International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 4, 2023

Original Article

INCREASING SOLUTION IN THE DRUG SIMVASTATIN WITH SOLID DISPERSION TECHNIQUE USING POLYMER SOLUPLUS

IYAN SOPYAN[1,2*], MUHAMMAD RAIHAN RIYALDI[1], SORAYA RATNAWULAN MITA[1], MEYWAN HARIONO[3]

[1]Department Pharmaceutics and Technology of Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang-45363, West Java, Indonesia. [2]Center of study Drug Dosage Form Development, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang-45363, West Java, Indonesia. [3]Pharmaceutical Design and Simulation Laboratory, School of Pharmaceutical Sciences, Universiti Sains Malaysia-11800, Pulau Pinang, Malaysia

*Corresponding author: Iyan Sopyan; Email: i.sopyan@unpad.ac.id

Received: 25 Mar 2023, Revised and Accepted: 06 Jun 2023

ABSTRACT

Objective: Simvastatin is a bioactive compound belonging to the class II Biopharmaceutic Classification System (BSC), which has high permeability but low solubility. The low solubility of Simvastatin showed by low bioavailability so modification is required for its solubility.

Methods: There are many techniques to improve the solubility of poorly water-soluble drug; one of them is solid dispersion prepared by the solvent evaporation method. This study aims to determine the solid dispersion formulation of simvastatin using soluplus as a polymer with a ratio of 1:1, 1:2, 1:3, and 1:4 which is employed to increase the solubility and dissolution rate of simvastatin. Furthermore, characterization was carried out using IR spectrophotometry, differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD).

Results: The maximum solubility test yielded a 1:4 solid dispersion, which is up to 20 times more potent than pure simvastatin. Simvastatin's solubility increased from 17.33% to 82.50% for a 1:4 solid dispersion at 60 min, affecting the dissolution rate as well.

Conclusion: A solid dispersion was formed in an amorphous state, as evidenced by the fact that the results of characterization using IR spectrophotometry showed no new functional groups were formed in the solid dispersion, the results of characterization using Differential Scanning Calorimetry (DSC) showed a decrease in melting point, and the results of x-ray diffraction characteristics did not show a sharp peak.

Keywords: Solubility, Dissolution, Simvastatin, Solid dispersion, Soluplus

DOI: https://dx.doi.org/10.22159/ijap.2023v15i4.48293. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Simvastatin is a drug used to lower cholesterol levels in the blood. The mechanism of action of simvastatin is by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which competitively inhibits the cholesterol biosynthesis process in the body. Simvastatin will inhibit HMG-CoA reductase, so it will convert acetyl-CoA into mevalonic acid, which is a cholesterol precursor. Simvastatin given orally has a bioavailability of less than 5%, while as much as 95% is bound to plasma proteins [1]. Drugs that have low solubility are classified into BCS class II and IV. BCS class II has better permeability than class IV; therefore, drugs in class II need to be changed in terms of solubility to achieve the desired pharmacological effect [2]. In the case of low bioavailability, many are associated with poor solubility. In the pharmaceutical world, solubility is a very important thing. Solubility is also one of the various parameters that are important in determining the dose of drug administered in the systemic circulation to achieve a pharmacological response [3].

Simvastatin (fig. 1) is a strong antihyperlipidemic drug, especially in reducing LDL levels by up to 50%. Many studies on simvastain state that giving 40 mg of simvastatin can reduce the risk of myocardial infarction by about a quarter. Research conducted for about 5 y found that simvastatin can prevent about 70-100 per person from 1000 against coronary heart disease [4]. All drugs have side effects. Simvastatin also has side effects such as an increase in serum aminotransferase in some patients and also a minor increase in plasma keratin kinase [5].

Solid dispersion is a solid product that consists of at least two components, namely a hydrophobic drug and a hydrophilic matrix. The solid dispersion technique is a relatively simple and inexpensive method. In addition, solid dispersion can reduce particle size, increase the degree of porosity, increase wetting power, and make the drug in an amorphous form so that it can increase its solubility. The advantage of choosing a solid dispersion technique is that it can increase the solubility of drugs with low water solubility [6].

