Indonesian Journal of Pharmaceutics
IdJP
ISSN : 2597-8748

Vol. 6, Issue 2, 2024 (95-108)
http://journal.unpad.ac.id/IdJP

Increasing Solubility of Simvastatin Via Salting Form Using Isonicotinamide As Co-Formers : Insilico and Invitro Studies

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Submitted: 15/07/2024, Revised: 20/07/2024, Accepted: 30/07/2024, Published: 14/08/2024

ABSTRACT

Simvastatin is a drugs used to lower plasma cholesterol. Simvastatin is a class II BCS drug that has low solubility and high permeability. One of the efforts made to increase the solubility of simvastatin is the formation of multicomponent crystals (co-crystals and salts). The purpose of this study was to determine the solubility and dissolution profile of multicomponent crystal simvastatin with the best co-former candidate from the in silico test. Simvastatin-co-former multicomponent crystal were prepared using solvent drop grinding method with a mol ratio of 1:1 ; 1:2 and 2:1. Based on the result of value of binding affinity and ability to form hydrogen bonds, isonicotinamide was chosen as the co-former in this research. Evaluation of multicomponent crystals was carried out by solubility and dissolution tests. The evaluation results showed an increase in the solubility and dissolution of the simvastatin-isonicotinamide multicomponent crystal with the highest increase occurring in the simvastatin-isonicotinamide multicomponent crystal with a mol ratio of 1:2. Multicomponent crystal characterization was carried out to determine physicochemical characteristics. The results of characterization using infrared spectrophotometry showed a spectrum shift. The results of the Differential Scanning Calorimetry (DSC) analysis show a decrease in the melting point. The results of Powder X-ray diffraction analysis showed that there were differences in the shape of the crystals indicated by the formation of new peaks on the diffractogram. So, it can be concluded that simvastatin-isonicotinamide multicomponent crystals are able to increase solubility and dissolution compared to pure simvastatin.

Keywords: Dissolution, in silico, solubility, multicomponent crystal, simvastatin.

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https://doi.org/10.24198/idjp.v6i2.60538

1. Introduction

Hypercholesterolemia is a condition of high cholesterol levels in the blood [1]. Hypercholesterolemia is one of the main causes of cardiovascular disease along with increasing age, male sex, diabetes and increased blood pressure. Based on the World Health Organization (WHO) report, the death rate caused by cardiovascular disease reaches 17.9 million people every year and 32% is the cause of all deaths worldwide. The death rate from cardiovascular disease is predicted to continue to increase from year to year and it is estimated that by 2030 it will reach 23.3 million deaths [2]. In Indonesia, based on data from Basic Health Research (Riskesdas) in 2018, The incidence of cardiovascular disease is increasing from year to year. At least 15 out of 1,000 people or currently there are 4.2 million people suffer from cardiovascular disease.

Simvastatin is a drug that belongs to the statin family and is a first-line drug in the treatment of hypercholesterolemia. The way simvastatin works is to inhibit the work of the HMG-CoA reductase enzyme which is a precursor of cholesterol synthesis so that the production of cholesterol in the body is reduced. Simvastatin is available in oral tablet form with an initial dose of 10-20 mg/day and a maximum dose of 80 mg/day [1].

Solubility is one of the important parameters to achieve the desired drug concentration in the systemic circulation to achieve the required pharmacological response [3]. Drugs with poor solubility require higher doses to achieve therapeutic plasma concentrations after oral administration. Most drugs are weak acids or weak bases which have poor solubility [4]. More than 40% of new compounds developed in the pharmaceutical industry are practically insoluble in water [5].

Based on the Biopharmaceutical Classification System (BCS), simvastatin is included in BCS class II which has low solubility in water but has high permeability [6]. For drugs that are classified as BCS class II, the dissolution process is the determining step for drug absorption so that an effort is needed to increase dissolution which can be done by increasing the solubility of the drug to accelerate the absorption process and the onset of drug action [7].

Various approaches that can be taken to increase the solubility and dissolution rate of drugs include changes in physical and chemical form, changes in chemical form, addition of hydrophilic excipients, to modifying and changing the structure of the substance by converting it into its salt form or its cocrystal form [8]. Cocrystal is an approach that combines two or more compounds to obtain better physical and chemical properties using hydrogen bonding, van der walls and stucking phi-phi interactions.

Several methods have been used to increase the solubility and dissolution of simvastatin including physical modification (formation of cocrystals and solid dispersion) and addition of a carrier system. However, there are still some weaknesses from the method that has been used. One effort to increase drug solubility without changing pharmacological activity is to modify the solid form of the drug through the formation of multicomponent crystals, such as salts and cocrystals [9]. The formation of multicomponent crystals, such as salts and cocrystals is known to increase the solubility of some drugs. Salts of acidic and basic drugs generally have a higher solubility than the corresponding acidic or basic forms.

