Indonesian Journal of Pharmaceutics
IdJP
ISSN : 2597-8748

Vol. 6, Issue 2, 2024 (66-83)
http://journal.unpad.ac.id/IdJP

Comparative Dissolution Formulation and Test Simvastatin Ko-Crystal Tablets With Isonicotinamide As Coformer

Ina Novianti, Iyan Sopyan*, Marline Abdassah Bratadiredja, Raira Salsabila Hapsari, Ervina Setiawati.

Faculty of PHarmacy, Padjadjaran University, Jl. Raya Bandung-Sumedang KM 21, Jatinangor 45363, Indonesia

Submitted: 06/06/2024, Revised: 12/06/2024, Accepted: 11/07/2024, Published: 14/08/2024

ABSTRACT

Simvastatin is a statin drug used to lower plasma cholesterol in all types of hyperlipidemia. Simvastatin is included in BCS class II with poor solubility. One of the efforts made to increase the solubility of simvastatin is the formation of co-crystals. Co-crystal is a modified type of crystal habit, which consists of two or more molecules in the same crystal lattice. The purpose of this study was to obtain the best excipient combination formula on the simvastatin co-crystalline tablet with isonicotinamide as a coformer and its comparable dissolution test results. The excipient combination optimization was carried out using a two-level factorial method. The optimized Avicel pH 102 and Primogel produced four combination designs on ready-made formulas, namely F1 Avicel pH 102: Primogel (79:2), F2 Avicel pH 102: Primogel (79:8), F3 Avicel pH 102: Primogel (85: 2) and F4 Avicel pH 102: Primogel (85: 8). The evaluation includes evaluating the mass of the print and the quality of the tablets. The excipient combination design solution in the best formula is Avicel pH 102 and Primogel with a ratio (79: 8). The method used in a comparable dissolution test is to compare the values of F1 (difference factor) and F2 (similarity factor) using BootStrap software. The F2 values observed were 50.3 at pH 1.2, 56.09 at pH 4.5, and 59.23 at pH 6.8, which indicates that the simvastatin co-crystalline tablet has similarities with the innovator tablet. The excipient combination design solution in the best formula is Avicel pH 102 and Primogel with a ratio (79: 8). The method used in a comparable dissolution test is to compare the values of F1 (difference factor) and F2 (equation factor) using BootStrap software. The F2 values observed were 50.3 at pH 1.2, 56.09 at pH 4.5, and 59.23 at pH 6.8, which indicates that the simvastatin co-crystalline tablet has similarities with the innovator tablet.

Keywords: Simvastatin, co-crystal, two-stage factorial, comparable dissolution test.

*Corresponding author,
e-mail: I.sopyan@unpad.ac.id I. Sopyan)

https://doi.org/10.24198/idjp.v6i1.55250

1. Introduction

Simvastatin is a therapy that has a mechanism of action as an HMG-CoA reductase inhibitor for the treatment of hyperlipidemia. Simvastatin is a white crystalline powder and non-hygroscopic which is practically insoluble in water (30 mg/mL), therefore Simvastatin is included in BCS class II drugs, because it has very low water solubility but has high permeability [1]. By knowing the low solubility of simvastatin, it is necessary to increase the solubility of simvastatin, namely by forming co-crystals with the help of coformers.

o-crystals are complex molecules consisting of two or more different molecules and coformers bonded together by hydrogen bonds [2], So, that it can increase solubility [3]. The cocrystallization technique that will be used is the solvent evaporation method because it has been used in previous studies to increase the solubility of simvastatin. The formulation is needed to be done to observe in enhancement of a dissolution rate and bioavailability of the drug in related preparation like tablet [4].

One of the methods used to determine the optimal formula is Design Expert, a two-level factorial design is conducted to get an optimal formula, It is a design that is used to determine the effects of several factors as well as their interactions. where each factor is limited to only two levels, namely low and high levels. In this case the factor is any amount of the independent variable that is varied and can affect the response. Whereas effect is the response form of what is produced when there is a change in the level of a quantifiable factor [5].

Comparable dissolution test (UDT) is a comparative test conducted on the innovator drug product with the test drug product to compare the similarity of the dissolution profiles. UDT is used to determine the equivalence and properties of the two medicinal products [6]. UDT was carried out in vitro using 3 different dissolution media according to the simulation of the original state of the body, namely pH 1.2 to simulate the state of the stomach without enzymes, pH 4.5 and 6.8 to simulate the state of the intestine without enzymes [7]. This study aims to determine the profile of the dissolution test between the two products. So, it is hoped that the use of isonicotinamide as a coformer can be one of the developments in the next stage of drug formulation.

2. Methods

2.1. Tools

The tools used consisted of a basket-type dissolution test apparatus (Sotax Type PTW II), a hardness tester (Erweka), a fragility test apparatus (Varian), a compressibility test apparatus (Varian), a disintegration time test apparatus (Erweka), a stative funnel, caliper (Tricle Brand), single punch tablet press (TDP), water bath, Bootstrap® software, Design Expert® software, pH meter (Mettler Toledo), spectropHotoUV-Vis meters (Jena Analytics - Specord 200), and analytical balance (4 digits) (Toledo).

2.2. Materials

The materials used are Avicel pH 102 (p.a Merck), buffer pH 1.2 containing hydrogen chloride, buffer pH 4.5 contains potassium dihydrogen phosphate, buffer pH 6.8 contains potassium dihydrogen phosphate, isonicotinamide (pro-analysis, Sigma Aldrich), magnesium stearate (Pro-analysis, Merck), methanol (pro-analyst, Merck), primogel (pro-analysis, merck), simvastatin (p.a Teva, Bulgaria), innovator tablets (Zocor® tablets).

2.3. Simvastatin Co-crystal Manufacturing

The simvastatin co-crystal was made by solvent evaporation method with a ratio of (1:2) simvastatin:isocotinamide, then put into an evaporating dish. Then add sufficient methanol with constant stirring until completely dissolved. Then the solvent was evaporated by leaving it at room temperature for 24 hours [8].

2.4. Formula Optimization with Design Expert® Software

Prior to the optimization, the excipients to be varied, namely Primogel and Avicel pH102, were analyzed using the two-level factorial design in Design Expert® software to get some of the best formulas [9].

