

A Comparison of the Technical Quality of American and Japanese Ranitidine Tablets

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Abstract

The purpose of this study was to compare the technical quality of commercial American and Japanese ranitidine tablets. Five brands of 150-mg USP tablets and six brands of 150-mg JP tablets were compared on hardness, friability, average weight, average content, content uniformity, and dissolution.

The difference in hardness between American and Japanese tablets was significant. Dissolution profiles of Japanese tablets were not significantly different from one other, whereas those of American tablets were significantly different. However, all brands complied with USP 27. Since all brands can be expected to be in therapeutic use, this result supports the use of the USP criterion as an indicator for therapeutic efficacy.

Introduction

Since generic drugs are safe, effective, and lower cost, they have many advantages from a medical-financial viewpoint. However, there must be assurance that generic drugs on the market are quality products. Since there is risk in the selection of generic drugs by the pharmacy or hospital for use by consumers and healthcare professionals, it is important to ensure that safe, effective, high quality, and equivalent generic products are available. Therefore, proof of safety and effectiveness is required before generic drugs can be used. The dissolution test is a method of testing the release of active ingredients from oral solid preparations and is aimed at confirming their quality according to a fixed standard, which also aids in preventing significant bioequivalence (1, 2). For the approval of a generic drug in the United States, bioequivalence to the brand-name drug is satisfied by showing that an acceptable in vitro dissolution standard is met (3). Since 1999, the Japanese Orange Book (4) has been published by the Society of Japanese Pharmacopoeia to specify the quality of Japanese products. There are many reports on quality control of generic drugs with dissolution tests (5). While international pharmaceutical harmonization has been promoted, for example, through the "International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use in Japan, the United States, and the European Union" (6-8), there are reports concerning the comparative

studies of the quality of generic drugs between different countries.

Ranitidine belongs to a class of drugs known as H₂-blockers, which block the action of histamine on stomach cells, thus reducing stomach acid production (1). The difference in dissolution behavior between innovator and generic ranitidine tablets has been previously reported (9). In a previous study, the quality of American and Japanese ibuprofen tablets was compared (10); in the present study, the quality of American and Japanese ranitidine tablets is compared, including the innovator product and generics.

Experimental

Materials

Five types of 150-mg USP ranitidine tablets and six kinds of 150-mg JP tablets were purchased. Information on these tablets is summarized in Table 1. All samples were stored at room temperature, and all tests were performed within product expiration dates.

Ranitidine hydrochloride reference standard (Lot No. SER 7018) was purchased from Wako Pure Chemicals Co. Ltd., Tokyo, Japan.

The quality requirements for ranitidine immediate-release tablets in the United States and Japan are as follows:

In USP 27:

Uniformity of Dosage Units: The amount of active ingredient is between 85 and 115% and the

Table 1. Tablets included in the study.

Code	Brand	Package	Lot	exp.	Company
JAPAN-A	Zantac tablet	PTP	ED1F2	2005.04	GlaxoSmithKline
JAPAN-B	Ranitac150	PTP	E123A1	2005.06	Nichi-Iko Pharmaceutical Company
JAPAN-C	Hattosuka Tab150 mg	PTP	CH04	2004.06	Ohara Pharmaceutical
JAPAN-D	Ranimerck Tab150	PTP	001AH5	2005.04	Merck-Seiyaku
JAPAN-E	Raden Tab150	PTP	2501	2005.06	Sawai Pharmaceutical Co., Ltd.
JAPAN-F	Ranichizan Tab150	PTP	B77	2004.05	Nihon Pharmaceutical Industry Co., Ltd.
USA-A	Zantac150	PTP	1ZP0786	2003.03	Glaxo Wellcome Inc.
USA-B	Ranitidine Tablets, USP	PTP	131360	2003.07	Geneva Pharmaceuticals, Inc.
USA-C	Ranitidine Tablets, USP	Bottle	GA5354	2003.09	Apotex Corp.
USA-D	Ranitidine Tablets, USP	Bottle	123747A	2003.05	Novopharm USA Inc.
USA-E	Ranitidine Tablets, USP	Bottle	M256	2003.07	MAJOR Pharmacruticals, Inc.

relative standard deviation (RSD) is less than or equal to 6.0%.