Several potential coformers were selected based on the presence of ionized functional groups, pKa difference values, stability, toxicity, solubility, hygroscopicity, successful salt formation, and availability of materials. The coformers used were arginine, lysine, isonicotinamide, and monopotassium phosphate. These research would be focusing on increasing the solubility of one of the BCS Class II drugs, namely simvastatin with a multicomponent crystal approach, especially salt. Increasing the solubility of simvastatin can improve the dissolution rate and bioavailability of the drug. It is also hoped that this research can provide innovation in further drug development.

2. Method

2.1. Materials

The materials and tools that will be used for this research include aquades (Global Scientific), isonicotinamide (SigmaAldrich), monobasic potassium phosphate (Merck), potassium bromide (Sigma-Aldrich), methanol (SigmaAldrich), sodium hydroxide (Merck), and simvastatin (Hungarian Teva), agitator (IKA HS 260 Basic).

2.2. Equipment

Type II dissolution test equipment (SOTAX CH-4008 Basel), glass pestle, AutoDock Tools application, PyRx application, DSC (DSC Model-60, Shimadzu), 50mL beaker , 100mL, 1000mL (Pyrex), parchment paper, filter paper (Whatman No.42), 10 mL, 50mL, 100ml (Pyrex) volumetric flasks, FTIR spectroscopy (IR Prestige-21 Shimadzu), pH meter (HI 2211), UV-Vis spectrophotometry (Specord 200), Bruker D8 Advance X-Ray Diffractometer (XRD).

2.3. Study In Silico

In silico studies were carried out to determine the coformer that could provide the best interaction with simvastatin as determined by molecular docking studies. The coformer and simvastatin structures were generated through the ChemDraw program and then converted into .pdbqt format using AutoDock Tools. The simvastatin and coformer structure files in the form of .pdbqt are run on the PyRx application to see the binding affinity of each coformer when interacting with simvastatin. Then, docking was carried out on simvastatin and coformer using the AutoDock Tools 1.5.6 application and observed whether there was an interaction formed. Later, the best coformer that interacts with simvastatin is selected which is characterized by the presence of hydrogen and ionic bonds and has the most negative binding affinity [10].

2.4. Preparation of Multicomponent Crystal Simvastatin

Simvastatin salt is prepared using the solvent drop grinding method. A number of selected mixtures of simvastatin and coformer were made with a mole ratio of 1:1, 1:2, and 2:1, respectively, ground together in a mortar at a constant speed for 20 minutes while adding 3-5 drops of methanol during the grinding process [11].

2.5. Preparation of Phosphate Buffer pH 7.0

Dissolve 6.8 g of monobasic potassium phosphate P in approximately 250 mL of CO2-free water. Add a sufficient amount of 0.2 N sodium hydroxide (approximately 100 mL) to a pH of 7.0 and then add water to make up to 1000 mL [12].

2.6. Maximum Wavelength and Zero Crossing Setting

Long wave maximum simvastatin was determined by scanning using UV-Vis spectrophotometry. 10 µg/mL of drug solution was dissolved in methanol and measured at a wavelength of 200 – 400 nm [13]. Then derivatives were carried out from the absorbance results obtained until zero crossing was found where only simvastatin provided absorption while the coformer did not provide absorption [14].

2.7. Preparation of Calibration Curve

A total of 10 mg of simvastatin was dissolved in a solvent in the form of a mixture of methanol-aquades (solubility test) and phosphate buffer pH 7.0 (dissolution test) in a 100 mL volumetric flask. From the stock solution, as much as 0.1; 0.2; 0.3; 0.4; 0.5, and 0.6 ml were transferred to a 10 ml volumetric flask and added up to 10 ml with solvent, respectively. The absorbance of the solution was then measured at wavelengths of 238 nm, 254 nm (second derivative) and 257 nm (second derivative) with distilled water and phosphate buffer as blanks. The absorbance data is calculated in the standard curve equation so that the line equation $y = ax + b$ is obtained [15,13].

2.8. Evaluation of Simvastatin Crystal Multicomponent

Solubility Test

A total of 10 mg of simvastatin was dissolved with 10 ml of distilled water in a glass vial and then placed in a mechanical stirrer for 24 hours at room temperature (25 ℃) at a speed of 120 rpm. Saturated solubility was measured by UV spectrophotometry at wavelengths of 238 and 254 nm (second derivative) [11].

Dissolution Test

The dissolution test was carried out using Tool II (paddle) at a speed of 50 rpm for 60 minutes. The media used in the form of a buffer solution (phosphate buffer) pH 7 as much as 900 mL at a temperature of 37±0.2°C. Periodically every 10 minutes, 10 ml of sample and medium were replaced with the same volume during the test. The samples were then measured using UV spectrophotometry at wavelengths of 238 nm and 257 nm (second derivative) to calculate the percent dissolution [11].

