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Original Article

Multicomponent crystals: Solubility enhancement of simvastatin using arginine and glycine coformers

[Cristales multicomponentes: Mejora de la solubilidad de la simvastatina utilizando coformadores de arginina y glicina]

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Abstract

Context: Simvastatin can be modified by the formation of multicomponent crystals to increase its solubility.

Aims: To compare the solubility of multicomponent simvastatin crystals to pure simvastatin.

Methods: The *in silico* study of simvastatin and the coformers arginine and glycine revealed non-covalent interactions, so multicomponent preparations of simvastatin crystals were prepared by solvent evaporation using a mole ratio of 1:1; 1:2 and 2:1.

Results: Each simvastatin-arginine and simvastatin-glycine ratio increased the solubility, with the highest increase observed for the 1:2 ratio compared to pure simvastatin.

Conclusions: Simvastatin-arginine multicomponent crystals (1:2) showed the best dissolution profile in phosphate buffer medium pH 7.0 with 67.69% dissolution, while simvastatin-glycine multicomponent crystals (1:2) exhibited the best dissolution profile in buffer media pH 1.2 with 16.19% dissolution. Characterization of the multicomponent crystals revealed a shift in the peaks, a decreased melting point, and enthalpy, indicating decreased % crystallinity and the formation of a new solid phase.

Keywords: arginine; glycine; multicomponent crystal; simvastatin; solubility enhancement.

Resumen

Contexto: La simvastatina puede modificarse mediante la formación de cristales multicomponentes para aumentar su solubilidad.

Objetivos: Comparar la solubilidad de cristales multicomponentes de simvastatina con la simvastatina pura.

Métodos: El estudio *in silico* de la simvastatina y los coformadores arginina y glicina reveló interacciones no covalentes por lo que se prepararon preparaciones multicomponente de cristales de simvastatina por evaporación de disolvente utilizando una proporción molar de 1:1; 1:2 y 2:1.

Resultados: Cada relación simvastatina-arginina y simvastatina-glicina aumentó la solubilidad, observándose el mayor aumento para la relación 1:2 en comparación con la simvastatina pura.

Conclusiones: Los cristales multicomponentes de simvastatina-arginina (1:2) mostraron el mejor perfil de disolución en medio tampón fosfato pH 7,0 con un 67,69% de disolución, mientras que los cristales multicomponentes de simvastatina-glicina (1:2) exhibieron el mejor perfil de disolución en medio tampón pH 1,2 con un 16,19% de disolución. La caracterización de los cristales multicomponente reveló un desplazamiento de los picos, una disminución del punto de fusión y de la entalpía, lo que indica una disminución del % de cristalinidad y la formación de una nueva fase sólida.

Palabras Clave: arginina; cristal multicomponente; glicina; mejora de la solubilidad; simvastatina.

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INTRODUCTION

Solubility is an important physicochemical property of drug compounds and can be used to predict their absorption in the gastrointestinal tract (Khadka et al., 2014). Solubility can also affect the dissolution rate, with a low dissolution rate due to low drug solubility causing poor bioavailability of drugs given orally (Kawabata et al., 2011). Indeed, nearly 40% of drugs on the market have low solubility in water.

Drugs are classified into four classes based on solubility and permeability using the biopharmaceutical classification system (BCS). Simvastatin (SV) is a low solubility compound (BCS class II) but has high permeability (Amidon et al., 1995; Takagi et al., 2006) and is the main drug of the statin class with antihyperlipidemic and anticholesterol activity. SV is the drug of choice for the management of hypercholesterolemia due to its recognized efficacy and safety profile (Seeren et al., 2012). However, drugs that have low solubility in water are often less bioavailable, and their rate of dissolution impacts their absorption in the body (Amidon et al., 1995; Shargel and Yu, 1999). The solubility of simvastatin in water is 0.03 mg/L, and it has a bioavailability of only 5%(Murtaza. 2012); therefore, a solution is needed to increase its bioavailability. Several methods have been developed to increase the solubility, such as forming an SNNEDS, adding a surfactant, and reducing particle size by microemulsion technology (Jeevana and Sreelakshmi, 2011). However, these methods have some disadvantages, such as requiring several matrices, high energy requirements, and a complicated up-scaling process (Nemichand and Laxman, 2016).

Another technique to increase drug solubility without changing its pharmacological activity is to modify the solid form of the drug through the formation of multicomponent crystals, such as salts and cocrystals (Domingos and Duarte, 2015; Elder et al., 2013; Thakuria et al., 2013). This simple method is effective because the drug is in a crystalline form, which is stable and does not require other additives in a formulation. Multicomponent crystals are formed when more than one molecule of a different substance crystallizes in a crystal lattice with a specific stoichiometric ratio through non-covalent bonds (Kumar and Nanda, 2018; Martin et al., 2013). The formation of cocrystals occurs due to hydrogen bonding between active pharmaceutical ingredients and cocrystal-forming materials, which are commonly called cocrystal formers (Alatas et al., 2020). Suitable coformers must be able to form hydrogen bonds with drug compounds and be included in the generally recognized as safe (GRAS) category (Patole and Deshpande, 2014), for example, arginine and glycine.

Arginine is a complex amino acid that is generally found at active sites in proteins and enzymes due to the amine-containing side chains (PubChem, 2022). Nensi (2019) reported the formation of multicomponent piperine crystals with arginine as a coformer can increase the solubility of piperine compared to pure piperine. Glycine is the simplest proteinogenic amino acid with a hydrogen atom in its side chain. Amino acid coformers for salt formation have been studied extensively and proven to improve the stability and dissolution profile of an active substance with solubility problems. Glycine is used as a coformer because it has amino and carboxylic groups that can act as hydrogen bond donors and acceptors (Nugrahani and Jessica, 2021). Shete et al. (2015) found that the interaction of itraconazole with glycine increased the solubility of itraconazole up to three times higher than pure itraconazole.

