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A Comparative Dissolution Test between Generic and Branded Name of Furosemide Tablets

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Abstract

A study on comparative dissolution rates betwen two generic tablets and two branded name of furosemide tablets has been undertaken. Method applied was paddle method as required by FI IV, and furosemide concentration was measured spectrophotometrically at maximum wavelength of 277.5 nm. The dissolution profiles were drawn from the plot between percentage of furosemide dissolved versus time, and linearized according to Langenbucher equation. Results showed that at 5 th minute of dissolution, the dissolution rates between generic tablet A_1 and brand name tablets B_1 and B_2 were not significantly different but there was a significant difference between tablets A_1, B_1, B_2 and generic tablet A_2. At 10th minute, the dissolution rates between brand name tablets (B_1 and B_2) were not significantly different, but there was a significant difference between brand name tablets (B_1 and B_2) and generic tablets (A_1 and A_2). At 15th minute, all tablets showed a significant difference in dissolution rates.

Keywords: comparative dissolution, furosemide tablet, dissolusion profile

Introduction

Furosemide (4-chloro-N-furfuryl-5-sulfamoilanthranilic acid) is a potent and short duration diuretic used for the therapy of oedema, and hypertension (Katzung, 1995). This compound is widely used and also a fast moving drug (Gemari, 2006). Being practically insoluble in water (Indonesia Pharmacopeia IV), the bioavailability of furosemide is dissolution rate-limited (Waller, 1982). It is a polimophous substance which consisted of 7 forms (4 true polymorphs, 2 sovates and 1 amorphous) (Bauer et al., 2002) which has significant contribution to variability in the dissolution profile among its dosage forms.

Furosemide tablets are found commercially in several brands with different prices. The branded names are much more expensive than the generic tablets, for example the price of branded name "L" is 32 times higher than that of the generic tablet (ISFI, 2003). It is our interest to ensure whether higher price correlates with better quality and vice versa. Further, the results might support the production and the use of generic tablets for common people.

Method

Equipments: Spectrophotometer UV-Vis (Shimadzu 1061), tablet hardness tester (Stokes-Monsato), disintegration tester (Sinsho), tablet friability tester (Friabilator-Roche), dissolution tester (Pharma Test PT-DT7), pH meter (Metrohm Herisau E 520), analytical balance (Denver Instrument M-220 D) and stopwatch.

Materials: Furosemide (courtesy of Kimia Farma), generic furosemide tablets: A1 and A2, branded furosemid tablets: B1 and B2, phosphate buffer pH 5,8, NaOH, methanol, ethanol and aqua destilata.

Sample collection

Samples were randomly taken from commercially available furosemide tablets (drug content was 40 mg) in Padang, consisted of 2 generic tablets A_1 and A_2 and 2 branded name furosemide tablets B_1 and B_2 which were 62 tablets each.

Determination of the maximum wavelength and the calibration curve of furosemide in phosphate buffer pH 5.8

Ten mg of furosemide was dissolved in a 100 mL flask which then diluted with pH 5.8 phosphate buffer to obtain a series of solutions with concentration of 4, 6, 8, 10, 12, dan 14 µg/ml respectively. The absorption of each solution was measured at maximum wavelength of furosemide.

Tablet evaluation

Evaluations of each product including organoleptic, expiration date, weight uniformity, size uniformity, friability, hardness, disintegration time and quantitative analysis of furosemide in each brand

were done according to the Indonesia Pharmacopeia IV.

Comparative dissolution test of furosemide (Indonesia Pharmacopeia IV)

Dissolution test of 6 tablets from each brand was performed by using paddle method (stirring rate of 50 rpm) with a medium of 900mL pH 5.8 phosphate buffer solution at 37° ± 0,5°C. Samples were taken at 5, 10, 15, 30, 45, 60 minutes respectively. The concentration of furosemide dissolved were determined by spectrophotometry UV-visible. The dissolution profile of each brand was plotted and data were then analyzed according to Langenbucher equation:

$$\left[\log\left[-\ln(1-m)\right] = b\log(t-Ti) - \log a\right]$$

Where: m = fraction of drug dissolved at time t
a = scale parameter
t = time
Ti = lag time
b = curve parameter ; where
b = 1 for exponential curve
b > 1 for S curve
b < 1 for curve with higher slope than lag time

Parameters such as Td and $T_{85\%}$ of each brand were then submitted to statistical analysis. The percentage of furosemide dissolved from each brand at 5th, 10th and 15th respectively were analyzed by using t sudent analysis.