2.9. Characterization of Multicomponent Crystal Simvastatin

Fourier-Transform Infrared Spectroscopy (FTIR)

A total of 2 mg of each sample was mixed with 248 mg of potassium bromide crystals and ground until homogeneous, then compressed with a pressure of 60 Psi. The spectrum was measured in the range of 400-4000 cm-1 using an FTIR spectrophotometer [11].

Differential Scanning Calorimetry (DSC)

Samples of 3-5 mg were placed in a programmed device in a temperature range of 25-180 ℃ with a heating rate of 10 ℃/min [11].

Powder X-Ray Diffraction (PXRD)

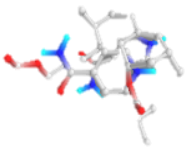
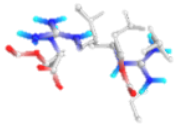
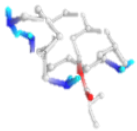
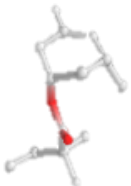
The crystal structure was analyzed using an X-Ray Powder Diffractometer with the provisions of a Cu target/filter (monochromator), a voltage of 40 kV, a current of 30 mA, a slit width of 0.2 inches, with a scanning speed of 0.2–0.5°/min and a scanning distance. $2\theta = 5–60°$ [11].

3. Result

3.1. Determination of Coformers by In Silico Method

Results of docking between simvastatin and coformers with the in silico method can be seen in table 1. In this method, it can be seen that there are 2 coformers that have the opportunity to form multicomponent crystals with simvastatin because they have hydrogen bonds, namely isonicotinamide and arginine. The two coformers form hydrogen bond interactions with simvastatin as a macromolecule. The interaction of hydrogen bonds affects the hydrophilicity of a substance. In addition, the value of bond affinity affects the intermolecular activity of the compound and affects the bond strength. The smaller the bond affinity, the stronger the bond formed [16].

Table 1. Coformer Selection by In Silico Method

No.	Coformer	3D Structure	Interaction	Ei (kcal/mole)
1.	Isonicotinamide		1 hydrogen bond No phi phi interaction	-2.5
2.	Arginine		1 hydrogen bond No phi phi interaction	-2.3
3.	Lysine		0 hydrogen bonds No phi phi interaction	-2.3
4.	Monopotassium Phosphate		0 hydrogen bonds *Phi phi interaction*	-1

3.2. Results of Making Simvastatin Cocrystals Using the Solvent Drop Grinding Method

Simvastatin has poor solubility in water but good solubility in methanol. Isonicotinamide is practically insoluble in acetone, but easily soluble in water and methanol, so that in the manufacture of multicomponent crystals of simvastatin-isocotinamide crystals using the solvent-drop grinding method, methanol is used. Multicomponent crystal simvastatin and isonicotinamide coformer made by solvent drop grinding method with mole ratios of 1:1, 1:2, and 2:1. The mole ratio used is based on the synthonic relationship between the active pharmaceutical ingredient (simvastatin) and its coformer (isocotinamide). Synthonic relationships involve non-covalent interactions such as hydrogen bonds, van der Waals, -stacking electrons, electrostatic interactions and halogen bonds [17]. The lactone groups contained in simvastatin are carbonyl, hydroxyl and ether which can form a hydrogen bond with coformers such as isonicotinamide. The results of the multicomponent preparation of simvastatin-isocotinamide crystals are shown in Figure 1.

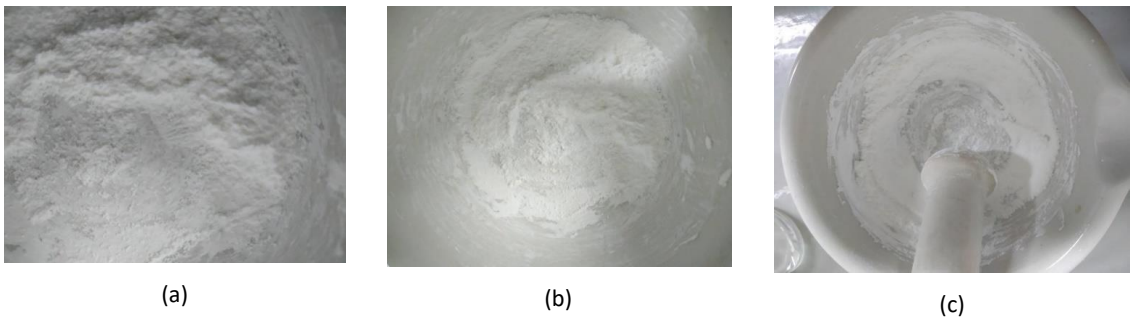


Figure 4.1 The results of the manufacture of simvastatin-isocotinamide multicomponent crystals (a) 1:1 mole ratio (b) 1:2 mole ratio (c) 2:1 mole ratio by solvent drop grinding method

3.3. Solubility Test Results

The results of the simvastatin solubility test and simvastatin-isocotinamide crystal multicomponent with a ratio of 1:1, 1:2, and 2:1 can be seen in Figure 2.