2.5. Preparation of Calibration Curve

Amount 100 mg simvastatin BPFI was weighed and dissolved in 100 mL of solvent to be used in the comparative dissolution test, namely a buffer solution of pH 1.2 containing hydrogen chloride, a buffer solution of pH 4.5 containing potassium dihydrogen phosphate, and a buffer solution of pH 6.8 containing disodium hydrogen phosphate. Then the preparation of isonicotinamide stock solutions with similar concentrations was also carried out. The absorbance of each solution was measured using a UV spectrophotometer at a wavelength range of 200-300 nm. Then derivatives were performed until zero crossing was found where only simvastatin provided absorption while the coformer did not provide absorption. Subsequently, the simvastatin solution was diluted in stages to obtain a solution with 5 variations in concentration. Each concentration was measured its absorbance using a UV spectrophotometer at a wavelength range of 200-300 nm and a standard curve was made. After obtaining the standard curve, linearity test, LOD, LOQ, accuracy test, and precision test were carried out with the help of Microsoft Excel 2017 software [10].

2.6. Tablet mass Evaluation

The formula resulting from Design Expert® optimization is weighed for each component and mixed in one container. Then evaluated as the mass of the impression of flow properties and compressibility.

Flow properties

The printed mass is put into a stationary funnel. The funnel cover is opened so that the print mass comes out and is accommodated on a flat surface. The mass flow time of the print is recorded and the angle of repose is measured by calculating the diameter and height of the pile of print mass coming out of the mouth of the funnel [11].

Compressibility

A total of 100 grams of the printed mass was put into a measuring cup on the compressibility test apparatus and the volume was recorded. Then the bulk density is calculated using the formula following :

$$bulk\ density = \frac{Weigh\ of\ granul}{volume\ granul}$$

The mass is compressed by tapping 10, 500, and 1250 times (V10, V500, and V1250). If the difference between V500 and V1250 is less than 2 ml, then V1250 is the compressed volume. If the difference between V500 and V1250 is more than 2 ml, then the knocking is repeated 1250 times until the difference is less than 2 ml. Then the incompressible density is calculated using the following formula:

$$Tapped\ density = \frac{granule}{volume\ tapped\ granule}$$

Carr's index and hausner ratio are calculated using the following formula:

$$\text{Carr's Index} = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100\%$$

[12].

2.7. Tablet Quality Evaluation

The printed mass of each formula that has been evaluated is then printed using a single punch tablet printer with the direct compression method. Furthermore, the quality of the tablets was evaluated for weight uniformity, size uniformity, tablet hardness, friability, disintegration time, dissolution and assay.

Weight uniformity

A total of 20 tablets were separated. Then the weight of the tablets was measured one by one using an analytical balance. The average weight for one tablet is calculated [13].

Size uniformity

A total of 20 tablets were separated and then the diameter and thickness of the tablets were measured using a caliper [14].

Tablet hardness

A total of 20 tablets were separated and then the hardness of the tablets was measured using a hardness tester one by one [15].

Friability

A total of 20 tablets were separated and their weight was measured using an analytical balance. Tablets are inserted into the friability test apparatus. The tool is turned on until it rotates 100 times. The tablet is removed and weighed again. Loss of tablet weight is calculated in percent [11].

Disintegration time

A total of 6 tablets were separated and put into each basket tube on the disintegration time test apparatus. The tool is turned on with water medium at 37º±2ºC. The disintegration time of each tablet was observed and recorded [16].

Dissolution test

A total of 6 tablets were separated. Make a buffer solution of pH 7 as much as 900 mL for each chamber. Set the type 2 dissolution apparatus (paddle type) so that it has a speed of 50rpm and a temperature of 37º±0.5ºC. Tablets are inserted into each chamber. Sampling of 5±0.1 mL was carried out at minute5, 10, 20, and 30. Then the concentration of the sample was measured using a UV-Vis spectrophotometer [17].

Tablet content evaluation

Separate 10 tablets and crush them. Then weighed 100 mg of mass and dissolved in100 mL of solvent mixture of methanol and water in a volumetric flask. Then dilution was carried out to obtain a solution with a concentration of 2 mg/L. The absorbance of the solution was measured using a UV-Vis spectrophotometer at a wavelength range of 200-300 nm. The tablet content was determined using the standard curve equation [18].

2.8. Analysis Using Two-Level Factorial Design Method in Design Expert®

The results of the evaluation of the print mass (flow properties and compressibility) and tablet quality

(disintegration and dissolution time) are entered into the “Response” column on the optimization results page. Then click the “Analysis” option on the left of Design Expert®to find out the results of Half-Normal Plot, ANOVA, Contour Plot and Actual Equation on each response. Then click the "Numerical" option on the left of Design Expert® to find out the desirability value and the best recommended formula solution [9].

2.9. Comparable Dissolution Test

Tests were carried out on 12 innovator tablets and 12 simvastatin co-crystal tablets. Prepared dissolution media, namely a buffer solution of pH 1.2 containing hydrogen chloride, a buffer solution of pH 4.5 containing potassium dihydrogen phosphate, and a buffer solution of pH 6.8 containing disodium hydrogen phosphate. Each dissolution medium is inserted into the chamber of the type 2 dissolution apparatus as much as 900 mL per chamber and the temperature is set to 37°C ± 0,5°C. Press the “Start” button on the device to start the comparative dissolution test. Comparative dissolution test was carried out for 60 minutes. Sampling of 5±0.1 mL was carried out at minute5, 10, 20, 30, and 60. Then the concentration of the sample was measured using a UV-Vis spectrophotometer. Furthermore, the concentration of the dissolution test results compared to the innovator simvastatin tablet and simvastatin co-crystal tablet was calculated using the BootStrap® software to obtain the f2 value and the dissolution grapH comparison [19].

3. Results and Discussion

3.1. Simvastatin Co-crystal Production Results

Simvastatin co-crystals were synthesized using the solvent evaporation method. The coformer in the manufacture of this co-crystal is isonicotinamide, this coformer was chosen because it complies with the requirements of a coformer, namely non-toxic substances, having better polarity than the active substance, pharmaceutical excipients and non-covalent with the active substance [20,21]. Methanol was selected as the solvent because of simvastatin's high solubility in it. The solvent evaporation method will provide time for simvastatin and coformers to move and form bonds and interact which is the basis for the alleged formation of co-crystals [21].

The equimolar comparison used was based on the synthone relationship between the active pharmaceutical ingredient simvastatin and the isonicotinamide coformer. Synthonic relationships involve non-covalent interactions such as hydrogen bonds, van der Waals, -stacking electrons, electrostatic interactions and halogen bonds [21]. The lactone groups contained in simvastatin are carbonyl, hydroxyl and ether groups who can form hydrogen bonds with coformers such as isonicotinamide. The solvent evaporation method promotes the formation of cocrystals with enhanced hydrogen bonding [22].

The results of optimization using the two-level factorial design method on Design Expert® yielded 4 formula designs. Each formula contains co-crystal simvastatin as active substance, primogel as disintegrant, Avicel pH 102 as filler-binder, mg stearate as lubricant and talcum as anti-adherent or glidan as follows.

