

Method validation of simvastatin in PCL-PEG-PCL triblock copolymer micelles using UV-vis spectrophotometric for solubility enhancement assay

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METHOD VALIDATION OF SIMVASTATIN IN PCL-PEG-PCL TRIBLOCK COPOLYMER MICELLES USING UV-VIS SPECTROPHOTOMETRIC FOR SOLUBILITY ENHANCEMENT ASSAY

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ABSTRACT

Objective: This study aims to increase the solubility of simvastatin (SIM), a hydrophobic drug, by incorporating it into PCL-PEG-PCL triblock copolymer micelles and validating the assay method used, namely UV-Vis spectrophotometric.

Methods: The shake flask method was used to determine the increase in solubility experienced by SIM after being incorporated into the micellar system. The values of maximum wavelength (λ_{max}), linearity, LOD, LOQ, accuracy, and precision were used as parameters measured to assess the validity of the assay method used.

Results: The results showed that PCL-PEG-PCL triblock copolymer micelles could increase SIM solubility by 9.7 times (89.49±5.75 µg/ml) compared to SIM without modification (9.19±0.24 µg/ml). The validation results show the λ_{max} value of 239 nm, a linear calibration curve with an R-value of 0.9994, LOD and LOQ of 0.33 µg/ml and 1.00 µg/ml, accurate measurement with recovery at concentrations of 80%, 100%, and 120% were 102.93±1.32%, 100.78±0.40%, and 104.58±0.79% and also had good precision with RSD<2%.

Conclusion: The PCL-PEG-PCL triblock copolymer micelles can increase SIM solubility and the UV-Vis spectrophotometric method has been validated successfully for the quantitative analysis of SIM in PCL-PEG-PCL triblock copolymer micelles.

Keywords: Simvastatin, Triblock copolymer, PCL, PEG, Validation, UV-Vis spectrophotometric

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INTRODUCTION

Solubility is one of the physicochemical properties of drugs that need to be considered because it can affect the formulation and effectiveness of therapy. Drugs with low solubility (hydrophobic drugs) will provide low bioavailability so that the desired therapeutic effect is not perfect [1, 2].

SIM (C₂₅H₃₈O₅) is an anti-cholesterol drug of the statin class with the mechanism of action of inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). SIM belongs to the class II biopharmaceutical classification system (BCS) with a solubility of 0.01 g/l (practically insoluble) and a bioavailability of <5% [3-6].

Many attempts have been made to increase the solubility of SIM, including hydrogels [7], complexes with arginine [8], solid dispersions [9, 10], micellar polymers with derivatives of tocopherol [11], spherical crystal [12], and co-crystal formation [13, 14]. In this study, the increase in the solubility of SIM was carried out by being incorporated into PCL-PEG-PCL triblock copolymer micelles which would then form a micellar polymer. PCL-PEG-PCL triblock copolymer micelles are an ideal drug carrier candidate for SIM with an entrapment efficiency of 87.74% [15].

To determine the increase in solubility experienced by SIM, it is necessary to determine the concentration of SIM in the PCL-PEG-PCL triblock copolymer micelle. According to the pharmacopeia, SIM levels were determined by the High-Performance Liquid Chromatography (HPLC) method. However, a simpler method, UV-Vis spectrophotometry, has been reported to be used for the assay of SIM in several pharmaceutical preparations showing results that meet the required acceptance criteria [16-19].

MATERIALS AND METHODS

Materials

SIM is provided free by Dexa Medica (Palembang-Indonesia). All other chemicals and reagents used in this study met the criteria for an analytical grade.

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Preparation of PCL-PEG-PCL triblock copolymer and SIM loaded PCL-PEG-PCL triblock copolymer micelles

The preparation of PCL-PEG-PCL triblock copolymer and incorporated SIM into the micelles system was obtained from our previous study. Where PCL-PEG-PCL triblock copolymer is made by reacting 5 g of PEG and 10 g of *ε*-CL using Sn (Oct); 0.5% w/w as a catalyst by the ring-opening polymerization method (ROP). While SIM was incorporated into the polymeric micelles by the solvent evaporation method (film formation), 1 ml of SIM stock solution in dichloromethane (100 mg/10 ml) was mixed with 50 mg of PCL-PEG-PCL triblock copolymer [15].