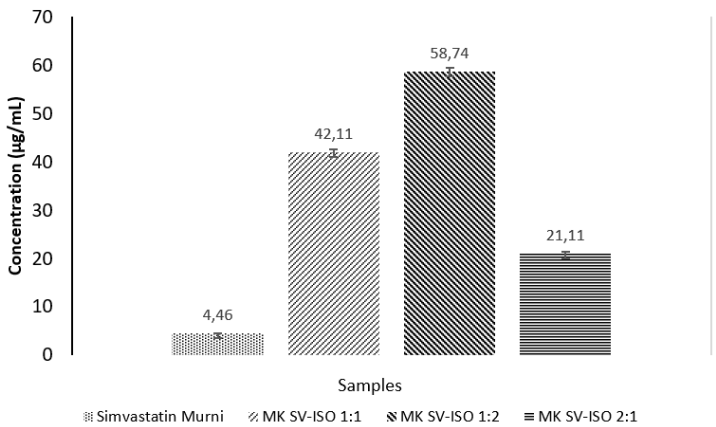


Figure 2. Graph of pure simvastatin solubility test results and multicomponent simvastatin-isocotinamide crystals

The results of the multicomponent crystal solubility test showed an increase in solubility when compared to pure simvastatin. The multicomponent crystalline simvastatin-isocotinamide with a mole ratio of 1:1 gave an increase in solubility of 42.11 mg/L (9.43 times) when compared to pure simvastatin, while the increase in the solubility of the multicomponent crystal simvastatin-isocotinamide with a mole ratio of 1:2 was 58.74 mg/L. (13.9 times) and simvastatin-isocotinamide with a 2:1 mole ratio of 21.11% (4.73 times) when compared to pure simvastatin.

3.4. Dissolution Test Results

The results of simvastatin dissolution test and simvastatin-isocotinamide crystal multicomponent with mole ratios of 1:1, 1:2, and 2:1 can be seen in Figure 3.

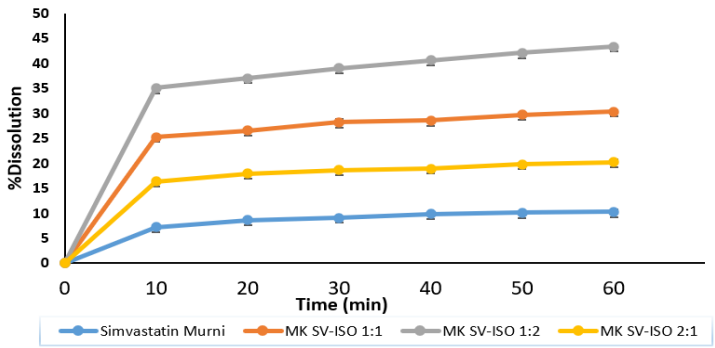


Figure 3. Graph of pure simvastatin solubility test results and simvastatin-isocotinamide crystal multicomponent

The amount of simvastatin dissolved after 60 minutes was 10.27%, simvastatin crystalline multicomponent with a ratio of 1: 1 was 30.34%, multicomponent crystal simvastatin was in a ratio of 1:2 was 43.38% and multicomponent crystal simvastatin was in a ratio of 2:1. by 20.21%. This shows that the number of simvastatin dissolution in the multicomponent simvastatin-isocotinamide crystal with a ratio of 1:1 increased by 295.45% (2.95 times), the multicomponent simvastatin-isocotinamide crystal with a ratio of 1:2 increased by 422.35% (4.22 times), multicomponent crystalline simvastatin-isocotinamide with a ratio of 2:1 increased by 196.78% (1.96 times) when compared with pure simvastatin.

3.5. Characterization Results with Fourier-Transform Infrared Spectroscopy (FTIR)

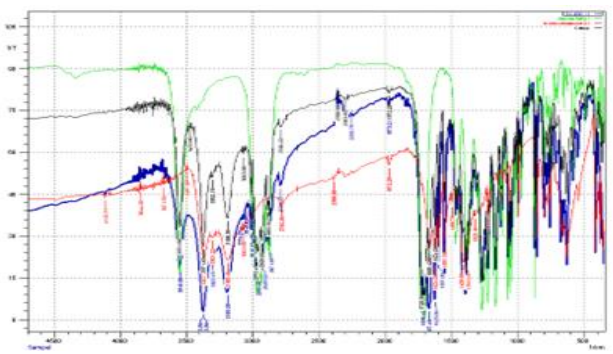


Figure 4. Spectrum results for pure simvastatin (green), simvastatin isocotinamide physical mixture 1:2 (black), multicomponent simvastatin-isocotinamide 1:2 crystals (blue), pure isonicotinamide (red)

The results of the characterization on the FTIR spectrum of simvastatin powder showed the presence of an OH functional group at a wave number of 3551.01 cm^{-1}, a CH functional group at a wave number; 3010.93 cm^{-1} and the functional group C=O at a wave number of 1725.36 cm^{-1}, these results are in accordance with the results of research conducted by [6]. Based on the results of the infrared spectrum between simvastatin, isonicotinamide, physical mixture, and the formed multicomponent crystals showed identical peak characteristics in the crystal multicomponent sample shown at 3373.56 cm^{-1} (NH stretching), 3040.83 cm^{-1} (CH stretching) , 2786.22 cm^{-1} (OH stretching) 1624.09 cm^{-1} (C=O stretching), 1394.56 cm^{-1} (CN stretching).

