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Original Article

A SIMPLE EFFORT TO ENHANCE SOLUBILITY AND DISSOLUTION RATE OF SIMVASTATIN USING CO-CRYSTALLIZATION

IYAN SOPYAN[ab], ACHMAD FUDHOLI[a*], MUCHTARIDI MUCHTARIDI[c], IKA PUSPITASARI[a]

Departement of Pharmaceutical and Technolgy Formulation of University of Gadjah Mada, Yogyakarta 55281 and University of Padjadjaran, Bandung, Indonesia
Email: i.sopyan@unpad.ac.id

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ABSTRACT

Objective: The main objective of this study was to explore co-crystallization as an effort to enhance the solubility of simvastatin (SV) using tartaric acid (TA) as co-former.

Methods: The simulation of molecular modeling of TA against SV has been done by *in silico* using auto dock 4.2. A preparation of co-crystal carried out by using solvent drops grinding (SGD) with an equimolar ratio. A co-crystal formed was confirmed by scanning electron microscopy (SEM), saturated solubility test, *in vitro* dissolution test, infrared spectrophotometry (FTIR), powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC).

Results: The *in silico* studies showed that the interaction of TA and SV has synthon molecular by hydrogen bonding. An increasing of solubility and *in vitro* dissolution profile of co-crystal resulted as compared to the value of pure SV and its physical mixer. Characterizations of a co-crystal SV: TA (1: 1) including SEM, FTIR, PXRD, and DSC have indicated the formation of new solid crystal phase that different compared to SV, TA, and its physical mixture.

Conclusion: The co-crystallization has been used to enhance the solubility and dissolution of simvastatin. All characterization either *in silico* and *in vitro* has shown the formation of co-crystal SV: TA (1:1).

Keywords: Simvastatin, Co-crystal, Solubility, Dissolution

INTRODUCTION

A drug with good solubility properties will show better absorption and bioavailability. Almost 40% of the drug in the market exhibit a low solubility in water. It is causing the drug slowly to be absorbed. In addition, the levels of the drug in the blood lower than levels that should be [1]. In the pharmaceutical industry, the shortage of properties of biopharmaceutical drugs such as toxicity and less effective medication is 1% of the major cases in a market [2]. It is due to the nature of the solubility of the drug. The effectiveness of drug therapy highly depends on the level of drug in the blood, thus directly depends on the nature of drug solubility [3, 4]. Approximately 70% of drug candidates have problems with the solubility. It is a big challenge in the field of pharmaceuticals to developing drugs and drug dosage form to obtain a good profile of the solubility and dissolution rate, especially for oral dosage forms [4].

Base on biopharmaceutical classification system (BCS), drugs are classified into four classes, including drugs with low solubility problems, such as simvastatin (SV). SV (fig. 1) is the drug in the BCS class II. It has a problem with the low solubility of about 30 µg/ml and a bioavailability is only 5% [5, 6]. Several methods have been developed to increase the solubility of SV such as the technique of forming an inclusion complex of cyclodextrin [7], solid dispersion [8], an addition of a surfactant, particle size reduction by microemulsion [9,10], and supercritical antisolvent (SAS) [11]. These methods have lacked, such as using the number of matrices and the energy of the process is high. According to the knowledge of the researchers, co-crystallization has not been applied to increase the solubility of the SV.

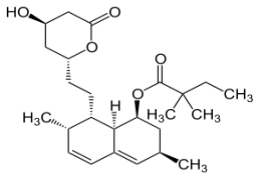

Fig. 1: Stucture of SV

The co-crystallization method is commonly used in the pharmaceutical field to change the features of the active pharmaceutical ingredients become a material with the desired properties [12]. Co-crystallization can generally be applied to acid, alkaline, neutral and ionic compounds [13]. Co-crystallization can improve the properties of the physiochemistry such as the level of solubility and the rate of dissolution using the simple technique [14, 15]. Co-crystal is complex solid compounds at room temperature. It is formed by two or more compounds with a co-former and connected by a synthon with certain of stoichiometry ratio [16, 17]. Synthon is a noncovalent interaction, including hydrogen bonds, Van der Walls and π-π electron [18-20]. The interaction of synthon can be predicted by *in silico* method. It is conducted to ensure the interactions of a active pharmaceutical ingredient (API) and co-former [21, 22].