Table 1. Formula of Co-Crystal Simvastatin Tablet

Ingredients	%concentration (w/w)			
	F1	F2	F3	F4
Simvastatin Co-crystal	10	10	10	10
Primogel	2	8	2	8
Avicel pH 102	79	79	85	85
Mg Stearate	1	1	1	1
Talkum	2	2	2	2

3.2. Results of Making Standard Curves and Validation of Analytical Methods

Validation of the analytical method aims to prove that the standard curve parameters meet the requirements for their use in determining sample levels. The parameters used to meet the standard curve characteristics used to assess the standard curve characteristics in a measurement, LOD (Limit of Detection), LOQ (Limit of Quantification), accuracy (% recovery), and precision (% coefficient of variation). All standard curves meet the desired parameter criteria. The results of the standard curve validation for the measurement of simvastatin and co-crystal levels can be seen in Figure/Table 2.

Table 1. Formula of Co-Crystal Simvastatin Tablet

Standard Curve	Regression Value (r2 0.98)	LOD (in ppm)	LOQ (in ppm)	Accuracy (80% - 110%)	Precision (< 2%)
SV (MeOH:H2O)	0.9988	0.0854	0.2589	97.0755	0.53
SV pH 1.2	0.9993	0.0867	0.2629	98,977	0.7944
SV pH 4.5	0.999	0.0429	0.1302	97,418	1.1084
SV pH 6.8	0.9985	0.2387	0.7235	93.496	0.4713
SV pH 7	0.9988	0.1572	0.4766	99.957	0.4092

Information:
SV = Pure Simvastatin

3.3. Tablet Mass Evaluation Results

The flowability test is determined by the flow rate and angle of repose. The results of the printed mass flow rate are listed in Figure 1. A good flow rate is more than 10g/s. Formulas 1, 2, 3 and 4 have flow times 15.21 g/s, 19.34 g/s, 9.7 g/s and 8.05 g/s for each formula. Consequently, only formulas 1 and 2 are eligible.

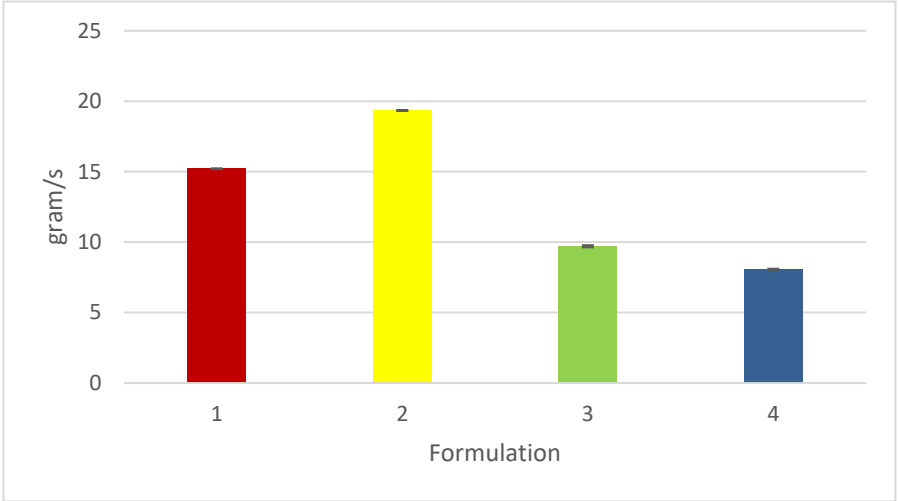


Figure 1. Flow rate test results (n=3)

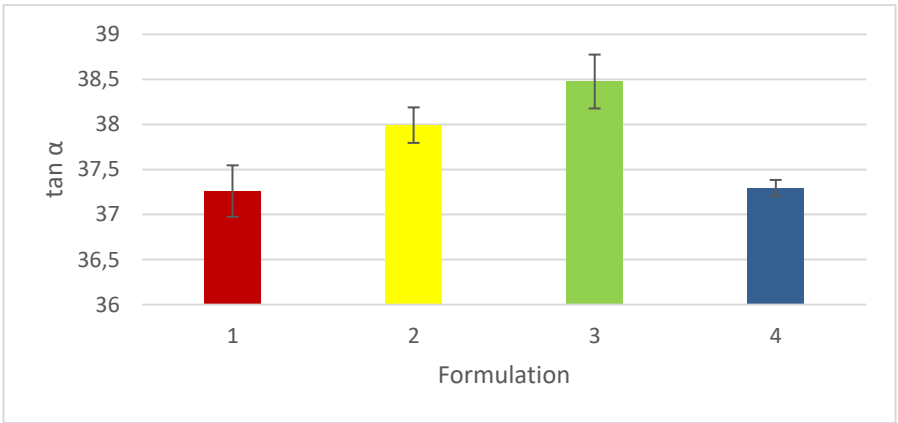


Figure 2. The result of angle of response (n=3)

The Carr index value affects the ability of the print mass to compact during the printing process. The smaller the Carr index value, the better the mass flow. In Figure 3, it can be observed that Formulas 1 and 2 exhibit relatively good Carr indices, while Formulas 3 and 4 have Carr indices that are sufficiently adequate.

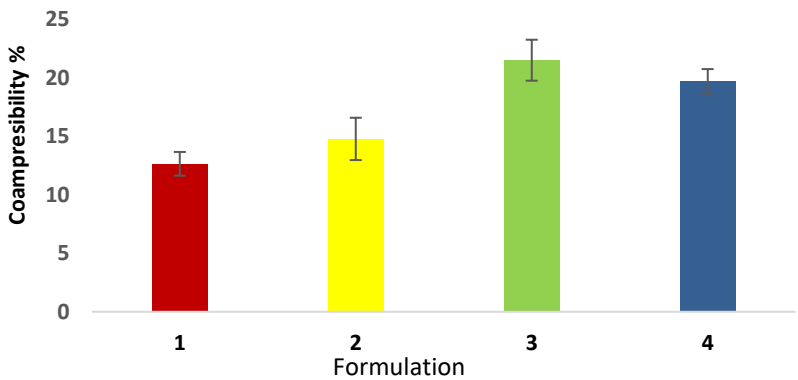


Figure 3. Compressibility test results (n=3)

3.4. Tablet Quality Evaluation Results

The weight of the tablets produced is 200 mg, ensuring compliance with the uniformity of weight requirements. These requirements stipulate that none of the tablets should deviate in weight by more than 15% or 30 mg, and no more than two tablets should have a deviation greater than 7.5% or 15 mg [24]. All formulas meet these requirements, as illustrated in Figure 4.