3.4. Dissolution Test Results

The pure simvastatin thermogram showed an endothermic peak with a peak temperature of 132.98°C which was the melting point of the pure simvastatin tested (fig. 5)

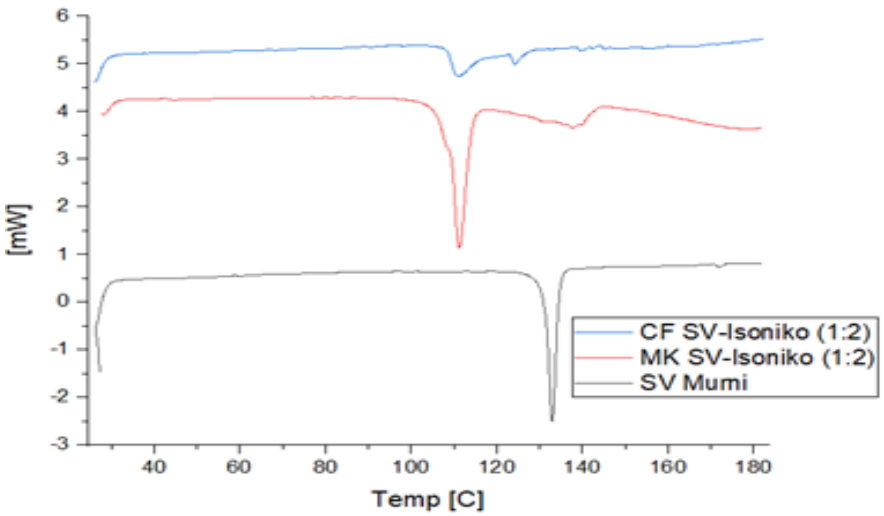


Figure 5. Results of Differential Scanning Calorimetry Test

The physical mixture thermogram shows that there are two endothermic peaks with a peak temperature of 111.07°C. Meanwhile, for the multicomponent crystal thermogram, there are two endothermic peaks with a peak temperature of 111.29°C. The decrease in melting point and heat content of multicomponent crystals will directly correlate with increasing solubility of API in multicomponent crystals [18].

4. Discussion

The insilico prediction results in table 1 that isonicotinamide has a better interaction than other coformers based on the energy affinity of the coformer-simvastatin complex. The docking energy is a parameter of the strength of the binding affinity between the ligand and its macromolecules. The lower the docking energy produced, the more stable the interaction formed between the coformer and simvastatin so that the

activity is expected to be better. Table 1 shows that isonicotinamide has the lowest bond affinity value of -2.5 kcal/mol. Thus, the chosen coformer is isonicotinamide. The difference in bond affinity values can be caused by differences in the hydrogen bond distance in the interactions of the ligands that occur. Hydrogen bonds are reported to be categorized based on the donor-acceptor distance where the distance is 2.2-2.5Å as a strong interaction, 2.5-3.2 Å as a moderate interaction and 3.2-4.0 Å as a weak interaction [19] The hydrogen bond distance of isonicotinamide-simvastatin is 2.9Å while the hydrogen bond distance of arginine-simvastatin is 2.4Å. Hydrogen bonding interactions between ligands can affect the activity of compounds. The smaller the hydrogen bond distance between the ligand and the greater the affinity strength of the two [20]. Isonicotinamide has a higher number of hydrophobic interactions than arginine. The interaction between simvastatin and isonicotinamide forms a salt compound due to proton transfer. Salt formation between simvastatin results in hydrogen bond interactions. Based on the analysis of the calculation of pKa values, the formation of simvastatin and isonicotinamide salts occurred because the difference in pKa values between the pKa of base (isonicotinamide) and pKa of acid (simvastatin) was more than 3 (10.61 – 4.21 = 6.4).

