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A Comparative Study on the Dissolution Profiles of Commercial Hydrochlorothiazide Tablets

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ABSTRACT

Dissolution profiles (DPs) of Dichlotride tablet containing hydrochlorothiazide, supplied by Merck Sharp & Dohme, N. J., U.S.A. and used as the reference formulation in this study, were compared with those obtained from sixteen commercial tablets. Dissolution tests were performed by employing a USP XXIII apparatus-I (Basket type) at 100 rpm. Pure water, 0.1N HCl and pH 7.4 buffer were used as the studied media. Released percentages of the active ingredient were measured at 10, 20, 30, 45, 60 and 90 minutes, respectively. The factor f_2 of the FDA's SUPAC Guide was applied to the qualitative determination of 'similarity' between pairs of dissolution profiles of Dichlotride and those of each investigated formulations. Results indicated that 5 out of 16 tested samples (ca. 31.3%) were suited to Dichlotride in all of three media. In addition, three other samples (ca. 18.8% each) were similar to Dichlotride in both water and 0.1N HCl. Two tested formulations gave similar in-vitro release profiles to those of Dichlotride only in corresponding pure water or the pH 7.4 buffer solution (ca. 6.3% each), in other words, different in both of the other two media. The last six samples showed completely different profiles compared with that of Dichlotride no matter what medium was used. In summary, the number of tested samples showing similar DPs as Dichlotride in individual media were as follows: 8 in water (50%); 9 in 0.1N HCl (ca. 56.3%); and 6 in pH 7.4 buffer solution (37.5%).

Key words : hydrochlorothiazide, dissolution profile, f_2 factor

INTRODUCTION

Pharmacodynamics concerns the relationship of formulations and pharmacological effects, especially how solid dosage forms are absorbed *in vivo*. Complicated factors are involved, among which, drug disintegration and dissolution are very important ones.

Drug dissolution experiments were first mentioned in U.S. Pharmacopeia XVII, and experimental items started to be covered in detail in XVIII[(1)], in order to assure that drugs have pharmaceutical equivalence in different batches or different brands with the same ingredients.

In principle, the regulated items of dissolution tests in Taiwan and the 4th Chinese Pharmacopoeia[(2)] require that the drug dissolution be measured in a single pH solvent at certain time points for quality control. This estimate hardly reflects the dissolution variation *in vivo* after taking medicine. However, it's not easy and remains in doubt to establish the correlation of *in vivo* bioavailability and bioequivalence (BA/BE) depending on the facts of *in vitro* dissolution experiments[(3,4,5)]. But it is perhaps more reliable to get a BA/BE reference from getting a drug dissolution profile in different pH value and time points by comparing dissolution curves. Even if we fail to establish the BA/BE relationship of *in vivo* and *in vitro*, it is still meaningful for comparison of the formulation quality of different brands.

The ROC Department of Health (DOH) has regulations on evaluation registration for control release formulations and for immediate release formulations of new drug surveillance[(6)]. In accordance with the DOH guidelines, it is required that the comparison data of dissolution profiles should be submitted, in some cases, when the BA/BE approved drugs are applied for the "minor" changes of formulation or for that of manufacturing site; or when the marketing approval application is proposed by the Taiwan manufacturing branch of the original drug developing company or its authorized contract manufacturers. On September 16, 1996, the managing principles concerning using drug dissolution profiles comparison as an alternative of the required BA/BE test report for applying oral dosage form evaluation registration[(7)] and notification of drug dissolution profiles comparison for low permeability, high solubility drugs and high permeability, low solubility drugs were proclaimed.

