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POLYMORPHISM OF SIMVASTATIN: AN EFFORT TO REPAIR SOLUBILITY AND DISSOLUTION RATE

Iyan Sopyan*, Thachaiyini Pallanisamy and Yoga Windhu Wardhana

Department of Pharmaceutics and Technology of Pharmacy and Pusdi Drugs Delivery and Drugs Disposition, Faculty of Pharmacy, Universitas Padjadjaran.

***Corresponding Author: Iyan Sopyan**
Department of Pharmaceutics and Technology of Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran.

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ABSTRACT

Objective: Simvastatin (SV) is most commonly used as a hypercholesterolemia drug, although it is poorly soluble in water and poorly absorbed by the gastrointestinal tract and has a bioavailability approaching 5%. This study tried to improve the solubility and dissolution rate of simvastatin through the evaporation solvent method. **Methods**: The evaporation solvent method has used the variation of solvent purification (recrystallization) of simvastatin compound. A difference of solvent would be formedsimvastatin a different crystal habit after being recrystallized. This study used a variation of equimolar mixed solvent methanol: ethanol (B), methanol: chloroform (C), and ethanol: chloroform (D). A Crystals that obtained from the purification are characterized by a solubility test, powder x-ray diffraction, and Fourier transforms infrared spectroscopy. **Results**: Powder X-ray diffraction results showed a significant difference compared to the diffractogram standard simvastatin, while the results of Fourier infrared spectroscopy transform showed no significant difference. Solubility test results obtained by an increase in solubility compared with the standard initial simvastatin (A). The dissolution test results showed an increase in dissolution rate at pH 1.2, 4.5, and 6.8 significantly compared to the standard simvastatin. **Conclusion**: Crystal modification using recrystallized by a mixture of solvents represented the modification results showed an increase in the solubility and dissolution test.

KEYWORDS: Simvastatin crystal, solubility, dissolution. Polymorpism.

INTRODUCTION

Among the hypercholesterolemia drugs, SV is the most commonly used, though it not very soluble in water and is poorly absorbed in the gastrointestinal tract. SV works by the mechanism of inhibition of the enzyme HMG-CoA reductase (Graeser, *et al.*, 20008; Vargas, *et al.*, 2013). SV has a stable crystalline form, does not have the type of hydrates. SV crystals are soluble and have a low bioavailability less than 5% (Murtaza, 2012). Crystal modification is one of the ways to improve the solubility, dissolution rate, and bioavailability of a drug, especially the drugs that have more than one polymorphic crystal forms (Graeser, *et al.*, 20008; Hušák *et al.*, 2010). Crystals with higher free energy will have a problem with solubility. This is ude to molecules in crystals with high energy have weaker solid-solid interactions and higher affinity for the solvent in the environments equated to crystals with lower free energy (Hušák *et al.*, 2010; Byrn, 2010). A crystalline drug can have different polymorphic forms if it's crystallized under various conditions such as different of the polarity solvent. Recrystallization is a straight forward method that can be done to convert a compound into its polymorph and it can make different physical properties, such as solubility and dissolution characteristics. (Lyn, *et al.*, 2011).

The present study has been designed to improve the solubility and dissolution rate of SV by crystal modification technique using recrystallization with different solvent mixtures. The habit of the crystal can be affected by the crystallization process via factors such as polarity of the solvent used in crystallization (Martínez-Ohárriz, *et al.*, 1999). The urgency of this study was to obtain SV crystals with better physicochemical properties of solubility and dissolution, thereby increasing the therapeutic effectiveness of SV and its dosage forms.

MATERIALS AND METHODS

Materials

Simvastatin (Teva purity >98%), methanol (Merck), ethanol (Merck), chloroform (Merck), sodium hydroxide (Bratachem), hydrochloric acid, sodium acetate and sodium phosphate Instrumentations.

Spectrophotometer UV-Vis (Specoord 200, Analytical Jena), powder X-ray diffractometer (X Philips Analytical PW1710, Germany), FT-IR (Specord 200, IR-Prestige,

Germany), dissolution tester (Sotax, USP type two paddle apparatus).

Methods

Manufacture of crystal polymorph simvastatin with method solvent evaporation.

