IMPROVEMENT OF SIMVASTATIN DISSOLUTION RATE USING DERIVATIVE NON-COVALENT APPROACH BY SOLVENT DROP GRINDING METHOD

IYAN SOPYAN[1,2], INSAN SUNAN KURNIWAN SYAH[1], DESI NURHAYTI[1], ARIF BUDIMAN[1]

[1]Departement of Pharmaceutics and Technology of Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia, [2]Pusdi Drug Delivery and Disposition, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia
Emai: i.sopyan@unpad.ac.id

ABSTRACT

Objective: This study aimed to enhance the solubility of simvastatin using noncovalent derivatives (NCDs) with oxalic acid (OA), fumaric acid (AF), and nicotinamide (NK) as conformers.

Methods: NCDs were prepared using by a solvent drop grinding (SDG). The NCDs formed were evaluated for saturated solubility test, NCDs with the highest saturation solubility were then characterized by Fourier transform infrared spectrophotometry (FT-IR), differential scanning calorimeter (DSC), powder x-ray diffractometry (PXRD) and the particulate dissolution using type II of USP test.

Results: SV-OA NCDs showed the highest solubility; thus NCDS of SV-OA were characterized by X-ray diffraction showing a new peak at 2θ = 28.96 °C and differential scanning calorimeter showed a change of endothermic peak from 134.3 °C to 69 °C. Infrared spectroscopy indicated that there were no functional group changes from simvastatin, while the dissolution rate increased from 68.22% to 76.08%.

Conclusion: SV-OA NCDs show an increased profile of solubility and dissolution compared to pure simvastatin.

Keywords: Simvastatin, Non-covalent derivative, Solvent drop grinding, Dissolution

INTRODUCTION

Biological availability is a rate value and the quantity of the drug that reaches the blood circulation. Solubility is an important factor in predicting the bioavailability of drugs in blood circulation. Often, drugs that have poor solubility in water also show low bioavailability, so the dissolution rate is the rate-limiting step in the absorption process of drugs in the body. The solubility of a drug is related to its physicochemical properties [1, 2].

Simvastatin is a drug that inhibits the action of the HMG-CoA reductase enzyme, thereby helping to reduce cholesterol levels in the blood. Based on the results of the Scandinavian Simvastatin Survival Study (4S) and The Heart Protect Study (HPS), simvastatin can reduce the incidence of ischemic stroke, myocardial infarction, and death in cardiovascular patients with atherosclerosis and hypercholesterolemia [3].

Based on the Biopharmaceutical Classification System (BCS), simvastatin is a class II drug group that has low water solubility but high permeability. High solubility can increase the bioavailability of drugs, so solubility is a determining factor in the quantity of the drug reaching the systemic circulation system [4]. Therefore, efforts should be made to increase the solubility of simvastatin to increase its bioavailability.

There are various ways to increase the speed of testing, the rate of dissolution or solubility of a drug, including the pro-drug approach, salt form synthesis, particle size reduction, complex formation, physical shape changes, solid dispersion, spray drying, and hot-melt extrusion. One technique with physical shape changes in the formation of co-crystalline techniques which causes changes in the arrangement of the molecules making up the crystal is caused by the formation of hydrogen bonds between the active substance and the co-former. Changes in the crystal lattice will cause increased changes in solubility [5]. In this study, an effort to increase the rate of dissolution of simvastatin will be investigated using oxalic acid, fumaric acid and nicotinamide as a coformer with a noncovalent derivative approach.

MATERIALS AND METHODS

Tools

Spectrophotometer UV-Vis (Specord 200), mechanic agitator (Ohm), Spectrophotometer FTIR (Specord), dissolution tester (Sotax AT7), X-Ray Diffractometer (Philips PW 1835), Differential Scanning Calorimetry (Pan analytical).

Materials

The following materials were used: simvastatin (98%, Teva, Belgium), nicotinamide (Sigma Aldrich), fumaric acid (Sigma Aldrich), oxalic acid (Merck), methanol (Merck), sodium dodecyl sulfate (Merck), sodium phosphate (Merck), and sodium hydroxide (Merck).

Methods

Production of simvastatin NCDs by the solvent drop grinding method

Simvastatin (SV) was mixed in a 1:1 ratio with nicotinamide (NK), oxalic acid (AO), or fumaric acid (AF) in a mortar and then crushed for 20 min with the dropwise addition of methanol.

