Effect of Dissolution Media on Disintegration and Dissolution of Hydrochlorothiazide Tablets

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Abstract □ The disintegration and dissolution times of hydrochlorothiazide tablets granulated with acacia, polyvinylpyrrolidone, or starch were measured in distilled water, 0.1 *N* hydrochloric acid, simulated intestinal fluid, and borate buffer at pH 10. The influence of 0.03% polysorbate 80 in the dissolution media on the disintegration and dissolution times is reported. No correlation is demonstrated between the disintegration and dissolution times.

Keyphrases □ Hydrochlorothiazide tablets, disintegration, dissolution—effect of dissolution media □ Dissolution media, hydrochlorothiazide tablets—effect on disintegration, dissolution □ Disintegration, dissolution times, hydrochlorothiazide tablets—effect of dissolution media

In the past decade, many rate studies on the release and dissolution of drugs were conducted (1–6). Various dissolution media were used.

In 1949, the Contact Committee[1] recognized that normally the stomach is acid in reaction, but the committee recommended distilled water as the test medium for the disintegration test in view of the variability of quantity and concentration of acid in both normal and sick persons. This recommendation was based on early observations that, in many instances, water and dilute acid gave closely comparable results (7). For the first time, simulated gastric fluid was specified in USP XV as the test medium for tablets containing ingredients that reacted more readily in acid solution than in water. This raised the question if gastric fluid should be used for all tablets since all orally administered tablets are subjected to the gastric juice. The USP XVIII disintegration test uses water; however, the unresolved question of which medium to use has been shifted to the dissolution test. At present, the USP monograph specifies the dissolution medium for each tablet that has a dissolution specification. The purpose of this investigation was to study the effect of several dissolution media on the disintegration and dissolution of three formulations of a hydrochlorothiazide tablet.

The incorporation of surface-active agents in tablets was reported to improve disintegration (8). The inclusion of a surface-active agent in the dissolution medium was reported to hasten the dissolution of powdered drugs (9–11) and drugs in tableted form (12–18).

Surface-active agents may enhance disintegration by a reduction of interfacial tension which promotes wetting and penetration of the liquid into the tablet. Surface-active agents may enhance dissolution processes of a poorly soluble drug in a tablet by a reduction of interfacial tension and micelle formation. This study was also undertaken to determine the influence of polysorbate 80 in several dissolution media used in tablet disintegration and dissolution tests.

EXPERIMENTAL

Preparation of Tablets—Each tablet contained 50 mg. of hydrochlorothiazide in a lactose base (19). All tablets were prepared by a wet granulation method using acacia, polyvinylpyrrolidone[2], or starch as a binding agent.

Disintegration—The USP XVIII tablet disintegration procedure and apparatus were used to determine the disintegration time.

Solubility and Dissolution—An excess of hydrochlorothiazide and the appropriate dissolution medium were rotated by a submersion rotor in a constant-temperature bath at 37 ± 0.1° for 24 hr. A portion was withdrawn from each bottle with a pipet fitted with a cotton filter. After a 200-fold dilution with the appropriate dissolution medium, the absorbance was measured spectrophotometrically using a blank solution of the appropriate dissolution medium. The wavelengths of maximum absorption in the various dissolution media were determined with a DK-2 spectrophotometer. In all dissolution media, a linear relationship was obtained between the absorbance and concentration of hydrochlorothiazide.

Dissolution Methods I and II are described in the NF XIII. For Method I, the rate of rotation was 60 r.p.m. The dissolution media are given in Table I. The intestinal fluid used was simulated intestinal fluid USP from which the pancreatin was omitted. The borate buffer was prepared by mixing 250 ml. of a 0.2 *M* boric acid and potassium chloride solution with 220 ml. of a 0.2 *M* sodium hydroxide solution and then adjusting to pH 10 by the addition of 28.0 ml. of the sodium hydroxide solution.

Since the surface tension of human gastric fluid ranges from 35 to 50 dynes/cm. (9), polysorbate 80 was added to the dissolution media so that their surface tensions would be within this range. The surface tension of each medium, given in Table I, was measured at 37° with a Fisher Du Nouy tensiometer.

The dissolution profile was obtained by plotting the percent of hydrochlorothiazide dissolved at 37° against time (19). From the dissolution profile of each tablet, the time required for 50 and 66.7% of the hydrochlorothiazide to dissolve was read and designated as $t_{1/2}$ and $t_{2/3}$, respectively. The value reported for the dissolution time represents the average of three tablets.

