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Study of Physical Characteristic and Equivalence between Generic and Branded Name of Phenylbutazone Tablet

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Abstract

Physical characterization and equivalence testing of generic and branded names of phenylbutazone tablets have been done. The information about quality of generic drugs is expected to increase the use of generic drugs by health practitioners and public. Dissolution test carried out by in vitro had correlation with bioequivalence by in vivo test. Sample of dissolution testing were generic (G) and branded (A and B) names of 200 mg phenylbutazone tablets. Physical characteristic test performed by uniformity weight test, hardness and disintegration time. Dissolution test were conducted by using basket and spectrophotometry ultra violet method in 200-400 nm wavelength. The result of uniformity weight of generic drug and branded drug was 352,02 mg and 352,82 mg, the hardness of generic was 9,58 kgf and branded was 9,50 kgf, and disintegration test result of generic was 16,1 minutes and branded was 3 minutes. The result of dissolution testing were dissolution profile and dissolved concentration at 30 minutes that compared to qualify of USP XXXII. Relative bioavailability testing of generic to A brand was 101.580 and generic to B brand was 105.275. Based on statistical test, there was no significant different or pharmaceutical equivalent. The generic tablets were equivalent to A and B branded names tablets with similar factors 82.120 and 74.271.

Keywords: *Equivalence, Dissolution, Salbutamol tablet; generic name, branded name*

1. Introduction

Medicines are important element of health implementation efforts [1]. Medicines in the market consists of innovator medicines (patent) and generic medicines. Generic medicines are included generic name and branded name that given by the manufacturer.

Production of generic medicines is one of the ways to provide quality medicine with affordable prices for general society. According to *the International Society for Pharmacoeconomics Outcome Research (ISPOR)* Indonesia, medicine costs in Indonesia are enough more expensive than some other countries. One reason of high medicine costs is most people are choosing to use branded medicines with more expensive cost than generic medicines [2]. Prescription of patents and branded medicines by physician can be the factor that caused patients difficult to fill the prescription. Whereas in 2010, the Health Ministry of the Republic Indonesia has revitalized the use of generic medicines. The revitalize is Permenkes RI No HK.02.02/Menkes/ 068/1/2010 about the obligation to use generic medicines that facilitated by health government in order to improve the quality of health.

Increasing of generic medicines uses is necessary in order to make society understanding and trust that generic medicines have quality, safety, and effectiveness same as with branded medicines [3]. Quality of medicines is a reference to establish the efficacy and safety, including physical and chemical stability that accordance with eligibility established criteria [4]. Difference of quality between generic and branded tablet can be done by in vitro tests. The tests aim to find strength and dissolution of tablet that shows profil of medicines in GIT (Gastro Intestinal) releasing, absorption rate in the systemic circulation, and therapeutic effect [5,6].

Phenylbutazone is one of the rheumatoid arthritis drug that consist of generic and branded name. Phenylbutazone acts as an anti-inflammatory by inhibiting the cyclooxygenase and inflammatory mediator, such as prostaglandins [7]. This study aims to determine physical properties and equivalences between

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generic and branded name of phenylbutazone tablets. Thereby the community that uses it can obtain the information about quality of generic and branded name of phenylbutazone tablet

2. Material and Methods

2.1 General

Generic phenylbutazone 200 mg tablet produced by PT. MA, phenylbutazone branded name tablet product of PT. DM, sodium hydroxide, potassium hydrogen phosphate, and distilled water, basket-type dissolution testparing apatus (Erweka®), disintegration test equipment (Erweka®), tablet hardness tester (Erweka®), UV-Vis spectrophotometer (Jenway®6800).

2.2 Physical Properties Test

Tablet Uniformity Test

Twenty tablets are weighed and calculated the average weight. For tablet with 300 mg, weighed one by one at a time, no more than two tablets weight deviates greater from 5% of the average weight, and no more than one tablet weight deviates from 10% of the average weight [6].