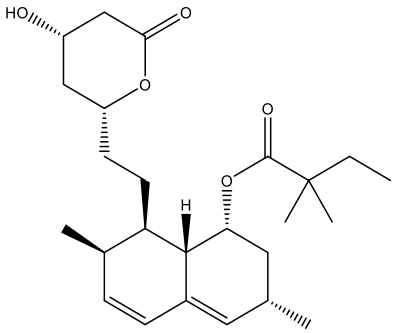

Fig. 1: Chemical structure of simvastatin (4)

Simvastatin was solidified in this study utilizing the soluplus polymer, which can interact with the medicine optimally by hydrogen bonding and boost system stability thanks to its unique structure through solvent evaporation. The bifunctional features of soluplus allow it to function as a matrix for solid solutions and dissolve pharmaceuticals with poor water solubility, making them appropriate for use in solid dispersion techniques. Soluplus has good water solubility properties [6].

MATERIALS AND METHODS

Materials

The materials used included simvastatin (Teva Hungary), aquadest (Global Scientific), soluplus (BASF), phosphate buffer pH 7, methanol (Sigma-Aldrich), and potassium bromide (Sigma-Aldrich).

Equipment

FTIR analytical zena (specord 100), Dissulotion apparatus (Sotax), DSC (Pan analytical), PXRD (Pan analytical).

Methods

Solid dispersion preparation

Solid dispersions were prepared by mixing simvastatin and soluplus polymer according to the ratios in table 3.1 using the solvent evaporation technique. The Simvastatin solution and Soluplus polymer were mixed until homogeneous using an evaporating dish, then allowed to evaporate at room temperature for 24 h. The dry mass obtained is taken and then ground and sieved using a sieve no. 80 and stored in vials [7].

Table 1: Dispersion formula with mass simvastatin to soluplus comparison (n=3)

Formula	Simvastatin	Soluplus
F1	1	1
F2	1	2
F3	1	3
F4	1	4

Preparation of the physical mixture

The physical mixture was prepared by weighing simvastatin and soluplus in a ratio of 1:1, 1:2, 1:3, and 1:4. Then it is mixed in parchment paper by stirring using a spatula, then put into a vial for storage.

Saturated solubility test

Several Simvastatin and solid dispersion (equivalent to 10 mg of Simvastatin) were each put into a vial containing 10 ml of aquadest. The vial must be closed using a cover layer. Then stirred using a linear shaker for 24 h to reach saturation at room temperature. After stirring, then the solution was filtered using Whatman filter paper no. 42. After that, the concentration of the sample was measured using a validated UV-Vis spectrophotometer at a wavelength of 238 nm [8].

Dissolution test

Simvastatin dissolution tests and solid dispersions were carried out according to the methods listed in the US Pharmacopeia using a type 2 dissolution test apparatus (paddle) at 37 °C, with constant stirring at 50 rpm. An amount of Simvastatin and the solid dispersion (equivalent to 40 mg of Simvastatin) was compressed to form a pellet. Then put into the dissolution medium (900 ml phosphate buffer pH 7). A total of 10 ml of samples were taken at intervals of 0, 5, 10, 20, and 30 min. The volume taken is replaced with a dissolution medium with the same volume. Furthermore, the samples were measured using a validated UV-Vis spectrophotometer at a wavelength of 238 nm [9-11].

Determination of spectra using fourier transform infrared (FTIR)

Tests were carried out on Simvastatin powder, solid dispersion, and physical mixtures. The sample in the form of powder was mixed with potassium bromide with a total sample of 2 mg and potassium bromide 248 mg, then ground until homogeneous and then compressed with a pressure of 60 psi. The infrared spectrum was measured using an infrared spectrophotometer. Measurements were carried out at a wavenumber of 4000-400 cm^{-1} using FT-IR [10].

Differential scanning calorimetry (DSC) analysis

This characterization test was carried out on Simvastatin, solid dispersion, and physical mixtures using a differential scanning calorimeter. 5 mg of the sample is placed in a closed aluminum frying pan. Then dry nitrogen was used as an inert gas with a flow rate of 50 ml/min and heating was measured at a temperature of 25-180 °C with a heating rate of 10 °C/minute [12].

