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Preparation of Simvastatin- β -Cyclodextrin inclusion complexes using co-evaporation technique

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ABSTRACT

Preparation of simvastatin- β -cyclodextrin inclusion complexes has been performed using co-evaporation technique. The aim of this study is to characterize the inclusion complexes of simvastatin - β - cyclodextrin and improve the solubility and dissolution rate of simvastatin. For comparison, pure simvastatin and its physical mixture were used. Characterizations of inclusion complexes of simvastatin with β - cyclodextrin in a solution state were carried out using phase solubility studies. Characterizations of solid inclusion complexes were performed using differential Thermal Analysis (DTA), powder X-ray diffraction, and scanning electron microscopy (SEM). Dissolution profiles were performed in a medium of pH 7.0 phosphate buffer solution containing sodium lauril sulfate 0.5% using type II USP apparatus. The results of solubility phase test showed a diagram of type A₁ solubility, with a constant value of stability of 227.827 M⁻¹, indicating that an inclusion complex of simvastatin - β - cyclodextrin (1: 1 molar) has been formed. The study results of dissolution rates and solubility showed that the inclusion complexes of simvastatin and β - cyclodextrin increased significantly in comparison to that of pure simvastatin and its physical mixtures.

Keywords: simvastatin, β -cyclodextrin, co-evaporation technique, inclusion complexes

INTRODUCTION

Drug solubility plays a major role in the development of drug dosage formulation. Active compounds in the form of oral solid drug dosage will be absorbed only when they are soluble in gastric fluids and shows high bioavailability. Various approaches have been exploited to improve the solubility of poorly soluble drug compounds, including co-grinding with a hydrophilic polymer, salt formation, formation of cocrystal phase and inclusion complexes using cyclodextrin [1,2,3,4]. A complexation method with cyclodextrins is one of the approaches already used to increase the solubility of drugs in water. Cyclodextrins can interact with a variety of drug molecules, hence forming inclusion complexes. Cyclodextrins (CDs) are cyclic toroidal-shaped molecules with an outer surface of hydrophilic and lipophilic central cavity that can form inclusion complexes with a variety of lipophilic drug molecules. Cyclodextrins are produced from starch by means of enzymatic conversion. The formation of drug inclusion complexes using cyclodextrin can improve its physicochemical properties such as solubility, dissolution rate, stability and bioavailability [5].

Simvastatin is a drug used to treat hyperlipidemia by reducing the levels of LDL-cholesterol and plasma triglyceride as well as apolipoprotein B. Simvastatin is categorized into the group of Biopharmaceutical Classification System

(BCS) drugs class II, meaning simvastatin poses a problem of low solubility in water and low bioavailability (5%); thus, it is essential to improve the dissolution rate of simvastatin, hence to improve the absorption and bioavailability of the drugs [6, 7].

The objective of this study is to characterize inclusion complexes of simvastatin and β -cyclodextrins (1: 1 molar) prepared using co-evaporation technique. The nature of solid inclusion complexes was characterized using scanning electron microscopy analysis, differential thermal analysis, and powder X-ray diffraction analysis. The solubility and dissolution rates profiles of simvastatin and β -cyclodextrin inclusion complexes were compared to those of pure simvastatin and its physical mixtures

EXPERIMENTAL SECTION

Materials

The materials used are simvastatin, obtained from PT. Kimia Farma Jakarta, β -cyclodextrin purchased from PT. Signa Husada, methanol (Merck, Germany), sodium phosphate (Merck, Germany), sodium lauryl sulfate (PT. Brataco), sodium hydroxide (PT. Brataco) and distilled water.

Method

Phase Solubility Diagram

Phase solubility diagrams of simvastatin with various concentrations of β -cyclodextrin in water were performed according to Higuchi and Connors [8]. The solution of β -cyclodextrin in water was prepared in various concentrations, namely: 0.000; 0.002; 0.004; 0.006; 0.008; 0.010; 0.012 and 0.014 M; then, an excess amount of simvastatin powder (50 mg) was added into the solution in a glass vials. Then the sample was mechanically stirred for 24 hours at 100 rpm at room temperature. After equilibrium was reached, the solution was filtered and analyzed spectrophotometrically at 239 nm. The curve of concentration of simvastatin was plotted against the concentration of β -cyclodextrin and to determine the type of diagram of the inclusion complexes formed, as well as the value of the slope; also, the stability constants (K_c) for complex was calculated using following equation :

$$K_c = \frac{Slope}{S_0 (1 - Slope)}$$

Preparation of inclusion complexes using co-evaporation technique

Inclusion complexes of simvastatin and β -cyclodextrin (1: 1 molar) were prepared using co-evaporation technique. Simvastatin was dissolved in an amount of ethanol and β -cyclodextrin in water. Next, a water phase was added to the ethanol phase, stirred, and then allowed to stand for 24 hours. The solids formed would precipitate, separated, and dried at a temperature of 45°C until a constant weight was reached and then sieved through mesh 60.