The diuretic in this project was Hydrochlorothiazide, a Thiazide deritive mainly used in the treatment of chronic heart failure-mediated edema and hypertension. Due to its low solubility in water, the Federal Register of the FDA categorizes it as questionable in BA/BE tests[(8)]. Formulations of different brands have different types and/or amount of adhesives, disintegrates, lubricants, or other excipients, as well as different compression forces which affect the disintegration and dissolution rate of a given formulation. Substantial related research has been published such as Ibrahim, H. G., who studied the influence of compression forces on the dissolution profile of Hydrochlorothiazide and Phenylbutazone. It

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was proven that dissolution is positive proportional to the logarithm of compression forces[9]. Tablet intensity is also functionally related with compression forces, so it is feasible to establish the relationship of tablet intensity and dissolution rate. Desai, D. S. documented the reduced dissolution stability of Hydrochlorothiazide formulation containing sodium starch glycolate without which the dissolution would be unacted[10]. Given different disintegrating and dissolution rates, those formulations will give lower drug effect and absorption *in vivo*. BA/BE problems are involved.

For Hydrochlorothiazide, a lot of research has been attempting to relate *in vitro* dissolution experiments and *in vivo* BA/BE test. Pandit, J. K. has conducted experiments on several Hydrochlorothiazide formulations (contain different disintegrates), and found the dissolution rate is proportional to the amount of Hydrochlorothiazide in urine[11]. Dakkuri, A. *et al*. also reported similar dissolution behavior[12].

At the second meeting of drug BA/BE held by the ROC Department of Health on May 24, 1995, it was suggested that some non-surveillant medicines should be subject to BA/BE inspection. Before that, we were asked to compare dissolution profiles of those medicines. So far, we have accomplished dissolution comparisons of Glyburide[13], Diltiazem HCl[14]. This article compares the dissolution profile of a single component formulation of Hydrochlorothiazide as a reference of BA/BE evaluation.

MATERIALS AND METHODS

I. *Materials*

(I) *Samples*

Each county bureau of health implemented the surveillance program on manufacturers with approval certificates of Hydrochloro-thiazide. 16 Samples were collected and each of them had 100 tablets per batch number per certificate. Four samples contained Hydrochlorothiazide 50 mg and the remainder contained 25 mg. One import product and 15 domestic products are in these 16 samples.

(II) *Control Brand*

200 Tablets of “Dichlotride Tab” are provided from Merck Sharp & Dohme, N. J. U.S.A. Each tablet contains Hydrochlorothiazide 50 mg.

(III) *Control Chemical*

Hydrochlorothiazide USP standard.

(IV) *Chemicals*

Potassium dihydrogen phosphate, sodium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, phosphoric acid, methanol and acetonitrile are purchased from Merck GR.

II. *Apparatus*

(I) *Dissolution Assay*

System including dissolution measuring apparatus (Logan D-800, U.S.), peristalsis pumps (Logan SP100, U.S.) and UV-Visible detector (Camspec M330, U.K.) was employed.

(II) *HPLC*

System including HPLC pump (Waters 510, U.S.) detector (Waters 484, U.S.), autosampler (TSP A100, U.S.) and integrator (Shimadzu C-R6A, JP) was employed.

III. *Methods*

(I) *Dissolution Profile Assay*

1. Solvent: Water, 0.1N HCl and pH 7.4 phosphate buffer was 900 mL each; 0.1N HCl and pH 7.4 phosphate buffer were prepared as USP method[15].
2. Apparatus: USP Apparatus I (Rotating Basket Apparatus).
3. Time points: Dissolution amount was measured separately at 10, 20, 30, 45, 60 and 90 minutes.
4. rotate speed: 100 rpm.
5. Preparation of Hydrochlorothiazide standard solution: 27.8 mg Hydrochlorothiazide USP standard was weighed precisely, put in 100 mL flasks for 25 mg/Tab. sample cases or 50 mL flasks for 50 mg/Tab. cases, dissolved in trace amount alcohol and diluted to certain volume by experimental solvent. 10 mL of this diluted liquid was drafted to another 100 mL flask and was diluted to certain volume by experimental solvents as standard solution.
6. Plot dissolution profile: Logan SP100 peristalsis pumps were program controlled to pump sampling liquid into Camspec M330 UV-Visible detector for UV315 nm absorption detection at 10, 20, 30, 45, 60, 90 minutes. Dissolution percentage was calculated and dissolution profile was plotted after comparing absorption of Hydrochlorothiazide standard solution.