Saturated solubility test

The equivalent to 20 mg simvastatin was dissolved with 10 ml aquades in an Erlenmeyer, placed in a mechanical agitator for 48 h at room temperature (25 °C) and then the saturated solubility was measured by UV spectrophotometry in the wavelength range of 247–257 nm [6].

Characterization of NCDs

X-ray diffraction analysis

The crystal structure was analyzed using a Powder X-Ray Diffractometer (Philips PW 1835), with the following conditions: target/filter (monochromator) Cu, voltage 40 kV, current 30 mA, slit width of 0.2 inches, with a scanning speed of 0.2–0.5 °/min and scanning distance 2θ = 5–60 ° [6].

Fourier-transform infrared spectroscopy (FTIR)

Powder-shaped samples were mixed with potassium bromide crystals at a molar ratio of 1:10 and crushed until homogeneous, then compressed with a pressure of 20 Psi using a KBr plate press. Spectra were measured in the range of 4000–400 cm^{-1} using a FTIR spectrophotometer [6].

Differential scanning calorimetry (DSC)

A sample of 3–5 mg was placed in the device programmed in a temperature range of 50–350 °C with a heating speed of 10 °C/min [6].

Dissolution test

The dissolution rate test was conducted based on USP30-NF25 using Apparatus 2 (paddle) with a speed of 50 rpm for 30 min and 900 ml media buffer solution pH 7 at 37±0.2 °C. Periodically every 10 min, 5 ml was sampled and the media replaced with the same volume during the test. Samples were then measured using UV spectrophotometry in the wavelength range of 247–257 nm to calculate the dissolution rate [6].

RESULTS AND DISCUSSION

Production of simvastatin NCDs by the solvent drop grinding method

Simvastatin co-crystals are made using the solvent drop grinding (SDG) method. This method is used because it requires only a few solvents where the solvent is dropped during grinding so it is more cost-effective and more environmentally friendly than the solution-based method [7]. Co-crystals are made by mixing simvastatin with co-former using a 1: 1 equimolar ratio (table 1). The comparison used refers to some previous research journals and theses that report the best results of NCDs formed with a 1: 1 equlmolar ratio [8, 9]. Co-former is used to help the formation of simvastatin co-crystals where the ethanol solvent functions as a catalyst. The active and co-former substances must have a number of donors and hydrogen bond acceptors. This hydrogen bond is an important bond in the formation of NCDs because the more hydrogen bonds, the solubility of a substance will increase. Another requirement of the co-former is that it must be pharmacologically acceptable, non-toxic and pharmacologically inert and can be easily dissolved in water. Three co-former used in this study fulfills these requirements. In addition, these three co-formers were reported to be proven to form co-crystals through hydrogen bonds [5, 8, 9, 11, 12]. In the process of making NCDs, weight loss ranges from 16-20%. Losses occur because there is material left behind at the time of final weighing after grinding.

Table 1: Comparison of simvastatin and co-former weights

API: co-former	Molar comparison	Weight comparison (mg)
SV: NK	1:1	100: 29
SV: AF	1:1	100: 22
SV: AO	1:1	100: 24

Number of experiment (n=3)

Solubility test results

The solubility test was conducted on simvastatin and the simvastatin NCDs with the three co-formers, namely nicotinamide, fumaric acid and oxalic acid. The solubility test was conducted to determine the effect of the co-former which gave the highest increase in the solubility of the three co-formers used. From the solubility test results, the co-former which formed the highest solubility was oxalic acid (3 ppm; fig. 1)**.**

NCDs characterization

Powder X-ray diffraction

The results of X-ray diffraction showed the formation of a new peak on the diffractogram at 2θ at 28.96°. Changes in diffraction patterns and the formation of new peaks on diffractograms indicate the formation of NCDs [13].

FT-IR spectrophotometric analysis

Infrared spectroscopy tests were performed on standard simvastatin, oxalic acid, and simvastatin co-crystals. Infrared spectroscopy is often used to detect interactions between drugs and coformer in NCDs. Infrared spectroscopy can detect cocrystal formations, as seen from the presence of hydrogen bonds. Cocrystallization between simvastatin with oxalic acid causes complexation between the two.

The interaction between the two substances is linked by hydrogen bonds. Hydrogen bonds are formed due to the presence of a carbonyl group from simvastatin which will bind to the hydroxy group on oxalic acid. The hydrogen bonding spectrum will appear at wavenumbers 3600-3200 cm^{-1} [14].