Preparation of physical mixture

A physical mixture of simvastatin and β -cyclodextrin was prepared with a molar ratio the same as that of the inclusion complexes (1: 1 molar). Both components were lightly mixed with a pestle and mortar. Subsequently, the mixture was sieved through mesh 60 and stored in a desiccator.

Scanning electron microscopy analysis

SEM micrographs of samples were analyzed using a SEM (Phenom world, The Netherlands) tool. The samples were placed in an aluminum holder and coated with gold to a thickness of 10 nm, the voltage set at 20 kV and current at 12 mA. Then, the samples were observed at various magnifications.

Differential Thermal Analysis

DTA thermogram of samples were obtained by using the Differential Thermal Analysis (DTG-60, Shimadzu, Japan). A number of samples (3-5 mg) were weighed and then placed in sealed aluminum pans and heated at a constant speed of 10° C per minute with a range of temperatures of 30-450 ° C.

Powder X-ray diffraction analysis

Powder X-ray diffraction analysis was conducted at room temperature by using a diffractometer (X-Pert Pro PanAnalytical, The Netherlands). The measurement condition was the metal target of Cu, $K\alpha$ filter, voltage of 40

kV, and current of 30 mA, with a measurement analysis at the range between 2 theta 5-100°. The powder was placed in the sample holder (glass) and made even to prevent particle orientation during sample preparation.

Solubility Test

The powder of inclusion complexes and physical mixture were weighed equivalent to 50 mg of simvastatin. The powder was introduced into an erlenmeyer, and 25 ml of distilled water was added. Then, it was stirred for 24 hours at the speed of 100 rpm at room temperature. After equilibrium was reached, the solution was filtered and the filtrate was suitably diluted and analyzed by spectrophotometrically at 239 nm.

Dissolution Profile

Determination of the dissolution rates profile was performed using type II USP dissolution tool (Copley Scientific, NE4-COPD, UK) with a medium of phosphate buffer (pH 7.0), containing 0.5% sodium lauryl sulfate of 900 ml and the temperature was regulated at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. And then a sample equivalent to 20 mg was placed into the dissolution vessel. The paddle was stirred at 50 rpm. As much as 5 ml solution samples were withdrawn at minutes 5; 10; 15; 30; 45 and 60, and replaced by a fresh dissolution medium. Drug dissolved was assayed by spectrophotometrically at 239 nm. All experiment were performed in triplicate.

RESULTS AND DISCUSSION

Phase Solubility Study

Phase solubility diagram was obtained by plotting the saturated concentrations of simvastatin against the concentrations of β -cyclodextrin as shown in Fig. 1. The solubility of simvastatin increased linearly as a function of the concentration of cyclodextrin in water solution. This is an A_L -type phase solubility diagram, which shows the formation of inclusion complexes of simvastatin and β -cyclodextrin with a molar ratio of 1:1. This is the most common type in which one drug molecule forms a complex with one cyclodextrin molecule. At an A_L -type phase solubility diagram, with a small slope of 1 and a stability constant ($K_{1:1}$) of the complexes, calculations can be performed based on the slope and intrinsic solubility (S_0) of the drugs in a complexation media [9]. From the results of the phase solubility test, a stability constant ($K_{1:1}$) of the simvastatin complexes could be obtained at 227.827 M^{-1} . The optimum values of the complex constant ($K_{1:1}$) were between 200-1000 M^{-1} , in which the inclusion complexes formed was quite stable. A higher value might reduce the bioavailability of drugs as the complexes could not be absorbed and thus not sufficient to dissolve. If the value of K_c is too low, it will be difficult for a complex formation to occur [10].

