5 th International Conference on Multidisciplinary Approaches for Sustainable Rural Development (ICMA - SURE)

LETTER OF ACCEPTANCE AND INVITATION

Date : November 5, 2022
No. : 065/LoA/ICMA-SURE-2022

Dear **Dadan Hermawan, Annisa Mutiara Fitri, Cacu Cacu, Amin Fatoni, Suwandri Suwandri, Ponco Iswanto, Uyi Sulaeman**

Thank you for submitting your abstract for presentation at the 5th International Conference on Multidisciplinary Approaches for Sustainable Rural Development (ICMA-SURE) 2022. After reviewing your abstract, we are pleased to inform you that your abstract entitled:

High-Performance Liquid Chromatography Method for Chiral Separation of Sulconazole using Cyclodextrin as Chiral Column

ID Paper: 3414

meets preliminary acceptance requirements set forth by our Scientific Committee to be presented as Oral Presentation at the conference. The conference will be held online on 8-9 November 2022 using the Zoom application.

The Oral/Poster Presentation Guidelines can be found at the following link:
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Regarding the payment, you also need to re-register to get a bill number. Please make bill payments before 6 November 2022. The payment and re-registration steps are explained in the ICMA SURE 2022 Payment Guideline.

If you require any further information, please do not hesitate to contact us or visit our website.We look forward to seeing you at the conference.

Yours Sincerely,

Amin Fatoni, S.Si., M.Si., Ph.D.
Chairman of ICMA-SURE 2022

ICMA SURE 2022
INTERNATIONAL CONFERENCE ON MULTIDISCIPLINARY APPROACHES FOR SUSTAINABLE RURAL DEVELOPMENT

CERTIFICATE

THIS CERTIFICATE IS PRESENTED TO

Dadan Hermawan, Annisa Mutiara Fitri, Cacu Cacu, Amin Fatoni, Suwandri Suwandri, Ponco Iswanto, Uyi Sulaeman

WITH THE TITLE

High-Performance Liquid Chromatography Method for Chiral Separation of Sulconazole using Cyclodextrin as Chiral Column

IN RECOGNITION OF THE OUTSTANDING CONTRIBUTION AS

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" The Advanced Strategies To The Development of Rural Resources For A Smart Society "

Purwokerto - Indonesia, November 8-9, 2022

Prof. Dr. Rifda Naufalin, S.P., M.Si.
Head of LPPM Jenderal Soedirman University

High-Performance Liquid Chromatography Method for Chiral Separation of Sulconazole using Cyclodextrin as Chiral Column

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ABSTRACT

Chiral separation of sulconazole by the high-performance liquid chromatography (HPLC) method using cyclodextrin as stationary phase (25 cm x 4.6 mm x 5µm) has been successfully achieved in this research. The optimized HPLC method was obtained using acetonitrile: water (0.2% HCOOH) (13:87, v/v) as mobile phase, 1.0 mL/min flow rate, 2 µL injection volume, and 230 nm UV wavelength. This HPLC method has been successfully applied for the determination of sulconazole in the pharmaceutical sample with a percentage recovery of 102.47% (RSD = 0.80%).

Keywords: *Chiral Separation, Cyclodextrin, HPLC, Sulconazole.*

1. Introduction

A fungal infection that occurred in recent years has become the main disease that many people are worried about. Especially since there is an increase in invasive fungal infection [1] More than half of commercially manufactured drugs are active chiral (enantiomers) substances that are still racemate or mixed form [2–6]. Chiral compounds have no superimposable shadow on the mirror. Chiral compounds are composed of one atom of carbon (C) which bonding to four other groups [7].

Stereoselective interactions of chiral during the subsequent process will result in side effects [8]. Active enantiomer compounds have the same properties of physical and chemical as each other (smell, color, and solubility) [9]. The opposite optical rotation in enantiomers can cause different biological, toxicological, and pharmacological activities for the body [6,9–11]. Enantiomer activities can become active enantiomers (eutomers), then others are toxic (distomers). Drugs that are racemate when entered into the body can have a bad impact on liver and kidney function [12].