Dissolution test: Not less than 80% of the labeled amount of ranitidine is dissolved in 45 min.

In *JP 15*:

Uniformity of dosage units: The acceptance value (AV) of the preparation is less than 15%.

Dissolution test: There is no specification yet.

Dissolution

The dissolution profiles of the tablets were investigated using two dissolution apparatus (Toyama Sangyo, Japan) containing 3 rotors and vessels with 6 glass-fiber probes at each flask, linked to a UV spectrophotometer (Photal Otsuka Electronics, Japan). The glass-fiber probes (6 mm in diameter) were fixed at various locations in the flask. USP Apparatus 2 paddles were used for the dissolution test at 50 rpm for 50 min. The dissolution medium was 900 mL of distilled water at $37.0 \pm 0.5^\circ\text{C}$ in a 1000-mL covered round-bottom flask. The sample tablets were introduced into 900 mL of water in the flask, and the UV absorbance was measured every minute by the two-wavelength method (calculated at 350 nm, corrected at 410 nm). Absorbance values collected automatically were converted to percentages of tablet dissolved by dividing by the standard UV absorbance. Statistical tests were carried out using the analysis of variance procedure (ANOVA).

Content Uniformity

Ten sample tablets were randomly selected, and the following process was repeated ten times. A tablet was introduced into 900 mL of distilled water in a flask, and the solution was agitated at 300 rpm by a mixer for 60 min.

Ten milliliters of the sample solution was filtered through a 0.8- μm membrane filter, the UV absorbance of the solution was measured at 264 nm (UV 160A, Shimadzu Co. Ltd., Kyoto, Japan), and the drug concentration was calculated based on a calibration curve.

Hardness

The hardness of the tablets was measured five times using a hardness tester (Toyama Sangyo Co., Osaka, Japan).

Friability

Twenty tablets were placed into a drum (USP24 and JP14, Toyama Sangyo Co., Ltd, Osaka, Japan), and the drum was rotated at 25 rpm for 5 min following *USP 24*. The tablets were then placed on a No. 10 mesh sieve, and any loose dust was removed with a soft brush and weighed.

Statistics

Statcel programs (11) containing a normal distribution test, *F*-test, Student *t*-test, Welch's *t*-test, Mann-Whitney's *U*-test, Bartlett test, one-factor analysis of variance test (ANOVA), and Kruskal-Wallis test were used as statistical data analysis methods.

Results

Physical Parameters

Table 2 shows the weight variation of American and Japanese ranitidine tablets. The average tablet weights of American tablets were between 0.3235 and 0.2200 g, but those of the Japanese were consistently close to 0.25 g. The relative standard deviations (RSD_w) for American tablet weight variation are between 0.777 and 2.468, but

Table 2. Weight Variation and Tablet Friability.

	Average, g	s	RSD _w , %	WL, %
UA	0.3020	0.0037	1.235	0.036
UB	0.2200	0.0043	1.932	0.048
UC	0.2409	0.0040	1.649	0.007
UD	0.3235	0.0025	0.777	0.040
UE	0.2405	0.0059	2.468	0.021
average	0.26537	0.040597	15.30	-
JA	0.2512	0.0033	1.319	0.014
JB	0.2510	0.0014	0.540	0.021
JC	0.2505	0.0033	1.330	0.016
JD	0.2524	0.0034	1.364	0.015
JE	0.2577	0.0023	0.874	0.033
JF	0.2531	0.0043	1.715	0.016
average	0.252645	0.003876	1.53	-

those for Japanese tablets are between 0.540 and 1.715. The range of RSD_w for Japanese tablet weights is smaller than that of the American tablets, which may be related to the differences in average tablet weight and tablet shape. The weights of the Japanese tablets follow a normal distribution ($n = 36, \chi^2 = 2.96, p < 0.05$), but the American tablet weights do not ($n = 30, \chi^2 = 49.6, p > 0.05$). The average weight of American tablets is not significantly different from that of the Japanese tablets by Mann-Whitney's *U*-test ($n_1 = 30, n_2 = 36, Z = 0.178, p < 0.05$).