Simvastatin is modified by the way where it dissolved in the following solvent mixture; methanol-ethanol, methanol-chloroform or ethanol-chloroform at room temperature, 25^0C. In this case, the solvents used are methanol, ethanol, and chloroform, ethanol and chloroform is a solvent that listed on the monograph. After simvastatin dissolved, the solution was left at room temperature until the solvent is evaporated entirely, and crystals are thoroughly dried.

Characterization of Crystalline simvastatin

Solubility test

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 validated spectrophotometry UV-Vis (Analytical Jena).

Powder x-ray diffraction Examination

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 2Θ angle 5° to 48 ° at a continuous scan rate of 4 °/minute.

FT-IR Analysis

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

Dissolution test of simvastatin crystal with pH 1.2, 4.5, and 6.8

The in vitro release behaviors of the SV and Modified SV crystal were measured using a dissolution tester (USP type two paddle apparatus). A typical experiment equal consisted of 40 mg powders SV in a 900-ml simulated intestinal fluid (less enzyme) pH 1.2 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 to the system after each sampling. Each sampled solution was filtered through a syringe filter of 0.45 µM pore size, and its UV absorbance was determined at 240 nm [Rao *et al*., 2010]. Concentration was calculated using a validated pre-constructed calibration curve. The same procedure was performed for dissolution SV and modified SV with pH 4.5 and 6.8 accordance (USP 36).

RESULTS AND DISCUSION

Crystal modification of simvastatin

The results showed that the modified simvastatin crystal look (visible) more rugged and solid. Simvastatin without modification has a smaller particle size so that the crystal is more smooth and short. Meanwhile, modified simvastatin has larger particle sizes. This can be seen through the physical appearance of each of the crystal.

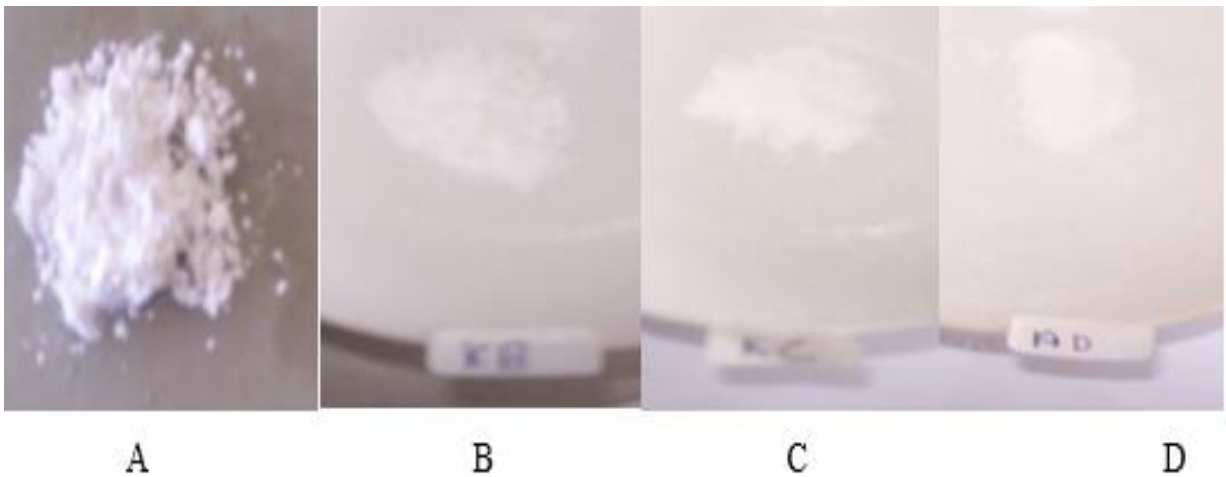

Figure 1: Results of modifications of simvastatin crystals: A (simvastatin without modification), B (methanol: ethanol), C (methanol: chloroform), and D (ethanol: chloroform).

Characterization of Simvastatin crystal

Solubility test

Solubility test results of simvastatin without modification (A) and modified simvastatin crystal with a mixture of solvent, a crystal of B with solvent methanol; ethanol, a crystal of C with methanol; chloroform, and crystal of D with ethanol; chloroform. Modified simvastatin crystals showed an increase in solubility in water than the simvastatin without modification. Simvastatin exhibits the solubility of 0.333 mg/l in distilled water. Crystal of C showed the highest solubility, 0.735 mg/l (120.72 % increase compared with simvastatin without

modification). Crystal of D shows the second highest solubility, 0.711 mg/ l (113.51 % increase compared to simvastatin). Crystal of B shows the solubility of crystals as much as 0.570 mg/l and incensement of 71.17 %.