Results and Discussion

The maximum wavelength of the absorption of furosemide solution in pH 5.8 phosphate buffer was 277,5 nm (Figure 1). The spectrometric analysis validation showed a linear plot of concentration vs absorption (y = 0,0588x + 0,0018; r = 0.9992).

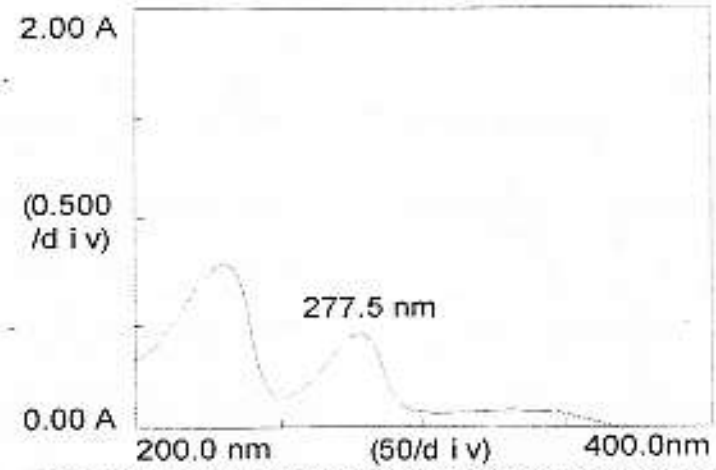

Figure 1. The UV spectrum of Furosemide in pH 5,8 phosphate buffer solution

Evaluation of the physicochemical and pharmaceutical properties of furosemide tablets showed that all brands fulfilled the requirements of The Indonesia Pharmacopeia IV (Table 1) except for the hardness of tablet A_2 which was slightly lower than required (4 – 8 kg/cm^2). Each brand showed a significant difference in disintegration time which corresponded to different mechanism of disintegration process. Tablet A_2 which had a low hardness but showed the highest disintegration time.

Table 1. Physicohemical and Pharmaceutical properties of furosemide tablets

Parameters	Brands			
	A_1	A_2	B_1	B_2
Colour	Green	White	White	yellow
Expiration date	July 2009	March 2010	September2010	February 2010
Weight (mg)	223.88 ± 2.037	169.09 ± 2.444	162.45 ± 1.959	211.53 ± 2.774
Diameter (mm)	8.26 ± 0.022	7.47 ± 0.024	7.57 ± 0.020	7.52 ± 0.006
Width (mm)	2.28 ± 0.022	2.08 ± 0.273	1.85 ± 0.021	3.04 ± 1.127
Friability (%)	0.223	0.307	0.123	0.026
Hardness (kg/cm^2)	6.65 ± 0.709	3.85 ± 0.626	6.85 ± 0.852	5.75 ± 1.208
Disintegration time (min)	0.73 ±0.177	7.95 ± 1.090	0.75 ± 0.078	1.34 ± 0.463
Drug content (%)	102.94	102.52	104.20	103.78

The dissolution profile of all brands of furosemide tablets (Figure 2) was obtained by plotting the percentage of furosemide dissolved versus time (Table 2). The profile showed that tablets A_1, B_1 and B_2 dissolved more rapidly than tablet A_2 . These correlated well with the disintegration time of each brands. Furosemide had 7 type of polymorph which may contribute to a different in solubility and hence dissolution time among brands (Bauer et al., 2002). Furthermore, the type of excipients used in the formula also determined the physicochemical and pharmaceutical properties of tablet.