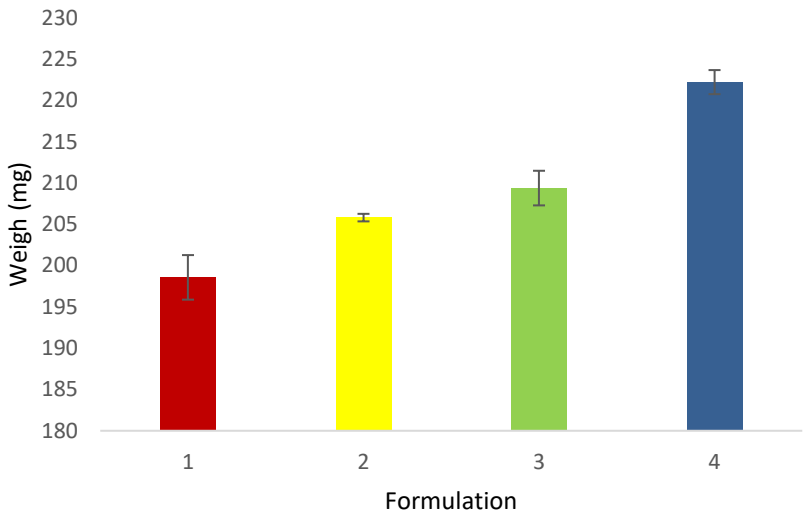
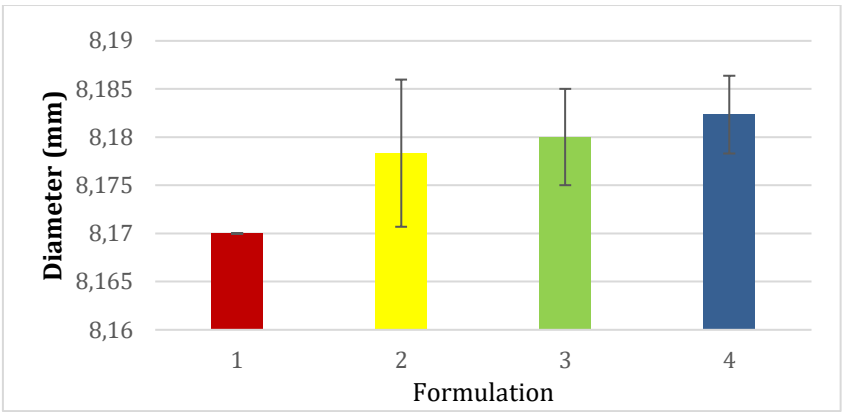
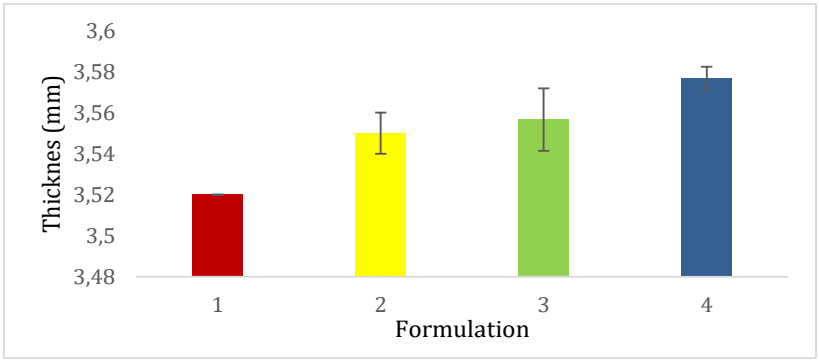


Figure 4. The results of the weight uniformity test (n=20)

The requirement for uniformity of size specifies that the tablet diameter should not exceed 3 times the tablet thickness and should not be less than 1 1/3 times the tablet thickness [24]. Consequently, the required diameter falls within the range of 4.66 mm to 10.5 mm. In Figure 5, it is evident that all formulas have uniform sizes that meet the requirements for both the diameter and thickness of the tablets."



(a)



(b)

Picture 5. The results of the uniformity test of size (a) diameter (b) thickness (n=20)

The tablet hardness test aims to assess the tablet's resistance to mechanical stress, such as shock during packaging, transportation, and use processes. Tablet hardness also significantly influences the disintegration and dissolution times of tablets. The results of the tablet hardness test are depicted in Figure 6. The tablet hardness requirements range from 70 to 100 N, and all formulas produced have met these requirements

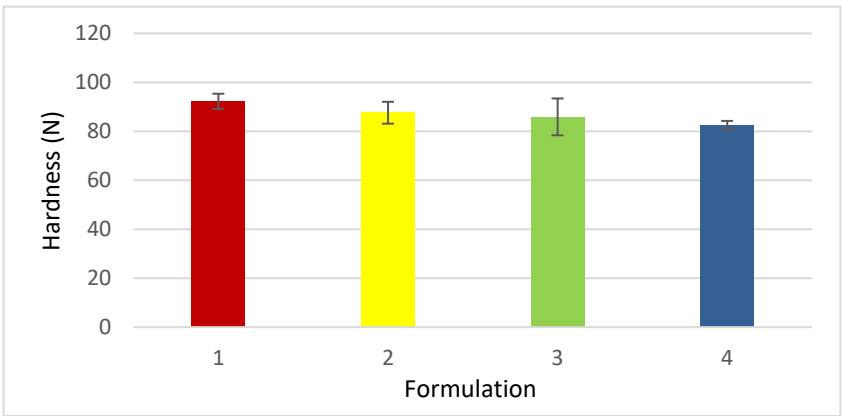


Figure 6. Hardness test results (n=20)

The requirement for friability testing is less than 1% [12]. As depicted in Figure 7, all the formulas meet this requirement. The value of friability can be influenced by the water content in the powder or the final product, namely tablets [25].

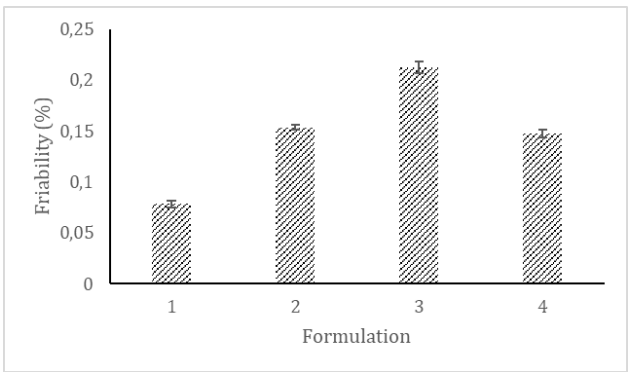


Figure 7. Friability test results (n=20)

The requirement for the disintegration time of uncoated tablets is 15 minutes [24]. As shown in Figure 8, all formulas disintegrate within 15 minutes, indicating that they meet the requirement.

