indones. J. Chem.*, 17 (2), 161–166.

[10] Ainurofiq, A., Mauludin, R., Mudhakir, D., and Soewandhi, S.N., 2018, Synthesis, characterization, and stability study of desloratadin multicomponent crystal formation, *Res. Pharm. Sci.*, 13 (2), 93–102.

[11] Wicaksono, Y., Wisudyaningsih, B., and Siswoyo, T.A., 2017, Enhancement of solubility and dissolution rate of atorvastatin calcium by co-crystallization, *Trop. J. Pharm. Res.*, 16 (7), 1497–1502.

[12] Tsutsumi, S., Iida, M., Tada, N., Kojima, T., Ikeda, Y., Moriwaki, T., Higashi, K., Moribe, K., and Yamamoto, K., 2011, Characterization and evaluation of miconazole salts and co-crystals for improved physicochemical properties, *Int. J. Pharm.*, 421 (2), 230–236.

[13] Surov, O., Volkova, T.V., Churakov, A.V., Proshin, A.N., Terekhova, I.V., and Perlovich, G.L., 2017, Cocrystal formation, crystal structure, solubility and permeability studies for novel 1,2,4-thiadiazole derivative as a potent neuroprotector, *Eur. J. Pharm. Sci.*, 109, 31–39.

[14] Moradiya, H., Islam, M.T., Woollam, G.R., Slipper, I.J., Halsey, S., Snowden, M.J., and Douroumis, D., 2014, Continuous co-crystallization for dissolution rate optimization of a poorly water-soluble drug, *Cryst. Growth Des.*, 14 (1), 189–198.

[15] Shevchenko, A., Bimbo, L.M., Miroshnyk, I., Haarala, J., Jelínková, K., Syrjänen, K., Veen, B., Kiesvaara, J. Santos, H.A., and Yliruusi, J., 2012, A new cocrystal and salts of itraconazole: Comparison of solid-state properties, stability and dissolution behavior, *Int. J. Pharm.*, 436 (1-2), 403–409.

[16] Zeng, Q.Z., Ouyang, J., Zhang, S., and Zhang, L., 2017, Structural characterization and dissolution profile of mycophenolic acid cocrystals, *Eur. J. Pharm. Sci.*, 102, 140–146.

[17] Chadha, R., Bhandari, S., Haneef, J., Khullar S., and Mandal, S., 2014, Cocrystals of telmisartan: Characterization, structure elucidation, in vivo and toxicity studies, *CrystEngComm*, 16 (36), 8375–8389.

[18] Qiao, N., Li, M., Schlindwein, W., Malek, N., Davies, A., and Trappitt, G., 2011, Pharmaceutical co-crystals: An overview, *Int. J. Pharm.*, 419 (1-2), 1–11.

[19] Félix-Sonda, B.C., Rivera-Islas, J., Herrera-Ruiz, D., Morales-Rojas, H., and Höpfl, H., 2013, Nitazoxanide cocrystals in combination with succinic, glutaric, and 2,5-dihydroxybenzoic acid, *Cryst. Growth Des.*, 14 (3), 1086–1102.

[20] Jung, S., Ha, J.M., and Kim, W.I., 2014, Phase transformation of adefovirdipivoxil/succinic acid cocrystals regulated by polymeric additives, *Polymers*, 6 (1), 1–11.

[21] Lahtinen, M., Kolehmainen, E., Haarala, J., and Shevchenko, A., 2013, Evidence of weak halogen bonding: New insights on itraconazole and its succinic acid cocrystal, *Cryst. Growth Des.*, 13 (1), 346–351.

[22] Pindelska, E., Sokal, A., and Kolodziejski, W., 2017, Pharmaceutical cocrystals, salts and polymorphs: Advanced characterization techniques, *Adv. Drug Delivery Rev.*, 117, 111–146.

[23] Shete, G., Puri, V., Kumar, L., and Bansal, A., 2010, Solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples, *AAPS PharmSciTech*, 11 (2), 598–609.

[24] Chadha, R., Bhalla, Y., Nandan, A., Chadha, K., and Karan, M., 2017, Chrysin cocrystals: Characterization and evaluation, *J. Pharm. Biomed. Anal.*, 134, 361–371.

[25] Sangeetha, M., and Mathammal, R., 2017, Establishment of the structural and enhanced physicochemical properties of the cocrystal-2-benzyl amino pyridine with oxalic acid, *J. Mol. Struct.*,1143, 192–203.

[26] Thomas, V.H., Bhattachar, S., Hitchingham, L., Zocharski, P., Naath, M., Surendran, N., Stoner, C.L., and El-Kattan, A., 2006, The road map to oral bioavailability: An industrial perspective, *Expert Opin. Drug Metab. Toxicol.*, 2 (4), 591–608.
Silva, E.P., Pereira, M.A.V., Lima, I.P.B., Lima, N.G.P.B., Barbosa, E.U., Aragao, C.F.S., and Gomes, A.P.B., 2016, Compatibility study between atorvastatin and excipients using DSC and FTIR, *J. Therm. Anal. Calorim.*, 123 (2), 433–439.

[27] Ober, C.A., and Gupta, R.B., 2012, Formation of itraconazole–succinic acid cocrystals by gas antisolvent cocrystallization, *AAPS PharmSciTech*, 13 (4), 1396–1406.

[28] Gao, Y., Gao, J., Liu, Z., Kan, H., Zu, H., Sun, W., Zhang, W., and Qian, S., 2012, Coformer selection based on degradation pathway of drugs: A case study of adefovirdipivoxil–saccharin and adefovirdipivoxil–nicotinamide cocrystals, *Int. J. Pharm.*, 438 (1-2), 327–335.

[29] Babu, N.J., Sanphui, P., and Nangia, A., 2012, Crystal engineering of stable temozolomide co-crystals, *Chem. Asian J.*, 7 (10), 2274–2285.

[30] Kim, M.S., Jin, S.J., Kim, J.S., Park, H.J., Song, H.S., Neubert, R.H.H., and Hwang, S.J., 2008, Preparation, characterization and in vivo evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process, *Eur. J. Pharm. Biopharm.*, 69 (2), 454–465.

[31] Hsu, P.C., Lin, H.L., Wang, S.L., and Lin, S.Y., 2012, Solid-state thermal behavior and stability studies of theophylline-citric acid co-crystals prepared by neat cogrinding or thermal treatment, *J. Solid State Chem.*, 192, 238–245.

[32] Jahan, R., Islam, M.S., Tanwir, A., and Chowdhury, J.A., 2013, In vitro dissolution study of atorvastatin binary solid dispersion, *J. Adv. Pharm. Technol. Res.*, 4 (1), 18–24.

[33] Thakuria, R., Delori, A., Jones, W., Lipert, M.P., Roy, L., and Rodríguez-Hornedo, N., 2013, Pharmaceutical co-crystals and poorly soluble drugs, *Int. J. Pharm.*, 453 (1), 101–125.