There are several advantages of cocrystals, namely that they can increase the physicochemical properties such as melting point, tablet ability, solubility, stability, bioavailability, and permeability due to the presence of coformers in the crystal structure without changing the pharmacological properties. They can be used for non-ionizable pharmaceutical active ingredients and complex drugs with sensitive functional groups that may not survive strong acid or base reaction conditions. In addition, cocrystals have the potential to shorten the development time for active pharmaceutical ingredients, thereby reducing production costs. Therefore, this study was designed to determine whether the use of arginine and glycine as coformers can increase the rate of dissolution and solubility of simvastatin.

MATERIAL AND METHODS

Materials

Hydrochloric acid (37%), arginine, glycine, potassium bromide (KBr), monobasic potassium phosphate, potassium chloride, methanol pro analysis (99.9%), sodium hydroxide (99.9%) were purchased by Merck and simvastatin 98% (Teva Pharmaceutical).

Tools and equipment

Type II dissolution test kit (Sotax A6), AutoDock Tools application, ChemDraw application, PyRx application, evaporator cup, glass funnel, differential scanning calorimetry (DSC Model-60, Shimadzu), powder X-ray diffractometer (Bruker D8 Advance), shaker (Memmert), FTIR spectrophotometer (IRPres-

tige-21 Shimadzu), UV-Vis spectrophotometer (Analytic Jena – Specord 200).

In silico studies

The structures of simvastatin and coformers (arginine and glycine) were made using the ChemDraw 12.0 application. The file format was then converted to the .pdbqt format using the AutoDock Tools application. Then the docking of the PyRx application with Autodock Vina software was performed. Parameters that were considered were bond interactions that occur, binding affinity, hydrogen bond energy, and hydrogen bond distance. Based on the study results, the interaction between simvastatin and the coformer was seen, which was characterized by the presence of hydrogen bonds and had the most negative binding affinity (Kong et al., 2018).

Perform docking using the PyRx application, then view the interaction using Autodock Vina software. The parameters that are considered are the bond interactions that occur, bond affinity, hydrogen bond energy, and hydrogen bond distance. With the hydrogen bonds formed between simvastatin and the coformers, the increase in solubility, which can be seen from the results of the solubility test and dissolution results and is also supported by the results of characterization using Fourier-transform infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction can show that the presence of coformers influences the increase in simvastatin solubility.

Preparation of multicomponent crystals simvastatin

The manufacture of multicomponent simvastatin crystals was carried out using the solvent evaporation method. Simvastatin and pure coformers (arginine and glycine) with molar ratios of 1:1, 1:2, and 2:1 were dissolved in methanol in an evaporation cup while stirring until simvastatin and coformer were completely dissolved. The solvent was allowed to evaporate for 24 hours or until all the solvent had evaporated.

Preparation of hydrochloric acid buffer pH 1.2

Accurately, 14.91 g of potassium chloride was weighed and dissolved in 1000 mL of carbon dioxide-free water. Hydrochloric acid buffer was made by adding 250 mL of potassium chloride and 425 mL of hydrochloric acid, then water to make 1000 mL was added (Kemenkes, 2020).

Preparation of phosphate buffer pH 7.0

An amount of 27.22 g of potassium phosphate P monobasic was dissolved in 1000 mL of carbon dioxide-free water. Phosphate buffer was prepared by adding 250 mL of monobasic potassium phosphate and 145.5 mL of sodium hydroxide, then adding water to make 1000 mL (Kemenkes, 2020).

Simvastatin maximum wavelength determination

The maximum wavelength of simvastatin was determined by scanning using a UV-Vis spectrophotometer of a solution of simvastatin dissolved in methanol and measured at a wavelength of 200-400 nm (Komal et al., 2018).

Preparation of calibration curve

An amount of 10 mg of simvastatin was dissolved into a 100 mL measuring flask using a combination of methanol-water solvent (solubility test), hydrochloric acid buffer at pH 1.2, and phosphate buffer at pH 7.0 (dissolution test). A 25 mL measuring flask was filled with each stock solution, and the solvent was then added to the mark. A validated UV-Vis spectrophotometer was used to measure absorbance. The line equation $y = ax + b$ was produced by calculating the absorption data using the standard curve equation (Gustaman, 2019; Komal et al., 2018).

Saturated solubility test

Pure simvastatin and multicomponent crystal samples (simvastatin-arginine and simvastatin-glycine) were the samples that were evaluated. Weighted of the multicomponent crystal samples was equal to 10 mg of pure simvastatin. After that, they were dissolved in 10 mL of distilled water in a beaker glass and shaken for 24 hours at room temperature (25°C) at 120 rpm using a shaker. The filter paper was then used to filter the sample. A validated ultraviolet spectrophotometer was used to determine saturated solubility (Sopyan et al., 2020).

Dissolution test

The dissolution test was carried out using a type II apparatus (paddle method) with the media used, namely a buffer solution (phosphate buffer) at pH 7.0 and a buffer solution (hydrochloric acid buffer) at pH 1.2 as much as 900 mL at a speed of 50 rpm and carried out for 60 minutes at 37 ± 0.2°C. The sample was put into the media. Samples were taken periodically every minute with a time span of 5, 10, 15, 30, 45, and 60 for a total of 10 mL of sample, and the medium was replaced with the same volume during testing. The sample was then filtered and measured using a UV spectrophotometer. The samples tested were pure simvastatin and multicomponent crystal samples (simvastatin-arginine and simvastatin-glycine). The multicomponent crystal sample was weighed in the

equivalent of 10 mg of pure simvastatin (Sopyan et al., 2017).

Characterization using Fourier-transform infrared (FTIR) spectroscopy

The samples used for reading the FTIR spectrum were pure simvastatin, coformers (arginine and glycine), multicomponent crystals (simvastatin-arginine and simvastatin-glycine), and physical mixtures (simvastatin-arginine and simvastatin-glycine). Each sample was mixed with potassium bromide (KBr) with a mole ratio 1:10 and ground until homogeneous, then compressed using 20 Psi pressure to form pellets. The spectrum was measured in the 400-4000 cm^{-1} range using an FTIR spectrophotometer (Sopyan et al., 2020).