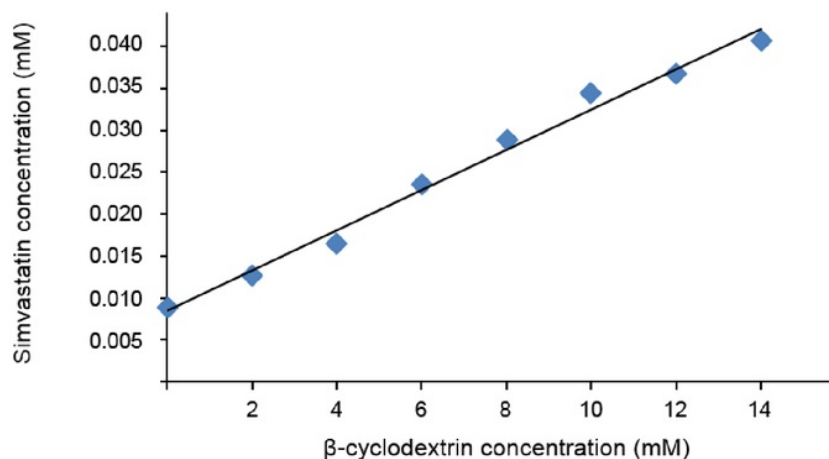


Figure 1. Phase solubility diagram of simvastatin with β -cyclodextrin in water at room temperature

Scanning Electron Microscopy(SEM) Analysis

SEM analysis was carried out to observe the morphology of sample and to provide the information about its surface texture. Observations were made at a magnification of 1000x. It could be seen that the morphology of simvastatin was in the form of crystalline solids, fused to form agglomerates with a rod shape (Figure 2a), indicating that the simvastatin was a crystalline phase. The morphology of β -cyclodextrin was in the shape of a large chunk with a rough surface texture (Figure 2b). In the physical mixture, the morphology of simvastatin and β -cyclodextrin could still be distinguished (Figure 2c); the simvastatin and β -cyclodextrin particles were still clearly visible. However, the inclusion complexes of simvastatin and β -cyclodextrin with co-evaporation method showed a morphological pattern of irregular shapes and a coherent form in which the morphology of the simvastatin and β -cyclodextrin is difficult to distinguish (Figure 2d). This indicated that the inclusion complexes were more amorphous than the simvastatin and its physical mixture because the complexation process has resulted in morphological changes, such as the structure and shape and size of the samples, resulting in a reduction in the degree of crystallinity of the simvastatin in the inclusion complexes [11].

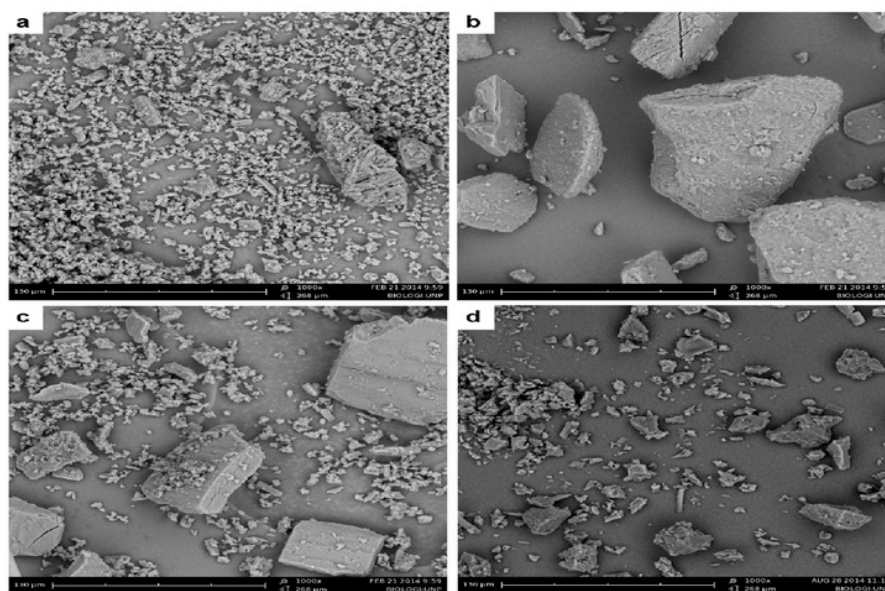


Figure 2. Scanning electron microphotographs of (a) simvastatin, (b) β -cyclodextrin, (c) physical mixture of simvastatin with β -cyclodextrin, and (d) inclusion complexes of simvastatin with β -cyclodextrin