Several techniques had been developed to synthesize co-crystal such as melting by using heat [23, 24], supercritical fluid (SFC) [25], slurrying assisted ultrasound [26], solvent evaporation, solid grinding [27], spray drying [28], liquid-assisted grinding (LAG) [29] and solvent drops grinding (SGD) [30]. An SGD is a co-crystal preparing method that employs a few chemical solvents, requires a less energy, having a good repeatability in the formation of crystals and could be used for a co-crystal screening [31]. In this project, we developed a simple method of co-crystallization in the terms procedures, process and it is also able to produce an increased solubility of API up to fifty times as much as previous studies [25]. In this work, we use a simple *in silico* method as a tool to ensure SV and TA interactions, especially for hydrogen bonds in the co-crystal form.

MATERIALS AND METHODS

Molecular docking simulation

The 3D-chemical structures of the SV and TA were designed using Hyperchem 7.0 (Ref) and energy minimization by MM+. Furthermore, the compound conformations were produced using the Discovery Studio 2.5 with CATALYST finest conformation module. CHARMM forced field was applied for energy optimization. The resulting compounds which had higher than 20 kcal/mol as compared to the

global minimum of conformation l minimum were refused, The utmost number of conformations was adjusted to 255 [32]. Docking simulations of the molecules were conducted using AutoDock 4.2 [33]. The AutoDockTools (ADT) script was employed to transform the ligand PDB to the pdbq format with adding Gasteiger charges, inspecting polar hydrogens and setting ligand flexibility.

Synthesis of co-crystal

Accurately weighed simvastatin (purity>99%, Teva, Belgium) and TA (Merck, Germany) equivalent to a molar ratio (1: 1), afterwards carried by grinding of the mixture of SV and TA assisted by methanol pro analysis (Merck, Germany) as solvent for 10 min, later stored in a water bath at 30 °C for 24 h.

Characterization of co-crystal

Scanning electron microscopy (SEM)

The surface of morphology of the samples was analyzed using a scanning electron microscopy SEM analytis (JSM6360A, JEOL, USA), Samples were measured with a double-faced adhesive tape, sputtered with platinum. Scanning electron photographs were taken at an accelerating voltage of 5 kV.

Saturated solubilty studies

Accurately weighed of dried co-crystal equivalently to SV 100 mg, then input into vial and reconstituted with 50 ml of distilled water, later shaken for 24 h using an agitator shaker, afterward calculate the amount of SV was dissolved by validated spectrophotometric Uv-Vis method using Spectrophotometry UV-Vis (Analytical Zena, Germany). The same way was done for pure SV, and a physical mixture of SV: TA (1:1).

***In vitro* dissolution studies**

The *in vitro* release behaviors of the SV and its co-crystals were measured using a dissolution tester (USP type two paddle apparatus). A typical experiment equal consisted of 40 mg crystal powders SV in a 900 ml simulated intestinal fluid (less enzyme) pH 6,8, stirred at 100 rpm. Sampling (5 ml) was done until 60 min at pre-determined time points, and a fresh 5 ml SIF solution was added into the system after each sampling. Each sampled solution was filtered through a syringe filter of 0.45 µm pore size, and its UV absorbance were measured at 240 nm. A concentration of the SV was calculated using a validated pre-constructed calibration curve.

Powder x-ray diffraction (PXRD)

The powder X-ray diffractometer (X Philips Analytical PW1710, Germany) patterns were collected using Cu Ka radiation (l = 1.54 Å), a tube voltage of 40 kV and a tube current of 40 mA. Data were collected from 2 Θ angle 5 ° to 48 ° at a continuous scan rate of 4 °/minute.

FT-IR spectrophotometry

Samples in the form of powder mixed with potassium bromide crystal with the molar ratio (1:10) and crushed until homogeneous and then compressed to a pressure of 20 psi. The spectra were analyzed over a range of wavenumbers 4000-400 cm^{-1} using FT-IR (Specord 200, Germany)

Differential scanning calorimetry (DSC)

The thermal analysis was performed on a DSC/TGA apparatus (Linseis PTA ST 1600, USA) that was calibrated for temperature and cell constants using indium. Samples (1–3 mg) crimped in the aluminum pan were analyzed from 50 °C to 300 °C with a heating rate of 10 °C/min. Samples were continuously purged with nitrogen at 50 ml/min.