Preparation of SIM stock solution

SIM was weighed as much as 10 mg, put into a 25 ml volumetric flask, and methanol was added to the mark and then homogenized to obtain a concentration of 400 ppm [16].

Determination of the λ_{max} of SIM

The 0.05 ml of the stock solution is pipetted, put into a 5 ml volumetric flask, distilled water is added to the limit mark and homogenized to obtain a solution with a concentration of 4 ppm, then the solution is measured using a UV-vis spectrophotometer over a 200-300 nm wavelength range. The λ_{max} of SIM is indicated by the wavelength that gives the highest absorbance [16].

Preparation of SIM calibration curve

The stock solution was pipetted as much as each 0.050, 0.075, 0.100, 0.125, 0.150, and 0.175 ml were put into a 5 ml volumetric flask, and then distilled water was added to the mark and homogenized to obtain a series solution with a concentration of 4, 6, 8, 10, 12 and 14 ppm. The serial solution was measured with a UV-vis spectrophotometer at the λ_{max} of SIM [16].

Solubility enhancement test of SIM in the PCL-PEG-PCL triblock copolymer micelles

SIM excess (10 mg) and loaded into PCL-PEG-PCL triblock copolymer was dissolved in 10 ml of distilled water and shaken for 24 h

at 25±1 °C. After 24 h, the solution was filtered with a 0.45 µm membrane filter and measured using a UV-vis spectrophotometer at the λ_{max} of SIM and the dissolved content was calculated using a calibration curve that had been prepared [20]. The instrument used was a UV-vis spectrophotometer (Thermo Scientific, Genesys 10S UV).

Method validation

Linearity test

The linearity test was carried out by analyzing the measurement results of the serial solution that had been made (4, 6, 8, 10, 12, and 14 ppm) then made a relationship between the absorbance and the concentration of the serial solution, a linear regression equation (y = ax+b) and correlation coefficient (R) was obtained [16].

Determination of limit of detection and limit of quantification (LOD and LOQ)

The LOD and LOQ was determined by measuring the absorbance of the serial solution on the calibration curve for 3 replications and then the standard deviation (SD) is determined [20].

LOD was calculated using the following equation:

$$\text{LOD} = \frac{3.3 \times \text{SD}}{\text{Slope}}$$

Table 1: The results for increasing solubility of SIM in triblock copolymer

Sample	Concentration of SIM (µg/ml)*	Increased solubility
SIM without modification	9.19±0.24	-
SIM in micelles	89.49±5.75	9.7 times

*All values are expressed as mean of n=3±standard deviation (SD)

SIM is a drug that has low solubility in water. Drugs with low solubility in water will be difficult to absorb into the gastrointestinal tract where the main component is water so that will cause low bioavailability. Therefore, one way that can be used to increase the bioavailability of a drug is to increase its solubility in water [1, 3]. Solubility enhancement test was carried out to examine the ability of PCL-PEG-PCL triblock copolymer to increase the solubility of SIM. A similar study was conducted by Alami-milani et al. using a hydrophobic drug model of dexamethasone, in that study, it was reported that the use of PCL-PEG-PCL triblock copolymers could increase the solubility of dexamethasone by 11.7 times (1.17 mg/ml) [23].

The PCL-PEG-PCL triblock copolymer was composed of PCL as a hydrophobic block and PEG as a hydrophilic block. In aqueous media, PCL-PEG-PCL triblock copolymer will spontaneously form

LOQ was calculated using the following equation:

$$\text{LOQ} = \frac{10 \times \text{SD}}{\text{Slope}}$$

Accuracy and precision test

The stock solution was pipetted as much as each 0.100, 0.125, and 0.150 ml, were put into a 5 ml volumetric flask containing 25 ml of PCL-PEG-PCL triblock copolymer solution in water, then distilled water was added to the mark, and then homogenized. The test solution was measured with a UV-vis spectrophotometer at the λ_{max} of SIM. The accuracy test is assessed based on the % recovery, while the precision test is determined based on the relative standard deviation (RSD) value [16, 21].

