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THE STABILITY EVALUATION OF LOSARTAN POTASIUM TOWARDS THE INFLUENCE OF pH AND LIGHT USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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Abstract–Considering the patient condition, some solid dosage form need to be suspended in water before administration to patient either in single or togather with other drugs. This preparation may change the the condition of the solution and affect to the drugs in it. The objective of this research was to evaluate the influence of pH and light towards losartan potassium that suspends in water. The percentage of losartan potassium suspension concentration was measured using High-Performance Liquid Chromatography based on the method of United Stated Pharmacopeia. Losartan potassium suspension was tested in several conditions, i.e suspended in pH 4 and pH 7 with protected and unprotected light, the testing was done by sampling at a time series, i.e 0, 15, 30, 45, and 60 minutes. The results showed that the suspension of losartan potassium could be stored for 45 minutes with the concentration of 98.63% for pH 4 with unprotected light condition; 98.89% for pH 7 with unprotected light condition; 98.55% for pH 4 with protected light conditions; and 99.06% for pH 7 with protected light condition. The result of this study showed that after 45 minutes, losartan potassium suspension did not meet the requirement in the monograph which was 101.0 to 98.5%. This research showed that the effect of pH and light on losartan potassium suspension did not give a significant difference.

INTRODUCTION

Losartan potassium is an antihypertensive drug class of angiotensin receptor blockers (ARB), which is used for the treatment of hypertension with the risk of heart disease, kidney disorders, or diabetes [KDOQI Evidence Review Team. 2012; Munger M.,A.2010; U.S. Departement of Health and Human Service, 2003). Some patients may be prescribed this drug alone or in combination with other drugs that called polypharmacy. This choice depends on their therapy needs. Polypharmacy is found when many drugs administered for one patient. The drug is usually administered to patients in the form of solid dosage form such as tablet or capsule. In certain condition such as when a patient can not be administered with drug in the form of solid dosage form, the drugs can be administered in the suspension by diluting them in water before administration (Hajjar et al. 2007; Kurata, 2006). Diluting process can be done by crussing the tablet before diluting them in water or let the suspended by themselves in water as what recently conducted by many hospital in japan. Change the dosage form when dispensing may affect the stability of the active compound moreover degradation reaction grows faster in liquid dosage form than tablets.

Losartan potassium is salt form compound that can be hydrolyzed in water (Bhatnagar et al. 2011). It will dissociate to anion in water until reaching the equilibrium state. As a result of the withdrawal of protons from water molecules by anion, the rest of OH- ions cause the solution becomes more alkaline and destabilize the drug. The presence of other drugs that are suspended together will affect the pH of the preparation which can also influence the rate of degradation of the drug (The United States Pharmacopeial Convention. 2007).

Previous research suggested that the losartan potassium hydrolyzed by strong acids, formed the degradation products from the dimerization of two molecules (Elshanawane et al., 2012). In another study, the degradation was known to occur during the dispensing suspension of losartan potassium.

This degradation increases rapidly when the suspensions are tested by light exposure. It is known that degradation occurs as a result of the destruction of the imidazole ring in losartan potassium due to the presence of light and oxygen (Seburg et al., 2006). Therefore, in this study, losartan potassium is used as subjects of research on the influence of pH and light towards tablet dosage form that suspends in water.

MATERIALS AND METHODS

Materials

losartan potassium standard (Sigma-Aldrich), losartan potassium tablets from market, Acetonitrile HPLC grade (Merck), Methanol HPLC grade (Merck), KH_2PO_4, aqua bidest, Aquadest, HPLC instrument (Dionex Ultimate 3000).

Methods

System Suitability Test

Losartan potassium solution was made by diluting reference standard to 100 ppm concentration of losartan potassium. 10µL of solution was injected into the HPLC instrument with a mobile phase of 0.1% phosphoric acid in water: acetonitrile 3: 2 (v / v) using column C18 (5 µm 4,6x250mm), repeated six times [The United States Pharmacopeial Convention. 2007; International Conference on Harmonisation/ICH. 2005). The number of theoretical plates, RSD (Relative Standard Deviation), peak area, retention time and tailing factor were calculated. This system was used for verification and stability determinitaion.

Verification Test of the Assay

Accuracy and Precision

Test was performed using the concentration of 80, 100 and 120 ppm of losartan potassium. Losartan potassium solution was made by diluting the reference standard of losartan potassium in methanol. The solution was injected and run in the suitable system. For the accuracy test, the solution was injected three times then the value of percentage recovery and percentage differentiation were calculated. While in precision test, the solution was injected three times then the value of standard deviation (SD) and RSD were calculated. In the test of interday, injection process was performed on the hour-0 and 6 while for the intraday test, it was performed on days 1 and 2. Then, the value of SD and RSD were calculated (International Conference on Harmonisation/ICH. 2005; Harmita, 2004).