(II) *Comparison with Control*

Dissolution profile of Dichlotride tablet control (50 mg/Tab.) from Merck Sharp & Dohme (N. J. U.S.A.) was plotted according to the average data from three dissolution tests (6 tablets every time) before, during and after sample experiments. Control was compared with the samples via f_2 factor[16] of SUPAC (Scale-up and Postapproval Change) suggested by FDA. Dissolution profiles of control and samples would be considered similar when f_2 is larger than 50:

$$f_2 = 50 \log\left\{\left[1+\frac{1}{\mathrm{T}}\sum_{t=1}^{\mathrm{T}}(\mathrm{X}_t-\mathrm{Y}_t)^2\right]^{-0.5} X100\right\}$$

X_t is disso lution percentage of control at time *t* and Y_t is dissolution percentage of samples at time *t*.

(III) *Content Uniformity Tests*

10 tablets of 5 mg/Tab. sample were separately ground into powders and put in 25 mL flasks (for 50 mg/Tab. samples, 50 mL flasks are used). Powders were dissolved in methanol to a certain volume and filtered. 5 mL filtrate was taken out and put in 50 mL flask and then diluted to a certain volume by mobile phase as sample solution. 0.1 mg/mL standard solution was prepared. 20 μL each of the standard and the sample solution was injected into HPLC for quantification. The analysis condition was as follows[17]:

column: μ-Bondapak C_{18} 10 μm 3.9 × 300 mm

mobile phase: 0.1M NaH_2PO_4 (pH3.0) / acetonitrile = 9/1

detector: 254 nm

flow rate: 1 ml/min

RESULTS AND DISCUSSION

I. *Sample Source*

Of the 33 known certificates of Hydrochlorothiazide single ingredient tablet, 29 were domestic products and 4 were imports. After we commissioned the board of health for spot-checks, 16 samples were obtained including 15 domestic products and one British import. Within these samples, number 1, 2, 6 and 10 were 50 mg/Tab and the rest were 25 mg/Tab.

II. *Experimental Conditions for Dissolution Profile of Hydrochlorothiazide Tablet*

Regarding the measurement of the dissolution profile of the Hydrochlorothiazide tablet, pharmacopoeia recorded its methods by the experiment done in 900 mL 0.1 N HCl at 100 rpm in a basket model apparatus. Moreover, in 1996, the Department of Health of the Executive Yuan required that the dissolution profiles comparison should be evaluated under at least three pH values enough for simulating a gastrointestinal duct environment[19]. Hence we used water and different pH phosphate buffers, pH 4.5, 5.5, 6.8 and 7.4 as solvent for analysis dissolution profiles of control in different environments. No obvious difference of dissolution profiles was found among each solvent in the first two hours, and therefore water and pH 7.4 buffer were chosen to serve as the other two solvents. The dissolution rates of Hydrochlorothiazide in three solvents were high and 90% dissolution was reached in the first half hour. Thus, we selected time points at 10, 20, 30, 45, 60 and 90 minutes.

III. *Analysis and Plot of Dissolution Profile of Control Dichlotride Tablet*

The dissolution profile of the control Dichlotride tablet was analyzed before, during and after sample analysis, totaling three times. The analysis result and relative standard derivation (RSD) is listed in Table 1. Information in table 1 is pictured in Figure 1. The RSD of all the time points in the dissolution profile were less than 0.9% except the time point at 10 minutes when the RSD was 4.0% with water as a solvent in Table 1, The RSD of all the time points was also less than 0.9% except at 10 minutes, and the RSD is 1.2% with 0.1N HCl as a solvent. The RSD of all time points was larger in pH 7.4 case from the minimum 2.1 to the maximum 5.2. The dissolution profiles of the control Dichlotride tablet were very similar in these three solvents, indicating that the dissolution rate of Hydrochlorothiazide was not affected by pH

