

IMPROVEMENT OF SIMVASTATIN SOLUBILITY USING HPMCAS, LOCUST BEAN GUM, SODIUM ALGINATE AND TPGS AS A POLYMER WITH SOLID DISPERSION METHOD

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ABSTRACT

Objective: Simvastatin (SV) is a cholesterol-lowering drug that classified in BCS (Biopharmaceutics Classification System) Class II class with high permeability but low solubility value. This study aims to obtain a solid dispersion formula that can increase the solubility of Simvastatin. HPMCAS, Locust Bean Gum, Sodium Alginate, and TPGS are four candidate polymers that will be selected by *in silico* study to make a solid dispersion formula.

Methods: The solid dispersion was prepared with two polymers, Locust Bean Gum (LBG), which has no hydrogen bonds with Simvastatin, and Sodium Alginate (SA), which has hydrogen bonds with Simvastatin, made by the ratio of mass 1:1, 1:2, 1:3, 1:4. Materials were evaluated by solubility and dissolution studies, then characterized using FTIR, DSC, and PXRD.

Results: Each drug-polymer ratio showed an increase in solubility and dissolution, but the SV-LBG formula (1:4) showed the largest increase, with a 4 folded increase in solubility and a roughly 2 folded increase in dissolution. The characterisation FTIR data demonstrate that the drug molecules are disseminated inside the polymer, and the PXRD diffractogram demonstrated a decrease in crystallinity to the amorphous phase, and the DSC thermogram also demonstrated changes in thermal behavior.

Conclusion: Solid dispersion is a promising method for increasing the solubility of simvastatin. The use of locust bean gum polymer was proven to increase the solubility and dissolution of simvastatin with the best formula SV-LBG (1:4).

Keywords: Solubility, Simvastatin, Solid dispersion

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INTRODUCTION

Drug solubility in water is the main parameter in drug formulation because it greatly affects the pharmacokinetic and pharmacodynamic properties of the drug. Recorded in 2015, compounds that are poorly soluble in water make up 40% of the top 200 oral drugs marketed in the United States [1]. Drugs that have low water solubility often require higher doses to achieve therapeutic plasma concentrations after oral administration. In addition, water-insoluble drugs have slow absorption resulting in inadequate and variable bioavailability, which causes gastrointestinal mucosal toxicity [2].

Simvastatin belongs to a group of drugs known as HMG-CoA reductase inhibitors or statins. This type of drug works by inhibiting certain types of enzymes needed to make cholesterol [3]. In the oral delivery route, there is a relationship between drug absorption and gastric permeability and solubility, namely Biopharmaceutics Classification System (BCS). Simvastatin belongs to BCS Class II, which has high permeability but low solubility (3×10^{-2} mg/l), with a bioavailability of 5%, indicating extensive first-pass metabolism in the liver. Therefore, it is very important to increase the solubility in water, dissolution rate and bioavailability of the oral solid dosage form [4, 5].

The solubility of poorly soluble drugs can be increased by various techniques. Some of them are forming a nanosuspension, co-crystallization, derivatization, solid dispersion, and salting [2]. Among the various methods, the drug solid dispersion system in a hydrophilic carrier is one of the most effective methods. Solid dispersion is the process of dispersing one or more active ingredients in an inert hydrophilic carrier in which the system can be prepared by various methods, such as melting, dissolving, and melting-dissolving [6]. The advantages of solid dispersions are simple to prepare, easy to optimize, and has reproducibility. In addition, this method has been used for 10-15 y so it is very promising to increase oral absorption and bioavailability of BCS Class II drugs [7].

The choice of carrier has a major influence on the dissolution characteristics of the dispersed drug since the dissolution rate of one surface component is affected by the other components in the mixture. Therefore, the carrier is hydrophilic, resulting in faster drug release from the matrix. The carrier must also be inert and drug compatible [8, 9].

The binding interaction and stability of the compound with the active drug ingredients can be seen through *in silico* studies. The interaction between drug and polymer is seen through *ligand-ligand* docking [10, 11]. HPMCAS, Locust Bean Gum, Sodium Alginate, and TPGS, are polymers that can be used to increase the solubility and dissolution of BCS class II drugs [12–15].

Locust bean gum (LBG) or commonly called carob gum or ceratonia is a natural plant material consisting of hydrocolloid polysaccharides consisting of D-galactose and D-mannose linked by glycosidic bonds [13]. Natural polymers when used in appropriate amounts can increase the dissolution rate due to their low viscosity and high swelling capacity making them a better alternative [16]. The use of LBG as a solid dispersion carrier has increased the dissolution of lovastatin by 53% compared to pure lovastatin, which only releases about 35% [17].