Determination of Calibration Curve

Losartan potassium concentration series solution was diluted to obtain the concentration of 25, 50, 75, 100, 125, 150 ppm of losartan potassium. The solution was injected and run in the suitable system. Analyzing the regression ratio of the peak area of each concentration of losartan potassium. Then, the calibration curve was made. LOD and LOQ were calculated by linear regression equation of the calibration curve [International Conference on Harmonisation/ICH. 2005; Harmita. 2004).

Stability Study

The stability of losartan potassium in water solution was evaluated in several condition as table 1 below. The test was conducted in a series of time, at minute 0, 15, 30, 45 and 60. The suspension was prepared by crushing the tablet and diluting them in water. It was homogenized by shake the suspension20 times.

150 µL of each sample was diluted with 1.2 mL of HPLC grade methanol and 150 µL of phosphate buffer to obtain a pH of 5.5 preparations with a concentration of 100 pg/mL.This was the sample test of minute 0. The same steps was conducted at the minutes 15, 30, 45, and 60. Furthermore, sample was vortex for 5 minutes, centrifuged for 5 minutes at a speed of 5000 rpm with a temperature of 25 °C. The supernatant was taken and filtered using a 0.45 filter syringe then put into vials for HPLC measurements. The area of the main peak was calculated using the regression equation obtained (Suryani et al., 2013).

RESULTS AND DISCUSSION

System Suitability Test

The test results showed the efficiency of the column, RSD of peak area, and RSD retention time meet the requirements in the system as follows: 10 µL losartan potassium injected into the HPLC instrument with a mobile phase of 0.1 % phosphoric acid in water: acetonitrile 3: 2 (v / v),

Verification Test

Accuracy and Precision

The test results show the recovery 103.547%, as required in the range of 95-105% [14]. The test results showed RSD each concentration with the value ≤ 2%, as required [11].

Table 1. Design of study

Sample test	pH 7	pH 4
Unprotected from Light	pH 7 Unprotected	pH 4 Unprotected
Protected from Light[a]	pH 7 Protected	pH 4 Protected

[a]Protected from Light =container covered with aluminum foil and prepared in dark conditions

Calibration Curve

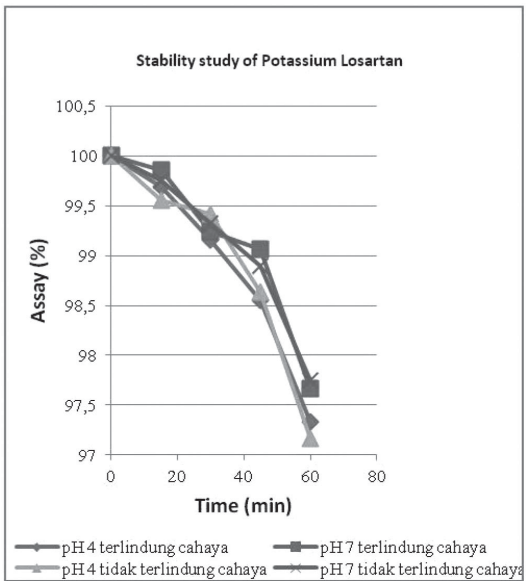
The test results show the value of r = 0.9998, y = 0,1699x + 0.2505, Coeff.Det value = 99.939%, Relative Standard Deviation value = 1.297%, Limit of detection is 3.364 mg/mL and the limit of quantitation is 10.193 mg / mL.

Stability Study

Referring to the significant value with 95% confidence level, it is known that the Losartan Potassium stability test data were not significantly different between experimental groups, both on the difference in pH and light conditions. According to compendial Losartan Potassium concentration that meets the requirements are not less than 98.5% and not more than 101.0% (The United States Pharmacopeial Convention, 2007; Health Departmenet of Indonesian Republic. 1995, Merck Canada Inc. 2014).

The test results show the suspension protected from light and suspensions are not protected from light both pH 4 and pH 7 can be storage until 45 minutes after the dispensing, the concentration of losartan potassium still meet the requirement.

The percentage content of the remaining respective amounted is 98.632% for pH 4 unprotected conditions; 98.892% for pH 7 unprotective conditions; 98.557% for pH 4 protected from light conditions; and 99.066% for pH 7 protected from light conditions. Calculation of reaction using order 1 kinetics function. The test results showed that in the losartan potassium suspend in the water does not undergo photolysis reaction, and found no major degradation results in the test for 60 minutes.



CONCLUSION

In the study of Losartan Potassium suspension stability the effect of pH between pH 7 and 4 as well as the storage conditions of light protected and unprotected light on the preparation does not have a significant influence. In addition, it was found that the information storage Losartan Potassium once made the suspension should be administered not more than 45 minutes after the preparations were made, this is indicated by the percentage of Losartan potassium concentration of less than 98.5% after 45 minutes in all experimental conditions, but not yet uncertain effects of changes in the dosage form at concentrations of losartan potassium in the body. Therefore, it is necessary to do clinical studies on Losartan Potassium preparations is suspended in water to determine the pharmacological effect on the response of the patient's body.

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