Powder X-ray diffraction (PXRD) analysis

The crystal structure of simvastatin, solid dispersion, and physical mixture were analyzed by Powder X-Ray Diffraction (PXRD) under the following conditions: target/filter (monochromator) Cu (wavelength = 1.5406), voltage 40 kV, and current 20 mA. Data were collected with a scanning mode of 0.02 °/min with a scanning distance of 2θ = 2°-60° [12].

RESULTS AND DISCUSION

Result of solubility test

A solubility test was carried out on pure simvastatin and all simvastatin solid dispersion formulas that had been prepared. The solubility test aims to determine and compare the dissolved concentration of Simvastatin in water between pure Simvastatin and Simvastatin solid dispersion.

In this study, the solubility test was carried out using the Higuchi and Connor method in which the sample was dissolved in water and shaken for 24 h to achieve saturation. The results of the solubility test can be seen in fig. 1.

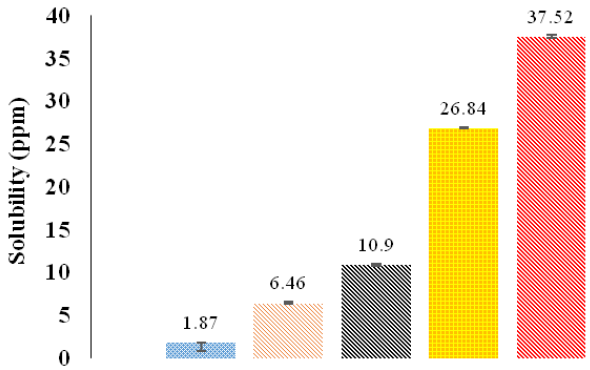

Fig. 2: Comparioson od solubilty value of simvastatin (blue), solid dispesion 1:1 (orange), solid dispesion 1:2(grey), solid dispesion 1:3 (yellow), solid dispesion 1:4 (red) (n=3)

Tests were carried out in triples. The results of the solubility test showed an increase in the concentration of Simvastatin dissolved in all Simvastatin solid dispersion samples. The optimum solubility increase was in formula F4 (with a saturated solubility of 37.52±0.18 µg/ml) compared to that of pure Simvastatin, which was 1.87±0 µg/ml. Solid dispersion was found to be significant (p<0.05). This shows a 20-fold increase in the solid dispersion formula compared to the solubility of pure Simvastatin.

Soluplus has a grafted structure of polyvinyl caprolactam-polyvinyl acetate-polyethyleneglycol giving Soluplus amphiphilic properties to produce micelles with a critical micelle concentration (CMC) of 7.6

mg/l [13]. As a consequence, the solubility of drugs that have poor solubility in water may increase [14].

The increase in solubility in Simvastatin solid dispersion can be caused by the formation of hydrogen bonds between Soluplus and the carbonyl group of Simvastatin so that the hydrogen bonds will arrest the movement of molecules in solid solution, prevent crystal formation, and make the solid dispersion stable in an amorphous form. Soluplus, with a carbonyl-amide group and a lipophilic chain is able to interact with hydrophobic drugs so as to cause hydration of the drug in aqueous solution. In addition, the amphiphilic nature of Soluplus will result in the formation of micelles in water so that it will dissolve the Simvastatin molecule [15–17].

Dissolution test result

The dissolution test is an important factor in drug quality control. The dissolution test was carried out to compare the dissolution profiles between tablet formulas, in the Indonesian Pharmacopoeia 6th Edition it was stated that the dissolution requirement of simvastatin tablets was 75% in the 30 min. fig. 2.