Sodium alginate is a hydrophilic polysaccharide consisting of the sodium salt of alginic acid. The use of alginate ester derivatives has proven to be a good solid dispersion carrier to increase the water solubility of poorly soluble compounds [14, 18, 19]. The use of sodium alginate as a carrier for telmisartan solid dispersion system can increase the drug dissolution rate by >80% within 30 min [14].

MATERIALS AND METHODS

Materials

Locust Bean Gum (YTBIO), Methanol (Sigma-Aldrich), Simvastatin (Hungary Teva), Potassium Bromide (Sigma-Aldrich), Potassium Phosphate Monobasic (Merk), Sodium Alginate (Kimica International), Sodium hydroxide (Merck KGaA).

In silico studies

The 2D structure of the polymer and Simvastatin was drawn using ChemDraw and saved in .cdx format. The structure file format was then converted to .pdb using the Chem3D and converted to .pdbqt by AutoDockTools. Through the PyRX with the Vina Wizard feature, the SV molecule is then inserted into the polymer cavity and observed whether there is an interaction [11].

Preparation of simvastatin solid dispersion

The solid dispersion system was made using the solvent evaporation method with the ratio of Simvastatin and polymer 1:1, 1:2, 1:3, and 1:4 w/w. Drug and polymer were mixed and partly methanol was added with continuous stirring until the mixture was completely dissolved. This mixture was evaporated at room temperature until a solid mass was obtained. This mass was pulverized using a mortar and pestle and then passed through an 80-mesh sieve to obtain a fine solid dispersion [20, 21].

Solubility studies

Drug substance and the solid dispersion equivalent to 10 mg SV were dissolved in 10 ml of distilled water in a vial and then placed in a shaker (IKA HS260 basic) for 24 h at room temperature (25 °C). Saturated solubility was measured by the validated UV-Vis spectrophotometer method (Analytik Jena Specord 200) at a wavelength of 238 nm [22].

Dissolution studies

The dissolution test was carried out using a paddle-type USP dissolution apparatus (Sotax AT7 Smart Dissolution Tester). Into the dissolution tube, 900 ml of phosphate buffer pH 7.0 was added. The speed is set to 50 rpm at 37±0.5°C. In each tube, a sample powder equivalent to 40 mg of SV was added. Aliquots (10 ml) were withdrawn at pre-determined time intervals of 0, 10, 20, 30, 40, 50 and 60 min with, replenished on each occasion with the same volume of dissolution fluid. The solution was measured using a UV-Vis spectrophotometer at 238 nm [23, 24].

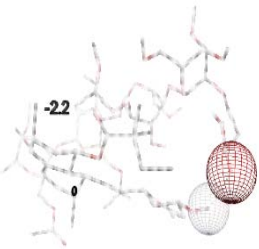
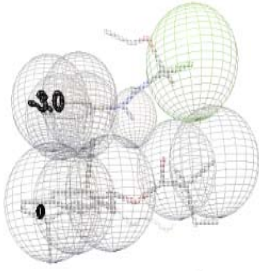
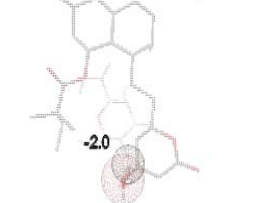
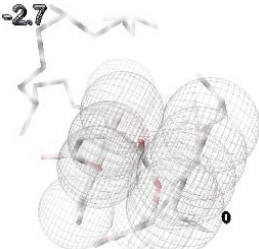
Fourier transform infrared (FTIR)

A total of 2 mg of sample was mixed with 248 mg of potassium bromide crystals and homogenized. The mixture then compressed with a pressure of 60 Psi. The spectrum was measured in the range of 400–4000 cm⁻¹ using an FTIR spectrophotometer (IRPrestige-21 Shimadzu) [22].

Differential scanning calorimetry (DSC)

The differential scanning calorimetric measurements were performed using DSC (DSC-60 plus Shimadzu). Each sample was taken an amount of 2 mg and sealed in an aluminum pan. The sample is heated at 10°C/min from 25°C to 180°C in an inert environment. The environment was maintained using nitrogen gas at a flow rate of 50 ml/min [6, 21].

