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CRUSHING COMPARED TO SIMPLE SUSPENSION METHOD IN PREPARING OF SPIRONOLACTONE TABLET SUSPENSION

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Abstract – In the case of patients can not take the medicine in the form of solid dosage form such as tablet and capsule, the drug has to be prepared in the solution before administration. Crushing the tablet is common method to be used in Indonesian hospital setting. Simple suspension method is recently used and developed in Japan. The objective of this research was to compare the two suspension in preparing spironolactone tablet. Spironolactone tablet was used based on the hospital case. The percentage of spironolactone concentrations of both suspension methods were measured by using High Performance Liquid Chromatography (HPLC) based on methods of United State Pharmacopeia. The test was conducted by sampling at 0, 15, 30, 45, and 60 minutes. The results showed that there was a change of spironolactone contents in both of methods. In crushing suspension method, the spironolactone content was 93.95% at 5 minute and decreased to - 89.23% after 60 minutes. Simple suspension method gives better results, i.e. 97.27% to 95.15%. Simple suspension method is better suspension method to be used because it can maintain spironolactone contents as monographic requirements which is 95% - 105%.

INTRODUCTION

Spironolactone is an aldosterone antagonist drug for the treatment of hypertension, congestive heart failure, primary hyperaldosteronism, hypokalemia, cirrhosis of the liver accompanied by edema or ascites (Charles and Lora *et al*., 2009). In some cases of geriatric patients who have difficulty in swallowing drugs and patients with hypertension who had a coma, gave the drug in the form of the suspension through enteral feeding tube. Currently there are two suspension methods that have been used, Crushing Suspension Method and Simple Suspension Method. Crushing Suspension Method is a commonly used where the tablet is destroyed and then mixed with water while simple suspension method is a new suspension method that has been recognized and implemented in Japan without crushing, suspended with water in temperature of approximately 55^0 C (White Rebecca and Vicky Bradnam, 2007; Kurata and Fujishima, 2010). The use of these two methods in suspensing may affect the stability of the drug. The drug degradation is caused by the hydrolysis reaction of lactone ring groups (cyclic ester) and thioester groups that easily attacked during its reaction (Basu Saskar Arindam *et al.* 2013). Previous studies have described that the weight of the drugs tested, *Ace Call*® (Temocapril), *Warfarin, Renivace*® (Enalapril Maleate), *Folli Amina*® (Folic Acid), and *Lendormin*® (Brotizolam) decreased by 70-90% by using crushing suspension method. Moreover, from the results of % recovery, warfarin experience instability with a value of nearly 50% while the simple suspension method is almost 100% (Zamami Yoshito *et al.,* 2014). From this case, simple suspension method is better than crushing suspension method. However, not all drugs can be prepared by the simple suspension method and further research is required to the other drugs. Therefore, spironolactone is used as a subject to compare the two methods to evalute the chage in its content during the praparation by using the high performance liquid chromatography instrument (HPLC).

MATERIALS AND METHODS

Reference standards of Spironolactone (Sigma-Aldrich), *Letonal*® (Spironolactone) tablets, Methanol of HPLC Grade (Merck), KH_2PO_4, HPLC

(Dionex Ultimate 3000).

Methods

System Suitability Test

The spironolactone solution was prepared by diluting the spironolactone standard to obtain 100 ppm of concentration. As much as 20 µL of this solution was injected into HPLC instrument with a mobile phase of methanol: water 6: 4 (v/v) and repeated six times (Anonim, 2007). The number of theoretical plates, % RSD (Relative Standard Deviation), peak area, retention time, and tailing factors are calculated. This system is used for verification test and sample test. Before applying to the suitability test, a maximum wavelength determination of standard raw materials is determined.

Verification Test of the Assay

Accuracy and Precision

The tests were performed at concentrations of 80, 100, and 120 ppm. Spironolactone solution is prepared by diluting the standard spironolactone solution with HPLC grade methanol. The solution is injected and run with the appropriate system. In the accuracy test, the solution is injected three times and the % recovery value and % differentiation are calculated. While in Precision test, the solution is injected three times with the value of SD and RSD calculated intra-day and inter-day. Intra-day injections were performed at 0, 8, and 24 hours. The Inter-day injection was performed on day 1 and 2 (Harmita, 2006).

Determination Calibration Curve

Spironolactone concentration series solutions were diluted to obtain concentrations of 25, 50, 75, 100, 125, and 150 ppm. The solution is injected and run on the appropriate system. After analysis ratio regression of the peak area, then the calibration curve was made. LOD and LOQ are calculated by the linear regression equation of the calibration curve (Harmita, 2006).

