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High Performance Liquid Chromatography Validation of Isoniazid Analysis Method in 2 Fixed-Dose Combination Dispersible Tablet

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ABSTRACT

Fixed-dose combination (FDC) dispersible tablets containing isoniazid and rifampicin are used in pediatric tuberculosis therapy; however, a specific analytical method for determining isoniazid in this dosage form has not been established in the Indonesian Pharmacopoeia VI. This study aimed to develop and validate a high-performance liquid chromatography (HPLC) method for the determination of isoniazid in 2 FDC dispersible tablets. Chromatographic separation was performed using a C18 column (4.6 mm × 250 mm, 5 µm) with UV detection at 254 nm. The mobile phase consisted of water, phosphate buffer, and methanol (850:100:50, v/v/v) delivered at a flow rate of 1.5 mL/min. Method validation showed good linearity with a correlation coefficient (r) of 0.9995. The limit of detection and limit of quantification were 0.00038724 mg/mL and 0.00117346 mg/mL, respectively. The method demonstrated acceptable accuracy with a recovery of 99.51% and precision with a %RSD of 0.41%. Selectivity evaluation showed that isoniazid was well separated from other components, indicating that the method was selective for isoniazid determination. Based on these validation parameters, the developed HPLC method is suitable for determining isoniazid levels in 2 FDC dispersible tablet formulations.

INTRODUCTION

Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide and is caused by *Mycobacterium tuberculosis* (Dewi et al., 2019). By 2021, ten countries accounted for 75% of the global estimated TB incidence, with Indonesia reported as the second highest contributor after India (World Health Organization, 2024). In Indonesia, 443,235 TB cases were reported in 2021, consisting of 434,967 drug-sensitive TB cases and 8,268 drug-resistant TB cases (The Ministry of Health, 2022). TB affects not only adults but also children. Pediatric TB treatment may involve combination therapy using isoniazid and rifampicin, which are first-line antituberculosis drugs for children (The Ministry of Health, 2020b).

A two-fixed drug combination (2 FDC) refers to a dosage form containing two active pharmaceutical ingredients in one preparation. A 2 FDC dispersible tablet contains rifampicin and isoniazid and is relevant for pediatric use because dispersible tablets are easier to administer to children. One of the quality requirements for dispersible tablet preparations is the dissolution test. In Indonesia, dissolution test requirements are generally determined based on the Indonesian Pharmacopoeia or other standard references. However, the Indonesian Pharmacopoeia Ed. VI (2020) does not list specific dissolution test requirements or analytical procedures for 2 FDC dispersible tablets containing rifampicin and isoniazid (The Ministry of Health, 2020a). The available method for 2 FDC capsule preparations cannot be directly applied to dispersible tablets because

the dosage form, excipient composition, disintegration characteristics, and drug release behavior may differ. Therefore, a specific analytical method needs to be developed and validated for isoniazid determination in 2 FDC dispersible tablet formulations.

Analytical method validation is required in pharmaceutical quality control to ensure that the method used produces reliable, accurate, precise, and reproducible results. Based on the monograph listed in the Indonesian Pharmacopoeia Ed. VI (2020), 2 FDC capsules containing rifampicin and isoniazid are analyzed using UV-Vis spectrophotometry for rifampicin and HPLC for isoniazid. Previous studies have reported analytical method development for FDC preparations containing rifampicin, isoniazid, and pyrazinamide using HPLC (Vilvamani et al., 2024), as well as UV-Vis spectrophotometric analysis of isoniazid and vitamin B6 in tablet preparations (Nasution et al., 2020) However, these methods were not specifically developed for determining isoniazid in 2 FDC dispersible tablets.

Therefore, this study aimed to develop and validate an HPLC method for determining isoniazid in 2 FDC dispersible tablet formulations. The developed method is expected to support quality control of pediatric antituberculosis dispersible tablets, especially for determining isoniazid levels in samples obtained from dissolution testing.