Based on the results of the infrared absorption spectrum, the interaction of hydrogen bonds between simvastatin and oxalic acid was evident as the absorption band C=O ester of the standard simvastatin at 1700.32 cm^{-1} shifted to 1704.18 cm^{-1} on the simvastatin co-crystals. This indicates that the expected hydrogen bonds have form3ed in the NCDs. Electronegative elements tend to attract electrons in between the carbon and oxygen atoms in the C=O bond, so that the bond becomes stronger; therefore the vibration band C=O bonds appear at higher frequencies [13]. From the shape of the spectrum image, it is evident that there is no change in the functional group of simvastatin.

Differential scanning calorimetry

The formation of physical interactions between two materials can be estimated using thermal analysis [14] if there is a change in the shape of the crystals, there will be changes in the thermodynamic aspects of a solid [15]. Screening the formation of physical interactions between simvastatin and oxalic acid was detected by DSC, as shown in fig. 4.
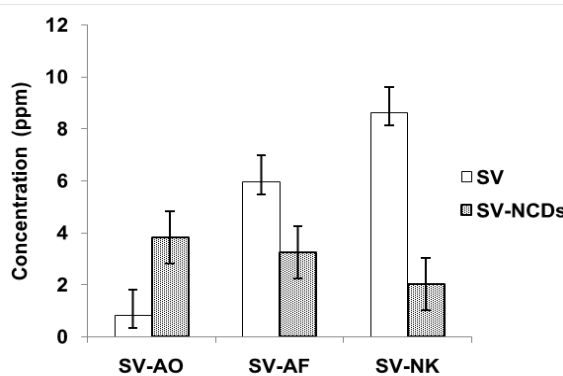

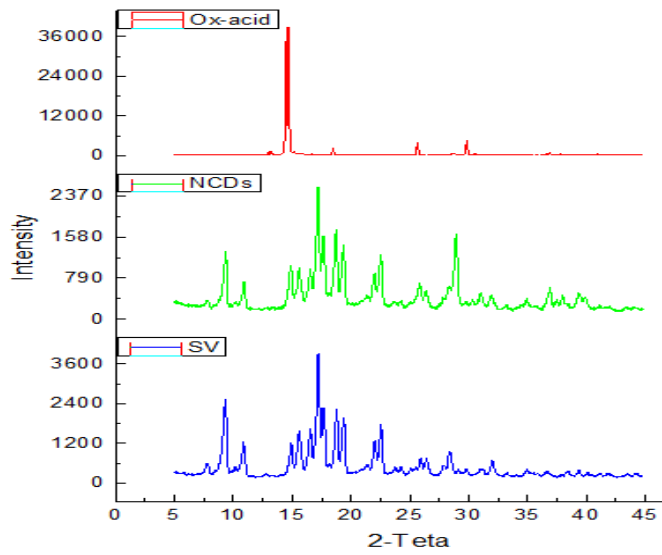Fig. 1: Solubility of SV and SV-NCDs (n=3)

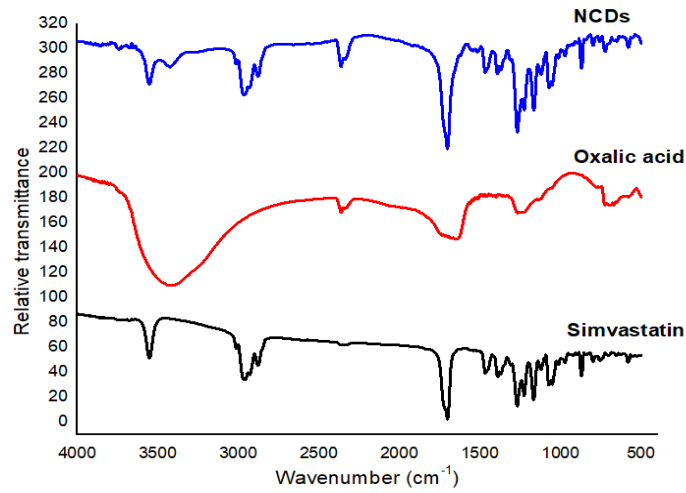**Fig. 2: X-ray diffractogram of SV, NCDs (SV-OXA), and oxalic acid (n=3)**