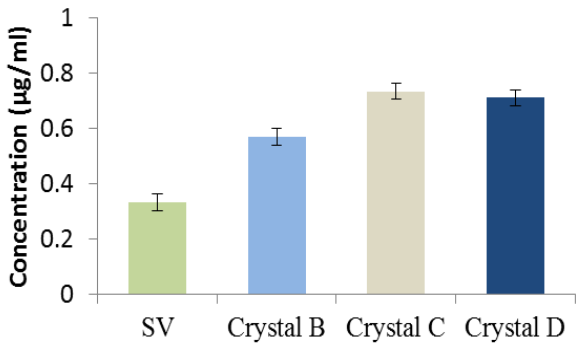

Figure 2: The results of the solubility of simvastatin before and after modification with a solvent mixture

Result of the dissolution test of simvastatin crystals

Following is a graph of the results of the dissolution test on hydrochloric acid buffer at pH 1.2 Based on the graph of the dissolution test, crystals A (simvastatin), B (methanol: ethanol), C (methanol: chloroform) and D (ethanol: chloroform) dissolve 0.18%, 0.70%, 12:57% and 0.67% respectively at 60 minutes in hydrochloric acid buffer at pH 1.2. This indicates that the dissolution rate of crystals B, C, and D are significantly increased than crystal A.

Based on the dissolution test graph above, crystal A (simvastatin) crystal B (methanol: ethanol), crystal C (methanol: chloroform) and crystal D (ethanol: chloroform) dissolved 2.82%, 4:02%, 4:40% and 4:56% at the 60th minute in acetate buffer at pH 4.5. This indicates that the dissolution rate of crystals B, C, and D are significantly 3-4 folded higher than crystal A.

Based on the dissolution test graph above, crystal A (simvastatin), crystal B (methanol: ethanol), crystal C (methanol: chloroform) and crystal D (ethanol: chloroform) dissolves 0.20%, 0.42%, 0.69% and 0.63% at the 60 minutes in a phosphate buffer at pH 6.8. This indicates that the dissolution rate of crystals B, C, and D are higher 3-4 times than simvastatin without modification (Keraliya RA. *et al*, 2010; Keraliya RA *et al*, 2016).

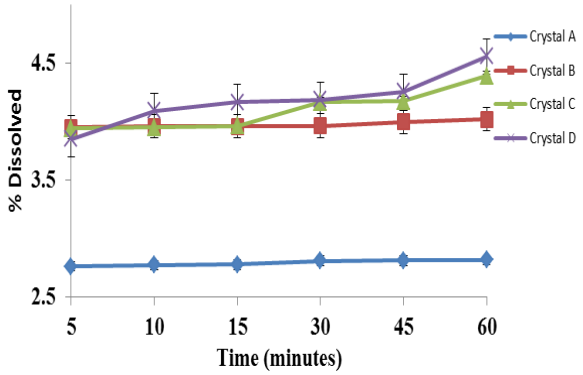

Figure 3: Result of dissolution test with pH 4.5 (acetate buffer).

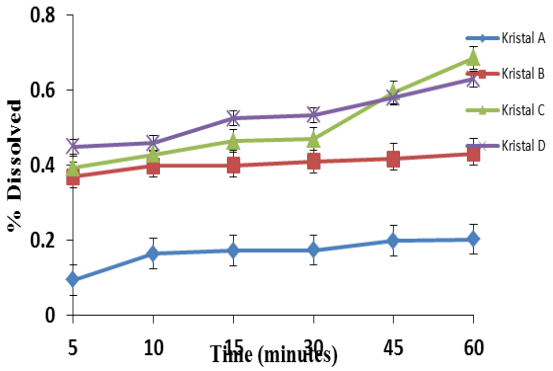

Figure 4: Results of dissolution testing with pH 6.8 (phosphate buffer).

Powder X-ray Diffraction studies

From the above results, there are significant differences between the diffractogram of simvastatin modification, so that it can be concluded that the modification of the crystal by recrystallization can result in simvastatin with different crystal form or morphology. According to table 1, it can be seen that a significant difference between crystals A, B, C and D. X-ray diffraction patterns of crystal A (simvastatin without modification), B and D show similar characteristics.