Antifungal drugs of azole are synthetic drugs consisting of imidazole and triazole molecules [1]. Imidazole antifungals have two atoms of nitrogen in the azole ring [13]. Azole antifungal drugs appearing in types of imidazole are miconazole, econazole, sulconazole, isoconazole, butoconazole, fenticonazole, ketoconazole, and bifonazole [6,13]. Sulconazole is an imidazole that acts as an antifungal and antibacterial [4]. Sulconazole has a widely of spectrum and very efficient for used in the treatment of superficial and mucosal fungal skin infections [4,6,14].

Sulconazole (SCZ) has the IUPAC name is 1-[2,4-dichloro-β-[(4-chlorobenzyl)thio]-phenethyl]-imidazole [3,15]. This type of imidazole compound is widely available in the form of nitrate salts in pharmaceuticals (ointments, powders, and solutions) at low concentrations (1%) [4]. This drug can be one of the alternative drugs that have been tested for effectiveness so that it can be tolerated well when compared to other topical imidazole drugs in the treatment of fungal infections. The disadvantage of sulconazole is that its solubility in water is low so when at higher doses required will cause side effects such as allergies and resistance phenomena (the ability of bacteria to stop the effect of antibiotic drugs) [16]. Sulconazole antifungal agents contain a chiral center where these enantiomers can be inactive or toxic (**Figure 1**) [6].

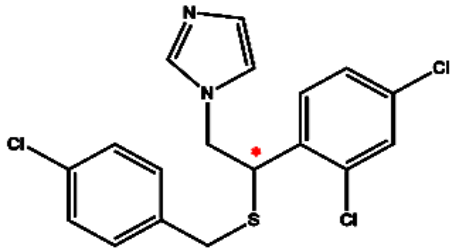

Figure 1. Sulconazole structure (The sign * indicates a chiral center) [6].

The chiral compound contained in the drug needs to be continuously separated between the two enantiomers by going through several testing stages on various pharmacological drugs circulating in the community [8]. Various methods were used as techniques in the separation of enantiomers to obtain high-purity drug content [7,9]. The method for drug analysis that is currently widely recommended by pharmacopeia is the chromatography method [17,18]. HPLC is one of the liquid chromatography methods with high separation, which is widely used to separate the various components contained in a racemate by the process of identification and validation of compounds [19,20]. HPLC separation occurs within the column where the mobile phase flows through the stationary phase [21].

Important characteristics of HPLC are efficiency, speed, and reduction in analysis cost [22]. Chiral separation with HPLC can be achieved by using an appropriate chiral selector to separate two enantiomers [23]. Cyclodextrin (CD) is one of typically the most widely used chiral selectors. CD derived from water-soluble cyclic oligosaccharide starch type has a good ability when it comes to accommodating aromatic rings in hydrophobic [24]. The use of CD as a chiral selector has been widely carried out by scientists to research the recognition and separation of enantiomers in pharmaceutical drugs [10,25].

Cyclodextrin as a chiral selector can be an occurrence of inclusion bond with a molecule in a drug [10]. The inclusion bond formed will be able to increase the process in solubility, dissolution, stability, and molecular bioavailability [23]. Testing the HPLC method and the use of CD Chiralpak Astec Cyclobond® (I 2000 HP-RSP 25 cm x 4,6 mm, 5 µm) as a chiral selector was carried out to separate the sulconazole enantiomer in samples (cream) of pharmaceutical preparations that had gone through the process optimization and validation analysis.

2. Materials and Methods

2.1. Materials and Instrumentation

Materials used in this study were standard sulconazole (Sigma-Aldrich), methanol (Merck), acetonitrile (Merck), formic acid (Merck), water (twice destination), and pharmaceutical samples sulconazole cream 30g (MYK-1® Sulconazole nitrate 10mg/g) (Will Pharma).

Experiments were carried out operated using HPLC Hitachi L (UV-Vis detector L-2420 set in 230 nm wavelength, L-2130 pump, L-2200 autosampler, and D-2000 Elite software), Sonicator Branson 1800, Chiralpak Astec Cyclobond column (I 2000 HP-RSP size 25 cm x 4.6 mm, 5 μm).