Tablet Hardness Test

Ten tablets are placed one by one on the anvil of hardness testing machine. Hardness scale of the tablets are shown in kgf units [8]. Generally, hardness of tablets are between 4-10 kgf [9].

Tablet Disintegration Test

Six tablet are inserted into the disintegration test tool. Artificial intestinal fluid (37 ± 2)° C was used as a medium. Run the tool of disintegration test and observe the tablet time for disintegrating. Standard of disintegration time for coated tablets is less than 30 minutes [10].

2.3 Dissolution test

Dissolution test is performed according to the Indonesian Pharmacopoeia fourth [10]. Total 900 mL of artificial intestinal fluid pH 7.5 are included in vitro dissolution test [11]. Medium temperature was maintained constant at 37±0,5^{o}C in order to remain the water in waterbath. Then tablets are put into the tube dissolution. The tool is run at a constant rate in 100 rpm [12]. Tests conducted for 30 minutes. Sampling is done at minute 5, 10, 15, 20, 25, and 30 respectively taken 10 ml [6].

2.4 Assay of Phenylbutazone

Determination of the Maximum Wavelength

Phenylbutazone 250 ppm standard solution was conducted by dissolved phenylbutazone 250 mg in 1000 mL of artificial intestinal fluid with pH 7.5 in volumetric flask. Standard solution is diluted to 25 ppm. 10 ml of the solution is measured the absorbance at of 200-400 nm [13].

The Calibration Curve

Standard solution of 250 ppm phenylbutazone was diluted in 1, 3, 5, 7 and 9 ppm for 10 ml and absorbance are measured by UV-Vis spectrophotometry. Based on absorbance, calibration curve and the equation are obtained [13].

Assay of phenylbutazone dissolution

Each 10 ml of dissolution test solution at 5, 10, 15, 20, 25, and 30 minute is measured the absorbance by using spectrophotometry at wavelengths that obtained previously. Concentration of phenylbutazone was obtained by using linear equations [13].

2.5 Data analysis

Data of Physical test

Each average weight, standard deviation (SD), and CV of generic and branded phenylbutazone tablets was compared with Pharmacopoeia Indonesia standard to obtaine the deviation.

Equivalence Determination

The obtained data of Phenylbutazone tablet dissolution test (Q) in the 30th minute was calculated by the following equation:

$$Q\ (\%) = \left(\frac{\text{tablet solute (mg)}}{tablet}\right) \text{x } 100\%$$

Dissolution efficiency of Phenylbutazone tablet for 30 minutes (DE30) was calculated by the following equation:

$$DE_t = \left(\frac{\text{y dt}}{\text{y 100t}}\right) \text{x } 100\ \%$$

DE_t : dissolution efficiency at $t_{(time)}$
Y_{dt} : area under the curve of dissolved active substance at $t_{(time)}$
Y_{100t} : wide rectangle 100% of dissolved active substance in medium at $t_{(time)}$

Value of relative bioavailability phenyl-butazone tablet was calculated by:

$$BA_{relative} = \frac{AUC_G}{AUC_B} \times \frac{Dose_B}{Dose_G}$$

AUC_G = area under the curve value of generic tablet
AUC_B = area under the curve value of branded tablet

3. Result and Discussion

3.1 Physical Properties Test

Weight uniformity test is intended to ensure that each tablet contains of right and equitable active ingredients dose. Deviations of each tablet Weight can affect on medication dose [14].

Uniformity different weights was obtained between generic and branded phenylbutazone tablets. Indonesian Pharmacopoeia Edition IV requires that all tablets must have CV value of weight uniformity less than 5%. CV values that obtained for weight uniformity between generic and branded name of phenylbutazone tablet are 2.55 and 0.42%. Based on the CV values, weight uniformity of branded phenyl-butazone tablet better than generic phenylbutazone tablet. However, CV values of the both products accordance to the weight uniformity standard.