Fig. 3: Infrared spectrum overlay cocrystalline simvastatin (purple) with standard simvastatin (black)
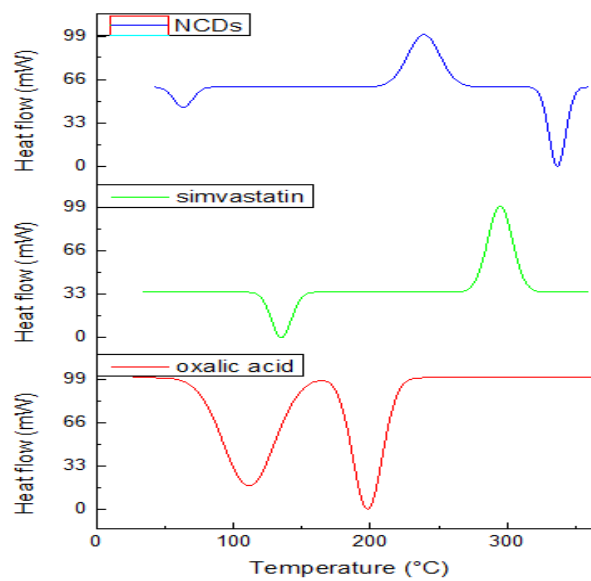

Fig. 4: Thermogram overlay of simvastatin, NCDs, oxalic acid

The standard simvastatin thermogram shows an endothermic peak, which is the melting process of crystal solids with an onset temperature of 120.8 °C, maximum peak at 134.3 °C and enthalpy of-105.68 J/g. The oxalic acid thermogram showed an endothermic peak with an onset temperature of 68.8 °C, maximum peak at 111.2 °C and enthalpy of-689.77 J/g. The co-crystal thermogram shows an endothermic peak with an onset temperature of 48.0 °C, maximum peak at 62.9 °C and enthalpy of-232.35 J/g. Changes in the values of the maximum onset, peak temperatures and enthalpy values show the different characteristics of standard simvastatin, co-former oxalic acid and the resulting NCDs. It appears that there is a decrease in the value of the onset temperature, the maximum peak and the enthalpy value, indicating that NCDs require less heat than the standard simvastatin (1).

Dissolution rate test

The dissolution rate was measured by the amount of active substance dissolved in a certain time in a known volume of the liquid medium at a relatively constant temperature to determine how much standard simvastatin and NCDs were dissolved in a certain condition. There was an increase in the dissolution rate of standard simvastatin with NCDs of 3.14% at the 10th minute; 5.53% at 20 min and 7.86% at 30 min [16, 17].
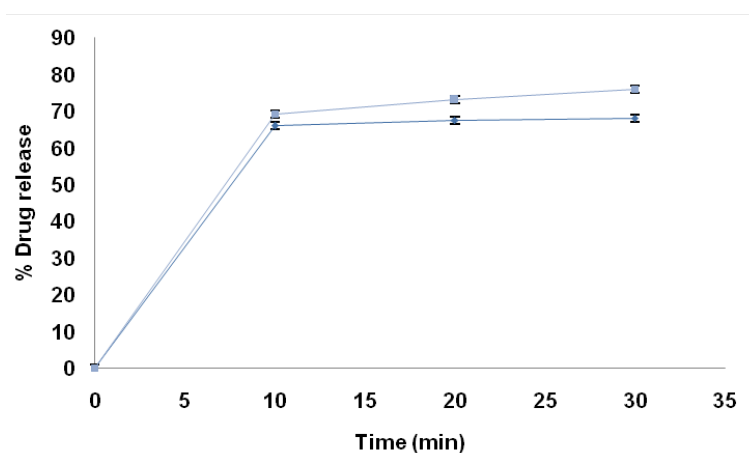

Fig. 5: Dissolution profile of simvastatin (■) and NCDs (▲) (n=3)

CONCLUSION

Simvastatin crystals were prepared using the SDG method. Characterization of the crystals by X-ray diffraction revealed a new peak on the diffractogram at 2θ = 28.96 ° and differential scanning calorimetry showed changes in the endothermic peak from 134.3 °C to 62.9 °C, while IR spectroscopy showed that there was no change in the functional group of simvastatin. The solubility test results showed the highest increase in solubility was achieved by co-crystals formed by oxalic acid (3 ppm) and the dissolution rate increased from 68.22% to 76.08%. Further research is needed to test the bioavailability and stability of the resulting co-crystals, as well as investigate other methods and co-formers to produce co-crystals that have the best solubility.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

No conflict of interest declared in this research

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