METHODS

Materials and Instruments

The instruments used in this study were an HPLC system equipped with a UV-Vis detector and Empower software for data acquisition and processing. The HPLC system consisted of a Waters e2695 separation module and a Waters 2489 UV-Vis detector operated at 254 nm. Chromatographic separation was performed using a C18 column, L1 USP category, with dimensions of 4.6 mm × 250 mm and particle size of 5 µm. Other instruments included a dissolution tester (Hanson), pH meter (Mettler Toledo), analytical balance (Mettler Toledo), ultrasonic bath (Hanson), volumetric glassware (Pyrex), HPLC vials (Waters), volumetric pipettes (Pyrex), and 0.22 µm membrane filters (Merck).

The materials used were isoniazid working standard (Second Pharma Co. Ltd.), 2 FDC dispersible tablets containing isoniazid and rifampicin (PT. Chemia Farma), methanol gradient grade for HPLC (Merck), dipotassium phosphate analytical grade (Merck), monopotassium phosphate analytical grade (Merck), hydrochloric acid analytical grade (Merck), placebo, and distilled water/aquadest (PT. Kimia Farma).

Development of Analytical Method

The analytical method was developed based on the monograph for rifampicin and isoniazid capsules in the Indonesian Pharmacopoeia Ed. VI. The method was adapted for the determination of isoniazid in 2 FDC dispersible tablets. Method development focused on chromatographic conditions, sample preparation, and dilution procedure suitable for dispersible tablet matrices. The final method used a C18 column, L1 USP category, with dimensions of 4.6 mm × 250 mm and particle size of 5 µm. The prepared sample solution was diluted with phosphate buffer at a ratio of 1:2 before HPLC analysis.

Chromatographic Conditions

The HPLC analysis was performed using isocratic elution. The mobile phase consisted of water, phosphate buffer, and methanol in a ratio of 850:100:50. The flow rate was set at 1.5 mL/min, and the injection volume was 50 µL. Detection was carried out using a UV-Vis detector at 254 nm. The solvents used during sample preparation were 0.1 N HCl, phosphate buffer, and distilled water.

Preparation of Standard Solution

Isoniazid working standard was accurately weighed and dissolved in 0.1 N HCl using an ultrasonic bath for 10 minutes. The solution was then diluted to volume with 0.1 N HCl and mixed until homogeneous. An aliquot of the standard solution was transferred into a volumetric flask, mixed with phosphate buffer, and diluted with distilled water to volume. The final solution was filtered through a 0.22 µm membrane filter before injection into the HPLC system.

Validation of Analytical Method

Linearity and range

Linearity was evaluated using isoniazid working standard solutions prepared at five concentration levels: 60%, 70%, 80%, 100%, and 120% of the target concentration. Each solution was filtered through a 0.22 µm membrane filter, and 50 µL was injected into the HPLC system. The calibration curve was constructed by plotting isoniazid concentration against peak area. Linearity was evaluated based on the regression equation and correlation coefficient.

$y = bx + a$.....(1)

y = the peak area

x = concentration of isoniazid

b = slope

a = intercept

Limit of Detection (LOD) and Limit of Quantification (LOQ)

The limit of detection (LOD) and limit of quantification (LOQ) were calculated from the calibration curve obtained during the linearity test. LOD and LOQ were determined using the standard deviation of the response and the slope of the calibration curve.

$LOD = \frac{3{,}3\,\sigma}{S}$ .....(2)

$LOQ = \frac{10\,\sigma}{S}$ .....(3)

σ = Standard Deviation

S = Slope

Accuracy and Precision

Accuracy was determined using the recovery method. Isoniazid working standard was added to placebo matrix at three concentration levels: 60%, 100%, and 120% of the target concentration. Each concentration level was prepared in triplicate. The solutions were analyzed using the validated HPLC conditions, and accuracy was expressed as percentage recovery.

$Recovery = \frac{Analysis\ Consentration\ (\%)}{Target\ Concentration\ (\%)}\ x\ 100\%$ ...(4)

Precision was evaluated at 100% of the target concentration using six replicate preparations of isoniazid sample solution. Each solution was injected into the HPLC system under the selected chromatographic conditions. Precision was expressed as the relative standard deviation (%RSD) of the measured isoniazid response or calculated concentration.

$\%RSD = \frac{SD}{mean}\ x\ 100\%$.....(5)

SD = standard deviation

Mean = average measured concentration or response.