According to the Indonesian Pharmacopoeia III, for tablet with 300 mg, weighed one by one at a time, no more than two tablets weight deviates greater from 5% of the average weight, and no more than one tablet weight deviates from 10% of the average weight. Average weights of generic and branded phenylbutazone tablet are 352.02 and 353.82 mg. Each and average weight of generic and branded phenylbutazone tablet have no deviation in weight uniformity. Weight uniformity test aimed to ensure that production quality content in each tablet are similarity and uniformity of [15]. Based on the Weight uniformity test, generic phenylbutazone tablet that has varied weight can cause variety of active substance in each tablet and medicine dosage for patient does not comply with the supposed therapeutic dose.

There are several factors can cause differences in weight uniformity of tablet that has different brands and same active substance. The factors are uniformity of mixing ingredients distribution in powders or granules, segregation of powder or granule during processes of production, and tablet weight deviation [8].

Table 1. Hardness of phenylbutazone tablet

Product	Average of hardness	Standard of hardness	SD
Generic	9,58 kgf	4-10 kgf	1,02
Branded	9,50 kgf	4-10 kgf	0,22

Tablet hardness test results show that average tablet of generic phenylbutazone with 7.73 to 10.83 kgf and phenylbutazone tablet branded name with 9.20 to 9.97 kgf are accordance to the the standard of tablet hardness. Tablets hardness greater than 10 kgf are still acceptable, as long as the tablets are accoedance to the disintegration and dissolution standard [9].

Tablet hardness describe resilience of tablet against the mechanical stress such as shocking, impacting and cracking that may occured during packaging, distribution, and storage of tablets. In addition, the tablet hardness may also affect on disintegration and dissolution of the tablet.

Tabel 2. Deviation tablet weight of phenylbutazone

Product	Average of weight	Accordance Deviance (>300 mg) [10]		CV
		5%	10%	
Generic	352,02	334,43-369,63	316,80-387,20	2,55
Branded	353,82	336,13-371,51	318,40-389,20	0,42

Tablet hardness describe resilience of tablet against the mechanical stress such as shocking, impacting and cracking that may occurred during packaging, distribution, and storage of tablets. In addition, the tablet hardness may also affect on disintegration and dissolution of the tablet. The hard tablet can not disintegrate within properly dissolved time [14]. Whereas, the too fragile tablet will not resistant in various shocks of packaging, storage and distribution process which can lead to reduction dose of medication. Hardness difference between the two products due to the variety and amount of additional ingredients used [8], and the difference in compression pressure and compressibility properties of the granules. The granules that have good compressibility, requiring slight pressure of compression to produce hard tablet.

3.2 Disintegration Test

Tablet disintegration time is the time for tablet to disintegrate into granules / constituent particles that can pass through the sieve mesh number 4 on the bottom of the disintegration tool test. Tablet can be absorbed after oral administration if the tablet are crushed, dissolved, and available in molecular size.

Tabel 3. Disintegration time of Phenylbutazone Tablet

Product	Requiring Time for Whole Tablet Disintegration	Standar
Generic	3 minutes	>30 minutes
Branded	16,1 minutes	>30 minutes

Disintegrating tablet time test of generic and branded phenylbutazone tablet are accordance with Indonesian Pharmacopoeia standard for coated tablets, i.e less than 30 minutes. Disintegrating time of Phenylbutazone generic tablets is 16.1 minutes and phenylbutazone branded tablet is 3 minutes.

Difference of disintegrating tablet time is caused by the level of hardness, the type and amount of ingredients, methods, compression pressure, granule compressibility, and physical chemical properties of tablet ingredients. Generally, hard tablets have long disintegrating time (more insoluble) and low dissolution. Hardness of tablet is also associated with the density and porosity [9]. The hard Tablets have low porosity so penetration and absorption of water into the tablet pores more difficult and results bonding between granules particles difficult to escape and long disintegration time.

Type and amount of excipients also affects in tablet disintegration time. Solubility and compressibility of filling material may affects on mechanism and time of tablet disintegration. Hydrophilic filler can increase the viscosity of penetrant. Meanwhile, increasing of binder amount may prolong the tablets disintegration time. Increasing or decreasing of binder concentration may also affects on tablet time disintegration. Hydrophobic lubricants may stick on surface of particles tablets constituent that will prevent wetting and improved tablets disintegration time [16].