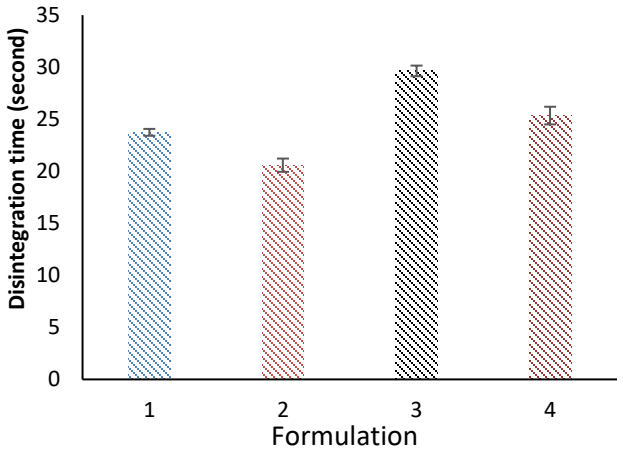


Figure 8. Disintegration time test results (n=6)

The dissolution test was conducted to observe and compare the dissolution profiles of all simvastatin co-crystal tablet formulas. According to PHarmacopoeia Edition VI, the dissolution requirement for simvastatin tablets is 75% at 30 minutes at pH 7 [17]. The percent dissolution of these tablets can be influenced by the tablet's disintegration time. From the results of the dissolution test shown in the figure, it is evident that all formulas meet the requirements. Figure 9 illustrates the percent dissolution of simvastatin co-crystal tablets at 30 minutes: formula 1 is 80.01%, formula 2 is 85.02%, formula 3 is 80.43%, and formula 4 is 81.52%.

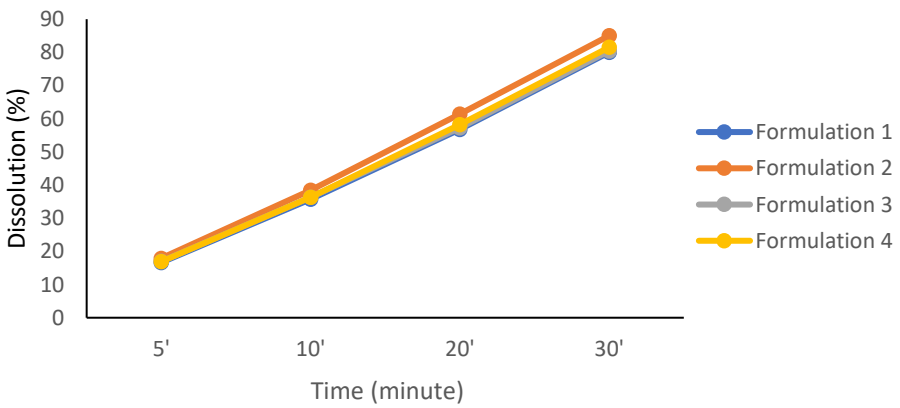


Figure 9. Dissolution test results (n=6)

The concentration of simvastatin co-crystal tablets was determined in methanol: water (4:6) solvent with zero crossing on derivative 1. According to PHarmacopoeia Edition VI, the requirement for simvastatin concentration in tablets is 90% - 110% [17]. As depicted in Figure 10, the levels of all formulas comply with the PHarmacopoeia requirements. Therefore, all formulas exhibit satisfactory levels of simvastatin in tablets.

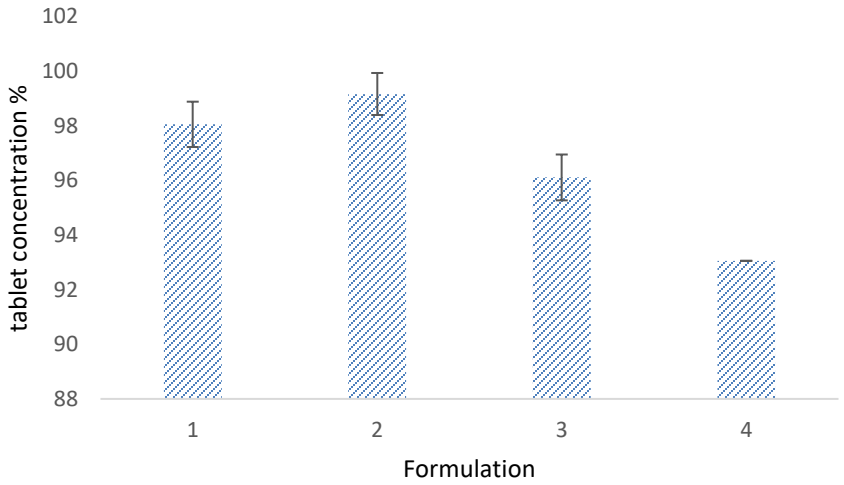


Figure 10. Assay results (n=10)

3.5. Analysis Results Using Two-Level Factorial Design Methods in Design Expert®

Data processing using a two-level factorial design method in Design Expert® works by sorting out the best formula based on the response (evaluation) of the specified parameter results. In addition, there is a linear model prediction to explain each excipient to the input response. Design Expert is validated by looking at the value of lack of fit and linearity (R2). The results of the validation of the design expert in this study are the lack of fit value of 0 and the linearity of 0.9969. The requirements for the Lack of fit value are less than 0.2 and the linearity is close to 1. So it can be said that the Design Expert® software in this study was validated. Data processing using the two-level factorial design method in Design Expert® worked by sorting out the best formula based on the response (evaluation) of the specified parameter results. In addition, there is a linear model prediction to explain each excipient to the input response. The ANOVA analysis results, indicating the effect of excipients on the evaluation of print mass and tablet quality, are presented in the table below.