Evaluation using differential scanning calorimetry

A quantity of 3-5 mg of sample is placed in aluminum containers in programmed devices within a temperature range of 50-350°C using a heating rate of 10°C/min from 25°C to 250°C in an inert environment and a nitrogen rate of 40 mL/min. The samples used for DSC readings were pure simvastatin, coformers (arginine and glycine), multicomponent crystals (simvastatin-arginine and simvastatin-glycine), and physical mixtures (simvastatin-arginine and simvastatin-glycine without treatment) (Sopyan et al. al., 2020; Thenge et al., 2020).

Characterization using powder X-ray diffraction

A sample of 1 g was placed in a sample container. The crystal structure was analyzed using an X-ray powder diffractometer using a Cu filter/target (monochromator), a current of 30 mA, a slit width of 0.2 inches, a voltage of 40 kV with a scanning speed of 0.2–0.5°/minute and a scanning distance of 2θ = 5–60°, The samples used for readings using PXRD were pure simvastatin, coformers (arginine and glycine), multicomponent crystals (simvastatin-arginine and simvastatin-glycine), and physical mixtures (simvastatin-arginine and simvastatin-glycine) (Sopyan et al., 2020).

Statistical analysis

Statistical tests were carried out using the ANOVA test with Tukey's advanced test on the results of increasing the percent dissolution of pure simvastatin and multicomponent simvastatin-glycine crystals using the IBM SPSS Statistics 25 application with a confidence level of 95% (n = 3). The aim was to find out the differences between two or more groups where only one factor was being considered, namely by conducting an ANOVA test. From the results obtained, it was concluded that there was a significant difference between pure simvastatin and crystalline multicomponent because the results of the ANOVA test showed that $p<0.05$, which means that H0 was rejected. Next, to find out which groups had significant differences with a significance level of 0.05, Tukey's further test was carried out, and the results showed significant differences between each other in all multicomponent crystal mole comparisons.

In silico data analysis

Data obtained from each measurement was then calculated using calculation formulas. The first test was the saturated solubility test. The data produced was the amount of sample dissolved in a solvent (in mg/L units). Then, the r coefficient and linear regression equation were calculated in the same way as the dissolution test. The data obtained from the docking simulation showed that hydrogen bonds, hydrophobic interactions, and energy bonds can be found using the Autodock tools. Data obtained from the characterization test was shown through comparison charts produced by each testing tool, which included infrared spectrophotometry, differential scanning calorimetry, and X-ray diffraction.

RESULTS

In silico studies

In silico studies were used to predict the interaction between simvastatin and coformers, namely arginine and glycine. A hydrogen donor and acceptor group are needed between simvastatin and the coformer to form hydrogen bonds, and i*n silico* interactions between SV-arginine and SV-glycine revealed negative values of enthalpy as -2.5 and -1.2 J/mole, respectively (Table 1).

Saturated solubility test

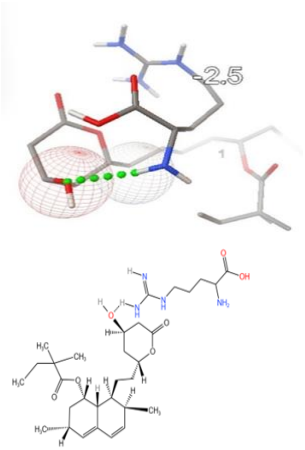
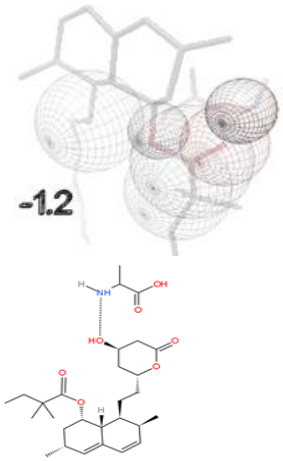
The multicomponent simvastatin-arginine (Fig. 1A) and simvastatin-glycine (Fig. 1B) crystals increased the solubility compared to pure simvastatin, with the greatest increase observed for the 1:2 ratio for both amino acids.

Dissolution test

The dissolution of the multicomponent crystals was evaluated in basic (phosphate buffer pH 7.0) and acidic (hydrochloric acid buffer pH 1.2) media to reflect the pH conditions in the digestive tract. The amount of simvastatin that dissolved in basic media after 60 minutes was 23.25%, lower than that observed for the 1:1 (40.95%), 1:2 (67.69%), and 2:1 (27.39%) multicomponent simvastatin-arginine crystals (Fig. 2A). Similarly, multicomponent simvastatin-

glycine crystals increased the dissolution of simvastatin in basic media (Fig. 3A). In contrast, multicomponent simvastatin-arginine crystals did not improve the dissolution of simvastatin in acidic media (Fig. 2B), whereas multicomponent simvastatin-glycine crystals increased the dissolution at 60 minutes with the highest value observed for the ratio of 1:2 (Fig. 3B). There was a significant difference ($p<0.05$) in the dissolution rate between pure simvastatin and crystalline multicomponent crystals.

Table 1. Simvastatin and coformer interactions.