RESULTS AND DISCUSSION

In determining the disintegration time by the USP method, it was noticed that occasionally a single tablet would require considerably longer to disintegrate than the other five tablets. Thus, it was thought that the average of the individual disintegration time of six tablets might be more representative of disintegration. As shown in Tables II and III, the average disintegration time for tablets granulated with acacia and starch was from one-half to two-thirds of the USP disintegration time. As shown in Table IV for tablets granulated with polyvinylpyrrolidone, the average disintegration time was approximately 15% faster than the USP disintegration time. Although the average disintegration time was less than the USP disintegration time, there was a rank correlation between the two disintegration times in all dissolution media.

[1] Combined Pharmaceutical Contact Committee (members appointed from American Drug Manufacturers' Association and American Pharmaceutical Manufacturers' Association).

[2] Plasdone K 29-32, registered trademark of GAF Corp., New York, N. Y., for pharmaceutical grade polyvinylpyrrolidone.

Table I—Wavelength of Maximum Absorption and Solubility at 37° of Hydrochlorothiazide in Various Dissolution Media and the Surface Tension at 37° of the Dissolution Media

Dissolution Medium	$\lambda_{max.}$, nm.	Solubility, g./l.	Surface Tension, dynes/cm.
Distilled water	270.5	0.830	71.0
Distilled water with polysorbate 80[a]		1.152	38.4
0.1 *N* Hydrochloric acid	271.5	0.823	70.9
0.1 *N* Hydrochloric acid with polysorbate 80[a]		1.070	39.2
Intestinal fluid[b]	270.5	0.884	71.7
Intestinal fluid with polysorbate 80[a]		0.998	38.4
Borate buffer, pH 10	273.0	4.070	71.2
Borate buffer with polysorbate 80[a]		4.820	39.1

[a] 0.03% polysorbate 80. [b] Simulated intestinal fluid USP without pancreatin.

Table II—Disintegration and Dissolution of Hydrochlorothiazide Tablets Granulated with Acacia in Various Dissolution Media at 37°

Dissolution Medium	Disintegration Time, min.		Dissolution Time, min.			
		Average of	Method I[a]		Method II[b]	
	USP	Six Tablets	$t_{1/2}$	$t_{2/3}$	$t_{1/2}$	$t_{2/3}$
Distilled water	12.4	8.3	32.8	45.6	14.4	25.7
Distilled water with polysorbate 80[c]	12.0	7.7	24.9	35.2	17.9	33.6
0.1 *N* Hydrochloric acid	22.0	11.9	20.8	30.5	14.1	26.4
0.1 *N* Hydrochloric acid with polysorbate 80[c]	15.2	9.9	15.8	25.3	11.3	24.4
Intestinal fluid[d]	21.3	13.9	29.0	40.4	16.8	28.3
Intestinal fluid with polysorbate 80[c]	19.2	14.2	27.0	37.6	14.5	24.8
Borate buffer, pH 10	13.8	8.4	16.7	24.4	10.4	14.0
Borate buffer with polysorbate 80[c]	14.1	9.4	17.3	25.6	7.7	11.0

[a] USP method using 60 r.p.m. [b] NF Method II. [c] 0.03% polysorbate 80. [d] Simulated intestinal fluid USP without pancreatin.

There was no marked difference in disintegration time in the various media. The 0.1 *N* hydrochloric acid produced the greatest variation. For tablets granulated with acacia and starch, the hydrochloric acid produced a longer disintegration time than the other media. For tablets granulated with polyvinylpyrrolidone, the hydrochloric acid produced a shorter disintegration time.

As shown in Table I, the addition of 0.03% polysorbate 80 to the dissolution media lowered the surface tension. With a reduction of surface tension, it is conceivable that the tablet would be wetted and more easily penetrated by the dissolving medium, with a more rapid disintegration. As shown in Table III, this effect was observed only in the disintegration in borate buffer of the tablet granulated with starch. In all other observations, within the variance of the disintegration test, the addition of polysorbate 80 to the dissolution medium did not significantly alter disintegration time.

As shown in Tables II–IV, the dissolution times within a given method were comparable with distilled water, 0.1 *N* hydrochloric acid, and simulated intestinal fluid. On the basis of the Noyes and Whitney equation, this would be anticipated because the agitation and volume of the liquid are constant and, as shown in Table I, the solubility of hydrochlorothiazide for practical purposes is the same. In the borate buffer, the solubility of hydrochlorothiazide is approximately 4 times as great as in the other media, and a faster dissolution would be expected (12, 20). This is experimentally verified by a shorter $t_{1/2}$ and $t_{2/3}$ for all formulations in the borate buffer.