3.3 Equivalences between Products

After contact with the medium, the tablets will be disintegrated, deagregasi, and dissolution in the medium. Observations of dissolution time was conducted in 5, 10, 15, 20, 25, and 30 minutes. Solute concentration of phenylbutazone tablets were analyzed by spectrophotometry. Test results show that phenylbutazone generic tablets slowly dissolve in every minute. In the 5th minute phenylbutazone dissolving of generic tablets is 15.39% and 87.51% in 30th minutes. Phenylbutazone dissolving of branded tablet is 58,19% for 5 minutes and 98,82% for 30 minutes (Figure 1).

Profile dissolution rate of phenylbutazone branded tablet in 5th, 10, and 15 minutes faster than phenylbutazone generic tablet so that onset of branded tablet faster than generic tablet. However profile dissolution rate of the both tablets are accordance with USP standard, i.e phenylbutazone concentration dissolution rate > 70% in 30th minutes. Similarity factor value of generic and branded phenylbutazone tablet that obtained by dissolution profile curves analyzed was 42.80. This value is under 50, so the conclusion is no resemblance between generic and branded of phenylbutazone tablet that may caused by differences in disintegrated and dissolved of both tablets. Disintegration and dissolution time of branded phenylbutazone tablet is faster than generic phenylbutazone tablet.

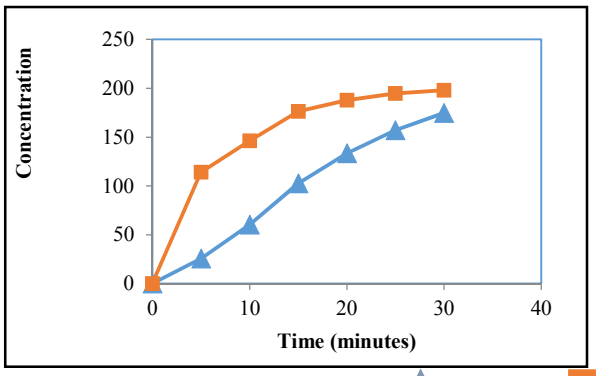

Figure 1. Dissolution Profile of generic ▲ and branded ■ product

Relative bioavailability equivalence can indicate quality of medicinal products, which the equivalence is formal comparative tests between generic and branded products to obtain the significant difference. The generic product is equivalent to branded product if there is not significant difference. Relative bioavailability of generic to branded phenylbutazone tablet was 63.07%.

Tabel 4. Dissolution of Phenylbutazone tablet

No	Time (min)	Dissolution of Generic Name		Dissolution of Branded Name	
		mg	%	mg	%
1	5	30,79	15,39	116,38	58,19
2	10	64,46	32,23	147,19	73,59
3	15	105,15	52,57	176,50	88,25
4	20	134,97	67,49	187,61	93,80
5	25	157,92	78,96	194,30	97,15
6	30	175,03	87,51	197,65	98,82

Standard: Q (cons. Of phenylbutazone) >70% in 30 mins [10]

These results indicate that the bioavailability of the two products is different. Relative bioavailability of branded to generic phenylbutazone tablet that obtained was 158.53%. These results indicate that bioavailability of branded phenylbutazone tablets are better than phenylbutazone generic tablet.

4. Conclusion

Physical properties of generic and branded phenylbutazone tablet that accordance to the Indonesia Pharmacopoeia standard are: 352,02 and 353,82 mg for weight uniformity; 9,58 and 9,50 kgf for tablet hardness; 16,1 and 3 minutes for disintegration time. Dissolution profile of generic and branded phenylbutazone tablets in

30 minutes that accordance to USP XXXII standard are 87,51 and 98,82%. Calculation of Similarity factor that obtained was 42,80% and relative bioavailability of the tablets was 63,07%. It concluded that generic and branded phenylbutazone tablet are not pharmaceutically equivalent.

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