Coformer	Structure	Interaction	Hydrogen binding energy (kkal/mol)
Arginine		1 hydrogen bond	-3.806
Glycine		1 hydrogen bond	-2.001

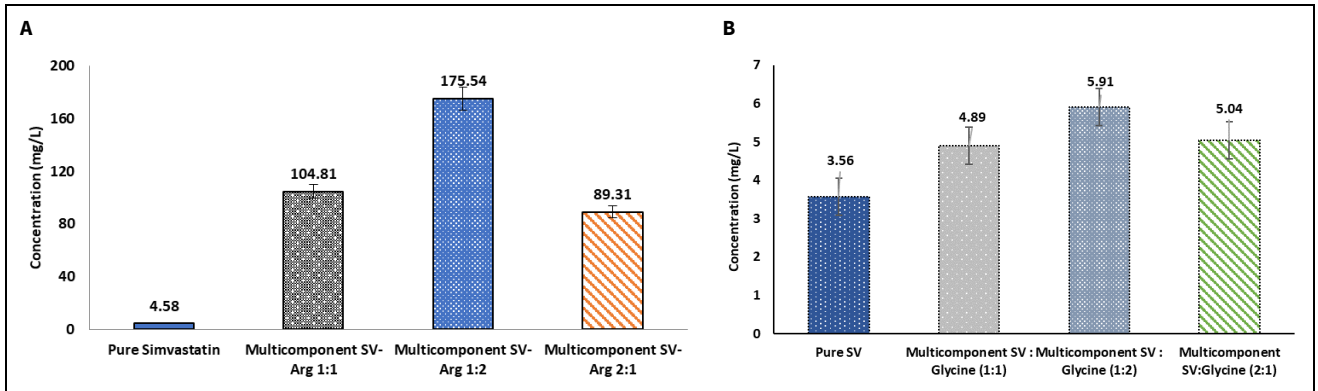


Figure 1. (A) Solubility of simvastatin and simvastatin-arginine and **(B)** simvastatin and simvastatin-glycine multicomponent crystals.

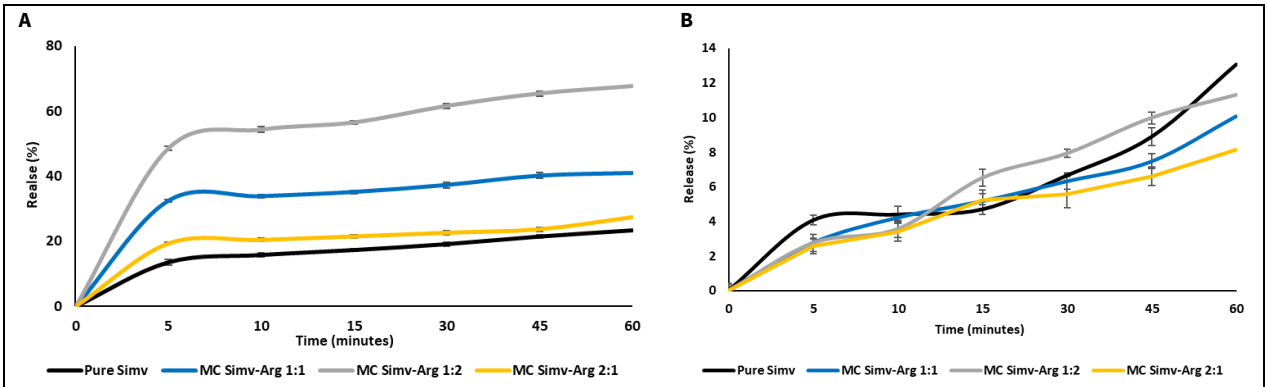


Figure 2. (A) Dissolution of simvastatin and simvastatin-arginine multicomponent crystals in phosphate buffer (pH 7). **(B)** Dissolution of simvastatin and simvastatin-arginine multicomponent crystals in HCl buffer solution (pH 1.2).

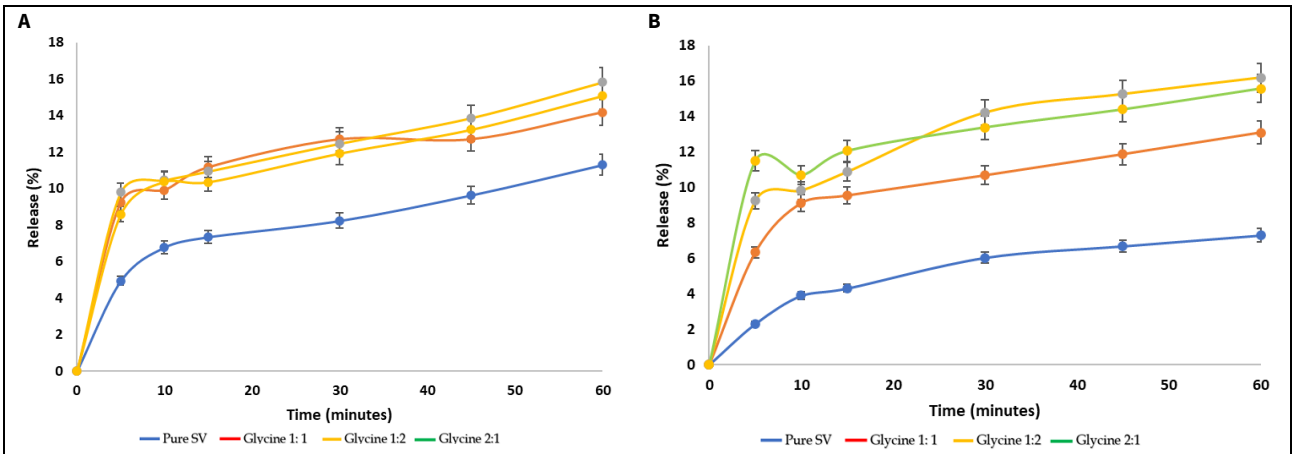


Figure 3. (A) Dissolution of simvastatin and multicomponent simvastatin–glycine crystals in phosphate buffer solution (pH 7). **(B)** Dissolution of simvastatin and multicomponent simvastatin–glycine crystals in HCl buffer solution (pH 1.2).