Table 1: The result of in silico studies (n=100)

Compound	Complex structure	Interaction	Binding energy (kcal/mol)	Hydrogend bond energy (kcal/mol)
SV-HPMCAS		1 hydrogen bond dan 9 hydrophobic interactions	-2,2	-0,144
SV-LBG		11 hydrophobic interactions	-3,0	-
SV-SA		1 hydrogen bond dan 10 hydrophobic interactions	-2,0	-4,431
SV-TPGS		15 hydrophobic interactions	-2,7	-

Powder X-ray diffraction (PXRD)

An X-ray powder diffraction study was carried out using an X-Ray Diffractometer (Bruker D8 Advance) to evaluate its crystallinity. XRD patterns were measured on 100 mg of the sample using a diffractometer and Ni-filtered Cu-K α radiation (1.5406 Å) under the voltage 40 kV, current 20 mA, receiver gap 0.2q inch, 2 θ range 5-60°C, scan rate 0.02 °/s [25, 26].

RESULTS AND DISCUSSION

In silico studies

In silico studies were carried out to predict candidate compounds to be made into solid dispersion formulas. By conducting this study, drug interactions with polymers, such as the presence of intermolecular interactions in the form of hydrogen bonds can be predicted. In solid dispersion systems, interactions between drugs and polymers do not always occur, so the selection of polymers for solid dispersion formulas is chosen based on the presence of interactions and the absence of interactions (table 1).

The *in silico* study showed that of the four candidate polymers, HPMCAS and Sodium Alginate (SA) were hydrogen bonded to Simvastatin (SV), while the other two polymers were not hydrogen bonded, which can be seen in table 1. Hydrogen bond is a non-covalent interaction between a hydrogen atom and an electronegative atom. The role of hydrogen bonding in the physicochemical properties of active pharmaceutical ingredients is in their solubility and dissolution properties [27, 28]. Meanwhile, the

binding energy indirectly indicates the ability of the drug to bind to the receptor. The binding affinity of the drug with the receptor will be higher as the binding energy decreases [29].

The binding affinity of a molecule is strongly influenced by the size, shape, and functional groups of the molecule. Hydrophilic molecules tend to have weaker binding affinity than hydrophobic molecules of the same size and shape. The number of hydrophobic interactions will affect the stability of the bond, where the more the number of hydrophobic interactions, the more negative the bond affinity so that the complex will be more stable. SV-LBG complex has the lowest binding energy with 11 hydrophobic interactions. The SV-TPGS complex has more hydrophobic interactions but lower binding energy. This could be due to the larger molecular size of TPGS than LBG. Molecular size that is too large will affect the binding affinity because there is a mismatch with the cavity space [30, 31].

Therefore, Sodium Alginate was chosen as the drug hydrogen-interacting polymer with the lowest hydrogen bond energy and Locust Bean Gum, which has no hydrogen-drug interaction with the lowest binding energy.

Solubility studies

Solubility is an important parameter to achieve the drug concentration in the systemic circulation in order to obtain the desired pharmacological response [2]. In the solubilization process, when the solid dispersion system is exposed to an aqueous medium, the carrier will dissolve and then the drug is released as fine colloidal particles [32].

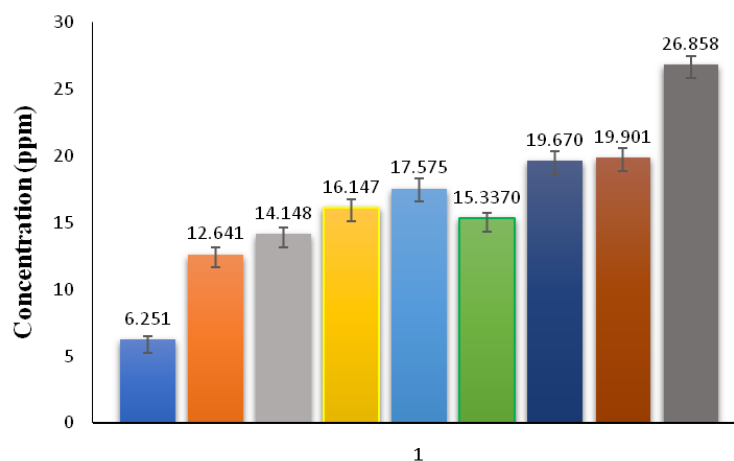


Fig. 1: Saturated solubility graph of simvastatin and solid dispersion system, simvastatin (blue light), SV: sodium alginate 1:1 (orange), SV: sodium alginate 1:2 (light grey), SV: Sodium alginate 1:3 (yellow), SV: sodium alginate 1:3 (light blue), SV: locust bean gum 1:1 (green), SV: locust bean gum 1:2 (dark Blue), SV: locust bean gum 1:3 (brown), and SV: locust bean gum 1:4 (dark grey) (n=3)

Saturated solubility studies (fig. 1) revealed that all drug-polymer solid dispersion formulas had increased solubility significantly ($p < 0.001$) compared to the native drug. The highest solubility was obtained in the solid dispersion of SV-LBG (1:4) with a concentration of 26.858 ± 0.59 ppm, which increased 4 times compared to native drug (6.251 ± 0.22 ppm). In each formula, it was seen that the solubility increase was higher as the ratio increased. So it can be concluded that the more polymer used, the solubility will be greater (fig. 1).