Table 3. Results of ANOVA Analysis on Flow Rate Response

Source	Sum of Squares	df	Mean Square	F-values	p-value	Statement
Model	34.45	3	11.48	4768.34	<0.0001	significant
A- Primogel	15.05	1	15.05	6250.30	<0.0001	
B- Avicel pH 102	11.33	1	11.33	4704.35	<0.0001	
AB	8.07	1	8.07	3350.37	<0.0001	
Pure Error	0.0193	8	0.0024			
Total Cast	34.47	11				

Table 4. Results of ANOVA Analysis on Compressibility Response

Source	Sum of Squares	df	Mean Square	F-values	p-value	Statement
Model	270.10	3	90.03	27645.43	<0.0001	significant
A- Primogel	19.29	1	19.29	5923.65	0.8944	
B- Avicel pH 102	167.29	1	167.29	51368.68	<0.0001	
AB	83.51	1	83.51	25643.95	<0.0001	
Pure Error	0.0261	8	0.0033			
Total Cast	270.12	11				

Table 5. Results of ANOVA Analysis on the Response Time of Disintegration

Source	Sum of Squares	df	Mean Square	F-values	p-value	Statement
Model	108.54	3	36.18	686.53	<0.0001	significant
A- Primogel	59.32	1	59.32	1125.59	<0.0001	
B- Avicel pH 102	43.70	1	43.70	829.24	<0.0001	
AB	5.52	1	5.52	104.77	<0.0001	
Pure Error	0.4216	8	0.0527			
Total Cast	108.96	11				

Table 6. Results of ANOVA Analysis on Dissolution Response

Source	Sum of Squares	df	Mean Square	F-values	p-value	Statement
Model	204.04	3	68.01	856.24	<0.0001	significant
A- Primogel	33.60	1	33.60	423.00	<0.0001	
B- Avicel pH 102	74.90	1	74.90	942.93	<0.0001	
AB	95.54	1	95.54	1202.79	<0.0001	
Pure Error	0.6355	8	0.0794			
Total Cast	204.68	11				

The initial hypothesis determined in this study, namely H0, there was no significant difference given by Primogel, Avicel pH 102 and both of the first formula to the fourth formula. The second hypothesis is H1 which is the opposite of H0. Determination of the hypothesis and the results of the hypothesis are very influential on decision making in research. The p-value or in software commonly known as p-value is one of the parameters used in deciding to reject or accept H0. It can be seen in the table of ANOVA analysis results above that all the resulting probability values are less than 0.05, this indicates that they are smaller than the specified level. The value of 0.05 can also be interpreted as the threshold we make mistakes when making decisions. The conclusion drawn then H0 is rejected. ANOVA results from this software indicate a significant difference

given by Primogel, Avicel pH 102 and both of the first formula to the fourth formula.

The next analysis is to choose the optimal formula based on each response. This analysis is related to the previous analysis, which examines the impact of each response on the selection of the optimal formula. The most optimal formulation is chosen when the color on the contour plot grapH becomes redder. The contour plot grapH illustrates how the combination of factors influences the response outcomes. If results falling within the blue area indicate a poor response, or very low results. A good response occurs when the results fall within the red area. The deeper the shade of red in the results area, the better the outcome [26].

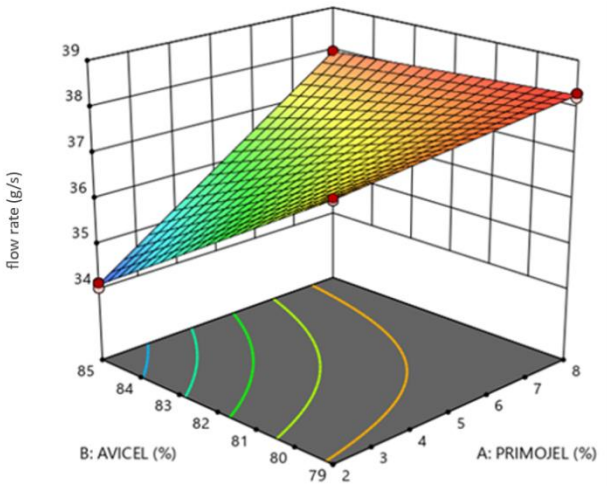


Figure 11. Contour Plot Against Flow Rate Response

The optimal formula based on the flowability response is formula 2 as shown in Figure 11. Primogel is very influential on the flowability so that the optimal formula is when concentration of Primogel is 8% and concentration of Avicel pH 102 is 79%. This is due to Primogel's ability to reduce cohesion induced by Avicel pH 102. Consequently, higher utilization of Primogel in the formula, the more it affects the flowability towards a positive response.

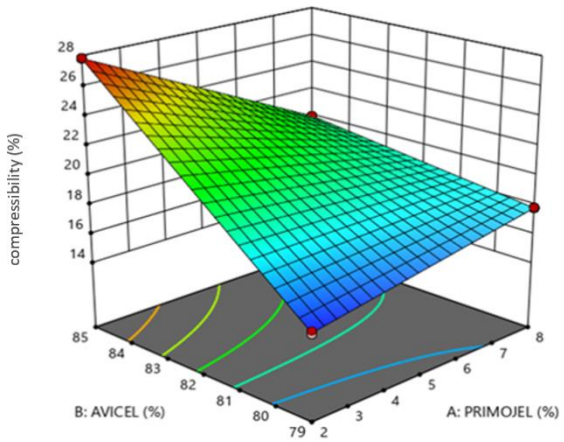


Figure 12. Contour Plot Against Compressibility Response

The optimal formula based on the compressibility response is formula 3 (Figure 12). In this formula, concentration of Avicel pH 102 is 85% and Primogel is 2%. This shows that Avicel pH 102 has good compatibility. Therefore, the higher the utilization of Avicel pH 102 in the formula, the better the compressibility value.

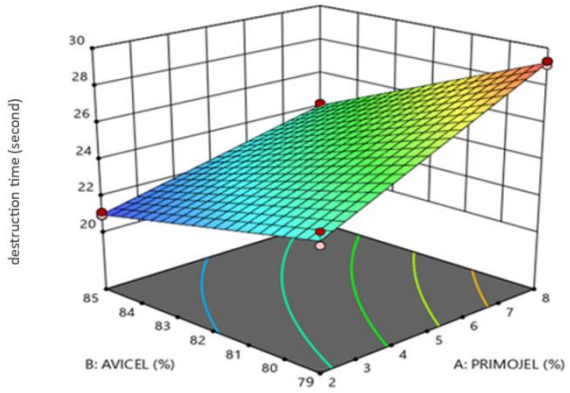


Figure 13. Contour Plot Against Destruction Time Response

The optimal formula based on the compressibility response is formula 3 (Figure 12). In this formula, concentration of Avicel pH 102 is 85% and Primogel is 2%. This shows that Avicel pH 102 has good compatibility. Therefore, the higher the utilization of Avicel pH 102 in the formula, the better the compressibility value.