Selectivity

Selectivity was evaluated by comparing chromatograms of the standard solution, sample solution, placebo, mobile phase, solvent, distilled water, phosphate buffer, and 0.1 N HCl. The method was considered selective when no interfering peak appeared at the retention time of isoniazid. If an adjacent peak was present, peak resolution should be reported to confirm adequate separation.

Determination of Isoniazid Dissolution

The dissolution test was performed using a basket apparatus. Each vessel was filled with 900 mL of 0.1 N HCl as the dissolution medium, and the temperature was maintained at 37 ± 0.5 °C. One 2 FDC dispersible tablet was placed into each dissolution basket, and the apparatus was operated at 100 rpm for 45 minutes. After 45 minutes, aliquots were withdrawn from each vessel, filtered if required, and diluted prior to HPLC analysis. The sample solution was prepared by transferring 1.0 mL of dissolution sample into a 20 mL volumetric flask, adding 1 mL of phosphate buffer, and diluting to volume with distilled water. The amount of dissolved isoniazid was calculated and expressed as a percentage of the labeled amount. The acceptance criterion was not less than 80% (Q) of isoniazid dissolved within 45 minutes, and the stage-one requirement was not less than Q + 5% for each dosage unit (The Ministry of Health, 2020a).

$Consentration = \frac{Sa\ x\ Stw\ x\ \%ci\ x\ 900\ x\ Sd}{Sta\ x\ Std\ x\ 100\ x\ Iso}\ x\ 100\%$.....(6)

Sa = Sample Area

Sta= Standard Area

Stw = Standard Weight (mg)

Sw = Sample Weight (mg)

Sd = Sample Dilution

%ci=Concentration Standard of Isoniazid (%)

900= Dissolution volume (mL)

Iso = Active Ingredient Content of Isoniazid in Tablet.

RESULT AND DISCUSSION

Development of Analytical Method

The analytical method was developed using reversed-phase HPLC with a C18 stationary phase and a polar mobile phase. This system was selected because isoniazid is a polar compound that can be separated using reversed-phase chromatography (Hakkimane & Guru, 2017). The C18 column is widely used in HPLC analysis because it provides suitable retention and separation for compounds with various polarity levels (Mishra et al., 2018; Prasanthi et al., 2015; Rusli et al., 2022).

In this study, the analytical method was modified from the previous L1 column, C18 3.90 mm × 300 mm, 10 µm, to an L1 column, C18 4.60 mm × 250 mm, 5 µm. The chromatogram comparison is shown in Figure 1. The modified column produced a shorter retention time and a sharper isoniazid peak. The retention time decreased from 5.811 minutes using the previous column to 3.599 minutes using the modified column. This result indicates that the modified column improved the efficiency of the analysis. The smaller particle size of the modified column may increase chromatographic efficiency, resulting in a sharper peak and faster elution of isoniazid.

The HPLC analysis was performed using a mobile phase consisting of water, phosphate buffer, and methanol with UV detection at 254 nm. Phosphate buffer was used to maintain the pH of the analytical system because pH can affect the elution strength and chromatographic behavior of the analyte (Alvarez-Segura et al., 2019; Gandjar & Rohman, 2012). The wavelength of 254 nm was selected because isoniazid provides adequate UV absorbance at this wavelength.

Method development was also carried out by comparing the ratio of sample solution to phosphate buffer. The previous preparation used a sample solution:phosphate buffer ratio of 1:2, whereas the modified preparation used a ratio of 1:1. As shown in Figure 2, the 1:1 ratio produced a cleaner chromatographic profile with lower interfering peaks than the 1:2 ratio. The isoniazid peak remained detectable at the expected retention time, indicating that reducing the amount of phosphate buffer did not interfere with isoniazid detection. Therefore, the 1:1 ratio was selected because it provided sufficient chromatographic performance, reduced buffer use, and minimized interfering peaks in the chromatogram.