Figure 1 shows tablet hardness of American and Japanese ranitidine tablets. There are significant differences in hardness by one-factor ANOVA among the American tablets ($F = 5.59, p < 0.05$) as well as the Japanese tablets ($F = 103.2, p < 0.05$).

Table 2 shows tablet friability. The results suggest that the percentage weight loss (WL) of American and Japanese tablets after the test was below 1%, which is the specification in *USP 24* and *JP 15*.

Drug Content and Drug Content Uniformity

The drug content of the American tablets was between 103.77 and 106.12% (Table 3), and the average content was 104.59%. The Japanese tablets ranged from 100.68 to 105.81%, and the average was 104.45%. The average drug contents of the American and Japanese tablets were 104.50 and 104.44%, respectively, and were not significantly different from the Japanese by Welch's *t*-test

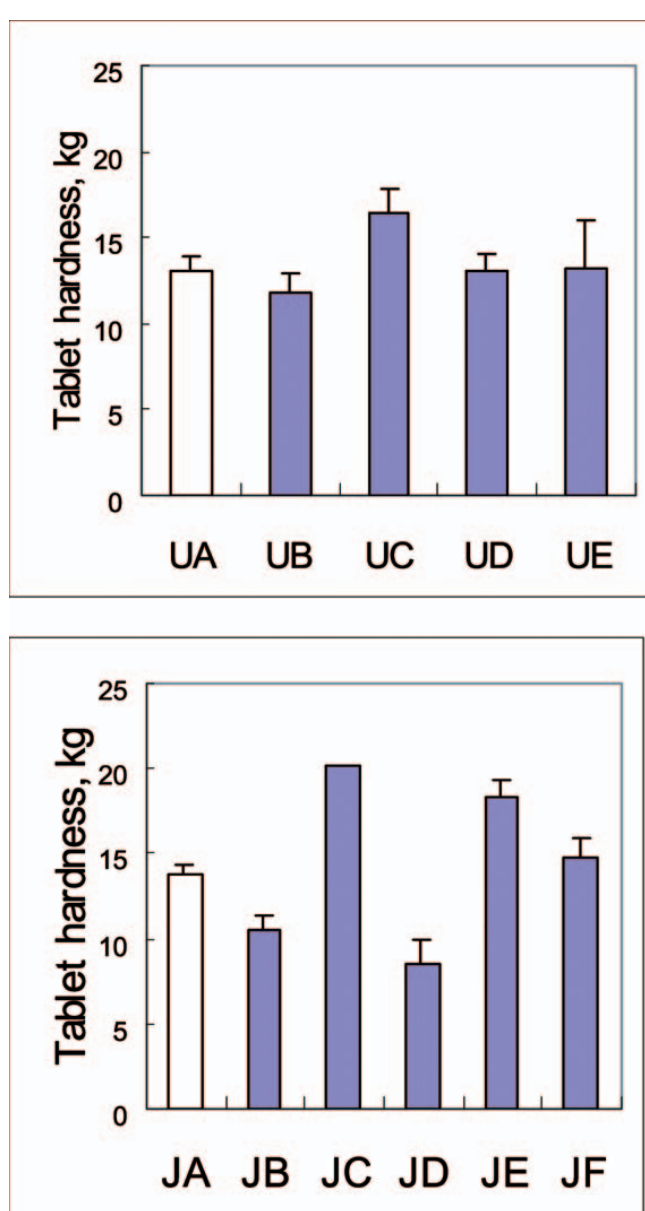


Figure 1. Tablet hardness (\pm SD) of American and Japanese ranitidine tablets.

($n_1 = 30, n_2 = 36, t = 0.0854, p < 0.05$). The AV for *JP 15* content uniformity test was calculated based on eq 2 and is summarized in Table 3. The RSD for the *USP* content uniformity test was calculated based on eq 3 following *USP 27* and is summarized in Table 1.

$$s = \sqrt{\frac{\sum_{i=1}^n (x_i - \bar{X})^2}{n-1}} \quad (1)$$

Table 3. Uniformity of Dosage Units.