Table 1: Intensity diffractogram of crystal A, B, C, and D.

Parameter	Crystal A	Crystal B	Crystal C	Crystal D
Intensity Angle 2θ	Highest=2625 16.5^{o}	Highest=3292 16.5^{o}	Highest=12020 9.3^{0}	Highest=4020 18.5^{o}

Crystals C has a diffractogram with fewer peaks that are not too high and resembles like the grass like diffractogram of the crystal A. This suggests that crystal C has high crystallinity and a low amorphous than crystals A, B, and D. Shifting in diffractogram for different crystal indicated a formation of various crystalline habit [Anger. *et al*., 2010; Sopyan *et al*., 2017].

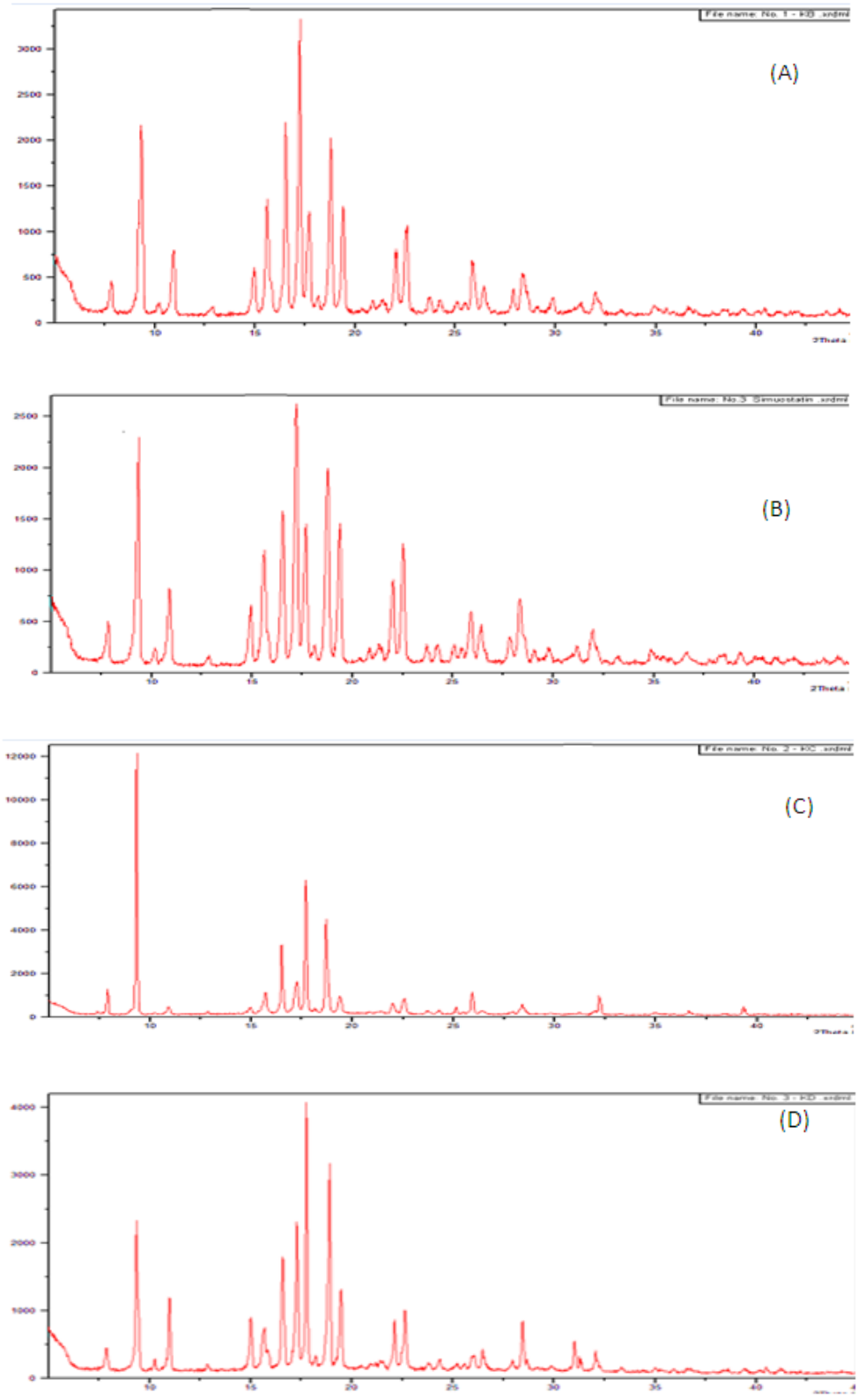

Figure 5: Diffractogram crystal A (simvastatin without modification), B (methanol: ethanol), C (methanol: chloroform) and D (ethanol: chloroform).