Differential Thermal Analysis

The DTA thermogram of simvastatin showed a sharp endothermic peak at a temperature of 142.39 °C which is a melting event of simvastatin with an enthalpy of -576.32 J/g (Figure 3a); this is consistent with the characteristics of simvastatin's melting points, ranging from 140 °C – 142 °C [7, 12]. Simvastatin is a crystalline solid with a regular structure and therefore the melting point serves as a transition change from the solid phase into melted. The β -cyclodextrin thermogram showed a broad endothermic peak at the temperature range of 88.59 to 100°C with an enthalpy of -2.77 kJ/g (Figure 3b), which is the process of water loss (dehydration) [13]. The physical mixture thermogram showed two endothermic peaks with a low intensity; this is an endothermic peak of each component. The first peak was at the temperature of 142.13°C, with an enthalpy of -101.32J/g, showing a simvastatin thermogram; the second, at a temperature between 86.20°C -100°C with an enthalpy of -1.92kJ/g, showing a β -cyclodextrin thermogram (Figure 3c). The decrease is due to the mixing of simvastatin and β -cyclodextrin that has caused a decline in the simvastatin's endothermic peak. The possibility is that both materials fused into the crystal lattice of other materials. This proves that the two components have interacted, but the complexation phenomenon has not yet occurred [12]. In the thermogram of the inclusion complexes of simvastatin - β -cyclodextrin with co-evaporation technique, the endothermic peak of simvastatin was slightly shifted to lower temperature and intensity

Figure 3d). These results indicate that interactions between simvastatin - β -cyclodextrin have occurred through the formation of inclusion complexes between simvastatin and β -cyclodextrin. Decreases of simvastatin endothermic peak are due to the formation of an amorphous solid, in which simvastatin fills the cavity of β -cyclodextrin [12, 14]. A non-crystalline phase will show a broad endothermic peak; when a guest molecule fills the cavity of β -cyclodextrin, its melting point will perish or shift into a lower temperature [15].

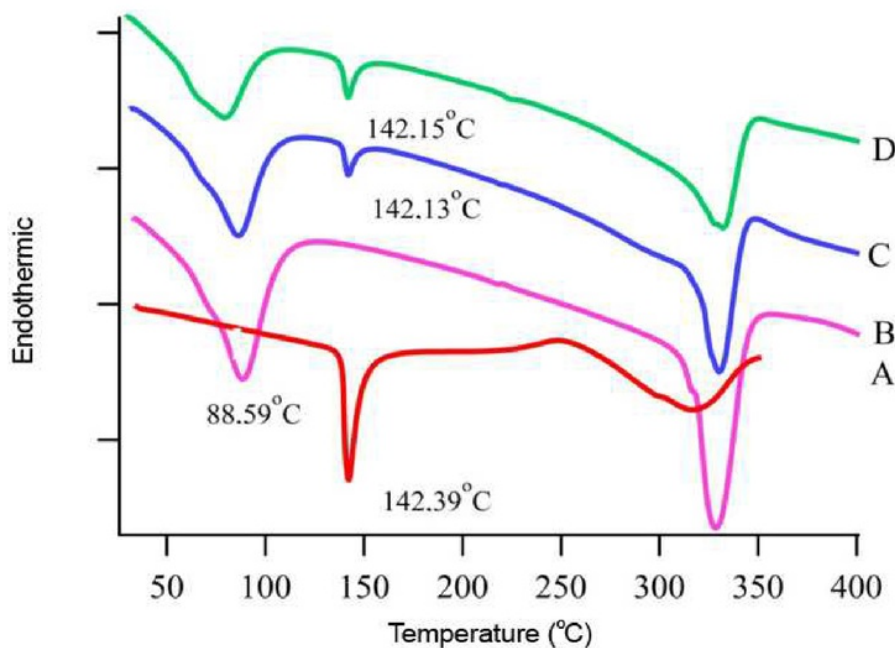


Figure 3. Differential thermal analysis thermogram of (A) simvastatin, (B) β -cyclodextrin, (C) physical mixture of simvastatin with β -cyclodextrin, and (D) inclusion complexes of simvastatin with β -cyclodextrin