The formation of multicomponent crystals in the form of salts and cocrystals has the advantage of increasing solubility and producing a more stable solid form than solid dispersion techniques. One of the simplest methods for the manufacture of multicomponent crystals is the wet milling method. Wet milling method or known as solvent-drop grinding (SDG) is a method of making multicomponent crystals, including salt and cocrystals by grinding together active pharmaceutical ingredients and salt/cocrystal-forming materials with the addition of a small amount of solvent [21]. The increase in bioavailability in the solvent drop grinding method is influenced by mechanical energy and solvent. Mechanical energy such as grinding is able to increase the degree of freedom of molecules so that they can open their conformations to interact with each other. Grinding together with the active substance which has low solubility in water will cause modification of the solid properties of the active substance compound so that the solubility and bioavailability of the active substance will increase. The milling process aims to reduce the particle size. The choice of solvent used is very important, it must be able to dissolve at least a small part of its constituent components. The solvent acts as a catalyst that can accelerate the formation of cocrystals [22]. SDG is the earliest method used for coformer screening because it is easy and requires less time and is simpler

The increase in bioavailability in terms of the coformer used and from the characteristics of the multicomponent crystal, namely the coformer must be able to form hydrogen bonds with the active substance because hydrogen bonding is an important bond in the formation of multicomponent crystals where the more hydrogen bonds, the solubility of a substance will increase and the formation of a crystalline phase. which can indicate an increase in the solubility of the active substance so that its bioavailability will also increase [11].

The derivative spectrophotometric method was used to analyze the results of the solubility test and dissolution test. This method is used because there is overlap between the absorbance of simvastatin and the coformer used, so the

effect of the coformer must be removed first so as not to interfere with the absorbance reading of the desired simvastatin sample. The derivative spectrophotometric method used is the zero crossing method in which the effect of the absorbance of the coformer is removed to close to 0 so that only the absorbance of simvastatin is the target substance. The purpose of this derivative is to get the effect of the coformer on the result to be as small as possible.

The results of solubility test shows in figure 2. Isonicotinamide is reported to be able to form complexes with drug compounds such as simvastatin through a mechanism as a donor and acceptor in the formation of hydrogen bonds. This also causes an increase in solubility through the formation of multicomponent crystals [23]. The increase in solubility in the multicomponent simvastatin-isocotinamide crystals occurred due to the formation of hydrogen bonds between simvastatin and isonicotinamide. In addition, the addition of the solvent serves as a contact conductor between simvastatin and the coformer so that it is in the form of a molecule that is longer than the bonds that occur in each molecule. The solubilizing effect of isonicotinamide which has water soluble properties also affects the increase in the solubility of simvastatin in water.

This increase in solubility can be caused by two possibilities, first due to the transfer of protons from isonicotinamide to simvastatin (salt formation) which causes ionization of simvastatin and secondly due to reduced energy required to break bonds between simvastatin molecules and water solvent due to hydrogen bonds (multicomponent formation). crystals) between simvastatin and isonicotinamide. In addition, the decrease in particle size due to the grinding process in the manufacture of multicomponent simvastatin-isocotinamide using the solvent-drop grinding method is thought to also increase the amount of solute dissolved in the solvent [24].

The dissolution evaluation was carried out to determine the levels of multicomponent crystals dissolved in the media at a certain time. The medium used is phosphate buffer pH 7.0 (adjusting to the pH conditions in the gastrointestinal tract) according to the characteristics of simvastatin which is well absorbed maximally in an alkaline body environment. The drug solubility process is also influenced by the shape of the ionized and non-ionized molecules in the carrier. According to the Henderson-Hasselbach equation, the amount of ionized and unionized is affected by the pKa or pKb of the compound and the pH of the environment [25].

Simvastatin as a weak acid compound will be more soluble in an alkaline environment, this is due to the increasing number of ionized forms. The ionized form will interact more easily with water molecules so it is more soluble. This solubility will affect the dissolution of simvastatin. As a result, simvastatin is more easily dissolved in an alkaline environment.

The results of dissolution test showed that there was an increase in the dissolution rate of the multicomponent simvastatin-isocotinamide crystals compared to pure simvastatin and the best increase in the dissolution rate occurred in the multicomponent simvastatin-isocotinamide crystals with a ratio of 1:2. The increase in the dissolution rate of the simvastatin-isocotinamide multicomponent crystal was due to various mechanisms, among which hydrogen bond interactions in the multicomponent crystal increased the polarity of simvastatin. The solubilization

effect of isonicotinamide, which is well soluble in water, increases the dissolution rate of multicomponent crystals. In addition, due to the formation of new crystalline multicomponent crystals which have physicochemical properties including a better dissolution profile than the previous crystalline phase [26,27].