Table 2. The amount of furosemide dissolved in pH 5.8 phosphate buffer solution at various times

t (minute)	% dissolved			
	A_1	A_2	B_1	B_2
5	79,6620 ± 4,5347	19,3304 ± 6,7670	86,8367 ± 6,767	86,5178 ± 5,5160
10	84,2220 ± 5,8484	38,2079 ± 11,4103	95,8609 ± 3,3170	94,4260 ± 2,8524
15	85,2742 ± 5,3841	68,4375 ± 17,3071	99,3048 ± 1,7173	98,1569 ± 1,9862
30	90,6314 ± 2,2205	88,6862 ± 7,3071	101,4413 ± 1,7660	101,3138 ± 2,2334
45	94,4260 ± 3,0652	99,0497 ± 1,4857	103,3546 ± 1,6324	102,6531 ± 2,8344
60	95,4783 ± 2,3257	102,4298 ± 2,9625	104,0242 ± 3,7409	102,9401 ± 2,3414

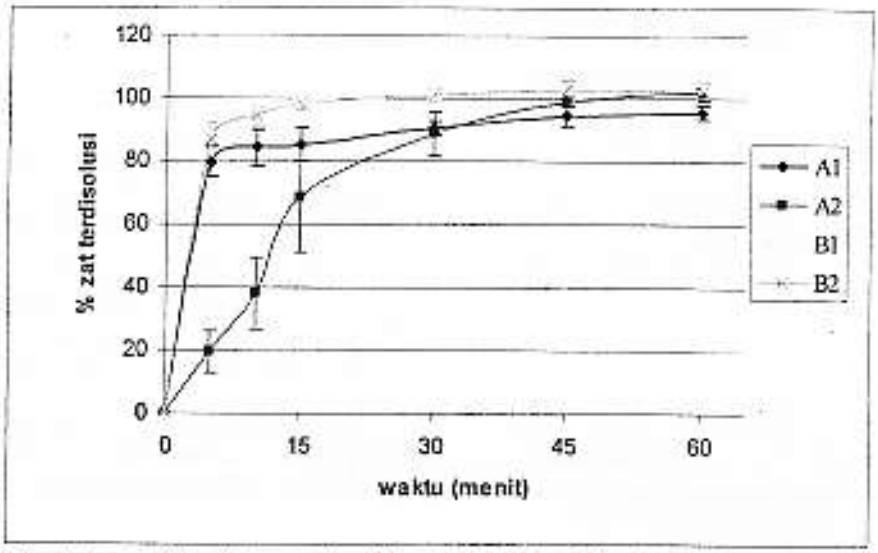

Figure 2. Dissolution profile of furosemide tablet A_1, A_2, B_1 dan B_2 in pH 5.8 phosphate buffer solution.

The dissolution data were then analyzed according to Langenbucher equation to determine the kinetic profile. All data showed a good agreement with this equation (Table 3 and Figure 3) which allowed the calculation of Td and $T_{80\%}$ parameters from the best fit curve .

Table 3. Regression analysis of dissolution data of various brands of furosemide tablets according to Langenbucher equation

Brand	Linear Equation	r
Tablet A_1	$y = 0,2877x - 0,0181$	$r = 0,9838$
Tablet A_2	$y = 1,4337x - 1,6918$	$r = 0,9924$
Tablet B_1	$y = 1,0214x - 0,4254$	$r = 0,9721$
Tablet B_2	$y = 0,6871x - 0,1878$	$r = 0,9911$