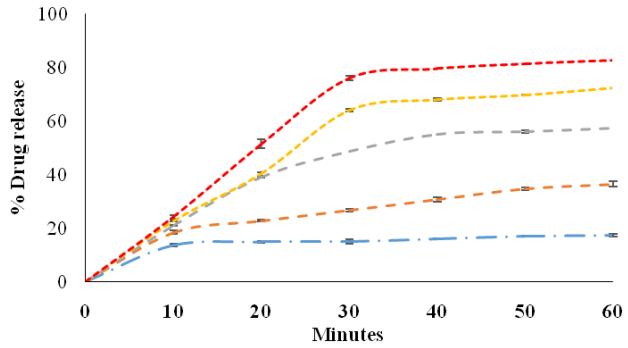

Fig. 3: Comparison disolution test of simvastatin (blue), solid dispesion 1:1 (orange), solid dispesion 1:2 (grey), solid dispesion 1:3 (yellow), solid dispesion 1:4 (red), (n=3)

This condition adapts to the dissolution of simvastatin tablets in the body. The dissolution test was carried out in triples. The results of the dissolution test showed that the solid dispersion of simvastatin had a higher dissolved concentration than pure simvastatin. In the 60 min, the dissolution of pure simvastatin was 17.33±0.524%, while the largest % dissolution was in the solid dispersion of Simvastatin: Soluplus (1:4) at the 60 min, which was 82.5±0.052%. Solid dispersion was found to be significant (p<0.05). In this case, the higher polymer content in the solid dispersion formulation results in higher and faster dissolution of drug particles. This is because soluplus can cause a decrease in the interfacial tension between the dissolution medium and the drug [18]. Increasing the dissolution rate in solid dispersion systems can be achieved through various mechanisms, including: Decreasing particle size of drug. When a solid dispersion is exposed to aqueous media, the carrier is dissolved first, followed by the release of the drug in the state of fine colloidal particles. As a result of increasing the surface area, it will cause an increase in the dissolution rate of the drug [19].

The drug is in an amorphous state, In the amorphous state, the drug will relatively have a higher solubility compared to its crystalline form, this is because in the amorphous state there is no energy needed to break the crystal lattice for the dissolution process [20]. Particles with increased wettability. Based on the research, there is a high effect of increasing drug limitations on increasing drug solubility in solid dispersion systems. Where the faster soluble polymer will increase the wettability of the active substance dispersed in it [21].

Particles with high porosity. Particles in solid dispersions are known to have high porosity; increasing this porosity will accelerate the drug-release process [22]. This increase is influenced by the shape and type of polymer used where polymers that have a linear shape will produce solid dispersions that have high porosity.

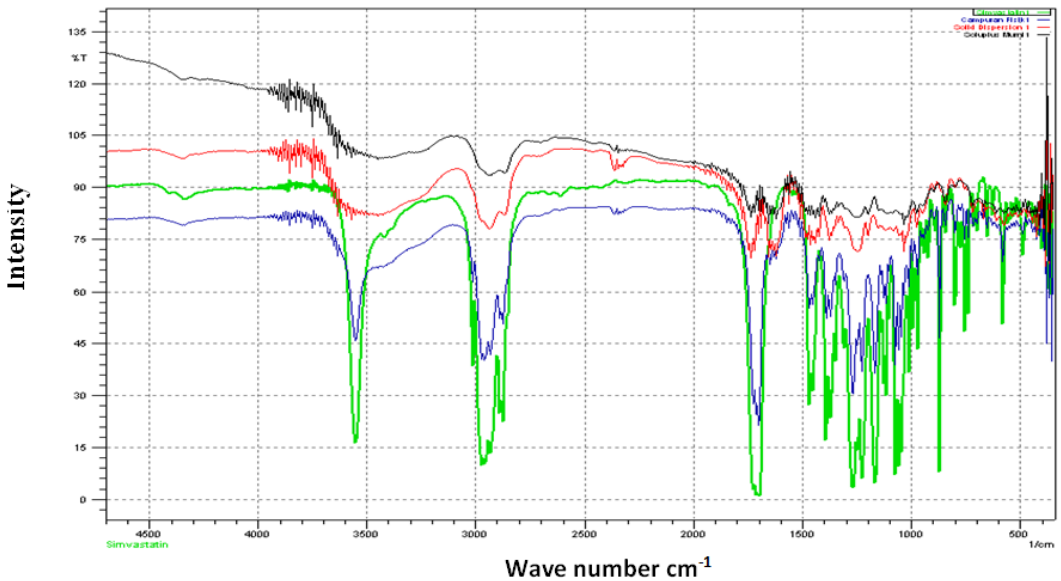

Fig. 4: Infrared spectrum overlay, simvastatin (green), physical mixture (blue), solid dispersion (1:4) (red), and soluplus (black)

FTIR analysis

Solid dispersion testing using an IR spectrophotometer was carried out to confirm whether a dispersion system was formed from the resulting solid. This test can also see if there are differences in functional groups between simvastatin and simvastatin solid dispersion by comparing the spectrum results obtained.