X-ray Diffraction Analysis

Powder X-ray diffraction analysis is the most reliable method to characterize an interaction between two components of solid material, either as a newly formed crystalline phase or not, and to investigate changes in the degree of crystallinity of the solid material [16]. Results of the diffractogram of simvastatin show its characteristic crystalline phase as the diffractogram show typical and sharp interference peaks at the angle of 2θ (10.92; 15.60; 16.56; 17.21; 18.79; 19.37 and 22.54) (Figure 4a). The β -cyclodextrin diffractogram (Figure 4b) also show the crystalline characteristics, clearly visible at the angle of 2θ (12.44; 15.40; 18.10; 21.10; 22.63 and 34.67) as the raw material of β -cyclodextrin used was in the crystalline form. The diffractogram with sharp interference peaks indicate a crystalline phase in which the crystal structures are arranged on a regular basis, hence the distance between parallel planes of molecules in the crystal lattice can be measured. The diffractogram pattern of the physical mixture of simvastatin - β -cyclodextrin (Figure 4c) indicates a superimposition of the interference peaks of each component, both simvastatin and β -cyclodextrin. However, the intensity of the interference peaks is significantly lower than that of the pure components. The diffractogram pattern of the inclusion complexes of simvastatin - β -cyclodextrin shows decreases of interference peaks, significantly typical of simvastatin (Figure 4d). This indicates the occurrence of amorphisation of parts of the simvastatin solids in the β -cyclodextrin cavity. In the process of the formation of inclusion complexes using co-evaporation technique, the drug compound and β -cyclodextrin that are in the molecular state will interact in a physical manner through attractive forces (hydrogen bonding), and therefore the molecules will occupy the cavity of simvastatin β -cyclodextrin polymers [17]. In other words, substituents or functional groups of the guest molecules (guest) interact with the group on the side or part of β -cyclodextrin and a formation of hydrogen bonds between guest molecules and β -cyclodextrin occur [18].

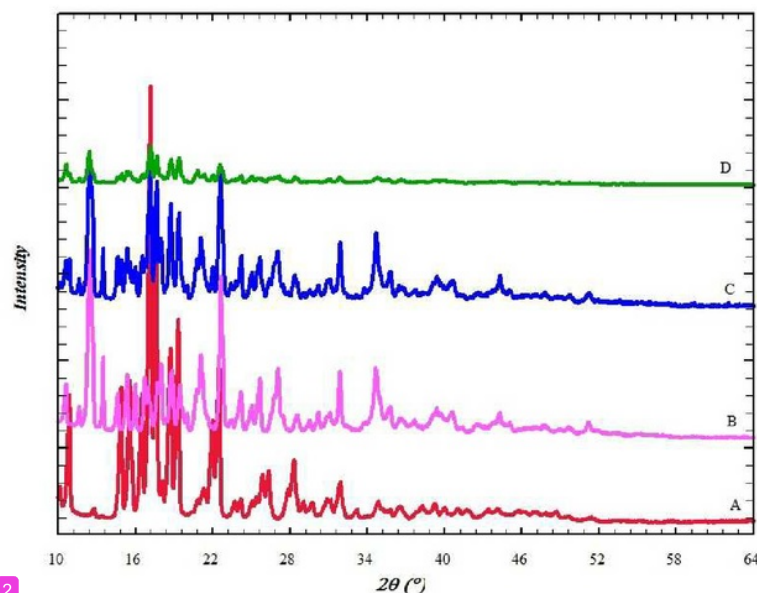


Figure 4. Powder X-ray diffraction pattern of (A) simvastatin, (B) β -cyclodextrin, (C) physical mixture of simvastatin with β -cyclodextrin, and (D) inclusion complexes of simvastatin with β -cyclodextrin

Solubility Test

Solubility tests of simvastatin, physical mixture, and inclusion complexes were conducted in distilled water as the medium. The results of the solubility test of pure simvastatin, the physical mixture and the inclusion complexes were 3.827 ± 0.186 g/mL; 6.752 ± 0.270 μ g/mL; and 13.598 ± 0.527 μ g/mL respectively. This shows increases of simvastatin solubility complexed with β -cyclodextrin, which is nearly 4-fold, in water medium, compared to that in pure simvastatin (Table 1). This is due to the inclusion complexes of drugs that are in the form of amorphous and included in β -cyclodextrin. Another factor that has contributed to the increase of the solubility of simvastatin is the increase in its wettability and dispersibility which, in turn, can also increase the dissolution rate of drug [7].