2.2. Preparation of Standards and Pharmaceutical Sample

An accurate weight of 10 mg sulconazole standard was dissolved in 10 mL methanol (1000 mg/L). The standard solution was then diluted to concentrations of 100, 150, 200, and 250 mg/L using methanol are then labeled and closed to avoid evaporation. The Sulconazole pharmaceutical sample was prepared with 100 mg of cream dissolved in 10 mL of methanol. It was sonicated for 10 minutes and filtered. All of the standards can be stored in the refrigerator before use. Then, the resulting solution was used for HPLC analysis.

2.3. Optimization of the HPLC Method

Standard solution of 100 ppm sulconazole was analyzed using the HPLC system with mobile phase of acetonitrile: water (0.2% HCOOH) in a variation of 20:80; 15:85; 13:87; and 11:89, flow rate 0.8; 0.9; 1.0; and 1.2 mL/min, injection volume 2; 3; 4; and 5μL, wavelength 210; 220; 230; and 240 nm. All variations were injected at room temperature. Optimum conditions are determined based on resolution values, retention time, area, and peak height.

2.4. Analytical Performance of the HPLC Method

Sulconazole standard solution (100-250 mg/L) was injected three times a repetition. The results were obtained for creating a calibration curve. The best results obtained were then evaluated visually on the plot (absorbance, peak area, and peak height). The resulting curve states between two quantities in the form of a curve or a straight line commonly referred to as regression [26]. Then determine the LOD and LOQ values. The next step is to precision (six times repetition), accuracy (three times repetition), and selectivity testing. Precision is performed, the accuracy test is measured by the number of analytes in percent recovery (% recovery), and selectivity was used to determine the difference and validate the analyte with the addition of other components in the sample [26].

Analysis of sulconazole pharmaceutical samples using the prepared sulconazole cream samples was repeated three times using HPLC to obtain valid results in determining the concentration in the cream sample preparation.

3. Result and Discussions

The optimization method using HPLC was carried out to determine the ideal/optimal conditions during the analysis process. The development of this method includes several parameters (resolution, peak shape, retention time, detection limit, quantitation limit, and the overall method) that will be used in the optimization process using HPLC [26]. Research of [27] regarding the determination of the enantiomer of sulconazole with the principle of the reverse phase, namely the stationary phase using a polysaccharide column of tris(3,5-dimethyl phenyl carbamate) or CDMPC type polysaccharide and the mobile phase in the form of acetonitrile and methanol, obtained the value of Rs (resolution) of sulconazole of 1.13 with a retention time of 35 minutes, but the results obtained are still less efficient so it needs to be redeveloped by using a cyclodextrin column for the separation of imidazole type compounds.

3.1. Optimization of HPLC

HPLC optimization was carried out using SCZ analyte which was injected into the column. This research uses CD as a stationary phase column. The stationary phase column used for enantiomer separation is commonly referred to as the modified column. This is based on the fact that is composed of porous solids of uniform size that are mostly made of silica. The diameters of the column that are widely used are 3, 5, or 10 µm. The surface of the column is composed of hydroxylated silica packaging then the polysaccharide groups will be attached to the silica matrix. Binding to a chiral polymer in its use will bind enantiomeric molecules in the chiral analytes separation process [28].

The sulfur atom (S) in sulconazole can interact strongly with the hydrogen in the stationary phase of CD to form a coordination bond. The bond in SCZ-CD has stronger than the oxygen atom (O) in miconazole and econazole [29]. CDs in the middle inside are hydrophobic and the outside is hydrophilic. Sulconazole has the property of being less soluble in water, so it can interact for arranged inclusion complexes with chiral selectors, especially cyclodextrin. The bond occurs in the middle cavity of hydrophobic cyclodextrin with lipophilic sulconazole[23,30]. This arrangement serves for makes hydrogen bond interactions and the formation of inclusion complexes on the enantiomers ligand with column [23,24]. The ability of CD is very good in accommodating hydrophobic aromatic rings [24].

a. Variation of mobile phase

Optimization is carried out in the early stages using mobile phase variations of acetonitrile: water (0.2% HCOOH). The selection of the mobile phase in optimization is based on the relative polarity of the mobile phase and stationary phase. Cyclodextrin as a stationary phase is a nonpolar compound that has hydrocarbons and sulconazole is polar, so the user of reversed-phase is a good way based on polar mobile phases such as water and acetonitrile. Reversed-phase chromatography with a polar compound will make the compounds eluted earlier and increasing the polarity of the mobile phase will increase the elution time. Cyclodextrin as nonpolar has a bonded phase packaging coating that can be bonded to the sulconazole group to be able to interact [28].