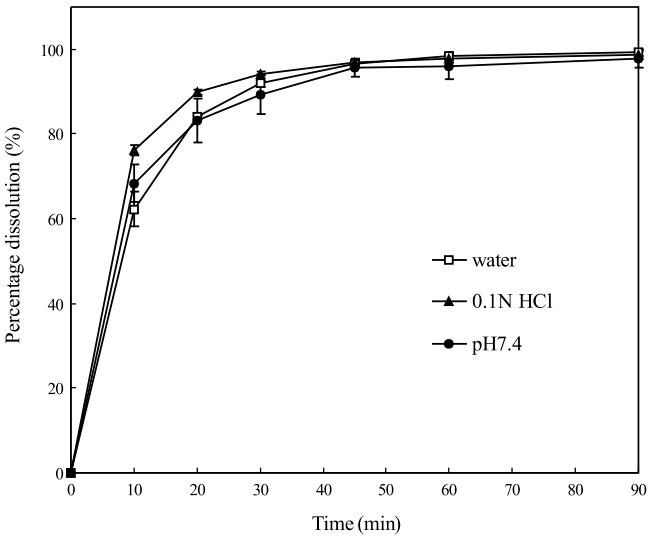

Figure 1. The dissolution profiles of Dichlotride tablet (as reference) in three different media.

Table 1. Percentage released and related standard deviation (RSD) in three different media of dissolution profiles of reference sample (n=3)

Medium \ Time (min) / Dissolutionrate		10	20	30	45	60	90
Water	Average	62.3	84.0	91.9	96.6	98.5	99.3
	RSD(%)	4.0	0.4	0.7	0.8	0.9	0.7
0.1N HCl	Average	76.3	89.8	94.3	96.9	97.8	98.7
	RSD(%)	1.2	0.6	0.6	0.7	0.9	0.9
pH7.4	Average	68.3	83.2	89.4	95.7	96.0	97.8
	RSD(%)	4.4	5.2	4.8	2.1	3.1	2.2

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Table 2. The summary of dissolution profile of commercial tablets

Sample No.	Lable Ammount (mg/Tab)	Results					
		Water		0.1N HCl		pH7.4	
		f_2 values	similarity	f_2 values	similarity	f_2 values	similarity
1	50	50.9	YES	73.1	YES	58.3	YES
2	50	64.4	YES	57.7	YES	68.5	YES
3	25	70.0	YES	83.0	YES	53.9	YES
4	25	66.1	YES	72.0	YES	71.3	YES
5	25	54.8	YES	60.6	YES	56.6	YES
6	50	57.8	YES	71.0	YES	30.3	NO
7	25	71.9	YES	67.8	YES	48.8	NO
8	25	55.7	YES	51.6	YES	49.5	NO
9	25	40.1	NO	51.8	YES	41.1	NO
10	50	41.6	NO	35.4	NO	66.4	YES
11	25	29.6	NO	27.7	NO	40.4	NO
12	25	18.2	NO	34.7	NO	13.0	NO
13	25	49.7	NO	44.6	NO	36.4	NO
14	25	49.2	NO	43.0	NO	36.0	NO
15	25	29.7	NO	34.2	NO	21.0	NO
16	25	35.1	NO	48.0	NO	28.7	NO

variation. This result is similar to the result of Sutton, J.E. in 1977[20].

IV. *Comparison of Dissolution Profiles of Merchandise Samples and Control*

(I) *Summary of Comparison of Dissolution Profiles of Three Solvents*

The FDA-suggested f_2 comparison of dissolution profiles of merchandise samples and controls were performed to check profiles' similarity. Detailed results and relative f_2 values are listed in Table 2. Five samples completely match the control in all three solvents (similarity ratio is 31.3%). Three cases were similar in water and 0.1N HCl but different in pH 7.4 buffer with similarity ratio 18.8%. One sample was similar in each pH 7.4 buffer or 0.1N HCl but different in the other two with a similarity 6.3%. The remaining 6 samples were completely different from the control. If the similarity of dissolution profiles of control and samples in each solvent is compared (Table 3), eight cases were similar in water (50%), nine were similar in 0.1N HCl (56.3%), and six were similar in pH 7.4 (37.5%).