The increase in solubility that occurs can be caused by the nature of the carrier polymer used. As a carrier, LBG can reduce particle size, has the ability to wet, and reduce drug crystallinity during the formulation of the mixture so that it can increase drug solubility [13]. Although not as good as SV-LBG solid dispersion, there is also an improvement in the SV-SA solid dispersion formula in each comparison. The increase in the solubility of the SV-SA solid dispersion system in water was due to a reduction in the particle size of SV and its molecular dispersion into a hydrophilic carrier

(SA), which caused a change in the original crystalline form to a soluble amorphous form [33].

Dissolution evaluation

The dissolution test was carried out on the pure drug and two solid dispersion formulas with the best-increasing solubility in each polymer (fig. 2). The solid dispersion formulas selected were SV-LBG (1:3), SV-LBG (1:4), SV-NA (1:3), and SV-NA (1:4). The ratios of 1:3 and 1:4 was chosen to see whether increasing the ratio affected the dissolution rate or not.

During the dissolution process, after the dispersion system is in contact with the dissolution medium, the media permeates to the drug carrier particles so as to form a carrier gel layer around the particles. The carrier particles must be dispersed rapidly throughout the dissolution medium in order to promote drug release. High carrier viscosity will result in the formation of agglomerates of drug carrier particles during dissolution, thereby inhibiting the dissolution process [17].

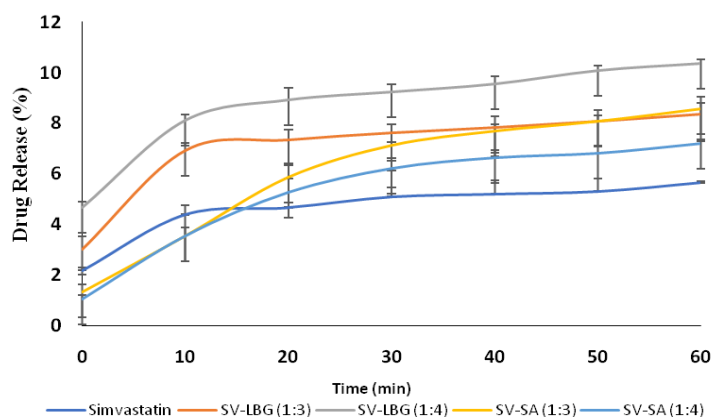


Fig. 2: Comparative dissolution study of simvastatin and solid dispersion in various comparison (n=3)

As seen in fig. 2, there is an increase in the dissolution of each solid dispersion formula compared to the native drug. Similar to the results of the solubility studies, the highest increase in dissolution rate was found in the SV-LBG formula (1:4), which was $9.241 \pm 0.30\%$ at 30 min. The dissolution rate in the SV-LBG formula (1:4) has a significant increase ($p < 0.05$), approximately 2 times greater than the native drug ($5.091 \pm 0.36\%$ at 30 min). Meanwhile, the best solid dispersion formula with sodium alginate is in the SV-SA ratio (1:3) with a dissolution rate of $7.136 \pm 0.10\%$ in 30 min with an increase of approximately 1.4 times. This shows that the ability of SA to increase the dissolution of solid dispersion systems is only up to a certain concentration. A higher number of polymers allows an increase in the viscosity of the system, thereby reducing the diffusivity of the drug and its dissolution rate [34]. Therefore, the SV-LBG formula (1:4), which is the formula with the best solubility increase and dissolution rate, was chosen for characterization.

In the SV-LBG solid dispersion formula, the increase in dissolution rate is most likely due to an increase in wettability, a decrease in drug particle size, and a reduction in drug crystallinity [35]. The sodium alginate in the SV-SA solid dispersion has an influence on the solid-state properties and dissolution behavior of the solid dispersion. The particle size and crystallinity of the solid dispersion are reduced compared to the pure drug, thereby increasing the dissolution rate. At certain concentrations, the addition of SA to a solid dispersion system has the potential to reduce the energy required for drug dissolution [34].

Fourier transform infrared (FTIR)

FTIR spectroscopy is one of the characterization methods used to determine the presence of functional groups in a molecule (fig. 3). The interaction between the drug and the solid dispersion carrier can be seen in the infrared spectrum. Solid dispersion systems can cause changes in the molecular structure of the drug in the matrix [7, 35].