Starting from the highest concentration of acetonitrile, which is at 20% and has a resolution value (Rs = 1.04) with retention time at peaks 1 and 2 being 8.04 minutes and 8.80 minutes. The decreased concentration of acetonitrile to 13% (Rs = 1.43) experienced make an increase in retention time at peaks 1 and 2 was 20.73 and 23.89 minutes, but if the concentration to 11% (Rs = 1.37) with retention time at peaks 1 and peak 2 was 27.44 and 31.81 minutes. The addition of water or polar solvents needs to be carefully considered because if the water content is too little then it may not be able to elute the solute, but if it is too much it will cause the column to become less active [28]. Although the concentration of acetonitrile at 20% has the lowest retention time, the resolution at a concentration of 13% is the highest result compared to others, so it is used for further optimization.

b. Variation of variable flow rate

Optimization of flow rate using mobile phase acetonitrile: water (0.2% HCOOH) (13:87, v/v) with flow rate variation of 0.8-1.2 mL/min. the flow rate of 0.8 mL/min (Rs = 1.14) with a retention time was 26.76 and 30.74 minutes, then the flow rate was increased at 0.9 to 1.0 mL/minute, the higher flow rate will cause the shorter retention time and high-resolution value, like in 1.0 mL/minute as optimum (Rs = 1.43) with retention time 20.73 and 23.89 minutes.

c. Variation of injection volume

Optimization of the injection volume was carried out with a variation of 2–5 µL. The injection volume of 2 µL (Rs = 1.43), then was increased retention time at 3-5 µL to get a more efficient retention time but the resulting resolution value decreased, which at a volume of 5 µL (Rs = 1,35) the lowest retention time was obtained in 20.30 and 23.36 minutes.

d. Variation of wavelength

Wavelength optimizing is carried out by variations of 210–230 nm. 210 nm has a shorter retention time than 220-240 are obtained longer retention time, but Rs in 210, 220, and 240 nm smaller than Rs in 230. The optimum wavelength at 230 nm (Rs = 1,43) with the retention time at 20.73 and 23.89 minutes. The parameters of the separation results of the sulconazole enantiomer are shown in **Table 1**.

Table 1. Separation of Sulconazole enantiomers

Optimization	Solvent retention time (minutes)	Retention time (minutes)		Rs
		Peak 1	Peak 2	
Acetonitrile: Water (0.2% HCOOH)				
20:80	3.1467	8.0400	8.8067	1.04
15:85	3.1733	15.0333	17.1400	1.26
13:87	**3.1867**	**20.7333**	**23.8933**	**1.43**
11:89	3.2000	27.4400	31.8133	1.37
Flow rate (mL/minutes)				
0,8	3.9867	26.7600	30.7467	1.14
0,9	3.5400	23.6333	27.3733	1.08
1,0	**3.1867**	**20.7333**	**23.8933**	**1.43**
1,2	2.7965	16.7533	19.3400	1.30
Injection volume (µL)				
2	**3.1867**	**20.7333**	**23.8933**	**1.43**
3	3.1867	20.5267	23.4600	1.27
4	3.1867	20.3533	23.4467	1.36
5	3.1867	20.3000	23.3667	1.35
Wavelength (nm)				
210	3.0000	20.5333	23.7267	1.16
220	3.0200	20.6600	23.7333	1.27
230	**3.1867**	**20.7333**	**23.8933**	**1.43**
240	3.1900	20.83.00	23.9953	1.01

Important parameters in reversed-phase HPLC are the mobile phase and polarity. Polarity has a parameter that plays an important role in the separation indicated by the strong continuity between the mobile phases. Polarity decrease can affect the retention time of the polar analyte in the stationary phase becomes lower. Increasing the polarity of the mobile phase will increase the retention time of the analyte in the stationary phase [31].