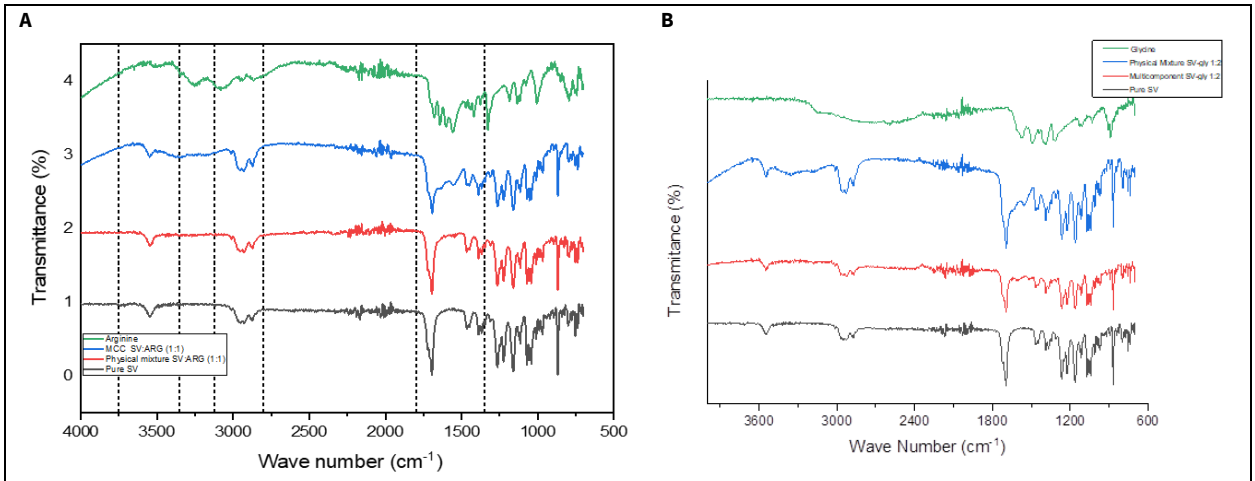


Figure 4. (A) FTIR spectrum of simvastatin-arginine crystals. **(B)** FTIR spectrum of simvastatin-glycine.

Fourier-transform infrared spectroscopy

Multicomponent crystals were characterized by infrared spectrophotometry, showing the formation of new peaks, peak shifts, and changes in the intensity of the peaks (Fig. 4 and Table 2-3).

The simvastatin-arginine multicomponent crystals with a 1:1 ratio were characterized because even though a 1:2 ratio increased the solubility and dissolution of simvastatin, the multicomponent simvastatin-arginine crystals with a 1:2 ratio were too sticky and could not be characterized. The 1:1 ratio was chosen

Table 2. The functional groups of pure simvastatin, multicomponent crystal SV:ARG (1:2), and physical mixture SV:ARG (1:2).

No	Simvastatin		Arginine		Multicomponent crystal SIM:ARG (1:1)		Physical mixture SIM:ARG (1:1)	
	Wave number	Functional group	Wave number	Functional group	Wave number	Functional group	Wave number	Functional group
1	3550.80	O-H	3222.08 and 1641.36	N-H	3547.20	O-H	3551.29	O-H
2	2969.01	C-H	3079.50	C-H	3288.24	N-H	3239.43	N-H
3	1694.78	C=O	1679.62	C=O	2953.86	C-H	2968.38	C-H
4	1264.88	C-O	1557.42	C≡N	1693.99	C=O	1694.69	C=O
5					1556.71	C≡N	1547.56	C≡N

Table 3. The functional groups of pure simvastatin, crystal multicomponent SV:GLY (1:2), and physical mixture of SV:GLY (1:2).

No.	Pure simvastatin		Glycine		SV-GLY crystal multicomponent (1:2)		SV:GLY physical mix (1:2)	
	Wave number	Functional group	Wave number	Functional group	Wave number	Functional group	Wave number	Functional group
1	3551	O-H	3560	O-H	3550	O-H	3547	O-H
2	3010	C-H	3473	N-H	3330	N-H	3010	C-H
3	1694	C=O	2170	C≡C	3014	C-H	2156	C≡C
4	1390	C-N	1573	C=C	2589	O-H	1696	C=O
5			1388	C-H	2168	C≡N	1391	C-N
6					1688	C=O		
7					1389	C-N		
8	1224	C-O	1154	C-O	1126	C-O	1224	C-O

for further testing because the multicomponent simvastatin-arginine crystals in this comparison also gave the second-best result of increased solubility and increased dissolution rate after a 1:2 ratio.

Differential scanning calorimetry

Multicomponent crystals were characterized by DSC to determine changes in the thermodynamic properties (Fig. 5). The pure simvastatin thermogram showed an endothermic peak with a peak temperature of 133.02˚C, which is the melting point of pure simvastatin with an enthalpy value of -5.69 J/g. There were two endothermic peaks in the simvastatin-arginine physical mixture with a ratio of 1:1. The first endothermic peak lies at 133.12˚C which is very close to the melting point of pure simvastatin, while the second endothermic peak at 93.01˚C approaches the melting point of pure arginine. Meanwhile, in the thermogram of multicomponent simvastatin-arginine crystals in a 1:1 ratio, there are two endothermic peaks with a peak temperature of 130.84˚C with an enthalpy value of -2.66 J/g and another endothermic peak at 177.09˚C. The thermogram of the simvastatin-glycine physical mixture had two exothermic peaks at a peak temperature of 133.16°C, and the multicomponent crystals had two peaks at a peak temperature of 129.15°C.