Making a solid dispersion between simvastatin and soluplus causes an interaction between the two. The interactions between the two substances are linked by hydrogen bonds. Hydrogen bonds are formed due to the carbonyl group of simvastatin which will bind to the hydroxy group on the soluplus, or vice versa. The hydrogen bond spectrum will appear in the wave number 3600-3200 cm^{-1} [23].

Based on the spectrum, the absorption peaks of simvastatin were observed at 3548 cm^{-1} (O-H stretch), 2929 cm^{-1} (C-H stretch), 1743 cm^{-1}, and 1695 cm^{-1} (C=O for esters and lactones). Then for soluplus, the peak widths were 3476 cm^{-1} (O-H stretch), 2934 cm^{-1} (C-H stretch), 1739-1653 cm^{-1} (C=O stretch), and 1478 cm^{-1} (C-O-C stretch for ether). which can be observed via the FTIR Spectrum. The spectrum in the physical mixture displays the characteristic peak of the drug simvastatin at 3548 cm^{-1} (O-H stretch) but it is clear that in the solid dispersion spectrum the peak disappears. The absence of stretching on the O-H has been previously reported for drugs that are molecularly dispersed in polymers which can be evidenced. amorphous properties of the drug [12]. The resultant spectrum of solid dispersion is more similar to that of polymer, this is because simvastatin is already dispersed in soluplus polymer, therefore the spectral properties of solid dispersion are more similar to soluplus polymer. In addition, the stretching of the carbonyl ester functional group showed a shift from 1743 to 1735 cm^{-1}. This shift of ester bond peaks represents intermolecular hydrogen bonding, which is also in agreement with the literature reported by Zhang, *et al.*, 2016 [24] and Löbmann, *et al.*, 2012 [25]. FTIR results show a favorable interaction between drug and polymer. In addition, the amorphicity of the drug in solid dispersions can be beneficial, as it usually shows an increase in drug dissolution, while the surrounding polymer matrix can prevent recrystallization of the drug [12].

Differential scanning calorimetry (DSC)

Characterization of solid dispersion using Differential Scanning calorimetry (DSC) was carried out to see the solid-state interaction between two or more materials by observing changes in thermodynamic properties when a substance is given heat energy. (fig. 4.) Changes in the crystallinity or amorphous nature of a solid can be seen by the enthalpy change when each diffractogram is compared. The decrease in the melting point of the solid dispersion correlates with the increase in the solubility value of the active substance in the solid dispersion. The melting point of the solid dispersion is between or below the melting point of the active substance and its polymer so that the physicochemical properties of the solid dispersion depend on the polarity of the polymer [26].

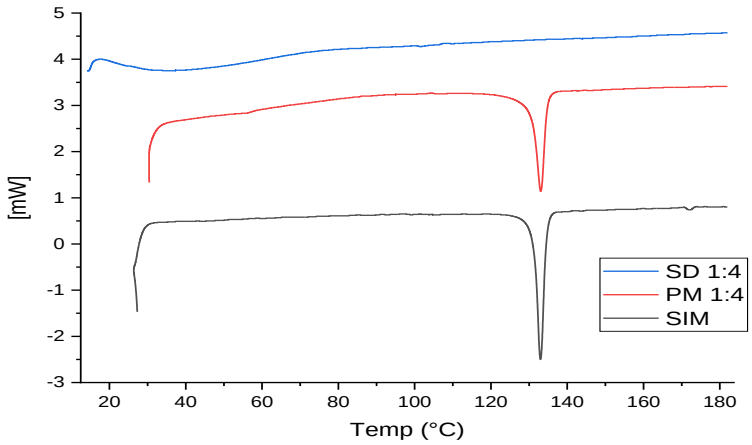

Fig. 5: Differential scanning calorimetry results SD 1:4 (blue), physical miture (PM) (red), simvastatin (black)