	Content (%)	RSD	AV
UA	104.30	4.82	14.90
UB	106.12	5.58	18.39
UC	103.11	4.06	12.05
UD	103.77	2.58	9.45
UE	105.67	2.60	11.38
average	104.50	4.11	-
JA	105.15	1.47	8.38
JB	104.75	2.44	10.13
JC	104.55	1.45	7.75
JD	105.77	2.28	10.78
JE	100.68	2.72	6.66
JF	105.81	2.51	11.34
average	104.44	2.73	-

$$AV = |M - \bar{X}| + ks \quad (2)$$

$$RSD = \frac{100s}{\bar{X}} \quad (3)$$

M is label claim (100%), \bar{X} is the mean of individual contents, n is the sample size, x_i is the individual content of the units tested, k is the acceptability constant ($k = 2.2$), and s is the standard deviation.

Dissolution

Figures 2 and 3 show the dissolution profiles of American and Japanese tablets in distilled water. Tablets UA and JA were the innovator products in the United States and Japan, respectively. The Japanese tablets started to dissolve after 2–3 min, and drug concentrations reached almost 100% after 20 min. The dissolution profiles of the Japanese tablets are almost identical at all measurement times. On the other hand, the dissolution profiles of the American tablets show a wide range of variability and are significantly different from one other. Figure 4 shows T80 of the American tablets. Since each data set is small ($n = 6$), it was assumed that the data in each group follow a normal distribution. The distributions of T80 of American tablets are significantly different from one other by the Bartlett test (USA, $n = 30$, $\chi^2 = 24.9$, $p < 0.05$) and by the Kruskal-Wallis test ($H = 25.8$, $p < 0.05$). The T80 of tablet UA is significantly higher than those of tablets UB, UC, and UE by individual Welch's t -test ($p < 0.05$). However, the T80 of

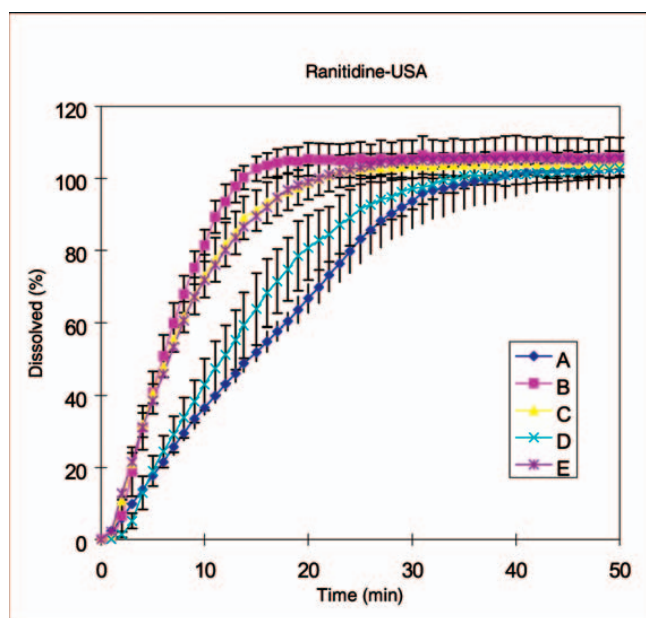


Figure 2. Dissolution profile (\pm SD) of American ranitidine tablets in distilled water.

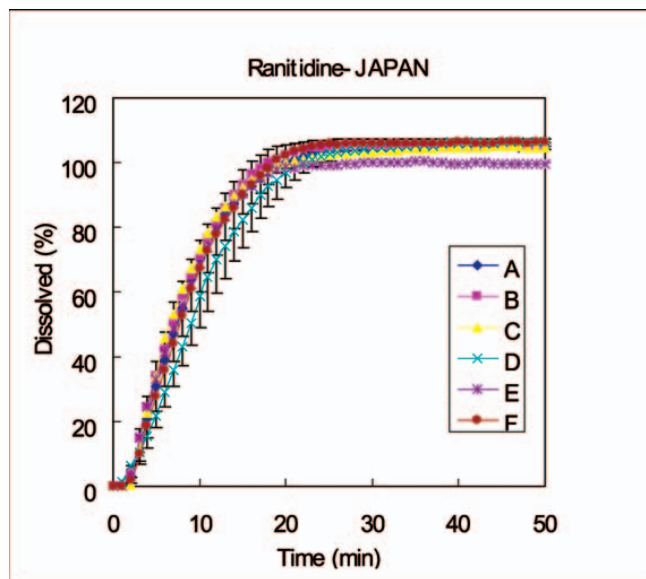


Figure 3. Dissolution profile (\pm SD) of Japanese ranitidine tablets in distilled water.