(II) *Details of Dissolution Profile Comparison in Three Solvents*

As the results in Table 2, dissolution profiles in sample 1 to 5 in three solvents are similar, and among them, sample 1 is the only import, a product of the British branch of the original development company. Moreover, the control in pH 7.4 solvent has a higher RSD value. For example, samples 6, 7 and 8 were different in pH 7.4 but similar in water and 0.1N HCl solvent. Sample 10 was only similar in pH 7.4 but different in the other two solvents. Sample 9 was only similar in 0.1N HCl. But the special cases only fell on sample 9 and sample 10. From checking f_2 values from sample 11 to 16 which were different in all three solvents, it was found that the f_2 values in pH 7.4 were lower than those in the other two solvents, implying a larger difference in the pH 7.4 solvent. Table 3 also shows there are less similar cases in pH 7.4 solvent (only 6 samples). Summing up these results, we can probably infer that it is easy to see the difference in pH 7.4 solvent.

Figure 2 to Figure 4 have dissimilar dissolution profiles

Table 3. The similarity of dissolution profile in three different media between reference sample and commercial products

Medium	Water	0.1N HCl	pH7.4
Similar	8/16	9/16	6/16
(%)	(50)	(56.3)	(37.5)
Different	8/16	7/16	10/16
(%)	(50)	(43.7)	(62.5)

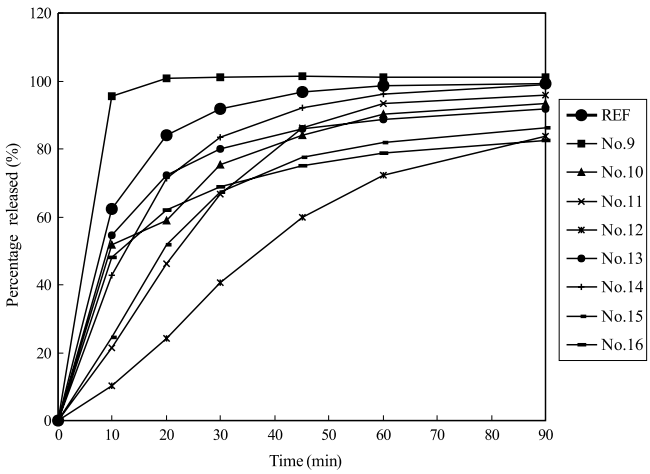

Figure 2. Dissolution profiles of Dichlotride tablet (REF) and commercial samples of which dissolution profiles, obtained in water medium, are different from that of refernece tablet.

in each solvent when samples and control are compared. Figure 2 shows the cases in water. The dissolution profile of sample 12 is obvious low. It was also shown in Table 2 that it carried the lowest f_2 value (18.2) among the total 16 samples. Sample 13 and 14 have f_2 values above 49 which means not similar but close. Figure 3 plots the dissolution profiles in 0.1N HCl. The dissolution profiles of samples are different from the control but more centralized than the other two solvents which implies smaller deviation. Sample 11 in these 7 dissimilar cases had the largest dissimilarity with a f_2 value 27.7. Figure 4 shows the situation in pH 7.4 phosphate buffer, and demonstrate a large deviation of each dissolution profile, especially on sample 12,15 and 16, with the corresponding f_2 under 30. The dissolution profiles of the samples are very different from the control ones.

(III) *Sample 10 and Dissolution Dissimilarity in All Three Solvents*

As we infer from above, there is a larger profile difference in pH 7.4 solvent but sample 10 is similar in pH 7.4 solvent yet dissimilar in the other two solvents (water and 0.1N HCl). Therefore, we list dissolution percentage in all sampling points in three solvents in Table 4 including the data of sample 11 to 16 of which the dissolution profiles are different from control.