Based on the infrared spectrum of pure simvastatin, pure isonicotinamide with multicomponent simvastatin-isocotinamide crystals. FTIR can be used to differentiate between crystal and salt formation by the vibration of the carbonyl bond. The observed carbonyl vibrations indicate an ionic bond. The presence of ionic interactions such as deprotonation drives a shift in C=O vibrations [28,29]. The results of the multicomponent spectrum of simvastatin-isocotinamide crystals showed a shift in the carbonyl group around the wave number of 1625.06 cm-1, while in pure simvastatin what carbonyl group was at the wave number of 1725.36 cm-1 so this could indicate the formation of salt in the simvastatin-isocotinamide multicomponent crystal. Melting point changes indicate that the interactions that occur affect the formation of the internal crystal structure [30]. Based on the thermogram in Figure 5 shows that there is an endothermic peak in the simvastatin-isocotinamide multicomponent crystal, so it can be concluded that there is an intermolecular interaction in the simvastatin-isocotinamide multicomponent crystal that is able to change the physicochemical properties of the compound. If salt formation occurs, the DSC thermogram will show an endothermic peak and a higher melting point than its constituent components [30]. However, based on the results of the tests that have been carried out as shown in Figure 5, the endothermic peak of multicomponent simvastatin-isocotinamide crystals is below pure simvastatin so that it can be indicated that there is no salt formation in the multicomponent simvastatin-isocotinamide crystals that have been prepared. This decrease in melting point can be correlated with an increase in the solubility of the sample. The higher tthe melting point (melting point), the lower the solubility. Conversely, the lower the melting point (melting point), the higher the solubility. This is in line with the results of the solubility tests that have been carried out where the multicomponent crystal simvastatin-isocotinamide 1:2 which has a lower melting point than pure simvastatin is able to show a higher solubility level.

The X-ray diffractrogram of powder from solvent drop grinding of simvastatin and isonicotinamide in Figure 6 shows the formation of several new peaks (black arrows) that are not present in the diffractogram, pure simvastatin where these results indicate the formation of multicomponent crystals of simvastatin-isocotinamide [26]. The decrease in peak intensity indicates a change in the degree of crystallinity. This is due to the mechanical energy that occurs during grinding so that simvastatin and isonicotinamide attract each other and form hydrogen bonds with coformers [31]. This is in line with the test results where the multicomponent crystalline simvastatin-isocotinamide has a higher degree of crystallinity, which is 80.3%, compared to pure simvastatin, which is 78.4%. The simvastatin-isocotinamide 1:2 crystalline multicomponent x-ray diffractogram has almost the same diffraction pattern as the physical mixture. However, the difference in the number of peaks indicates that the two are structurally different [32]. Physical chemical stability tests need to be carried out at least accelerated stability tests to

be carried out at least accelerated stability tests to see the stability of the interaction of simvasttain and coformer with temperature and humidity conditions that could influence

5. Conclusion

Based on this research, it can be concluded the results of virtual screening of coformers through in silico studies showed isonicotinamide has the most negative binding affinity energy compared to arginine, lysine, and monopotassium phosphate. The solubility and dissolution rate of simvastatin-isocotinamide multicomponent crystals increased when compared to pure simvastatin where simvastatin-isocotinamide multicomponent crystals with a mole ratio of 1:2 had the best increase, which increased by 13.9 folded in the solubility test and 4.55 folded in the dissolution test when compared with pure simvastatin. The results of characterization using infrared spectrophotometry showed a. In vivo studies needed to be conduct as next experiment to completed the data related to bioavailability studies.

6. References

[1] PERKENI. Guidelines for the Management of Dyslipidemia in Indonesia. Jakarta: PB Perkeni; 2015.

[2] Thomas Gaziano TA, Cardiovascular Diseases Worldwide, Public Health Approach to Cardiovascular Disease Prevention & Management. CRC Press, 2022. p 11.

[3] Savjani KT, Gajjar AK, Savjani JK. Drug Solubility: Importance and Enhancement Techniques, Wiley Online Lib. 2012;1:1-10.

[4] Vemul VR, Venkateshwarlu Lagishetty. Lingala S. Solubility, Enhancement Techniques. Int. J. Pharm. Sci. Rev. Res. 2010;5(1):41-51.

[5] Sharma A, Saragi V.V, Chen CR, Buddhi D. Review on thermal energy storage with phase change materials and applications. 2009;13(2): 318-345

[6] Octavia MD, Zaini E, and Halim A. Characterization of Simvastatin – -Cyclodextrin Inclusion Complex prepared by the Kneading Method. Indonesian Pharmacy Journal. 2015;7(3):149–156.

[7] Martin et al, 2011

[8] Savjani KT, Gajjar AK, and Savjani JK. Drug Solubility: Importance and Enhancement Techniques. International Scholarly Research; 2012.

[9] Thakuria R, Delori A, Jones W, Lipert MP, Roy L, and Rodríguez-Hornedo N. 2013. Pharmaceutical cocrystals and poorly soluble drugs. International Journal of Pharmaceutics. 2013;453(1): 101–125.

[10] Kong R, Zhu X, Meteleva ES, Dushkin AV, and Su W. Physicochemical characteristics of the complexes of simvastatin and atorvastatin calcium with hydroxypropyl-β-cyclodextrin produced by mechanochemical activation. Journal of Drug Delivery Science and Technology. 2018;46: 436–445.