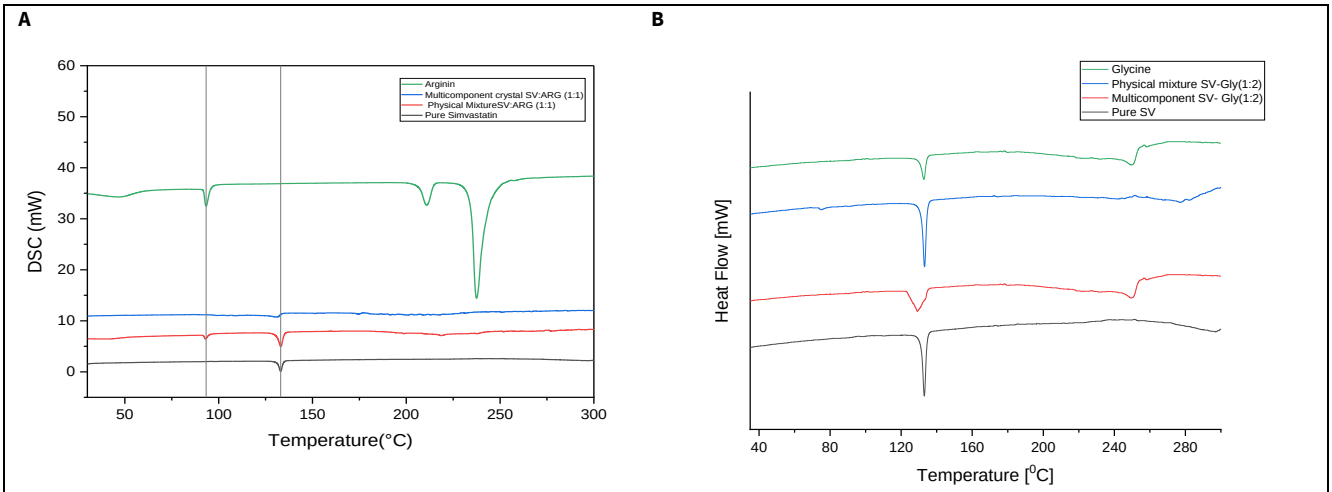


Figure 5. (A) DSC thermogram of simvastatin-arginine. **(B)** DSC thermogram of simvastatin-glycine.

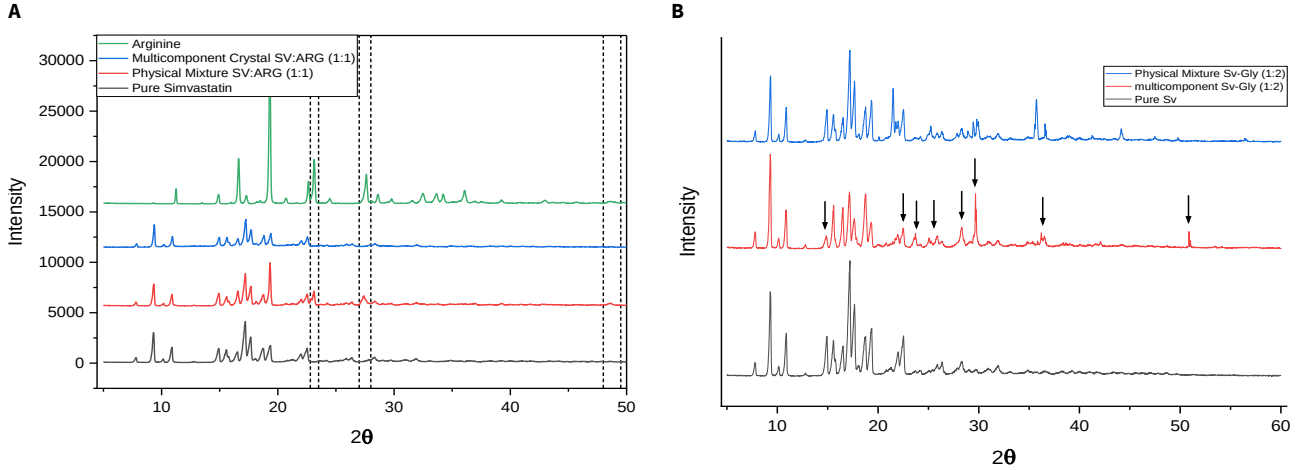


Figure 6. (A) PXRD diffractogram of simvastatin-arginine. **(B)** PXRD diffractogram of simvastatin-glycine.

Powder X-ray diffraction

The PXRD results in Fig. 6 show the 2θ characteristic of the pure simvastatin diffractogram with sharp and high peaks at an angle of 2θ (7.8°, 9.32°, 10.82°, 14.95°, 15.56°, 17, 2°, 22.55°). The spectrum of pure simvastatin showed characteristic absorption peaks at 3550.80 cm^{-1}, indicating the presence of the O-H functional group; 2969.01 cm^{-1}, indicating the presence of the C-H functional group; 1694.78 cm^{-1}, indicating the presence of the C=O functional group, and 1264, 88 cm^{-1}, which indicates the presence of the C-O functional group.

Meanwhile, the 2θ characteristic of the pure arginine diffractogram shows characteristic peaks at an angle of 2θ (11.32°, 16.67°, 19.27°, 23.19°, 27.56°, 48.61°). These characteristic sharp peaks indicate that simvastatin and pure arginine are crystalline. There are also several new peaks (marked with black arrows) in the simvastatin-glycine diffractogram (Fig. 6B), which are not present in the pure simvastatin diffractogram, indicating the formation of multicomponent crystals of simvastatin and glycine. The new crystalline phase of the simvastatin-glycine multicomponent crystal is marked by the presence of a new peak located at an angle of 2θ, namely 22.46°, 23.71°, 25.88°, 28.32°, 29.67°, and 36.21°. The change in the degree of crystallinity is indicated by a decrease in the intensity of the peaks caused by the mechanical interaction that occurs during stirring in the solvent evaporation method, resulting in intermolecular attractions and the formation of hydrogen bonds between simvastatin and glycine.

DISCUSSION

The *in silico* studies indicated strong hydrogen bonds between simvastatin and arginine or glycine, as evidenced by a hydrogen bond distance of 2.147 Å and 2.2 Å, respectively. Negative enthalpy of interaction between SV and coformer showed a spontaneous reaction. The activity of the compounds can be affected by the interaction of hydrogen bonds between the ligands because the lower the distance between the

hydrogen bonds between the ligands, the greater the energy strength. Hydrogen bonds are non-covalent interactions between hydrogen atoms and electronegative atoms that affect the hydrophilicity of a compound (Sathisaran and Dalvi, 2018). Hydrogen bonds are formed between the oxygen atom in the hydroxyl group of simvastatin, which acts as a hydrogen acceptor, with the hydrogen atom in the amine group, which acts as a hydrogen donor. This is a heterosynton supramolecular interaction because the hydrogen bonding occurs between two different groups and increases the solubility (Thakuria et al., 2013). In addition, the number of hydrophobic interactions formed determines the stability of the bond (Sopyan et al., 2020).