3.2. Method Validation

Validation of the analytical method is carried out as a determination that the parameters to be used are sufficiently capable to overcome analytical problems [28]. Appropriate method validation will be obtained if the method used successfully passes the optimization stage [26]. All variations of the parameters used in the validation depend on the expected analysis

objectives [28]. The parameters used in the validation include linearity, LOD, LOQ, accuracy, precision, and selectivity [32].

a. Linearity

Linearity is a method used to make a proportionality curve between the peak area response (y) and the concentration (x) of a particular analyte. The best results obtained were then evaluated visually on the plot of the relationship between the analyte concentration function and the measured signal (absorbance, peak area, and peak height). The resulting curve between two quantities is in the form of a curve or a straight line as regression [26]. The ability of the analysis method to give a direct response using a variety of data equations around the direction of regression line as straight line equations against the least-squares method [28]. The linearity test was carried out by making a standard calibration curve of sulconazole using a concentration variation of 100-250 ppm. At each concentration, measurements were carried out with three repetitions using HPLC under optimum conditions. The results equation of the line at peak 1 was y=1428.5x–60743 with the coefficient of determination 0.9977 and the correlation coefficient (r) being 0.9989. result of peak 2 was y=298.38x+28575 with coefficient determination 0,9976 and correlation (r) 0.9988.

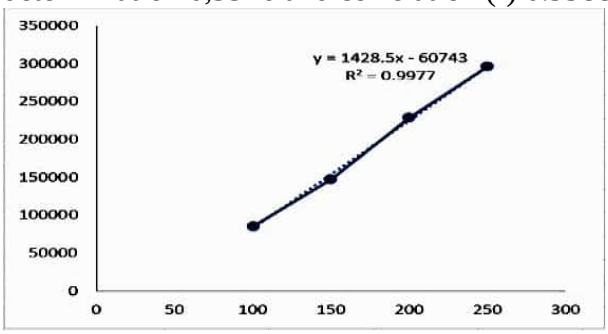

Figure 2. Peak curve 1 linearity test

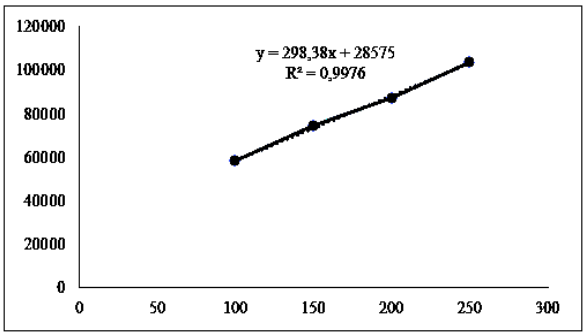

Figure 3. Peak curve 2 linearity test

b. Limit of detection (LOD) and limit of quantitation (LOQ)

LOD and LOQ are used as parameters to detect sensitivity in the tested analytical method. The detection limit can be said to be the sample with the lowest concentration of analyte that can still be detected, which will determine the test limit specifically to detect the presence or absence of the analyte within a certain value. The quantitation of the sample with the lowest analyte concentration is determined quantitatively with appropriate precision and accuracy values. The method of calculating LOD and LOQ is based on the standard deviation (SD) response and slope (S) values [26]. The measurement value used in the linear equation y = bx+a, while the blank standard deviation is the same as the residual standard deviation (Sy/x) [28]. The results of LOD value in peak 1 and 2 was 11.37 ppm and 11.62 ppm, indicating the lowest concentration of sulconazole standard that could be detected by HPLC. The LOQ value obtained at peaks 1 and 2 was 37.90 and 38.75 ppm which is the lowest concentration of sulconazole standard which is still inside in criteria for the lowest limit of concentration.