RESULTS AND DISSCUSION

***In silico* modeling**

An *In silico* studies by molecular modeling (fig. 2) has been employed as a simple tool to make sure the hydrogen bonding interactions of the SV-TA [21]. The lowest Gibbs-free energy of molecule conformation was-1,8 kcal/mol. The negative value indicates SV and TA interactions has occurred. The interaction type of the SV and TA is the hydrogen bond with bond distances 2, 27 Å. It is indicated a very close bond and allow hydrogen bonds.

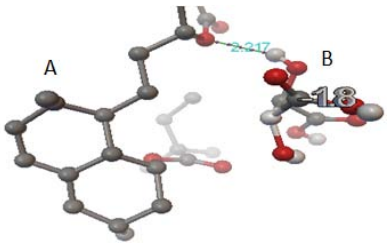

Fig. 2: *In silico* interaction model of (A) SV and (B) TA

An SV has a lactone group that contains a carbonyl, ether, and hydroxyl groups. TA has carboxylic acid and hydroxyl groups. Therefore, both of compounds could be as hydrogen donor and acceptor for hydrogen bonds. Analysis of molecular structure to design a co-crystal is very important to predict a synthon [34].

Preparation of co-crystal SV: TA (1:1)

A preparation of co-crystal had been carried out by SGD. It is done because SGD method was more effective and environmentally friendly [30, 35]. SGD method was also reliable for the discovery of a new co-crystal when a presence of a small amount of the liquid phase can improve the rate of co-crystal formation [36]. Photo of SEM (fig. 3) had revealed a comparison of particle size and surface morphology of pure SV and its co-crystal. The co-crystal of SV-TA (1:1) had displayed a more compact structure with a higher density. It was due to the interaction of hydrogen bonding of the SV and TA in co-crystal form. As we knew, a hydrogen bonding has a dominant role in the intermolecular interaction of co-crystallization [37].

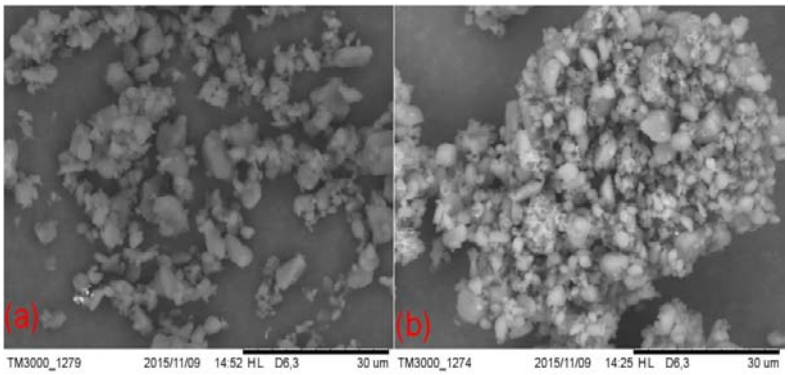

Fig. 3: Photo of SEM (a) pure SV and (b) co-crystal SV-TA (1:1)

Evaluation of co-crystal of SV-TA (1:1)

Saturated solubilty studies

Test of saturated solubility has conducted to the SV, a physical mixture of SV-TA and co-crystal SV-TA (1:1) (fig. 4). Evaluation of the saturated solubility of co-crystal SV-TA (1:1) has shown an increase up to 2.4 fold as compared to the physical mixture and SV. It is due to an affinity of the solvent against SV was more intense and another factor was a decrease in energy of crystal lattice by co-crystal formation [38, 39].