The solubility of simvastatin was increased due to the effect of the coformers, arginine, and glycine, which have good solubility in water, with the best increase in solubility obtained at a ratio of 1: 2. The increase in solubility of simvastatin in water (Alatas et al., 2020) occurs due to the polarity of the coformer (Nugrahani and Jessica, 2021).

The dissolution rate of the multicomponent crystals of simvastatin-arginine was lower than pure simvastatin, and both compounds dissolved better in basic phosphate buffer (pH 7.0) because simvastatin is a weak acid (pKa of 4.21) and maximally absorbed in an alkaline environment (Sopyan et al., 2017). The multicomponent simvastatin-glycine crystals in the ratio of 1:2 were dissolved better in the acid buffer because glycine is a weak base and has good characteristics for maximum absorption in an acidic environment (Nugrahani and Jessica, 2021). The presence of coformers increased the dissolution rate by the formation of hydrophilic-ionic interactions between the hydrophilic sites of simvastatin and the coformer ions and hydrophobic-ionic interactions between the hydrophobic sites (aromatic rings) of simvastatin molecules and dissolved coformer ions (Sopyan et al., 2020).

The spectrum of the simvastatin-arginine mixture shows a characteristic pattern similar to its constituent components, namely simvastatin and pure arginine, with no new functional groups, indicating that only a physical interaction occurs in the simvastatin-arginine mixture. In contrast, the spectrum of multicomponent simvastatin-arginine crystals shows similar characteristics to its constituent components with a peak change between 3600-3000 cm^{-1}, probably due to the interaction of hydrogen bonds in the O-H stretch group. The emergence of a new peak at 3288.24 cm^{-1} is probably due to the formation of hydrogen bonds between simvastatin and arginine in the N-H stretch groups. These results are in line with the *in silico* test results where simvastatin and arginine form hydrogen bonds with oxygen in the hydroxyl group of simvastatin, which acts as a hydrogen acceptor with the hydrogen atom in the arginine amine group, which acts as a hydrogen donor (Alatas et al., 2020). The carbonyl group in the pure simvastatin spectrum is at 1694 cm^{-1} but at 1688 cm^{-1} in the multicomponent simvastatin-glycine spectrum. This peak shift in the carbonyl group indicates salt formation in the multicomponent crystals (Thakuria et al., 2013). The molecular docking analysis predicted the formation of a hydrogen bond between simvastatin and glycine. This hydrogen bond forms between the hydroxyl group at 3550 cm^{-1} and the carbonyl group at 1688 cm^{-1}.

The multicomponent simvastatin-arginine crystals in the ratio of 1:2 were characterized because this ratio also gave the best results of increased solubility and dissolution rate. FTIR was applied to characterize the multicomponent crystals through the vibration of carbonyl bonds to distinguish between the formation of cocrystals and salts. Ionic bonding is shown due to carbonyl vibrations such as deprotonation, which can cause a shift in C=O vibrations (Kong et al., 2018).

Two endothermic peaks were observed in the physical mixture of simvastatin-arginine with a 1:1 ratio at the melting points of simvastatin and arginine, indicating no interaction between arginine and simvastatin in this physical mixture. Simultaneously, there was a decrease in the melting point and enthalpy in the thermogram of multicomponent simvastatin-arginine crystals with a 1:1 ratio, which can be attributed to an increase in the solubility of the multicomponent crystals (Nugrahani and Jessica, 2021). A decrease in the melting point of the multicomponent crystals corresponds to an increase in the solubility of active medicinal substances within these crystals. Solubility decreases with increasing melting point (melting point), whereas increased solubility corresponds to a lower melting point. Since these multicomponent crystals have a lower melting point than pure simvastatin and increased solubility in multicomponent simvastatin-glycine crystals in a ratio of 1:2, this is attributed to the solubility test of multicomponent simvastatin-glycine crystals that have been performed (Nugrahani and Jessica, 2021).

The PXRD analysis indicated a change in the degree of crystallinity with a decrease in the degree of crystallinity of the multicomponent simvastatin-arginine (1:1) crystals from 78.4% to 59.0% compared with pure simvastatin. A decrease in the degree of crystallinity indicates that there is a change from the crystalline phase, which will affect the physicochemical properties. Therefore, this is in line with the results obtained; namely, there is an increase in solubility and dissolution rate of the multicomponent simvastatin-arginine (1:1) crystals (Sopyan et al.,

2020). Similarly, the multicomponent simvastatin-glycine crystals had a slightly lower degree of crystallinity than pure simvastatin (77.3% vs. 78.4%). This is in line with the multicomponent simvastatin-glycine (1:2) crystals, which have greater solubility and rate of dissolution than pure simvastatin.

There was a new peak at an angle of 2θ (23.24°, 27.44°, 48.67°) on the diffractogram, and the physical mixture of simvastatin-arginine (1:1) has a similar pattern to pure simvastatin. A mixture of overlapping simvastatin and arginine peaks was observed in the physically mixed diffractogram, demonstrating a physical interaction between the two substances. Simvastatin-arginine crystals with a 1:1 ratio likewise had a nearly identical pattern to pure simvastatin, but no additional peaks existed.

The limitation of this study was the use of in silico software, and HPLC and/or spectrophotometry should be performed for quantitative analysis. Future studies should include a stability test and an *in vivo* test, at least with an *in vivo* correlation test (IVIVC), for an overview of the biopharmaceuticals and their bioavailability.

CONCLUSION

Hydrogen bonds increased the solubility and dissolution of simvastatin between the coformers arginine and glycine to form multicomponent crystals of simvastatin-arginine and simvastatin-glycine.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

Alatas F, Azizsidiq FA, Sutarna TH, Ratih H, Soewandhi SN (2020) Improvement of albendazole solubility through multicomponent crystal formation with malic acid. Galenika J Pharm 6(1): 114–123. https://doi.org/10.22487/j24428744.2020.v6.i1.14998

Amidon GL, Lennernas H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 12: 413–420. https://doi.org/10.1023/a:1016212804288

Domingos S, Duarte MT (2015) New forms of old drugs: Improving without changing. J Pharm Pharmacol 67(6): 830–846. https://doi.org/10.1111/jphp.12384

Elder DP, Holm R, De Diego HL (2013) Use of pharmaceutical salts and cocrystals to address the issue of poor solubility. Int J Pharm 453(1): 88–100. https://doi.org/10.1016/j.ijpharm.2012.11.028

Gustaman F (2019) Pengaruh Penambahan Cremophor EL Terhadap Peningkatan Laju Disolusi Simvastatin. J Pharmacopolium 2(1): 45-52.