It can be seen from the thermogram above that pure simvastatin has an endothermic peak at an onset temperature of 131.48 °C and a peak at a temperature of 134.42 °C with an enthalpy value of-21.51 J/g. The physical mixture of simvastatin: soluplus shows an endothermic peak at an onset temperature of 130.98 °C with a peak temperature of 134.56 °C and has an enthalpy of-17.80 J/g. Then based on the above thermogram, it can be seen that the solid dispersion of simvastatin: soluplus (1:4) shows an endothermic peak at an onset temperature of 22.14 °C with a peak temperature of 61.89 °C and has an enthalpy of-16.14 J/g. Based on the data above, it can be seen that the physical mixture of simvastatin: soluplus (1:4), and the solid dispersion of simvastatin: soluplus (1:4) showed a decrease in melting point when compared to pure simvastatin. This indicates the presence of most of the simvastatin dissolved in the polymer melt. The difference in melting point also allows an increase in the solubility of the active pharmaceutical ingredients in the form of solid dispersions [27]. The absence of a sharp peak in the drug melt indicates the presence of a glass transition, where simvastatin is mostly dispersed in the polymer matrix [12]. In addition, seen from the enthalpy of each solid dispersion, it can be seen that there is a decrease in enthalpy which is related to a change in the relative energy required to break bonds between solute molecules so that the smaller the enthalpy, the energy required to break the bonds of the solute. Becomes lower and solubility becomes higher.

Powder X-ray diffractometer (PXRD)

Solid dispersion testing using a powder X-ray Diffract meter aims to see whether or not there is a change in crystallinity after the solid dispersion manufacturing process. From the solid dispersion formula simvastatin: soluplus (1:4) was compared with pure simvastatin. X-ray diffraction can see changes in crystal properties and or the formation of a new phase [28].

The diffractogram of simvastatin has sharp peaks with high intensity at angles of 2θ = 7.7°, 9.1°, 10°, 10.9°, 17°, 19.1°, 22.4°, 29.3°, and 31.9°. This shows that simvastatin is naturally present in crystalline form. As for solid dispersions, the diffractogram pattern forms a halo diffractogram which is a characteristic of the formation of amorphous solid dispersions. The presence of this pattern indicates a decrease in the crystallinity of the solid dispersion compared to pure simvastatin [29]. The halo diffractogram formed in the amorphous solid dispersion system is caused by the fact that amorphous materials do not have long periodicity (regularity) unlike crystals so the root X-rays are diffracted in all directions, which form a "large bump" with an angle of 2θ which tends to be larger. The amorphous nature resulting from the formation of a solid dispersion is related to the increased solubility of simvastatin compared to the pure drug. The increase in solubility and dissolution rate of amorphous solids compared to their crystalline

form is related to interactions between molecules where in the amorphous state there is an increase in interactions between molecules compared to crystal forms which tend to be more rigid in structure (crystals have higher periodicity or regularity) [30-32].

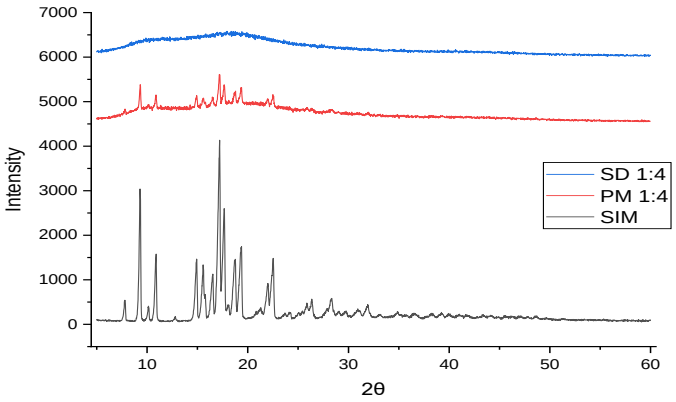

Fig. 6: Powder X-ray Diffractometer results SD 1:4 (blue), physical miture (PM 1:4) (red), simvastatin (black)