The seven samples in pharmacopoeia-stated 0.1N HCl solvent have f_2 value smaller than 50. But all match the

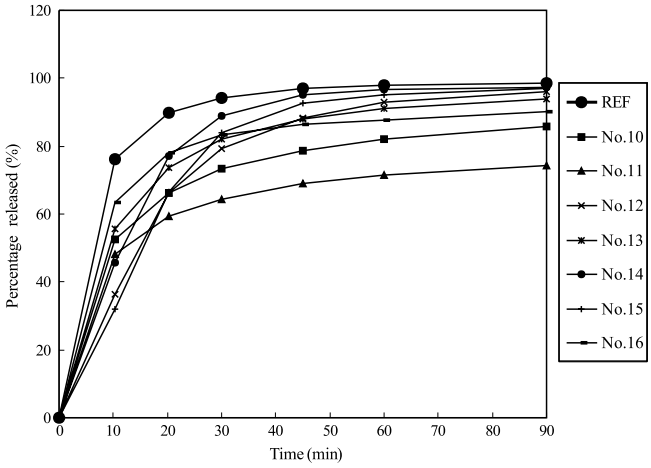

Figure 3. Dissolution profiles of Dichlotride tablet (REF) and commercial samples of which dissolution profiles, obtained in 0.1N HCl medium, are different from that of reference tablet.

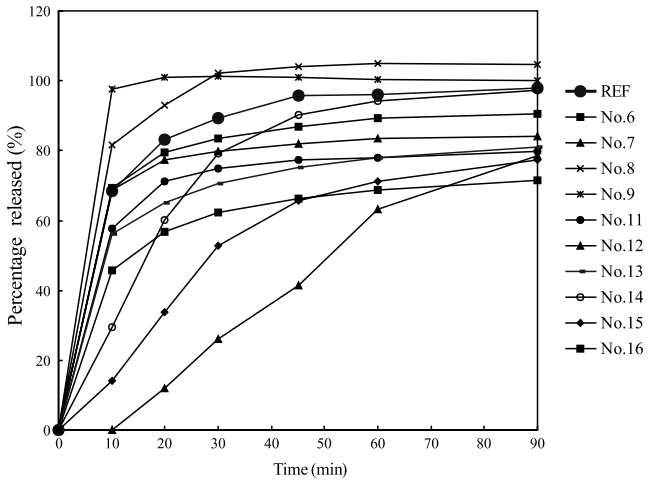

Figure 4. Dissolution profiles of Dichlotride tablet (REF) and commercial samples of which dissolution profiles, obtained in pH7.4 medium, are different from that of reference tablet.

Table 4. The released percentage of hydrochlorothiazide and f_2 values of sample 10~16

Sample No.	Medium	The Released Percentage of Hydrochlorothiazide						f_2 values
		10 min	20 min	30 min	45 min	60 min	90 min	
10	Water	52.8	60.9	74.4	80.9	84.8	88.8	41.6
	0.1N HCl	52.7	66.3	73.3	78.7	82.1	85.8	35.4
	pH7.4	66.8	80.4	85.5	88.7	90.5	93.0	66.4
11	Water	21.3	46.2	66.6	86.2	93.3	95.7	29.6
	0.1N HCl	48.3	59.4	64.5	69.0	71.4	74.2	27.2
	pH7.4	57.7	71.3	74.2	77.2	78.1	79.8	40.4
12	Water	10.3	24.3	40.4	59.8	72.2	83.8	18.2
	0.1N HCl	36.4	66.1	79.4	88.4	93.0	96.0	34.7
	pH7.4	0.1	11.9	26.0	41.4	63.3	78.6	13.0
13	Water	54.6	72.1	80.0	85.8	88.7	91.9	49.7
	0.1N HCl	55.6	73.8	81.9	87.9	91.2	93.9	44.6
	pH7.4	56.3	65.2	70.4	75.1	77.9	80.9	36.4
14	Water	42.8	71.2	83.4	92.2	96.1	99.0	49.2
	0.1N HCl	45.6	77.2	88.8	95.0	96.8	97.4	43.0
	pH7.4	29.4	60.3	79.3	90.3	94.2	97.4	36.0
15	Water	24.5	51.9	67.4	77.6	81.9	86.3	29.7
	0.1N HCl	32.0	66.4	83.8	92.5	95.0	96.9	34.2
	pH7.4	14.1	33.7	52.7	65.6	71.1	77.5	21.0
16	Water	48.1	62.0	68.9	75.0	78.7	82.5	35.1
	0.1N HCl	63.3	78.1	83.3	86.3	87.6	90.2	48.0
	pH7.4	45.7	56.7	62.3	66.4	68.7	71.6	28.7