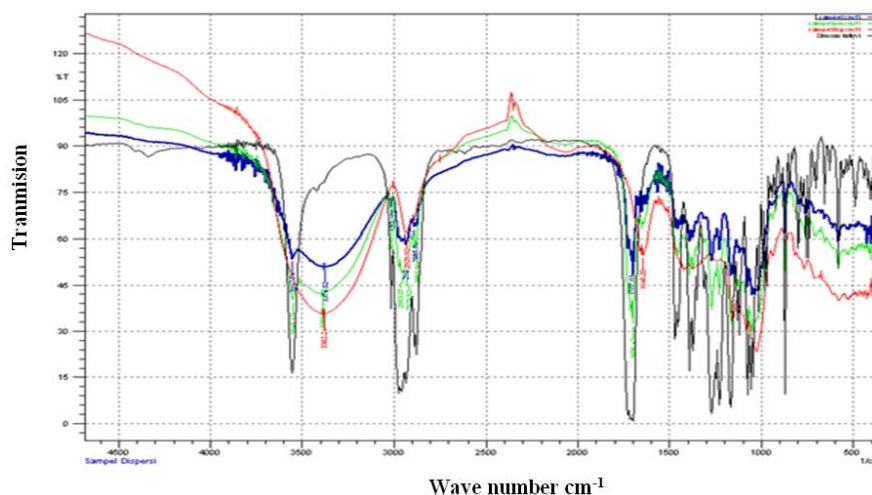


Fig. 3: FTIR spectra of simvastatin (black), locust bean gum (red), solid dispersion SV-locust bean gum (1:4) (blue), physical mixture SV-LBG (1:4) (green) (n=3)

Fig. 3 shows the IR spectra of the pure drug, Locust Bean Gum, solid dispersion (SD) SV-LBG (1:4), and physical mixture (PM) SV-LBG (1:4). The native SV spectrum showed peaks at 1669.42 cm^{-1} (C=O stretching vibration), 2970.43 cm^{-1} (C-H stretching vibration), and 3551.98 cm^{-1} (O-H stretching vibration). On the other hand, the spectrum of LBG showed peaks at 2929.92 cm^{-1} (C-H stretching vibration) and 3382.2 cm^{-1} (O-H stretching vibration). The main peak of the SV spectrum was also seen in the SD SV-LBG (1:4) and the PM SV-LBG (1:4), which indicated that there was no chemical interaction between the pure drug and the carrier polymer [20].

Comparing the spectrum of SD SV-LBG (1:4) and CF SV-LBG (1:4) with the native drug, the peak of O-H stretching vibration was more

similar to the peak in pure LBG. This may be due to the dispersed drug molecules in the carrier polymer. It was found that the peak of the carbonyl group (C=O) in the solid dispersion formula shifted towards a higher wave number with lower intensity. Solid dispersion spectrum showed no change or addition of new functional groups, which indicates that the overall symmetry of the molecule is not affected [25].

Differential scanning calorimetry (DSC)

In solid dispersion, DSC was performed to characterize the sample by observing endothermic peaks on the thermogram. The endothermic peak generally corresponds to the melting point of the pure drug and

indicates the crystalline nature. If no peak is observed, it indicates that the particles have been dispersed into amorphous [6, 33].

In DSC studies (fig. 4), the endothermic peak of native drug was found at 132.98 °C near the melting point of the drug (135–138 °C), indicating its crystalline nature [36]. The SD SV-LBG (1:4) had a peak

of 41.55 °C, which may be due to moisture loss, and a peak of 130.88 °C. The shift of the peak to lower temperature indicates a decrease in the melting point of the drug. In addition, the peak intensity of the solid dispersion formula also decreased. This minor difference in peak angle and intensity indicates a slight change in drug morphology, from crystalline to amorphous form [13, 37].

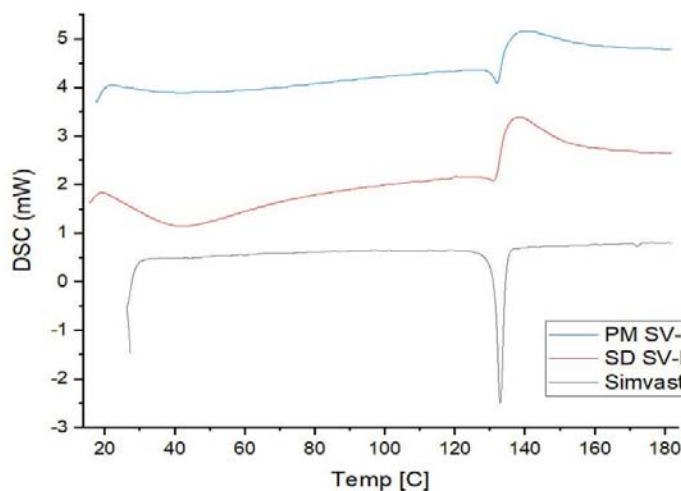


Fig. 4: DSC thermograms of simvastatin (black), SD SV-LBG (1:4) (red), PM SV-LBG (1:4) (blue) (n=2)