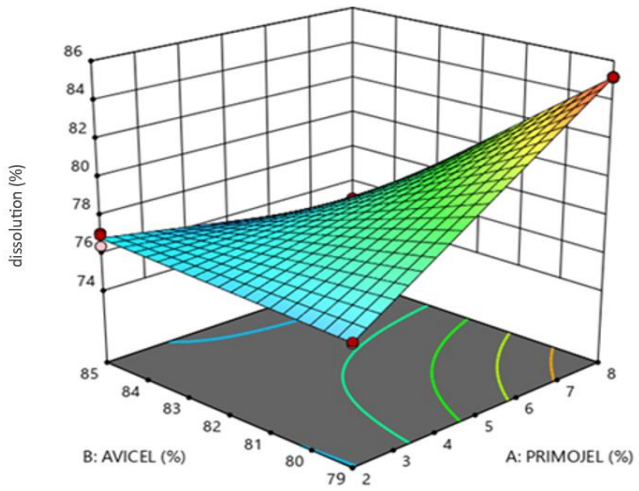


Figure 14. Contour Plot Against Dissolution Response

The optimal formula based on the response to dissolution is formula 2 (Figure 14). Dissolution is closely related to disintegration time, where dissolution increases with disintegration time. Therefore, the optimal formula selected for both disintegration and dissolution response times is the same.

The final analysis is the provision of solutions from the software. The solution given is the best formula solution that produces the most optimum disintegration time and dissolution,

from the software. The solution given is the best formula solution that produces the most optimum disintegration time and dissolution, which are then used in the comparative dissolution test. The solution given is one formula that has the highest desirability value. The prediction formula recommended by the software is Formula 2, which has a desirability value of 0.942. The desirability value itself is the value of the optimization function that shows the ability of the program used to fulfill the desire based on the criteria set in the final product. The desirability value describes the closeness between the resulting response (evaluation results) and the ideal value (actual value). The software uses the desirability value as a measure of the accuracy of the numbers given with the actual results that will occur. This value ranges from 0 to 1, where a value close to 1 indicates the program's ability to produce the optimum formula.

The purpose of optimization using the program is not only to produce a desirability value of 1.0, but also to identify the most optimum conditions from many formulas that consider all responses, factors and functions [26]. The results provided by the Design Expert® software are as follows:

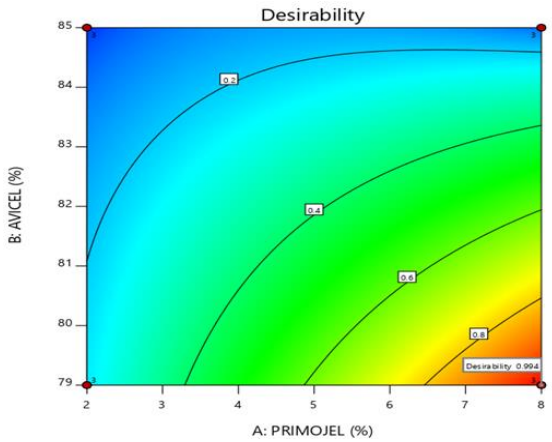


Figure 15. Contour Plot Against Desirability

Comparative dissolution test was conducted by comparing simvastatin co-crystal tablets with the optimal formula analysis results from Design Expert® software against 12 tablets of simvastatin innovator each. The comparative dissolution test was carried out at 3 pH. The variation in pH levels simulates the pH conditions of the human body. The following grapH illustrates the results of the comparative dissolution test at pH 1.2; 4.5, and 6.8.