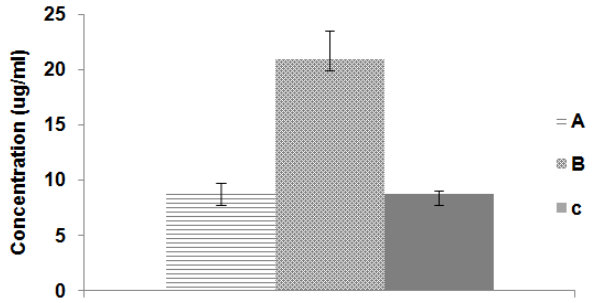

Fig. 4: Saturated solubility profiles (A) pure SV, (B) co-crystal SV: TA (1:1) and (C) physical mixture SV: TA (n=6)

***In vitro* dissolution studies**

In vitro dissolution studies had been carried out to pure SV and co-crystal SV-TA 1: 1 (fig. 5). The dissolution profile of co-crystal SV-TA (1:1) has shown the increasing approximately twofold compared to the dissolution profile of the pure SV in 60 min. The Increasing of dissolution rate was correlated with a function of surface area, a diffusion constant, boundary-layer thickness as well as solubility [40]. SGD also could modify the diffusion of a molecule of the API by affecting the hydrodynamic properties and to influence the release behavior of the API [41].

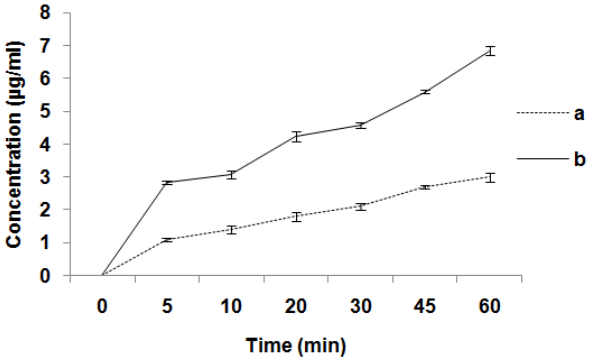

Fig. 5: Dissolution profile of (a) SV and (b) co-crystal SV: TA (1:1) (n=6)

FT-IR studies

FT-IR analysis of co-crystal was employed to determine the hydrogen bonding between the SV and TA (fig. 6). The spectrum overlay of pure SV, TA and co-crystal SV-TA (1:1) has exhibited the tape widening of the co-crystal absorption band at 3600-3200 cm^{-1}. It is specific for intermolecular hydrogen bonding. The characteristic peak absorption of an SV was found at 3,545 cm^{-1}(free O-H stretch), 2,970 cm^{-1} (methyl C-H asymmetric stretch), 1,695 cm^{-1} (ester C=O stretch, associated), 1,265 cm^{-1}(l-C-O-C stretch) [42]. In co-crystal form, the peaks of a SV were not prone and intensively also reduced.

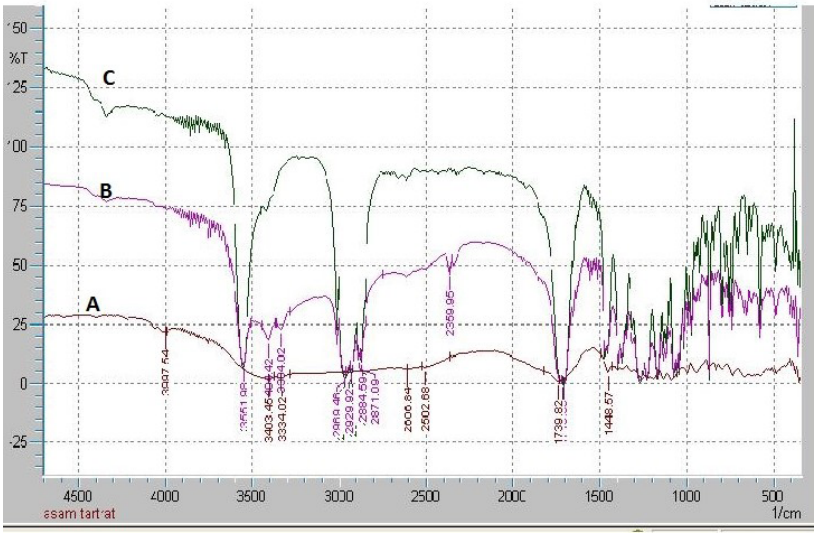

Fig. 6: FT-IR spectrum (a) TA, (b) co-crystal SV: TA (1:1) and (c) pure SV

The absorption band of free OH will be observed at the wavenumber 3500 cm^{-1}. A widening of OH peak on wavenumber 3500 cm^{-1} was due to the interaction of hydrogen bonding of co-crystal SV–TA 1:1.