c. Precision

The precision of a homogeneous sample is a measure of the closeness between a series of analytical processes that are measured repeatedly with the same analytical method. Precision is measured using the linearity equation[28]. Precision must include the value of standard deviation, relative standard deviation (RSD), coefficient of variation (CV), and the minimum % recovery range on certain conditions [26]. The value of standard deviation (SD) at peak 1 and

peak 2 are obtained at 0.7858 and 0.8744. The CV value at peak 1 was 0.762% and at peak 2 was 0.897%. In the results of RSD and CV values which has a value below 5.3% so this method has good repeatability and still be accepted well by the % RSD precision test which is <5.3% for concentrating solution >100ppm [33]. The HORRAT values at peaks 1 and 2 were 0.071 and 0.084, this indicates that the precision test on this sulconazole standard solution is valid, because the HORRAT value obtained is < 1 which indicates good repeatability.

d. Accuracy

Accuracy is a measure to show the results of the analysis with the actual concentration of the analyte, which can be expressed by the percent recovery from the determination of the amount of analyte whose concentration is known and then added to the sample. The accuracy test procedure must be repeated at least three times [26]. The average percent recovery obtained is 101.1%. The results of acceptance requirements for the percentage of recovery, which is in concentration >10 ppm at 80–110% and in a concentration >100 ppm at 90–107% [33].

e. Selectivity

Selectivity is an analysis method used to determine differences and validate analytes with the addition of other components in solution to measure each analyte to ensure that there are no disturbances during the analysis [26]. This selectivity test was carried out using 100 ppm sulconazole standard solution which was then added to 100 ppm ketoconazole standard solution. The mixture of the two solutions was analyzed using HPLC under optimum conditions. The selectivity (α) value is 1.21. This separation can be good if it has a value of $\alpha > 1$ because it shows that the stationary phase has a good ability to separate the two components during the elution, and it is proven that the procedure performed is not affected by the presence of impurities in the other components added in the sample matrix [28].

3.3. Determination of Sulconazole Sample Cream

The tested method has verified the separation of the sulconazole enantiomer in the pharmaceutical cream samples with the same optimized and validation steps as standard in three times repetition. The sulconazole chromatogram obtained showed a significant separation of chiral compounds between the two peaks. The enantiomer separation was carried out using a cyclodextrin-type stationary phase chiral column. The results obtained are in the pharmaceutical sample of sulconazole cream, which is a recovery of 102.47%. The results of acceptance requirements for the percentage of recovery, which is in a solution of concentration >100 ppm at 90–107% This HPLC method is proven to be valid and accurate so that it can be used for routine analysis purposes. The sulconazole chromatogram is shown in **Figure 4**.

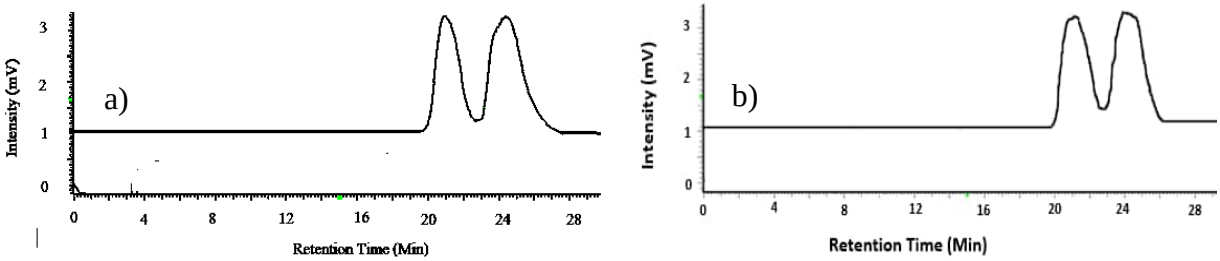

Figure 4. Chromatogram of sulconazole a) standard solution, b) pharmaceutical cream samples

4. Conclusions

Chiral separation using a cyclobond-based cyclodextrin chiral column in the HPLC method is considered very efficient in terms of separation, namely with Rs = 1.43 with a retention time of around 20 minutes. The sulconazole calibration curve was linear at R^2 = 0.997 respectively. LOD is 11.37 and 11.62 ppm, and LOQ is 37.90 and 38.75 ppm. Quantitative determination of sulconazole in the pharmaceutical sample cream obtained a percentage recovery of 102.47% (RSD = 0.80; n = 3). So it can be concluded that the HPLC method meets the efficiency requirements (both in time analysis, resolution, and validity) in separating HPLC.

Acknowledgment

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