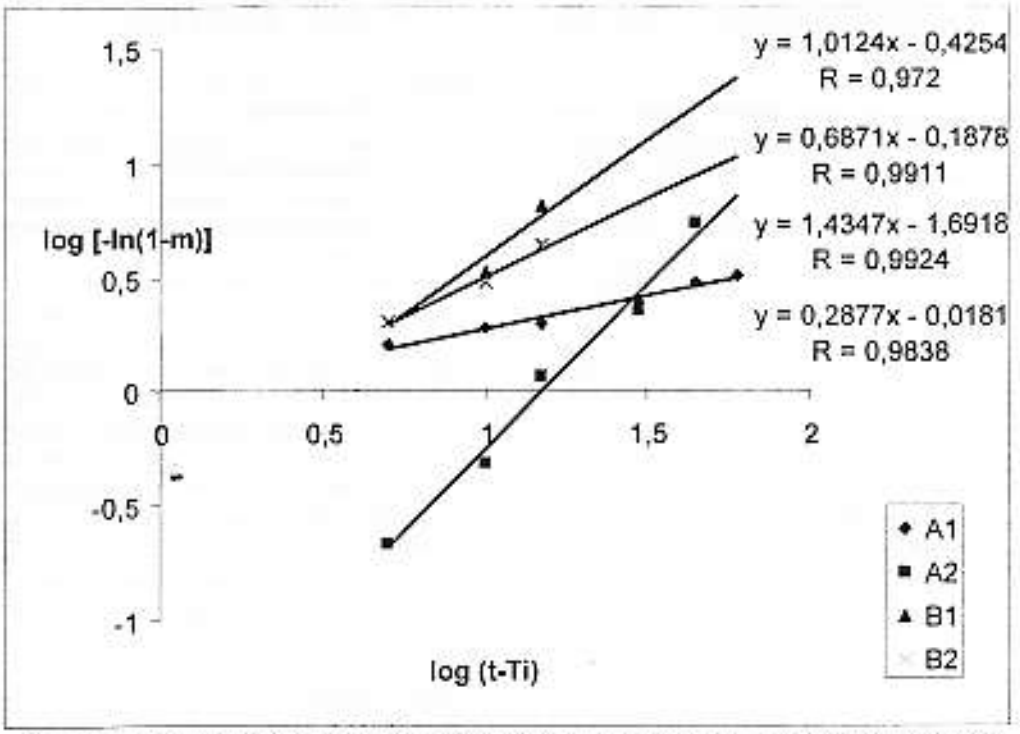

Figure 3. Langenbucher plot of the dissolution of furosemide tablet A_1, A_2, B_1 dan B_2 in pH 5.8 phosphate buffer solution.

Td is time needed for the dissolution of 63.2% from the tablet. Td for tablet A_1, A_2, B_1 dan B_2 respectively was 1,1559; 15,1078; 2,6314; and 1,8764 minutes. The $T_{80\%}$ parameter, the time needed for 80% dissolution, for furosemide tablet required by the Indonesia Pharmacopeia IV is 60 minutes. The $T_{80\%}$ for each brand was 4,5227; 21,0501; 4,2105, and 3,7507 minutes respectively for tablet A_1, A_2, B_1 dan B_2 which fullfiled the requirement. Again, both parameters showed the longest time for dissolution of furosemide from generic tablet A_2 which correlated well with its disintegration time.

The percentage of furosemide dissolved at 5th, 10th and 15th minutes respectively were analyzed statistically using T student test. Results indicated that there was a significant difference of % furosemide dissolved between tablet A_1 and A_2; $A_1$and B_2; A_2 and B_1; and between A_2 and B_2 (T calc > T tab) at 5th minutes of dissolution. However there was no significant difference between tablet A_1 and B_1; B_1 and B_2 (T calc < T tab). At 10th minutes, there was a significant difference of % furosemide dissolved between tablet A_1 and A_2; A_1 and B_1; A_1 and B_2; A_2 and B_1; and between A_2 and B_2 (T calc > T tab), only that between tablet B_1 and B_2 showed no significant difference. At 15th minutes of dissolution there were significant differences of % furosemide dissolved among all brands (T calc > T tab).

In summary, all brands met the requirements of the Indonesia Pharmacopeia IV especially in dissolution time ($T_{80\%}$), with the fastest was branded name tablet B_2 and the slowest was generic tablet A_2 while that of generic tablet A_1 and branded name tablet B_1 showed a similar value. The bioavailability of furosemide is dissolution rate limited, thus the dissolution rate of furosemide may closely related to its fate in-vivo. These results also showed that higher price does not always correlate with better quality because the dissolution profile and also probably the bioavailability of generic tablet A_1 and branded name tablets B_1 and B_2 were not significantly different. Thus the use of furosemide generic tablet prescribed for common people is highly supported.

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