FTIR Spectroscopy

There is no significant difference in the FTIR spectra of before and after simvastatin modified. All major peaks were observed at wavenumbers Simvastatin 3553cm-1 (free OH stretching), 3011, 2959, and 2872 cm^{-1} (CH stretching), and 1714 cm^{-1} (stretching vibrations of ester and lactone carbonyl groups) maintained in modified simvastatin, which shows that there is no interaction between simvastatin and solvent.

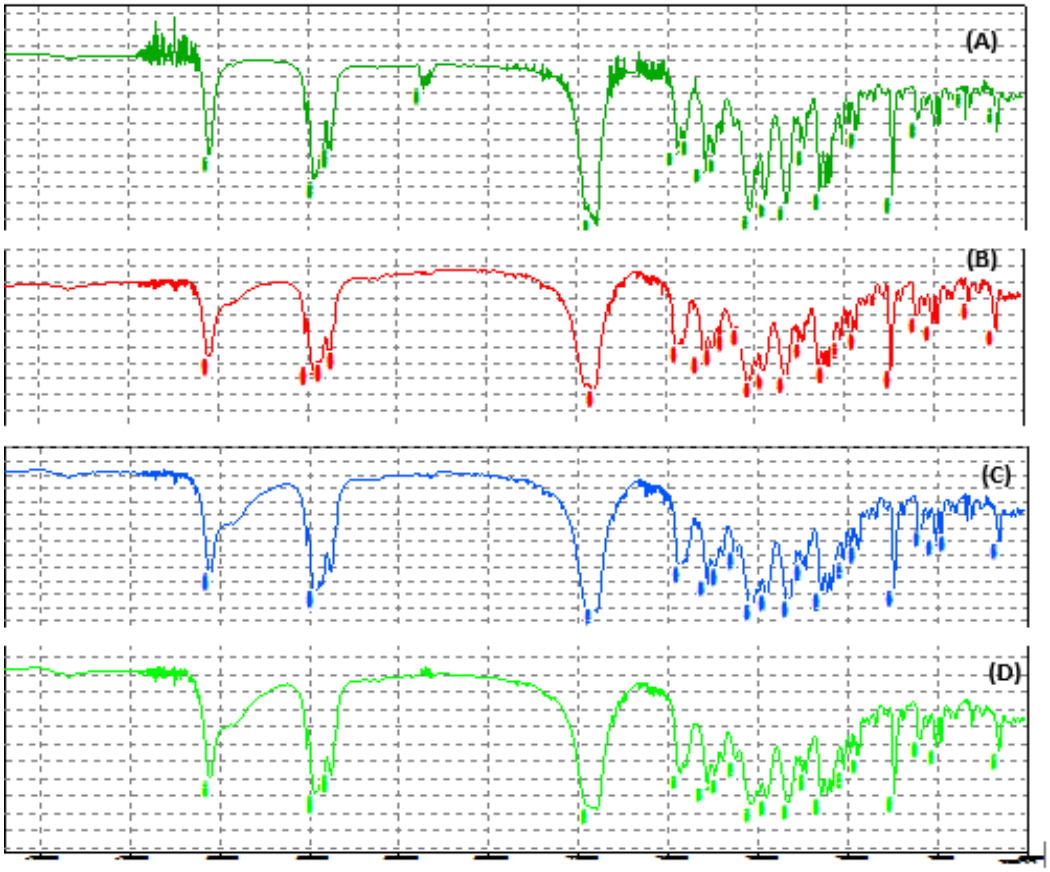

Figure 6: FT-IR spectrum of crystalline A, B, C and D.

CONCLUSIONS

Simvastatin polymorpism crystals formed after the modification process with solvent evaporation solubility test results of simvastatin crystal showed that modified crystal has a solubility in water better than simvastatin without modification, there are; crystal B increased 71.17 %, C increased 120.72 %, and D increased 113.51 %. The dissolution test results of simvastatin crystal showed that modified crystal has a better dissolution rate at hydrochloric acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8.

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