PXRD evaluation

A PXRD had performed to define the crystallinity of co-crystal of SV: TA (1:1) as compared to SV and its physical mixture. The overlay of diffractogram has showen distinct peaks and intensity at an angle 2Θ: 11 °, 35-37 °, and 39-41 °. A Powder x-ray diffraction is a specific technique to confirm the new solid state. All crystal forms of a compound have produced its own characteristic X-Ray diffraction pattern [43]. The difference of peaks indicates the formation of new solid crystalline phases [44] and it also allows for differences physiochemistry properties between co-crystal, pure SV, and TA.

Thermal analysis

The DSC studies can be used to observe of co-crystal formation from the difference in melting point of co-crystal as compared to its own

constituent via the endotherm phase [45]. Thermogram (fig. 7) had revealed the melting point (endotherm phase) of co-crystal SV-TA (67 °C)<pure SV (133 °C). The enthalpy of SV (87 Joule/g)>co-crystal SV-TA 1:1 (67,2 Joule/g). A decrease in melting point and heat content of co-crystal will directly correlate to increased solubility of API in the co-crystal. The melting point co-crystal will fall between melting point API and its co-former [2, 15]. We could predict to desire physiochemistry of co-crystal by a polarity of co-former [45].

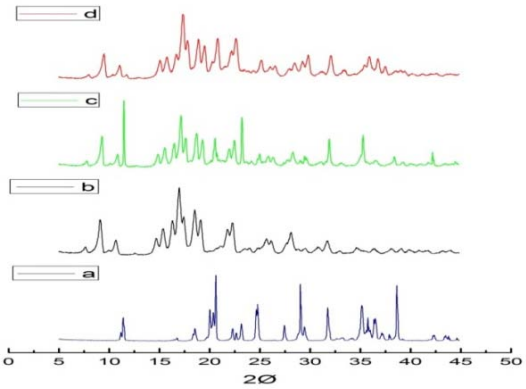

Fig. 7: Diffractogram of (a) TA, (b) SV, (c) physical mixture SV-TA and (d) co-crystal SV-TA (1:1)

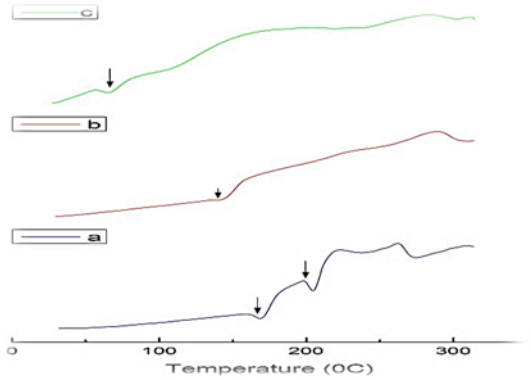

Fig. 8: Diffractogram pattern of (A) physical mixture SV: TA (1:1), (b) pure SV, and (c) co-cystal SV: TA (1:1)

CONCLUSION

Preparation of co-crystal SV with co-former TA (1:1) had been done with solvent drops grinding. The saturated solubility and *in vitro* dissolution evaluation of co-crystal SV: TA (1:1) had exhibited the rate of solubility and release behavior of co-crystal SV-TA (1: 1) increased significantly compared to pure SV. All confirmations against co-crystal SV: TA (1:1) had indicated the formation new solid crystalline phases that differ from SV, TA, and its physical mixture. Overall any linear correlation of *in silico* and *in vitro* evaluation.

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ABBREVIATION

SV-Simvastatin, TA-Tartaric Acid, API-Active Pharmaceutical Excipient, SGD-Solvent Drops Grinding, DSC-Differential Scanning Calorimetry, SEM-Scanning Electrons Microscopy, FT-IR-fourier Transform Infra Red Spetroscopy, PXRD-Powder X-ray Diffraction.

CONFLICT OF INTERESTS

Declared none

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