The enthalpy value of the solid dispersion formula was found to have decreased compared to that of pure SV, by -18.99 J/g and -21.61 J/g, respectively. This can be interpreted as a change in the relative energy required to break the solute intermolecular bonds. The smaller the enthalpy value, the lower the energy required to break the solute bonds. Therefore, the low enthalpy value can cause an increase in solubility indirectly [38].

Powder X-ray diffraction (PXRD)

PXRD is one of the characterization techniques used to see the solid properties of drugs. The diffractogram allows to know whether the drug state is in crystalline or amorphous state by comparing the peak heights of the solid dispersion compared to the native drug. In solid dispersions, the number of diffraction peaks indicates crystalline nature and the appearance of a halo diffractogram interprets the amorphous form [13, 25, 37].

The PXRD diffractogram can be seen in fig. 5. Diffractogram of native drug shows sharp peaks with high intensity. The pattern shows the crystalline nature of pure SV [21]. In the SD SV-LBG diffractogram (1:4), it was found that the peak angle was enlarged with a decrease in intensity. The decreased peak intensity in the solid dispersion system could be attributed to the reduction in the crystallinity of the drug leading to the formation of the dispersion in the amorphous phase. The absence of some characteristic peaks of the drug in the solid dispersion formula indicates the partial conversion of the crystalline form of the drug to its amorphous form [13, 37].

The decrease in crystallinity of the solid dispersion formula was proven by the results of the calculation of the obtained % crystallinity by 26.0%. The crystallinity of the solid dispersion system decreased by 3 times compared to native drug, with a crystallinity of 78.4%. The decrease in crystallinity that occurs indicates that in solid dispersion, some drugs have been converted into their amorphous forms [25].

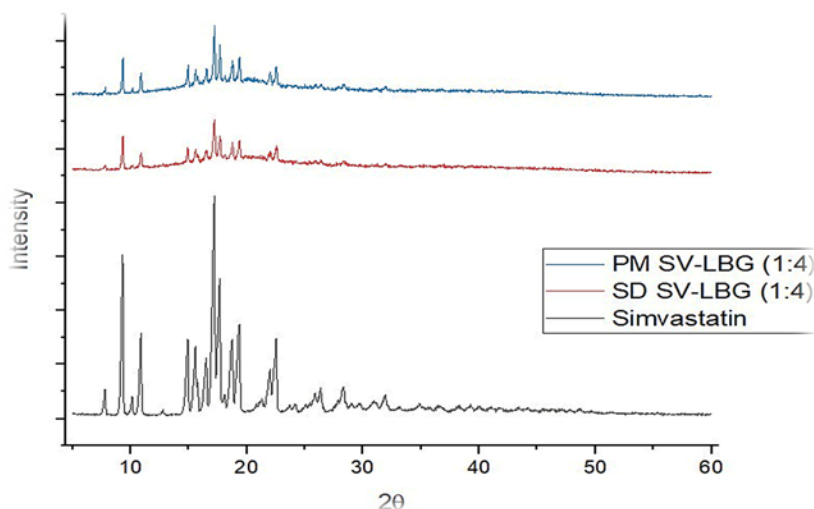


Fig. 5: Diffractogram of Simvastatin (black), SD SV-LBG (1:4) (red), PM SV-LBG (1:4) (blue) (n=2)

CONCLUSION

The insilico study showed hydrogen interactions between HPMCAS and Sodium Alginate polymers with Simvastatin, while Locust Bean Gum and TPGS polymers did not show hydrogen interactions with Simvastatin. Based on these studies, Sodium Alginate and Locust Bean Gum were selected as carrier polymers for solid dispersion systems. The results of the solubility and dissolution studies showed an improvement in the solid dispersion system compared to the native drug in both the SV-SA and SV-LBG solid dispersion formulas in each mass comparison. Formula SV-LBG (1:4) had the highest increase in solubility and dissolution of 26.858 ± 0.59 ppm and $9.241 \pm 0.30\%$ at 30 min. Characterization by FTIR showed that the drug was dispersed in the carrier molecule without the addition of new functional groups. DSC analysis showed a decrease in the melting point of the solid dispersion and the diffractogram of XRDP indicated a decrease in the crystallinity properties of the solid dispersion system compared to the native drug.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