RESULTS AND DISCUSSION

Increased solubility of SIM in PCL-PEG-PCL triblock copolymers micelles

Theoretically, SIM has a water solubility of 10 g/ml. The solubility of the modified SIM into the PCL-PEG-PCL triblock copolymer micelles was 89.49±5.75µg/ml, while the solubility of SIM without modification was 9.19±0.24µg/ml. These results indicate that there has been an increase in the solubility of SIM after being made into micelles [22]. The complete test results for increasing the solubility of SIM can be seen in table 1.

micelles with the hydrophilic part on the outside and the hydrophobic part on the inside as the core [24, 25]. The ability to increase solubility by triblock micellar copolymers is influenced by the length of the hydrophobic block and the ratio of the constituent polymers. The longer the hydrophobic block that makes up the triblock copolymer, the greater the solubility of the drug because more hydrophobic drugs can be loaded into the micellar system [26].

Analysis method validation

Method validation was carried out on the parameters of the λ_{max}, correlation coefficient (R) of the obtained calibration curve, LOD, LOQ, accuracy, and precision. The complete validation test results for various parameters can be seen in table 2.

Table 2: The summary of validation

Parameter	Result
λ _{max}	239 nm
Linearity	
y = ax+b	Y = 0.0499x-0.0249
a: slope	
b: intercept	
Correlation coefficient (R)	0.9994
LOD (µg/ml)	0.33
LOQ (µg/ml)	1.00
Accuracy (% recovery)*	
	80%
	100%
	120%
Precision (% RSD)	
	Intra-day
	1.371 (8 µg/ml)
	0.418 (10 µg/ml)
	0.786 (12 µg/ml)
	Inter-day (10 µg/ml)
	0.418 (1 st day)
	0.525 (2 nd day)

*All values are expressed as mean of n=3±standard deviation (SD)

λ_{max} of SIM measurement results

The λ_{max} is the wavelength that gives the maximum absorption of SIM. The determination of the λ_{max} of SIM aims to provide maximum

sensitivity of samples containing SIM, a calibration curve that is linear and produces fairly constant data if repeated measurements are made. Determination of the λ_{max} was carried out at a concentration of 4 ppm using a Uv-Vis spectrophotometer, the fig. 1

showed the λ_{max} of SIM was 239 nm, the results were not much different from the λ_{max} of SIM in the literature, which was 238 nm. The λ_{max} shift of the measurement results compared to the literature can be caused by several factors, such as differences in the source of

materials and the tools used. However, the wavelength shift is not more than 3% of the λ_{max} in the literature so it can be said that the results of the measurements carried out meet the requirements for use for analysis [16].

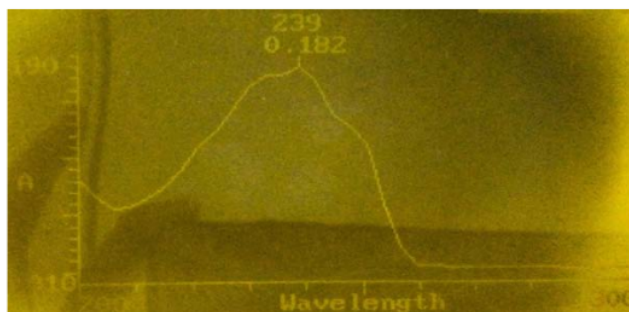


Fig. 1: The λ_{max} of SIM

The results of the calibration curve and linearity test

The calibration curve was used to determine the linear regression equation that would be used to calculate SIM levels in the PCL-PEG-PCL triblock copolymer. The linear regression equation was obtained from the relationship between the concentration of the prepared SIM series solution and its absorbance measured at a wavelength of 239 nm which is the λ_{max} of SIM used in this study, which was presented in table 3. SIM calibration curve graph can be seen in fig. 2, with intercept value = -0.0249 and slope value = 0.0499, so that the linear regression equation $y = 0.0499x - 0.0249$ with $R = 0.9994$ is obtained. The linearity test can be determined based on the correlation coefficient (R) of the obtained linear regression equation, where the acceptance criteria of the linearity test are $R > 0.9994$. When viewed from the R-value obtained in the test, it shows that the method used has good linearity [16, 17, 27].

Accuracy and precision test results

One of the fundamental requirements in the analysis is accuracy and precision. Accuracy indicates the closeness of the measurement results to the actual value which is expressed as % recovery, while precision indicates the degree of suitability of the test results as measured by the distribution of the results from the average when

repeated measurements are made which will produce an average value that is very close to the true value. The measuring parameter to determine precision is the percent relative standard deviation (% RSD) [16, 17, 28].

Table 4 presents that the average % recovery obtained in determining the accuracy is $102.93 \pm 1.32\%$, $100.78 \pm 0.40\%$, and $104.58 \pm 0.79\%$. % recovery is acceptable because it is in the range of 80-110% [17, 21, 28].