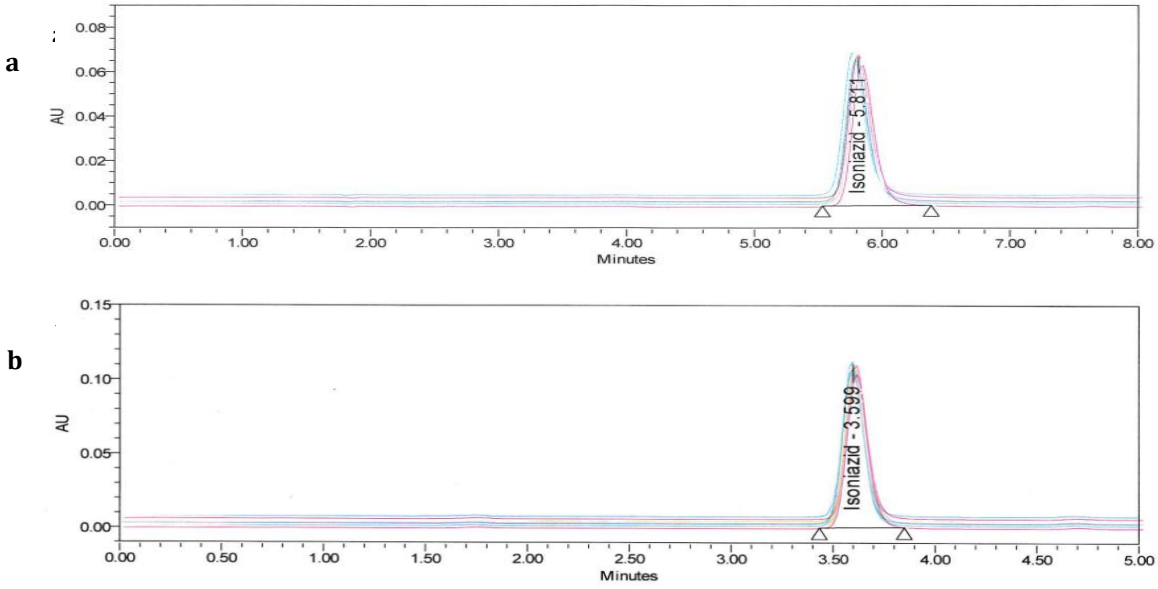

Figure 1: a. Column Chromatogram C18 3.90 mm x 300 mm, 10µm; b. Column Chromatogram C18 4.60 mm x 250 mm, 5µm

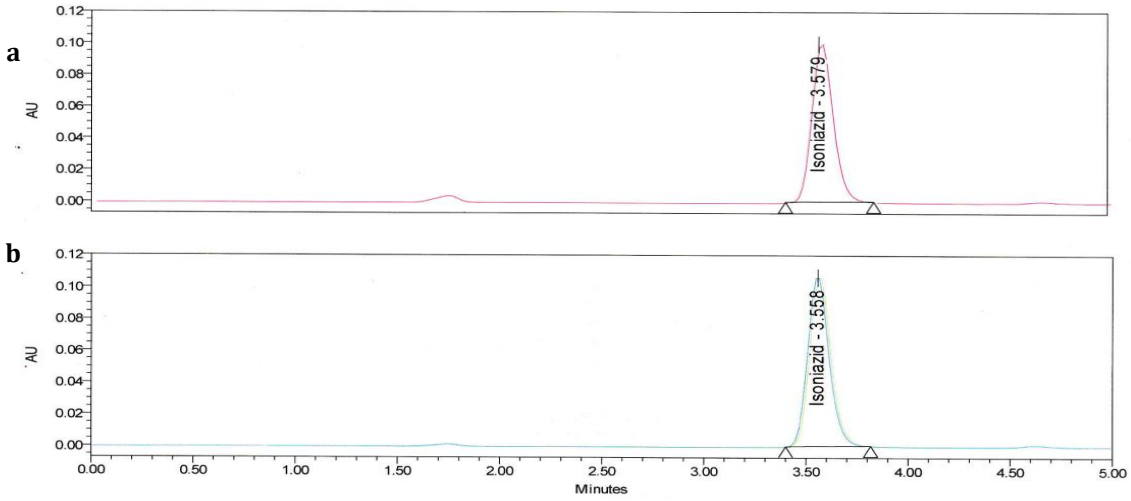

Figure 2: a. Chromatogram of sample solution:phosphate buffer (1:2); b. Chromatogram of sample solution:phosphate buffer (1:1)

Validation of Analytical Method

Validation of analysis is a technique that uses laboratory tests to ensure that the procedure's performance characteristics fulfill the requirements for its intended usage (The Ministry of Health, 2020a). The validation parameters evaluated in this study included linearity and range, LOD, LOQ, accuracy, precision, and selectivity.