CONCLUSION

Manufacturing of simvastatin solid dispersion with soluplus polymer by solvent evaporation method can increase simvastatin solubility. The solid dispersion that had the best solubility was the simvastatin-surplus 1:4 solid dispersion which was 20 times that of pure simvastatin. The dissolution rate of simvastatin-surplus solid dispersion 1:4 with a phosphate buffer medium of pH 7.0 was compared with pure simvastatin, from 17.33±0.524% to 82.50±0.052%. The results of characterization using FTIR showed that there were no new functional groups formed from the process of making solid dispersions, then for X-ray diffraction analysis showed the presence of amorphous formation in solid dispersions, and DSC analysis results showed a decrease in the melting point of solid dispersions.

ACKNOWLEDGMENT

We acknowledge DRPMI UNPAD research grant provider and KEMENDIKBUD RI.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFFERENCES

1. Alakhali K. Pharmacokinetic of simvastatin study in Malaysian subjects. IOSRPHR. 2013 Jan;3(1):46-51. doi: 10.9790/3013-31104651.
2. Levin M, editor. Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. In: Informa Healthcare; 2001. Pharmaceutical process scale-up. Available from: http://www.crcnetbase.com doi: 10.1201/9780824741969.
3. Di L, Kerns E. Drug-like properties: concepts, structure design and methods from ADME to toxicity optimization. Academic press; 2015.
4. Heart Protection Study Collaborative Group. Effects on 11 y mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 y in 20 536 high-risk individuals: a randomised controlled trial. Lancet. 2011;378(9808):2013-20. doi: 10.1016/S0140-6736(11)61125-2.
5. Katzung BG, Trevor AJ. Basic and clinical pharmacology; 2012.
6. Wairkar SM, Gaud RS. Solid dispersions: solubility enhancement technique for poorly soluble drugs. Int J Res Pharm Biomed Sci. 2013;4(3):847.
7. Singh P, Nanda A. Preparation, characterization and dissolution study of spray dried solid dispersions of simvastatin with PVP k 25 and Aerosil 200. Journal of Medical Pharmaceutical and Allied Sciences. 2021;10(6):3806-12.
8. Hosny KM, Khames A, Elhady SSA. Preparation and evaluation of orodispersible tablets containing hydroxylbutyl-β-cyclodextrin-simvastatin solid dispersion. Trop J Pharm Res. 2013;12(4):469-76. doi: 10.4314/tjpr.v12i4.4.
9. Gustaman F. Pengaruh penambahan cremophor El terhadap peningkatan laju disolusi tablet simvastatin. J Pharmacopolium. 2019;2(1). doi: 10.36465/jop.v2i1.471.
10. Sopyan I, Pallanisamy T, Wardhana YW. Polymorpism of simvastatin: an effort to repair solubility and dissolution rate. Pharm Lett. 2017;9(6):18-27.
11. Mehmood Y, Hammad Yousaf AK, Bashir I, Majeed I. Preparation and characterization of solid dispersion tablet of simvastatin employing starch phosphate as carrier. International Journal of Chemical and Pharmaceutical Sciences. 2014;5(2):79-84.
12. Nandi U, Ajiboye AL, Patel P, Douroumis D, Trivedi V. Preparation of solid dispersions of simvastatin and Soluplus using a single-step organic solvent-free supercritical fluid process for the drug solubility and dissolution rate enhancement. Pharmaceuticals (Basel). 2021;14(9):846. doi: 10.3390/ph14090846, PMID 34577546.
13. Compendium S. Solubility enhancement with BASF pharma polymers. Lampertheim, Germany: Pharma Ingredients and Services; 2011.
14. Zhu C, Gong S, Ding J, Yu M, Ahmad E, Feng Y. Supersaturated polymeric micelles for oral silybin delivery: the role of the Soluplus–PVPVA complex. Acta Pharm Sin B. 2019;9(1):107-17. doi: 10.1016/j.apsb.2018.09.004, PMID 30766782.
15. Zi P, Zhang C, Ju C, Su Z, Bao Y, Gao J. Solubility and bioavailability enhancement study of lopinavir solid dispersion matrixed with a polymeric surfactant–soluplus. Eur J Pharm Sci. 2019;134:233-45. doi: 10.1016/j.ejps.2019.04.022, PMID 31028820.
16. Prasad R, Radhakrishnan P, Singh SK, Verma PRP. Furosemide–soluplus® solid dispersion: development and characterization. Recent Pat Drug Deliv Formul. 2017;11(3):211-20. doi: 10.2174/1872211311666171129120020, PMID 29189186.
17. Hardung H, Djuric D, Ali S. Combining HME and solubilization: Soluplus®-the solid solution. Drug Deliv Technol. 2010;10(3):20-7.
18. Shamma RN, Basha M. Soluplus®: A novel polymeric solubilizer for optimization of carvedilol solid dispersions: formulation design and effect of method of preparation. Powder Technol. 2013 Mar;237:406-14. doi: 10.1016/j.powtec.2012.12.038.
19. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281-302. doi: 10.1002/jps.2600600902, PMID 4935981.

20. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of a low Tg drug. Powder Technol. 2006;167(1):20-5. doi: 10.1016/j.powtec.2006.05.012.
21. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. Eur J Pharm Biopharm. 2006;63(2):103-14. doi: 10.1016/j.ejpb.2006.01.016, PMID 16675209.
22. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23-24):1068-75. doi: 10.1016/j.drudis.2007.09.005, PMID 18061887.
23. Harmita H. Buku ajar analisis fisikokimia. Jakarta dep farm FMIPA ui. UI Press. 2006:120-3.
24. Zhang Y, Liu Y, Luo Y, Yao Q, Zhong Y, Tian B, et al. Extruded Soluplus/SIM as an oral delivery system: characterization, interactions, in vitro and in vivo evaluations. Drug Deliv. 2016;23(6):1902-11. doi: 10.3109/10717544.2014.960982, PMID 25268150.
25. Lobmann K, Strachan C, Grohganz H, Rades T, Korhonen O, Laitinen R. Co-amorphous simvastatin and glipizide combinations show improved physical stability without evidence of intermolecular interactions. Eur J Pharm Biopharm. 2012;81(1):159-69. doi: 10.1016/j.ejpb.2012.02.004, PMID 22353489.
26. Aakeroy CB, Fasulo ME, Desper J. Cocrystal or salt: does it really matter? Mol Pharm. 2007;4(3):317-22. doi: 10.1021/mp060126o, PMID 17497799.
27. Zaini E, Halim A, Soewandhi SN, Setyawan D. Peningkatan laju pelarutan trimetoprim melalui metode ko-kristalisasi dengan nikotinamida. J Farmasi Indones. 2011;5(4):205-12.
28. Mulye SP, Jamadar SA, Karekar PS, Pore YV, Dhawale SC. Improvement in physicochemical properties of ezetimibe using a crystal engineering technique. Powder Technol. 2012;222:131-8. doi: 10.1016/j.powtec.2012.02.020.
29. Mishra MK, Ray D, Barik BB. Microcapsules and transdermal patch: a comparative approach for improved delivery of antidiabetic drug. AAPS PharmSciTech. 2009;10(3):928-34. doi: 10.1208/s12249-009-9289-z, PMID 19629706.
30. Gracin S, Rasmuson AC. Solubility of phenylacetic acid, p-hydroxyphenylacetic acid, p-aminophenylacetic acid, p-hydroxybenzoic acid, and Ibuprofen in Pure Solvents. J Chem Eng Data. 2002;47(6):1379-83. doi: 10.1021/je0255170.
31. Sopyan I, Sari IM, K IS. Solid state characterization of a novel physical interaction (paracetamol-chlorphenoramine maleate). Int J Appl Pharm. 2018;6:21-5.
32. Sopyan I, Fudholi A, Muchtaridi M, Puspitasari I. A simple effort to enhance solubility and dissolution rate of simvastatin using co-crystalization. Int J Pharm Pharm Sci. 2016;8(8):342-6.