Table 3: The result of absorbance measured of the series solution

Concentration (ppm)	Absorbance*
4	0.181±0,002
6	0.264±0,008
8	0.379±0,003
10	0.468±0,007
12	0.580±0,006
14	0.672±0,004

*All values are expressed as mean of $n=3 \pm$ standard deviation (SD)

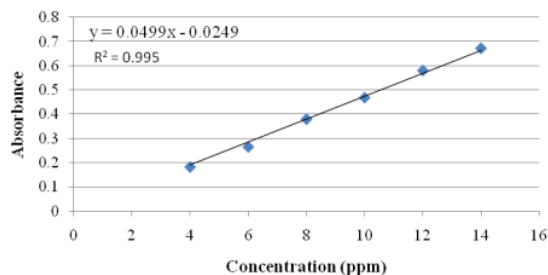


Fig. 2: The graph of SIM calibration curve

Table 4: The results of accuracy test of SIM in PCL-PEG-PCL triblock copolymer micelles

Concentration (%)	Theoretical level ($\mu\text{g/ml}$)	Calculated level ($\mu\text{g/ml}$)	Recovery (%)*	% RSD
80	8	8.234	102.93 ± 1.32	1.269
100	10	10.078	100.78 ± 0.40	0.398
120	12	12.549	104.58 ± 0.79	0.755

*All values are expressed as mean of $n=3 \pm$ standard deviation (SD)

The precision test results are shown in table 5 and 6 show that the % RSD of the average SIM absorbance obtained was 1.371, 0.418, and 0.786 for the intra-day measurement, while 0.418 for the first

day and 0.525 for the second day on the inter-day measurement with a concentration of 10 µg/ml. The value of % RSD<2 indicates that the method shows good precision [13, 14].

Table 5: The results of intra-day precision test of SIM in PCL-PEG-PCL triblock copolymer micelles

Concentration (µg/ml)	Absorbance*	% RSD
8	0.386±0.005	1.371
10	0.478±0.002	0.418
12	0.601±0.005	0.786

*All values are expressed as mean of n=3±standard deviation (SD)

Table 6: The results of inter-day precision test of SIM in PCL-PEG-PCL triblock copolymer micelles

Concentration (µg/ml)	Days-	Absorbance*	% RSD
10	1 st	0.478±0.002	0.418
	2 nd	0.479±0.003	0.525

*All values are expressed as mean of n=3±standard deviation (SD)

CONCLUSION

The solubility of SIM after being incorporated into PCL-PEG-PCL triblock copolymer micelles was successfully increased by 9.7 times compared to SIM without modification. The UV-Vis spectrophotometer used to measure dissolved SIM levels has been successfully validated. The validation results show the λ_{max} value of 239 nm, a linear calibration curve with an R-value of 0.9994, LOD and LOQ of 0.33 µg/ml and 1.00 µg/ml, accurate measurement with % recovery at concentrations of 80%, 100%, and 120% were 102.93±1.32%, 100.78±0.40% and 104.58±0.79% and also has a good precision value with RSD<2%.

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AUTHORS CONTRIBUTIONS

All of the authors listed in this manuscript have contributed equally.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interest related to this report.

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CLAIM

Take an arguable position on the scientific topic and develop the essay around that stance.

ADVANCED	The essay introduces a precise, qualitative and/or quantitative claim based on the scientific topic or text(s), regarding the relationship between dependent and independent variables. The essay develops the claim and counterclaim fairly, distinguishing the claim from alternate or opposing claims.
PROFICIENT	The essay introduces a clear, qualitative and/or quantitative claim based on the scientific topic or text(s), regarding the relationship between dependent and independent variables. The essay effectively acknowledges and distinguishes the claim from alternate or opposing claims.
DEVELOPING	The essay attempts to introduce a qualitative and/or quantitative claim, based on the scientific topic or text(s), but it may be somewhat unclear or not maintained throughout the essay. The essay may not clearly acknowledge or distinguish the claim from alternate or opposing claims.
EMERGING	The essay does not clearly make a claim based on the scientific topic or text(s), or the claim is overly simplistic or vague. The essay does not acknowledge or distinguish counterclaims.

EVIDENCE

Include relevant facts, definitions, and examples to back up the claim.