Jeevana JB, Sreelakshmi K (2011) Design and evaluation of self-nanoemulsifying drug delivery system of flutamide. J Young Pharm 3(1): 4–8. https://doi.org/10.4103/0975-1483.76413

Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S (2011) Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 420(1): 1–10. https://doi.org/10.1016/j.ijpharm.2011.08.032

Kemenkes RI (2020) Farmakope Indonesia Edisi VI. Jakarta: Kemenkes RI.

Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J (2014) Pharmaceutical particle technologies: An Approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci 9(6): 304–316. https://doi.org/10.1016/j.ajps.2014.05.005

Komal K, Kaur T, Singh AP, Sharma P (2018) Enhancement of solubility and dissolution of simvastatin by using solid dispersion technique along with different combination of polymers. J Drug Deliv Therapeut 8(2): 32–40. https://doi.org/10.22270/jddt.v8i2.1668

Kong R, Zhu X, Meteleva ES, Dushkin AV, Su W (2018) Physicochemical characteristics of the complexes of simvastatin and atorvastatin calcium with hydroxypropyl-β-cyclodextrin produced by mechanochemical activation. J Drug Deliv Sci Technol 46: 436–445. https://doi.org/10.1016/j.jddst.2018.05.018

Kumar S, Nanda A (2018) Approaches to design of pharmaceutical cocrystals: A review. Mol Cryst Liq Cryst Sci Technol 667(1): 54–77. https://doi.org/10.1080/15421406.2019.1577462

Martin FA, Pop MM, Borodi G, Filip X, Kacso I (2013) Ketoconazole salt and co-crystals with enhanced aqueous solubility. Cryst Growth Des 13(10): 4295–4304. https://doi.org/10.1021/cg400638g

Murtaza G (2012) Solubility enhancement of simvastatin: A review. Acta Pol Pharm 69(4): 581–590. https://pubmed.ncbi.nlm.nih.gov/22876598/

Nemichand SK, Laxman SD (2016) Solubility enhancement of nebivolol by microemulsion technique. J Young Pharm 8(4): 356–367. https://doi.org/10.5530/jyp.2016.4.11

Nensi H (2019) Pembentukan Multikomponen Kristal Piperin dengan Asam Siringat dan Arginin Menggunakan Metode Solvent Drop Grinding [Tesis]. Padang: Universitas Andalas.

Nugrahani I, Jessica M (2021) Amino acids as the potential co-former for co-crystal development: A review. Molecules 26(11): 3279. https://doi.org/10.3390/molecules26113279

Patole T, Despande A (2014) Co-crystallization a technique for solubility enhancement. Int J Pharm Sci Res 5(9): 3566–3576. https://doi.org/10.13040/IJPSR.0975-8232.5(9).3566-76

PubChem (2022) PubChem Compound Summary for CID 6322, Arginine. https://pubchem.ncbi.nlm.nih.gov/compound/Arginine

Sareen S, Mathew G, Joseph L (2012) Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig 2(1): 12–17. https://doi.org/10.4103/2230-973X.96921

Sathisaran I, Dalvi SV (2018) Engineering cocrystals of poorly water-soluble drugs to enhance dissolution in aqueous medium. Pharmaceutics 10(3): 108. https://doi.org/10.3390/pharmaceutics10030108

Shargel L, Yu A (1999) Applied Biopharmaceutics and Pharmacokinetics, 4th Ed. New York: Mcgraw-Hill.

Shete A, Murthy S, Korpale S, Yadav A, Sajane S, Sakhare S, Doijad R (2015) Cocrystals of itraconazole with amino acids: Screening, synthesis, solid state characterization, *in vitro* drug release and antifungal activity. J Drug Deliv Sci Technol 28: 46–55. https://doi.org/10.1016/j.jddst.2015.05.006

Sopyan I, Fudholi A, Muchtaridi M, Sari IP (2017) Co-crystallization: A tool to enhance solubility and dissolution rate of simvastatin. J Young Pharm 9(2): 186–186. https://dx.doi.org/10.5530/jyp.2017.9.36

Sopyan I, Syah ISK, Nurhayati D, Budiman A (2020) Improvement of simvastatin dissolution rate using derivative non-covalent approach by solvent drop grinding method. Int J Appl Pharm 12(1): 21–24. https://doi.org/10.22159/ijap.2020v12i1.35865

Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL (2006) A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Mol Pharm 3(6): 631–643. https://doi.org/10.1021/mp0600182

Thakuria R Delori A, Jones W, Lipert MP, Roy L, Rodríguez-Hornedo N (2013) Pharmaceutical cocrystals and poorly soluble drugs. Int J Pharm 453(1): 101–125. https://doi.org/10.1016/j.ijpharm.2012.10.043

Thenge R, Patel R, Kayande N, Mahajan N (2020) Co-crystals of carvedilol: Preparation, characterization and evaluation. Int J Appl Pharm 12(1): 42–49. https://doi.org/10.22159/ijap.2020v12i1.35640

AUTHOR CONTRIBUTION:

Contribution	Sopyan I	Megantara S	Elizabeth K	Kaffah S
Concepts or ideas	x	x		
Design	x			
Definition of intellectual content	x	x		
Literature search	x	x	x	x
Experimental studies	x	x	x	x
Data acquisition	x	x	x	x
Data analysis	x	x	x	x
Statistical analysis	x	x	x	x
Manuscript preparation	x		x	x
Manuscript editing	x			x
Manuscript review	x	x	x	x

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