Table 5. Results of content uniformity tests of sample 10, 11 and 16(%)

Sample No.	Content Uniformity(%)										Average
	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}	
10	95.1	100.6	99.1	98.2	92.6	96.9	97.9	99.9	95.5	94.7	97.0
11	106.5	101.0	97.3	94.6	100.8	102.8	106.1	98.7	96.3	104.5	100.5
16	105.2	101.9	103.4	106.3	105.3	100.0	100.3	106.8	105.9	103.6	103.9

requirement of pharmacopoeia if we estimate in terms of Q value 60% at the sixtieth minute. From this, it is understood that the dissolution profile comparison is more meaningful than a dissolution amount of a single point.

(IV) *Content Uniformity Test*

Table 4 shows the final dissolution percentage in each sample in different solvents. Except for sample 14, all are lower than 90%. To further confirm if assay and content-uniformity of the tablets were responsible for the dissimilarity of the dissolution profile, we tested the content by dissolving 10 tablets from each of the 3 samples, of which the dissolution amount was less than or close to 90% (including 90.2% for sample 16) in 0.1N HCl medium. Table 5 shows all samples matched the regulation of pharmacopoeia. Therefore, the possibilities of insufficient content found in the items of assay and content-uniformity were excluded. This could be due to the influence of formulation or the manufacture's techniques.

CONCLUSION

From this study of Hydrochlorothiazide single ingredient tablet, we determined the complexity of causes of dissolution rates. A proper content uniformity doesn't imply that comparison of dissolution profile is flawless. Because drug properties, size of granules, crystal forms, formulations and manufacturing techniques (such as compression forces) are involved, dissolution profiles among products have great differences. From the comparison of dissolution profiles of market merchandise and controls, we generated concepts of dissolution for commonly used domestic Hydrochlorothiazide formulations. And this can serve as reference for pharmacy regulators and industry.

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利尿劑Hydrochlorothiazide製劑之溶離曲線比對試驗

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摘　要

本研究旨在探討市售Hydrochlorothiazide單方錠劑與原開發廠美國默沙東藥廠（Merck Sharp & Dohme, N.J., U.S.A.）之Dichlotride 錠劑對照品溶離曲線之相似性，每一檢體均分別以水、0.1N HCl及pH 7.4磷酸緩衝液為溶媒，採用USP裝置I（Rotating Basket Apparatus），轉速100 rpm，測定10、20、30、45、60及90分鐘各時間點之溶離量，以繪製溶離曲線；並依照FDA所提SUPAC之f_2因子，與對照品比較其相似性。十六件檢體之溶離曲線與對照品比對結果，於三種溶媒之溶離曲線均與對照品相似者有五件（相似比率約31.3%），於水及0.1N HCl二溶媒中具相似性但於pH 7.4磷酸緩衝液不相似者有三件（約18.8%），而各只於單一溶媒，即0.1N HCl或pH 7.4磷酸緩衝液，具相似性者各一件（各約6.3%），其餘六件（37.5%）於三種溶媒之溶離曲線均與對照品不相似。綜合16件檢體與原廠對照品之溶離曲線的相似性，分別為水中溶離相似者八件（50%），0.1N HCl溶離相似者九件（56.3%）及pH7.4磷酸緩衝液溶離相似者六件（37.5%）。

關鍵詞：Hydrochlorothiazide，溶離曲線，f_2因子