tablet UA is not significantly different from the average T80 of American generic tablets (UB, UC, UD, and UE) by Student t -test ($n_1 = 6$, $n_2 = 24$, $t = 0.685$, $p > 0.05$).

Figure 5 shows T80 of the Japanese tablets. In contrast, the T80 distributions of the Japanese tablets are not

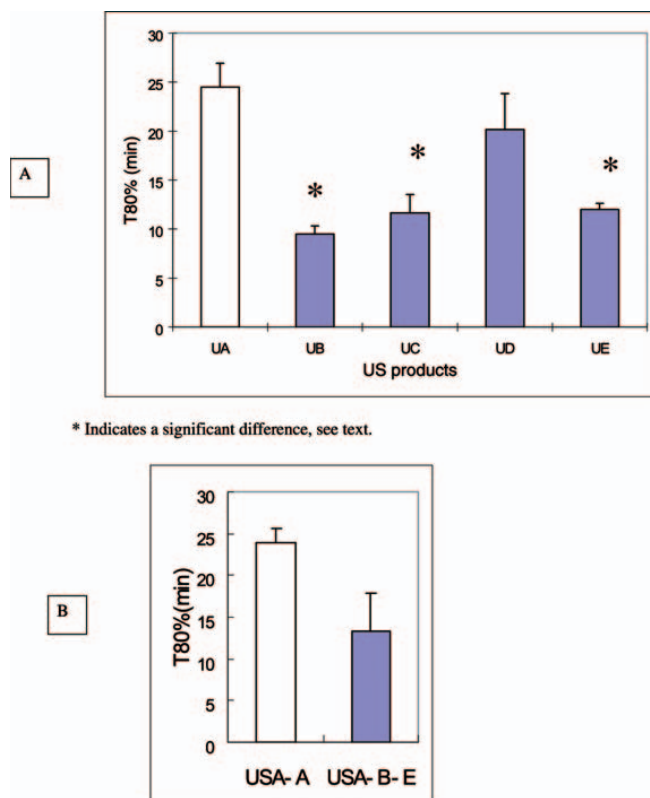


Figure 4. (A) T80 (\pm SD) of the American tablets. (B) T80 of the innovator (USA-A) and the average T80 of the USA generics.

significantly different from one other by the Bartlett test (USA, $n = 36$, $\chi^2 = 10.8$, $p > 0.05$) and one-factor ANOVA ($F = 2.00$, $p > 0.05$). The T80 of tablet JA is almost the same as that of the average T80 of Japanese generic tablets.

Figure 6 shows the percentage dissolved at 45 min (A45) of the American tablets. The A45 distributions for the American tablets are not significantly different from one other by the Bartlett test (USA, $n = 30$, $\chi^2 = 4.58$, $p > 0.05$) and one-factor ANOVA ($F = 1.02$, $p < 0.05$). The A45 of tablet UA is not significantly different from the average A45 of American generic tablets by Mann-Whitney's U -test ($n_1 = 6$, $n_2 = 24$, $Z = 0.570$, $p > 0.05$).