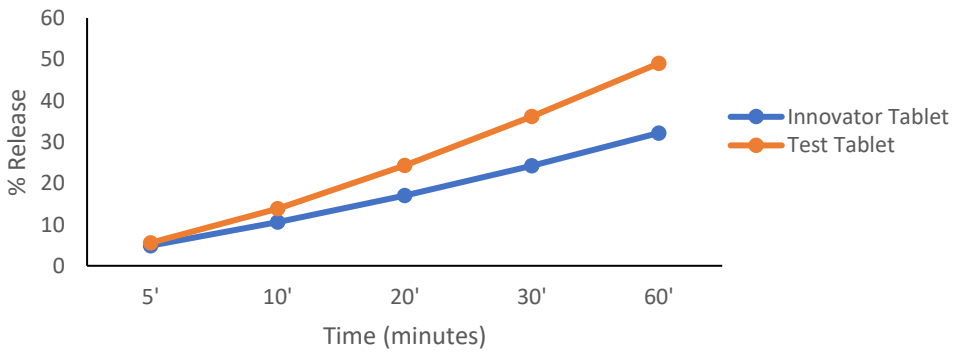


Figure 16. Comparable Dissolution Test pH 1.2

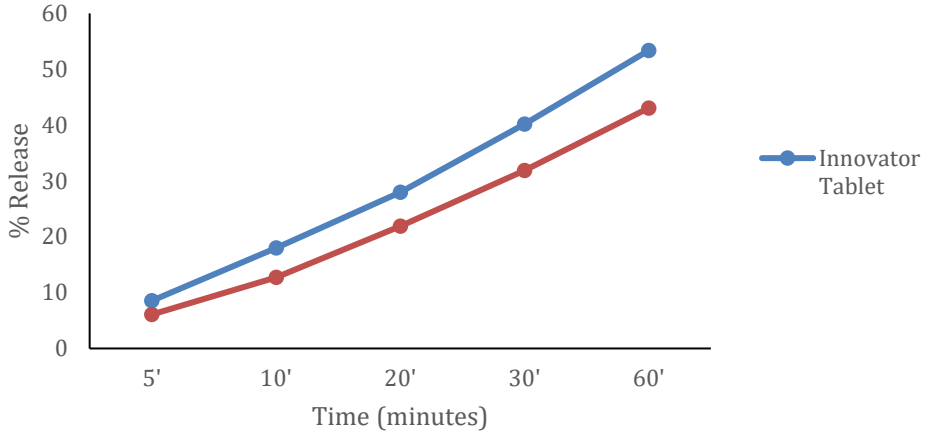


Figure 17. Comparable Dissolution Test pH 4.5

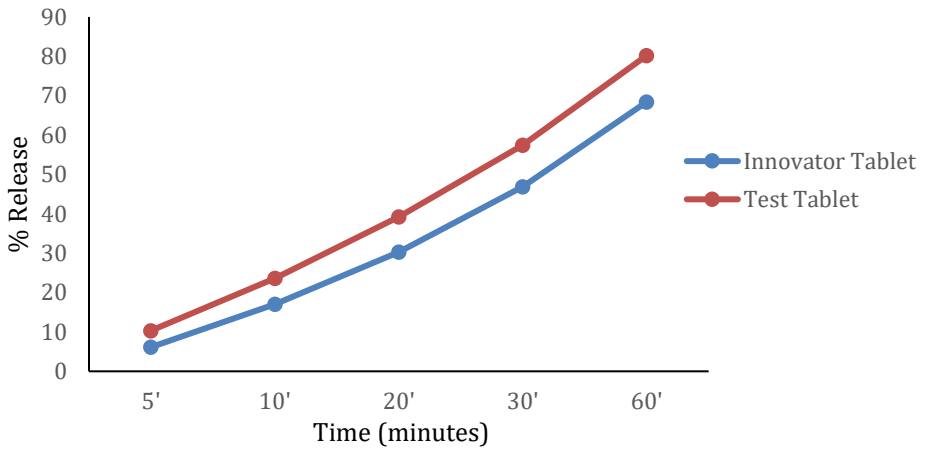


Figure 18. Comparable Dissolution Test pH 6.8

At all pH levels used, it can be seen that there is an increase in dissolution levels of both simvastatin co-crystal tablets and innovator tablets at 5 to 60 minutes. However, simvastatin co-crystal tablets and innovator tablets have a higher dissolution rate at pH 6.8, which means simvastatin is more soluble at alkaline pH than at acidic pH. Then, the dissolution is calculated by the value of f2 using the BootStrap software®which performs a similarity test between the innovator tablet and the test tablet. The f2 value obtained is 50.3 at pH 1.2; 56.09 at pH 4.5; and 59.23 at pH 6.8. It can be seen that the value of f2 in all pH conditions is more than 50 which indicates that the innovator tablet has the same release profile as the test tablet. Therefore, simvastatin co-crystal tablets show a similarity index to the innovator tablet at pH 1.2; 4.5, and 6.8. The grapH illustrates that the dissolution result line for the test tablets are always above the innovator tablet dissolution line at all pH values. This means that the dissolution rate of the test tablet is higher than that of the innovator tablet.

4. Conclusion

Based on the optimization results of Design Expert software, there are 4 optimal formulas for making simvastatin co-crystal tablets with variations of excipients Primogel

and Avicel pH 102. However, the formula that has the most optimal evaluation results is formula 2 which contains 8% Primogel and Avicel pH 102 79% with desirability 0.942.

The simvastatin co-crystal tablet produced comparable dissolution test results with an f2 value of more than 50 at all pH values, which means that the simvastatin co-crystal tablet had the same release profile as the innovator tablet. Overall the grapH shows that the test line is above the innovator tablet, which means the test tablet has a higher dissolution rate than the innovator tablet.

5. References

[1] Murtaza G. Solubility enhancement of simvastatin: A review. Acta Poloniae PHarmaceutica - Drug Research. 2012;69(4):581–590.

[2] Jayasankar A. et al. Cocrystal formation during cogrinding and storage is mediated by amorpHous pHase. Pharmaceutical Research. 2006;23(10):2381–2392.

[3] Mirza S, Heinämäki J, et al. L24 Co-crystals: An emerging approach to improving properties of pharmaceutical solids', European Journal of Pharmaceutical Sciences. 2008;34(1):S16–S17.

[4] Hairunnisa, Sopyan I, Gozali D. Cocrystal : nocotimide as the coformer. Scientific Journal of Farmako Bahari. 2019;10(2):113–122.

[5] Wulan PP. Identification of Process Variable Effects and Determination of Optimum Conditions for catalytic decomposition of methane by surface response method, National Seminar on Chemistry and Chemistry Education. 2012;1(1):443–452.

[6] Supervisor B. et al. Per KBPOM No. HK.03.1.23.12.11.10217 Year 2011 Compulsory Drug Equivalence. Journal of Chemical Information and Modeling. 2011;53(9):19.

[7] Shah VP, et al. FDA guidance for industry 1 dissolution testing of immediate release solid oral dosage forms. Dissolution Technologies. 1997;4(4):15–22.

[8] Sopyan I, et al. Co-crystallization: A tool to enhance the solubility and dissolution rate of simvastatin, Journal of Young PHarmacists. 2017;9(2):183–186.

[9] Riwidikdo H. Health Statistics. Yogyakarta: Mitra Cendekia Press.unite; 2008.

[10] Kharisma RM, Sopyan I. Dissolution Rate Repairing of Simvastatin as A New Approach in Cocrystallization, Scholars Research library. 2017;6(9):18–27.

[11] Lieberman, HA and Lachman, L. The Theory and Practice of Industrial PHarmacy, 2nd ed. PHiladelpHia: Lea and Febiger; 1986.

[12] United States PHarmacopeia. The United States PHarmacopeia: The National Formulary, Volumes 1-4. New York: United States PHarmacopeial Convention; 2013.

[13] Ministry of Health Republic of Indonesia. Indonesian PHarmacopoeia Edition IV. Jakarta: Ministry of Health of the Republic of Indonesia; 1995.

[14] Ansel H. Introduction to Pharmaceutical Dosage Forms Edition IV. Jakarta: UI Press; 2008.

[15] Parott E. Pharmaceutical Technology Fundamental PHarmaceutics 3th edition. Minneapolis: Burgess Publishing Company; 1971.
[16] Agoes G. Development of Pharmaceutical Preparations. Bandung: ITB Publisher; 2008.
[17] Ministry of Health of the Republic of Indonesia. Indonesian PHarmacopoeia Edition VI. Jakarta: Ministry of Health of the Republic of Indonesia; 2020.
[18] Chavhan V, Ghante M. Stability Indicating Uv SpectropHotometric Method Development and Validation of Simvastatin in Bulk and Tablet Dosage Form, Journal of Applied PHarmacy. 2014;6(2):235–246.
[19] FDA. Guidance for Industry: Waiver of In Vivo Bioavailibility and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a BiopHarmaceuticas Claasification Systems. US: Department of Health; 2000.
[20] Mirza S, Miroshnyk I, et al. Co - Crystals : an Emerging Approach for Enhancing Properties of Pharmaceutical Solids, Dosage. 2008;24(02):90–96.
[21] Qiao N, et al. Pharmaceutical cocrystals: An overview, International Journal of PHarmaceutics. Elsevier BV. 2011;419(1–2):1–11.
[22] Chandramouli Y, et al. Review on Cocrystal As an Approach With Newer Implications in Pharmaceutical Field, International Journal of Medicinal Chemistry & Analysis. 2012;2(2):91–100.
[23] Sopyan I, Wathoni N, Rusdiana T, Gozali D. Characterization of Solid Pharmaceutical Preparations. Yogyakarta: DeePublish; 2018.
[24] Ministry of Health of the Republic of Indonesia. Indonesian PHarmacopoeia Edition III. Jakarta: Ministry of Health of the Republic of Indonesia; 1979.
[25] Lachman L, Herbert A, JosepH L. Theory and Practice of the Pharmaceutical Industry III Edition. Jakarta: University of Indonesia Publisher; 2008.
[26] Nurmiah S. et al. Application of Response Surface Methodology in Optimizing Process Conditions for Processing Alkali Treated Cottonii (ATC)', Journal of Postharvest and Marine and Fishery Biotechnology. 2013;8(1):9.