Linearity and Range

Linearity refers to an analytical method's ability to deliver a proportional response to analyte concentration. Linearity is typically stated in terms of variation around the regression line's direction, which is derived using calculations based on data received from analyte test results in samples of varying concentrations (Raposo & Ibelli-Bianco, 2020; Riyanto, 2014). Linearity is reached under typical conditions when the correlation coefficient (r) value is ≥ 0.98. The range is defined as the interval between the highest and lowest limits of verified analyte levels that can be determined with sufficient accuracy, precision, and linearity using recognized analytical processes. The International Council for Harmonization (ICH) recommends that linearity be established use at least five commonly used concentrations. Dissolution Test ± 20% of the specific range (for example, in controlled release preparations, after 1 hour, 20%, and after 24 hours, more than 90%, then the range is from 0% to 110% of the concentration stated on the label) (5,11). Data from the regression line can help to show an approximate degree of linearity by relating the response (y) to the concentration (x). Linearity can be described in the form of a slope (b), an intercept (a), and a regression coefficient (r).

Linearity was evaluated using five concentration levels of isoniazid, namely 60%, 70%, 80%, 100%, and 120%. The calibration curve showed a linear relationship between isoniazid concentration and peak area, as presented in Figure 3. The regression equation obtained was y = 54389523x – 4007.7 with a correlation coefficient r = 0.9995. The correlation coefficient close to 1 indicates that the HPLC response was proportional to isoniazid concentration within the tested range. Therefore, the method demonstrated acceptable linearity for isoniazid determination.

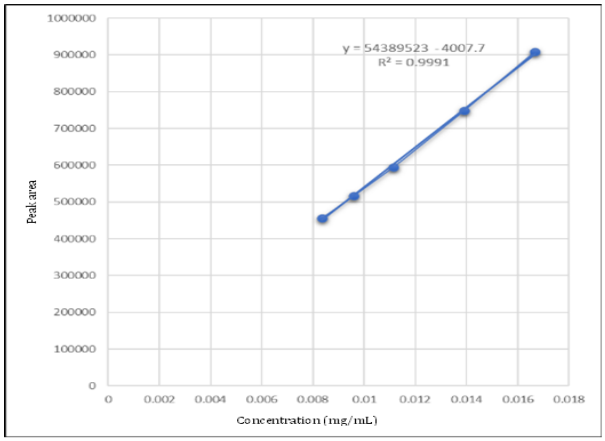

Figure 3. Calibration curve of isoniazi

Limit of Detection and Limit of Quantification

LOD and LOQ were determined based on the standard deviation of the response and the slope of the calibration curve (Raposo & Ibelli-Bianco, 2020; Riyanto, 2014). Testing the LOD and LOQ of an analyte can be seen from the standard deviation value of the response (σ) of the analyte being analyzed. The standard deviation of response was 6382.381, and the slope obtained from the regression equation was 54389523. The calculated LOD and LOQ values were 0.00038724 mg/mL and 0.00117346 mg/mL**,** respectively. These results indicate that the developed method was sufficiently sensitive to detect and quantify isoniazid at low concentrations. LOD and LOQ are important parameters in analysis because they help to determine reliable analyte concentration limits in the analytical method used.

Accuracy

Accuracy is a value that indicates how near the analyst's results are to the real analyte levels. The percent recovery of the additional analyte is used to calculate accuracy (Visconti et al., 2023). Accuracy was determined using the recovery method by adding isoniazid standard to the placebo matrix at three concentration levels: 60%, 100%, and 120%.

Table 1. Result of sample accuration

No.	Concentration (%)	Sample (mg/mL)	Recovery (%)
1	60	0.008363	99.79
2	60	0.008363	100.97
3	60	0.008350	99.26
4	100	0.013898	99.51
5	100	0.013913	99.83
6	100	0.013908	99.51
7	120	0.016678	98.57
8	120	0.016683	99.14
9	120	0.016683	98.99
Average			99.51
RSD			0.68

The accuracy results are presented in Table 1. The recovery values ranged from 98.57% to 100.97%, with an average recovery of 99.51% and RSD of 0.68%. These results met the acceptance criterion of 98–102%, indicating that the method was accurate for determining isoniazid in the 2 FDC dispersible tablet matrix (Gandjar & Rohman, 2012; Indonesian Food and Drug Authority, 2014; The Ministry of Health, 2020a).