Figure 7 shows the A45 of the Japanese tablets. The A45 distributions of the Japanese tablets are not significantly different from one other by the Bartlett test (Japan, $n = 36$, $\chi^2 = 4.47$, $p > 0.05$). However, the A45 of the Japanese tablets are significantly different from one other by one-factor ANOVA ($F = 10.8$, $p < 0.05$). The A45 of tablet JA is not significantly different from those of tablets JB, JC, JD, and JF by the individual Student t -test ($p > 0.05$), but is significantly different from that of tablet JE ($t = 5.65$, $p < 0.05$). The difference in tablet JE might be related to drug content difference. The A45 of tablet JA is not

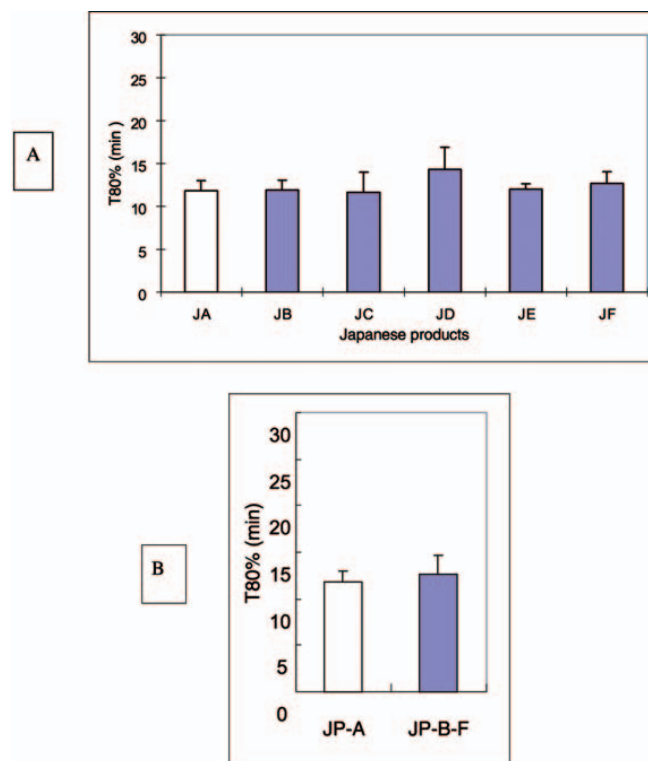


Figure 5. (A) T80 (\pm SD) of Japanese tablets. (B) T80 of the innovator (JP-A) and the average T80 of the Japanese generics.

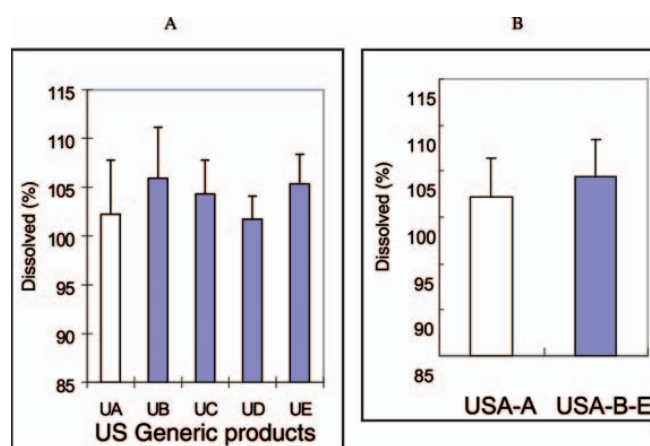
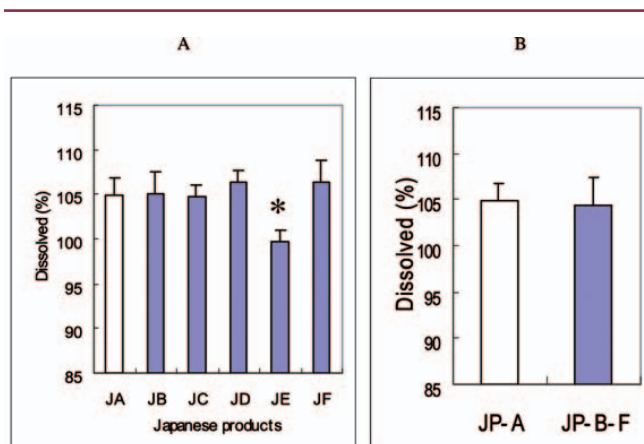


Figure 6. (A) A45 (\pm SD) of American tablets. (B) A45 of the innovator (USA-A) and the average A45 of the USA generics.

significantly different from the average A45 of the Japanese generic tablets by the Mann-Whitney's U -test ($n_1 = 6$, $n_2 = 30$, $Z = 0.021$, $p > 0.05$).