ADVANCED	The essay supplies sufficient relevant, accurate qualitative and/or quantitative data and evidence related to the scientific topic or text(s) to support its claim and counterclaim.
PROFICIENT	The essay supplies relevant, accurate qualitative and/or quantitative data and evidence related to the scientific topic or text(s) to support its claim and counterclaim.
DEVELOPING	The essay supplies some qualitative and/or quantitative data and evidence, but it may not be closely related to the scientific topic or text(s), or the support that is offered relies mostly on summary of the source(s), thereby not effectively supporting the essay's claim and counterclaim.
EMERGING	The essay supplies very little or no data and evidence to support its claim and counterclaim, or the evidence that is provided is not clear or relevant.

REASONING

Explain how or why each piece of evidence supports the claim.

ADVANCED	The essay effectively applies scientific ideas and principles in order to explain how or why the cited evidence supports the claim. The essay demonstrates consistently logical reasoning and understanding of the scientific topic and/or text(s). The essay's explanations anticipate the audience's knowledge level and concerns about this scientific topic.
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PROFICIENT	The essay applies scientific reasoning in order to explain how or why the cited evidence supports the claim. The essay demonstrates logical reasoning and understanding of the scientific topic and/or text(s). The essay's explanations attempt to anticipate the audience's knowledge level and concerns about this scientific topic.
DEVELOPING	The essay includes some reasoning and understanding of the scientific topic and/or text(s), but it does not effectively apply scientific ideas or principles to explain how or why the evidence supports the claim.
EMERGING	The essay does not demonstrate clear or relevant reasoning to support the claim or to demonstrate an understanding of the scientific topic and/or text(s).

FOCUS

Focus your writing on the prompt and task.

ADVANCED	The essay maintains strong focus on the purpose and task, using the whole essay to support and develop the claim and counterclaims evenly while thoroughly addressing the demands of the prompt.
PROFICIENT	The essay addresses the demands of the prompt and is mostly focused on the purpose and task. The essay may not acknowledge the claim and counterclaims evenly throughout.
DEVELOPING	The essay may not fully address the demands of the prompt or stay focused on the purpose and task. The writing may stray significantly off topic at times, and introduce the writer's bias occasionally, making it difficult to follow the central claim at times.
EMERGING	The essay does not maintain focus on purpose or task.

ORGANIZATION

Organize your writing in a logical sequence.

ADVANCED	The essay incorporates an organizational structure throughout that establishes clear relationships among the claim(s), counterclaims, reasons, and evidence. Effective transitional words and phrases are included to clarify the relationships between and among ideas (i.e. claim and reasons, reasons and evidence, claim and counterclaim) in a way that strengthens the argument. The essay includes an introduction and conclusion that effectively follows from and supports the argument presented.
PROFICIENT	The essay incorporates an organizational structure with clear transitional words and phrases that show the relationship between and among ideas. The essay includes a progression of ideas from beginning to end, including an introduction and concluding statement or section that follows from and supports the argument presented.
DEVELOPING	The essay uses a basic organizational structure and minimal transitional words and phrases, though relationships between and among ideas are not consistently

clear. The essay moves from beginning to end; however, an introduction and/or conclusion may not be clearly evident.

EMERGING

The essay does not have an organizational structure and may simply offer a series of ideas without any clear transitions or connections. An introduction and conclusion are not evident.

LANGUAGE

Pay close attention to your tone, style, word choice, and sentence structure when writing.

ADVANCED

The essay effectively establishes and maintains a formal style and objective tone and incorporates language that anticipates the reader's knowledge level and concerns. The essay consistently demonstrates a clear command of conventions, while also employing discipline-specific word choices and varied sentence structure.

PROFICIENT

The essay generally establishes and maintains a formal style with few possible exceptions and incorporates language that anticipates the reader's knowledge level and concerns. The essay demonstrates a general command of conventions, while also employing discipline-specific word choices and some variety in sentence structure.

DEVELOPING

The essay does not maintain a formal style consistently and incorporates language that may not show an awareness of the reader's knowledge or concerns. The essay may contain errors in conventions that interfere with meaning. Some attempts at discipline-specific word choices are made, and sentence structure may not vary often.

EMERGING

The essay employs language that is inappropriate for the audience and is not formal in style. The essay may contain pervasive errors in conventions that interfere with meaning, word choice is not discipline-specific, and sentence structures are simplistic and unvaried.