Precision

Precision is a parameter that represents the level of consistency between individual measurements, as assessed by the deviation of individual results from the average when the operation is repeated on samples drawn from the same mixture. The standard deviation or relative standard deviation (coefficient of variance) is used to calculate precision.

Table 2. Result of sample precision

No.	Concentration (%)	Sample (mg/mL)	Recovery (%)
1	100	0.013890	100.66
2	100	0.013915	101.19
3	100	0.013903	100.77
4	100	0.013898	100.63
5	100	0.013903	101.13
6	100	0.013903	100.32
Average			100.79
RSD			0.32

Precision was evaluated at 100% concentration using six replicate preparations. The precision results are presented in Table 2. The recovery values ranged from 100.32% to 101.19%, with an average recovery of 100.79% and RSD of 0.32%. The RSD value was less than 2%, indicating that the method showed good precision and produced consistent results for repeated isoniazid determination (Raposo & Ibelli-Bianco, 2020; Riyanto, 2014).

Selectivity

Selectivity is the degree to which an analytical method can reliably measure analytes in the presence of interference (error) under predetermined test situations for the sample to be examined. Selectivity describes an analytical method for measuring analytes specifically and precisely (Raposo & Ibelli-Bianco, 2020). Selectivity was evaluated by comparing chromatograms of the isoniazid standard solution, sample solution, placebo, mobile phase, phosphate buffer, dissolution medium, and distilled water. The method was considered selective when no interfering peak appeared at

the retention time of isoniazid. The chromatogram showed that the isoniazid peak in the sample appeared at the same retention time as the isoniazid standard, while placebo, distilled water, phosphate buffer, and dissolution medium did not produce peaks at the isoniazid retention time. HCl produced a peak, but it did not appear at the same retention time as isoniazid; therefore, it did not interfere with the analysis. These results indicate that the method was selective for determining isoniazid in the 2 FDC dispersible tablet matrix (Marson et al., 2020).

Determination of Isoniazid Dissolution

After the method was confirmed to be linear, accurate, precise, sensitive, and selective, it was applied to determine isoniazid levels in dissolution test samples of 2 FDC dispersible tablets. The dissolution test is the process of dissolving an active substance or compound from a solid dosage form into a certain medium (van der Merwe et al., 2020). This test is used to determine compliance with the dissolution requirements stated in each monograph for dosage forms used orally. The dosage unit in question is 1 tablet, 1 capsule, or a specified amount (The Ministry of Health, 2020a). The Q value for isoniazid was 80%, and the stage-one acceptance criterion required that each dosage unit should not be less than Q + 5%, equivalent to 85%. The dissolution results showed that the lowest isoniazid dissolution value was 94.63%, with an average value of 99.06%. The lowest value was higher than the stage-one acceptance criterion of 85%, indicating that all tested units met the dissolution requirement. The average dissolution value of approximately 99% indicates that isoniazid was effectively released from the 2 FDC dispersible tablet formulation. This result supports the quality expectation for dispersible tablets, which should disintegrate and release the active substance efficiently in the dissolution medium.

CONCLUSIONS

The developed HPLC method using an L1 C18 column and a sample solution:phosphate buffer ratio of 1:1 was successfully validated for the determination of isoniazid in 2 FDC dispersible tablets. The method met the validation requirements for linearity, sensitivity, accuracy, precision, and selectivity. The dissolution test results also showed that isoniazid release from the tested dispersible tablets fulfilled the acceptance criterion. Therefore, this HPLC method can be applied for determining isoniazid levels in dissolution test samples of 2 FDC dispersible tablets and may support routine quality control of pediatric antituberculosis formulations. However, further evaluation of robustness and solution stability is recommended to strengthen the applicability of the method for routine regulatory and manufacturing purposes.

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AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception and design of the study. Material preparation, data collection, and data analysis were performed by the authors. The first draft of the manuscript was written by the first author, and all authors reviewed, revised, and approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

ETHICAL CONSIDERATION

Ethical issues (including plagiarism, data fabrication, double publication, etc) have been completely observed by the author.

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