* Indicates a significant difference, see text.

Figure 7. (A) A45 (\pm SD) of Japanese tablets. (B) A45 of the innovator (JP-A) and the average A45 of the Japanese generics.

Figure 8 shows the average T80 and average A45 values of the American and Japanese tablets. The T80 of Japanese tablets follow a normal distribution ($n = 36, \chi^2 = 3.89, p < 0.05$), but the American tablets do not ($n = 30, \chi^2 = 8.87, p > 0.05$). The T80 of the American tablets is not significantly different from that of the Japanese tablets by the Mann-Whitney U -test ($n_1 = 30, n_2 = 36, Z = 0.837, p > 0.05$). On the other hand, the A45 of Japanese and American tablets follows a normal distribution ($n = 36, \chi^2 = 5.04, p > 0.05$ and $n = 30, \chi^2 = 0.881, p > 0.05$, respectively). The distribution of A45 of the American tablets is significantly different from that of the Japanese by the F -test ($n_1 = 30, n_2 = 36, F = 2.519, p < 0.05$). The A45 of the American tablets is not significantly different from that of the Japanese by the Welch's t -test ($t = 0.656, p > 0.05$).

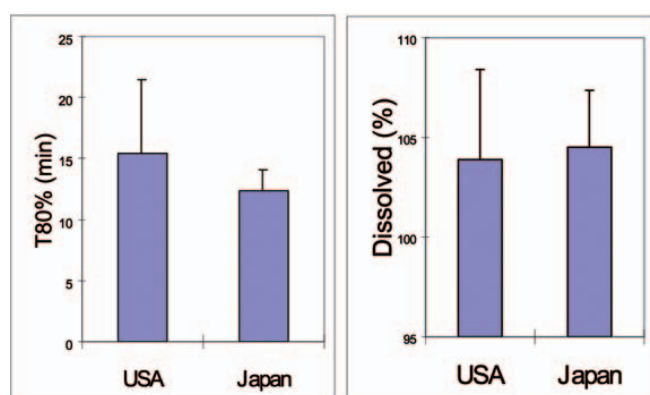


Figure 8. Average T80 and A45 of American and Japanese tablets.

Discussion

Physical Parameters, Drug Content, and Drug Content Uniformity

The tablet hardness results suggest that the hardness of tablets manufactured in both countries is sufficiently high and that there is greater variability among American tablets than among Japanese. The WLS of American and Japanese tablets in a tablet friability test were significantly low. Since ranitidine tablets are film-coated to resist humidity, it seems that the higher mechanical strength may be due to the film coating.

The average weight of the American tablets was almost the same as that of the Japanese, but the RSD_w of all American tablets was about 10 times higher than that of the Japanese. This may be because a direct compression method is commonly used, average tablet weights had a wide distribution between products, or because specific tablet shape was appraised in the United States. However, American tablets were in compliance with the USP.

The average drug content of the American tablets was not significantly different from that of the Japanese. The AVs of all American and Japanese tablet results are within 15% except for UB. On the other hand, the RSDs of both tablets are less than 6%. The results of the JP 15 content uniformity test indicate that all American and Japanese ranitidine tablets except UB met the JP content uniformity test specification. However, all tablets complied with the USP. This result suggests that the JP content uniformity test is slightly stricter than the USP test.

Dissolution

Since USP ranitidine tablets require at least 80% drug dissolution after 45 min, all dissolution profiles were evaluated for T80 and A45. The T80 and A45 of the American tablets were significantly different from one other. In contrast, the dissolution of the Japanese tablets differed only slightly. As ranitidine is very hygroscopic, film-coated tablets are made to resist high humidity and are stored in anti-humidity containers. Anti-humidity coating films resist water penetration and delay tablet dissolution. Since Japan has a climate of heat and high humidity, resistance to humidity is very important and is of concern to preformulation scientists. All American and Japanese products were in compliance with USP 27. Since all brands were purchased commercially, and hence can be expected to be in therapeutic use, this result supports the USP 27 dissolution criterion as an indicator for therapeutic efficacy.

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