- Rodriguez Aller M, Guillaume D, Veuthey JL, Gurny R. Strategies for formulating and delivering poorly water-soluble drugs. *J Drug Deliv Sci Technol.* 2015;30:342-51. doi: 10.1016/j.jddst.2015.05.009.
- Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. *ISRN Pharm.* 2012;2012:195727. doi: 10.5402/2012/195727, PMID 22830056.
- Pharm DMR. The essential guide to simvastatin: usage, precautions, interactions and side effects. *Interact Media Licensing.* 2021. p. 16.
- Murtaza G. Solubility enhancement of simvastatin: a review. *Acta Pol Pharm.* 2012;69(4):581-90. PMID 22876598.
- Sopyan I. Dissolution rate repairing of simvastatin as a new approach in cocrystallization. *Pharm Lett.* 2017;13(9):18-27.
- Bolourchian N, Mahboobian MM, Dadashzadeh S. The effect of PEG molecular weights on dissolution behavior of simvastatin in solid dispersions. *Iran J Pharm Res.* 2013;12Suppl:11-20. PMID 24250667.
- Dalvi PB, Gerange AB, Ingale PR. Solid dispersion: strategy to enhance solubility. *J Drug Delivery Ther.* 2015;5(2):20-8. doi: 10.22270/jddt.v5i2.1060.
- Mir K, Khan N. Solid dispersion: an overview of the technology. *Int J Pharm Sci Res.* 2017;8:2378-87.
- Tiwari R, Tiwari G, Srivastava B, Rai AK. Solid dispersions: an overview to modify bioavailability of poorly water-soluble drugs. *Int J PharmTech Res.* 2009;1(4):1338-49.
- Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. *J Biomol Struct Dyn.* 2021;39(16):6306-16. doi: 10.1080/07391102.2020.1796811. PMID 32698689.
- Siswandi S, Rusdiana T, Levita J. Virtual screening of co-formers for ketoprofen co-crystallization and the molecular properties of the co-crystal. *J App Pharm Sci.* 2015;5(6):78-82. doi: 10.7324/JAPS.2015.50613.
- Gao H, Wang W, Dong J, Ye Z, Ouyang D. An integrated computational methodology with data-driven machine learning, molecular modeling and PBPK modeling to accelerate solid dispersion formulation design. *Eur J Pharm Biopharm.* 2021;158:336-46. doi: 10.1016/j.ejpb.2020.12.001, PMID 33301864.
- Panghal D, Nagpal M, Thakur GS, Arora S. Dissolution improvement of atorvastatin calcium using modified locust bean gum by the solid dispersion technique. *Sci Pharm.* 2014;82(1):177-91. doi: 10.3797/scipharm.1301-23, PMID 24634850.
- Borba PAA, Pinotti M, de Campos CEM, Pezzini BR, Stulzer HK. Sodium alginate as a potential carrier in solid dispersion formulations to enhance dissolution rate and apparent water solubility of BCS II drugs. *Carbohydr Polym.* 2016;137:350-9. doi: 10.1016/j.carbpol.2015.10.070, PMID 26686139.
- Song IS, Nam SJ, Jeon JH, Park SJ, Choi MK. Enhanced bioavailability and efficacy of silymarin solid dispersion in rats with acetaminophen-induced hepatotoxicity. *Pharmaceutics.* 2021;13(5):628. doi: 10.3390/pharmaceutics13050628, PMID 33925040.
- Siraj N, Athar SHM, Khan DrG, Raza S, Ansari Mohd A. Review on solid dispersion of poor water soluble drug by using natural polymers. *The Pharma. Innov J.* 2019;8(1):631-6.
- Patel M, Tekade A, Gattani S, Surana S. Solubility enhancement of lovastatin by modified locust bean gum using solid dispersion techniques. *AAPS PharmSciTech.* 2008;9(4):1262-9. doi: 10.1208/s12249-008-9171-4, PMID 19115112.
- Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press (PhP) and American Pharmacists Association (AphA); 2009.
- Pawar SN, Edgar KJ. Alginate esters via chemoselective carboxyl group modification. *Carbohydr Polym.* 2013;98(2):1288-96. doi: 10.1016/j.carbpol.2013.08.014, PMID 24053805.
- Hosny KM, Khames A, Elhady SSA. Preparation and evaluation of orodispersible tablets containing hydroxybutyl- β -cyclodextrin-simvastatin solid dispersion. *Trop J Pharm Res.* 2013;12(4):469-76. doi: 10.4314/tjpr.v12i4.4.
- Nanda A. preparation, characterization and dissolution of solvent evaporated simvastatin solid dispersions. *JMPAS.* 2021;10(3):2813-28. doi: 10.22270/jmpas.V10I3.1179.
- Sopyan I, Syah ISK, Nurhayti D, Budiman A. Improvement of simvastatin dissolution rate using derivative non-covalent approach by solvent drop grinding method. *Int J App Pharm.* 2020;21-4. doi: 10.22159/ijap.2020v12i1.35865.
- Gustaman F. Pengaruh penambahan cremophor el terhadap peningkatan laju disolusi tablet simvastatin. *J Pharmacopolium.* 2019;2(1). doi: 10.36465/jop.v2i1.471.
- Mehmood Y, Yousaf H, Khursheed A, Bashir I, Majeed I. Preparation and characterization of solid dispersion tablet of simvastatin employing starch phosphate as carrier. *Int J Chem Pharm Sci.* 2014;5(2):79-84.
- Komal K, Kaur T, Singh AP, Singh P, Sharma P. Enhancement of solubility and dissolution rate of simvastatin by using solid dispersion technique along with diferent combination of polymers. *J Drug Deliv Ther.* 2018;8(2):32-40.
- Sonar PA, Behera AL, Banerjee SK, GaiKWad DD, Harer SL. Preparation and characterization of simvastatin solid dispersion using skimmed milk. *Drug Dev Ind Pharm.* 2015;41(1):22-7. doi: 10.3109/03639045.2013.845836, PMID 24160569.
- Li W, Zheng H, Ye C, Wu T, Fan M, Feng J. Effect of the Intermolecular Hydrogen Bond between Carbazole and N, N-Dimethylformamide/Isopropanolamine on the solubility of carbazole. *Energy Fuels.* 2012;26(10):6316-22. doi: 10.1021/ef301240t.
- Sathisaran I, Dalvi SV. Engineering cocrystals of poorly water-soluble drugs to enhance dissolution in aqueous medium. *Pharmaceutics.* 2018;10(3):108. doi: 10.3390/pharmaceutics10030108, PMID 30065221.
- Saputri KE, Fakhmi N, Kusumaningtyas E, Priyatama D, Santoso B. Docking molekular potensi anti diabetes melitus tipe 2 turunan zerumbon sebagai inhibitor aldosa reduktase dengan autodock-vina. *Chim Nat Acta.* 2016;4(1):16-20. doi: 10.24198/cna.v4.n1.10443.
- Arwansyah A. Simulasi molecular docking senyawa kurkumin dana sebagai selective androgen receptor modulators (SARMs) pada kanker prostat. *Dinamika.* 2015;5(2).
- Yao H, Ke H, Zhang X, Pan SJ, Li MS, Yang LP. Molecular recognition of hydrophilic molecules in water by combining the