Table. 1 Solubility of simvastatin

Formula	Solubility of simvastatin (μ g/ml) \pm SD
Pure simvastatin	3.827 ± 0.186
Physical mixture of simvastatin - β -cyclodextrin	6.752 ± 0.270
Inclusion complexes of simvastatin - β -cyclodextrin	13.598 ± 0.527

Dissolution profile

The dissolution percentage at the 5th minute of simvastatin, physical mixture, and inclusion complexes of simvastatin - β -cyclodextrin, is respectively 61.592 ± 3.667 % 56.878 ± 10.208 % and 61.714 ± 11.496 %. At 30th minute of dissolution are respectively 64.963 ± 4.618 %; 70.418 ± 1.767 %, and $72,389 \pm 10.042$ % (Figure 5). The overall results of the dissolution show the lowest percentage of dissolved substances belong to pure simvastatin when compared to the physical mixtures and inclusion complexes. The physical mixture of simvastatin - β -cyclodextrin has a faster dissolution rate than that of pure simvastatin although in the physical mixture there have been no inclusion complexes formed between β -cyclodextrin and simvastatin yet, when compared to the inclusion complexes, the dissolution rate of the physical mixture is slower than that of the inclusion complexes. The physical mixture of poorly water-soluble drugs such as simvastatin and β -cyclodextrin has a faster dissolution rate when compared to the pure simvastatin as a simple mixing between poorly water-soluble drugs such as simvastatin and β -cyclodextrin enhances the drug's molecule diffuse passively into the dissolution medium and enable the drug particles to easily dispersed in the dissolution medium, hence a faster dissolution rate than that of pure simvastatin [

18]. β -cyclodextrins have the ability to form complexes in situ in a dissolution medium so as to increase the dissolution rate of the drugs although in their solid state no inclusion complexes have been formed [19]. The formation of inclusion complexes of simvastatin - β -cyclodextrin increases the dissolution rate of simvastatin in comparison with the physical mixture and pure simvastatin. The increase of dissolution rate is due to formation of inclusion complexes in a cavity-shaped matrix in which the inner cavity of β -cyclodextrin is hydrophobic and the outer β -cyclodextrin hydrophilic. An inclusion complex of a drug that was initially poorly soluble in water will produce a complex hydrophilic nature of the drug itself because the complex would easily wetted and the drugs dissolve fastly. In addition, an increase in the rate of the dissolution of simvastatin in the inclusion complex is also caused by the decrease in the degree of its crystallinity [18].

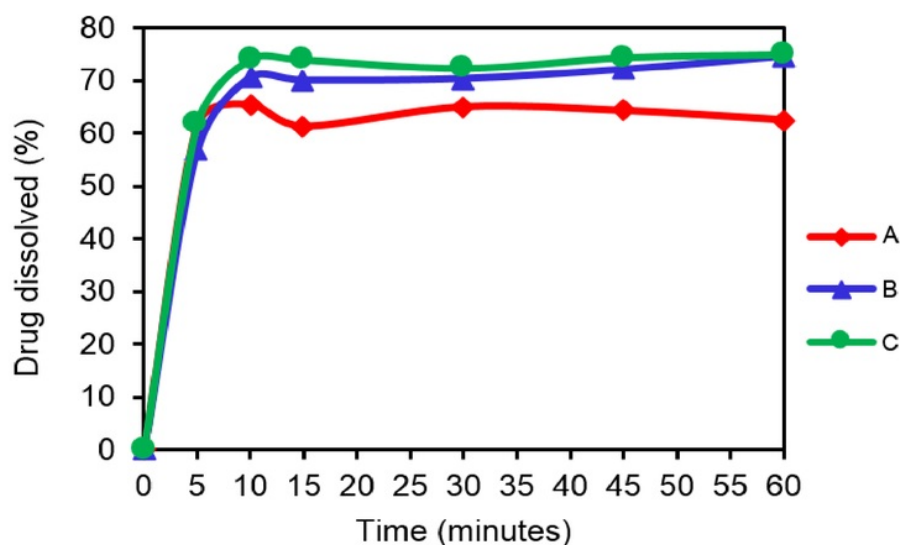


Figure 5. Dissolution profile of (A) simvastatin, (B) physical mixture of simvastatin with β -cyclodextrin, and (C) inclusion complexes of simvastatin with β -cyclodextrin

CONCLUSION

Phase solubility test demonstrated an A_L -type solubility diagram indicating the formation of inclusion complexes of simvastatin - β -cyclodextrin 1:1 molar ratio. Complexation with β -cyclodextrin could improve the solubility and dissolution rate of simvastatin. The other factors contributed to higher dissolution rate of simvastatin such as increase wettability and decrease in crystallinity of the solid drug.

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