Sample Content Analysis

Each of suspended drug samples was tested at 5, 15, 30, 45, 60 minutes. Samples were taken as much as 300 µL, mixed with 150 µL of phosphate buffer and 1050 µL of HPLC grade of methanol. The samples were shaken 20 times in order to disperse the drug which was then 1 minutes before the time of sonication. Every samples of it would vortex for 5 minutes and centrifuged for 5 minutes at room temperature and 5000 rpm. The obtained supernatant was taken and filtered using a 0.45 syringe filter then fed into the HPLC vials performed on the appropriate system. The main peak areas were calculated using the linear regression equations obtained (Suryani Nelly *et al.*, 2013).

RESULTS AND DISCUSSION

System Suitable Test

The test results as in Table 1 show that the efficiency of the column, Peak Asymmetry, RSD peak area and retention time meets the requirements with the following system: 50 mL of spironolactone parent solution injected into HPLC instrument with mobile phase of methanol: water 6.5: 3.5 (v / v), column C-18 (4.6 X 250 mm, 5 mm), wavelength 237.5 nm, flow rate 1 ml/min, and ambient column temperature. Based on the USP 30, the optimum condition of HPLC for spironolactone is the mobile phase of methanol: water 6: 4 (v / v), a column with a length of 15 cm and a volume of 20 mL injection.

Verification Test

Accuracy and Precision

Test results show % recovery is 99.5508 as required in the 90-110% range (Anonim, 2007). The test results show each concentration with RSD value <2% as required Harmita, 2006).

Calibration Curve

The test results show that the r = 0.9998, y = 2.5175 +1.785x, standard deviation = 1.176023%, limit of

Table 1. System Suitable Test Parameters

Test Parameters	Requirement (USP 30)	Results
Column Efficiency	>2000 theoretical plates	2630
Peak Asymmetry	<2	0.914
Standard Deviation (RSD)	<1.5%	0.0704%
Peak Retention		0.1978%
Peak Areas		

detection = 2,1743 µg/mL, limit of quantitation 6,5862 µg/mL.

Sample Content Analysis

As can be seen in Table 2, the sample with crushing suspension method gave the percentage of spironolactone at time 5 minute as much as 93,9505% compared to 97,2743% in simple suspension method. The more drug content lost in crushing method could be caused by drugs that left in the mortar or the use of a crushing machine such as blender. In addition, individual factors in grinding and removing scours at mortar also affect drug levels. Based on the USP 30, spironolactone tablet contents allowed is not less than 95% and not more than 105% of the number of spironolactone listed. This result indicate that simple suspension method could prevent the lost of the drug at the first preparation.

Table 2. Percentage of Spironolactone Content with Crushing Suspension Method and Simple Suspension Method

Time (minute)	Method of Suspension	
	Crushing Suspension Method	Simple Suspension Method
5	93.9505 %	97.2743%
15	92.8724 %	96.9515%
30	90.7848 %	96.3080%
45	89.7550 %	95.2458%
60	89.2399 %	95.6394%

Table 3 showed that degradation of drug were found in both suspension methods from the beginning of preparation to 60 minutes. The number of degradation was quite similar. It indicate that the drug content decrease is due to chemical reactions.

Table 3. Percentage Level Degradation of Spironolactone Content on Crushing Suspension Method and Simple Suspension Method

Time	Percent Degradation	
(Minute)	0	6,0495%
Crushing	15	7.1276%
Suspension Method	30	9.2152%
	45	10.2450%
	60	10.7601%
	0	2.7257%
Simple Suspension	15	3.0485%
	30	3.6920%
Method	45	4.7542%
	60	4.8441%

Drug degradation from the both suspension methods is caused by the spironolactone changing form tablet into suspension from which effect to the stability of the drug, especially for the film-coated tablet. Changing the tablet dosage form with both methods can cause the active ingredients exposed to the water easily, so it caused a hydrolysis reaction, which decreased the drug content.

The hydrolysis reaction to the spironolactone can be occured because of the spironolactone group consist of chemical groups which are susceptible to hydrolysis reaction such as lactone group (cyclic ester) and thioester group (Harmita, 2006). The degradation form of the spironolactone drug is 7α tiometilspironolakton and kanrenon. This degradation result is formed by the hydrolysis of the thioacetate group to form 7α-thiospironolactone (as an intermediate agent) followed by S-methylation thus forming 7α-thiomethylspironolactone. The lactone ring group at 7α-thiometil spironolactone can hydrolysis to be kanrenone (World Health Organization, 2001).

CONCLUSION

Changes in the dosage form of spironolactone tablets to be reconstituted in the form of a suspension, both crushing suspension method and simple suspension method give different concentration level. In crushing suspension method 93,9505% - 89,2399% while simple suspension method 97,2743% - 95,1559%). The results of this study can be concluded that simple suspension method is the ideal suspense method to be used because it can maintain the level of spironolactone drug which suitable with the monograph requirements at USP 30 that is 95% - 105%. Both methods have decreased levels of the drug, but did not give large change and influential until 60 minutes. However, further investigation of spironolactone is needed. Because the drug is commonly used in combination with other antihypertensive drugs.

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