[11] Sopyan I, Syah UTI, Nurhayati D, and Budiman A. Improvement of Simvastatin Dissolution Rate Using Derivative Non-Covalent Approach By Solvent Drop Grinding Method. International Journal of Applied Pharmacy. 2020;12(1):21–24.

[12] Depkes RI, Farmakope Indonesia edisi VI. Jakarta: Kementrian Kesehatan Republik Indonesia; 2015.

[13] Komal K, Kaur T, Singh AP, Singh AP and Sharma P. Enhancement Of Solubility And Dissolution Of Simvastatin By Using Solid Dispersion Technique Along With Different Combination Of Polymes. Journal of Drug Delivery and Therapeutics. 2018;8(2):32–40.

[14] Kharisma RM, and Sopyan I. Dissolution Rate Repairing of Simvastatin as A New Approach in Cocrystallization. Der Pharm Lett. 2017;9(6):18–27.

[15] Gustaman F. The Effect of the Addition of Cremophor El on the Increase Simvastatin Dissolution Rate. Journal of Pharmacopolium. 2019;2(1).

[16] Nisha CM, Kumar A, Shulakari C. et al, Current and novel therapeutic molecules and targets in Alzheimer's disease. J. Formosan Med. Ass.2016: 115(1): 3-10.

[17] Miroshnyk I, Mirza S, Sandler N. Pharmaceutical co-crystals–an opportunity for drug product enhancement. Expert Opinion on Drug Delivery. 2009;6(4):333-341

[18] Pevorlich G. Melting points of one- and two-component molecular crystals as effective characteristics for rational design of pharmaceutical systems. Acta Crys. (2020). B**76**, 696-706

[19] Hanif AH, Alawamy JS. Detecting and Analyzing Land Use and Land Cover Changes in the Region of Al-Jabal Al-Akhdar, Libya Using Time-Series Landsat Data from 1985 to 2017**.** Sustainability MDPI**.** 2020; 12(11):4490

[20] Qoonita & Daryono, Analisis Molekuler Docking Senyawa Daun Sirsak (Annona muricata L.) sebagai Antidepresan Terhadap Reseptor Monoamine Oxidase A. Jurnal ilmiah ilmu Hayati. 2012;9(3): 247 -257.

[21] Braga D, Maini L and Fabrizia Grepioni. Mechanochemical preparation of co-crystals, Chem. Soc. Rev., 2013;42 (13):7638-7648.

[22] Erliyanti NK, Hanny F. Susianto SS, Altway A. THE PREPARATION OF FIXED CARBON DERIVED FROM WASTE TYRE USING PYROLYSIS. Chemistry & Chemical Engineering, Biotechnology, Food Industry. 2015;16 (4):343 – 352

[23] Gozali E, Kamnis S, Gu S, Numerical investigation of combustion and liquid feedstock in high velocity suspension flame spraying process. Surface and Coatings Technology. 20013; 228 (15):176-186.

[24] Jessica MA, Nugrahani I. Amino Acids as the Potential Co-Former for Co-Crystal Development: A Review. Molecules. 2021;26(11):3279.

[25] Sinkó, K, Géza S; Miklós Z. Liquid-Phase Synthesis of Cobalt Oxide Nanoparticles. Journal of Nanosci. Nanotech. 2011;119(5):4127-4135.

[26] Zaini E, Halim A, Soewandhi SN, and Setyawan D. Increasing the Dissolution Rate of Trimethoprim Through Cocrystal Method With Nicotinamide. Indonesian Pharmacy Journal. 2011;5(4):205–212.

[27] Okky Dwichandra Putra & Hidehiro Uekusa. Pharmaceutical Multicomponent Crystals: Structure, Design, and Properties. Springer Nature. 2020. pp 153–184

[28] Bal & Pn. Systemic Thrombolysis in Patients With Acute Ischemic Stroke and Internal Carotid ARtery Occlusion: The ICARO Study. Stroke. 2012;43(1).

[29] Bolourchian N, Mahboobian MM, Dadashzadeh S., The Effect of PEG Molecular Weights on Dissolution Behavior of Simvastatin in Solid Dispersions. Iran JP Res. 2013;12(suppl):11-12.

[30] Ainurofiq A, Mauludin R, Mudhakir D, and Soewandhi. Synthesis, Characterization, and Stability Study of Desloratadine Multicomponent Crystal Formation. Research in Pharmaceutical Science. 2018; 13(2):93–102.

[31] Wang H, Zhao P, Ma R, Jia J, Fu K. Drug–drug co-amorphous systems: An emerging formulation strategy for poorly water-soluble drugs. Drugs Discovery today. 2024; 9(2): 1359-6446

[32] Khan H, Aditya S. Yerramilli, Adrien D'Oliveira, Terry L. Alford, Daria C. Boffit. Experimental methods in chemical engineering: X-ray diffraction spectroscopy—XRD. Wiley online lib. 2020;98(6)1255-1266.