- hydrophobic effect with hydrogen bonding. *J Am Chem Soc.* 2018;140(41):13466-77. doi: 10.1021/jacs.8b09157, PMID 30244569.
32. Bikiaris DN. Solid dispersions, part I: Recent evolutions and future opportunities in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs. *Expert Opin Drug Deliv.* 2011;8(11):1501-19. doi: 10.1517/17425247.2011.618181, PMID 21919807.
33. Pradhan R, Tran TH, Choi JY, Choi IS, Choi HG, Yong CS. Development of a rebamipide solid dispersion system with improved dissolution and oral bioavailability. *Arch Pharm Res.* 2015;38(4):522-33. doi: 10.1007/s12272-014-0399-0, PMID 24895145.
34. França MT, O'Reilly Beringhs A, Nicolay Pereira R, Martins Marcos T, Bazzo GC, Stulzer HK. The role of sodium alginate on the supersaturation state of the poorly soluble drug chlorthalidone. *Carbohydr Polym.* 2019;209:207-14. doi: 10.1016/j.carbpol.2019.01.007, PMID 30732801.
35. Nagpal M, Kaur L, Chander J, Sharma P. Dissolution enhancement of domperidone fast disintegrating tablet using modified locust bean gum by solid dispersion technique. *JPTRM.* 2016;4(1):1-11. doi: 10.15415/jptrm.2016.41001.
36. National Center for Biotechnology Information. Simvastatin; 2021. Pubchem Compound Summary for CID. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/54454>. [Last accessed on 01 Sep 2021].
37. Kaity S, Isaac J, Ghosh A. Interpenetrating polymer network of locust bean gum-poly (vinyl alcohol) for controlled release drug delivery. *Carbohydr Polym.* 2013;94(1):456-67. doi: 10.1016/j.carbpol.2013.01.070, PMID 23544563.
38. Augustijns P, Brewster M. Solvent systems and their selection in pharmaceuticals and biopharmaceuticals. Springer Science+Business Media; 2007. p. 466.