As shown in Table I, the addition of 0.03% polysorbate 80 increased the total solubility of hydrochlorothiazide in all dissolution media. The critical micelle concentration (CMC) of polysorbate 80 is 0.01 and 0.03%, as determined by the surface tension and the

Table III—Disintegration and Dissolution of Hydrochlorothiazide Tablets Granulated with Starch Paste in Various Dissolution Media at 37°

Dissolution Medium	Disintegration Time, min.		Dissolution Time, min.			
		Average of	Method I[a]		Method II[b]	
	USP	Six Tablets	$t_{1/2}$	$t_{2/3}$	$t_{1/2}$	$t_{2/3}$
Distilled water	3.3	2.0	27.4	43.9	24.8	45.6
Distilled water with polysorbate 80[c]	3.3	2.3	23.2	40.0	22.5	44.0
0.1 *N* Hydrochloric acid	5.8	2.8	19.3	35.4	14.8	31.6
0.1 *N* Hydrochloric acid with polysorbate 80[c]	2.9	2.0	21.9	44.6	18.1	37.0
Intestinal fluid[d]	3.3	2.1	25.0	40.0	18.6	40.5
Intestinal fluid with polysorbate 80[c]	4.0	2.6	26.3	47.6	18.1	40.1
Borate buffer, pH 10	3.7	2.5	6.6	10.2	4.4	7.0
Borate buffer with polysorbate 80[c]	2.0	1.8	7.0	10.4	4.8	7.0

[a] USP method using 60 r.p.m. [b] NF Method II. [c] 0.03% polysorbate 80. [d] Simulated intestinal fluid USP without pancreatin.

Table IV—Disintegration and Dissolution of Hydrochlorothiazide Tablets Granulated with Polyvinylpyrrolidone in Various Dissolution Media at 37°

Dissolution Medium	Disintegration Time, min. USP	Disintegration Time, min. Average of Six Tablets	Dissolution Time, min. Method I[a] $t_{1/2}$	Dissolution Time, min. Method I[a] $t_{2/3}$	Dissolution Time, min. Method II[b] $t_{1/2}$	Dissolution Time, min. Method II[b] $t_{2/3}$
Distilled water	11.9	10.5	27.3	39.1	17.7	32.0
Distilled water with polysorbate 80[c]	13.1	10.9	28.5	41.2	16.8	27.7
0.1 *N* Hydrochloric acid	9.5	7.5	29.4	43.5	12.1	20.7
0.1 *N* Hydrochloric acid with polysorbate 80[c]	11.3	9.9	24.6	37.0	12.6	24.3
Intestinal fluid[d]	13.6	11.9	21.1	33.4	15.3	29.0
Intestinal fluid with polysorbate 80[c]	12.9	11.4	23.7	35.4	15.0	25.3
Borate buffer, pH 10	13.6	11.3	17.7	26.1	8.8	13.1
Borate buffer with polysorbate 80[c]	14.3	11.8	16.7	24.4	8.9	12.9

[a] USP method using 60 r.p.m. [b] NF Method II. [c] 0.03% polysorbate 80. [d] Simulated intestinal fluid USP without pancreatin.

solubility method, respectively (21). Thus, there is sufficient polysorbate 80 to solubilize some hydrochlorothiazide.

Inspection of Table II indicates a slight increase in dissolution of tablets granulated with acacia upon the addition of polysorbate 80 to the dissolution medium. As shown in Tables III and IV with tablets granulated with polyvinylpyrrolidone and starch, the addition of polysorbate 80 did not change the dissolution time. In this limited investigation, the addition of a wetting agent did not significantly affect the dissolution of hydrochlorothiazide from the three tablet formulations. This seems to indicate that the inclusion of a wetting agent in a routine dissolution test is questionable until further studies are made.

Schroeter *et al.* (22), in a study of the dissolution and disintegration times of 76 lots of tablets, demonstrated that there is an extreme specificity in the presence or absence of a relationship between the disintegration and dissolution times. Undoubtedly, there are occasions when the relationship between dissolution time and disintegration time is significant (23); however, in general it appears that one should not expect a correlation between disintegration and dissolution (24–27).

With the three formulations studied, there is no correlation between disintegration and dissolution. For example, in comparing tablets granulated with starch to those granulated with polyvinylpyrrolidone, it is seen that the disintegration of the tablet containing starch is approximately 3 times as fast as the tablet prepared with polyvinylpyrrolidone; yet the dissolution times are of the same magnitude. Conversely, the disintegration in borate buffer of tablets granulated with acacia and polyvinylpyrrolidone is approximately the same as in other media, but the dissolution is faster in the borate buffer than in any other medium studied.

Unquestionably, the tablet granulated with starch disintegrates most rapidly in distilled water, 0.1 *N* hydrochloric acid, and simulated intestinal fluid, and in these media to which 0.03% polysorbate 80 has been added; however, there is no difference in the dissolution time from the three formulations. In the borate buffer, both the disintegration and dissolution are more rapid for the tablet granulated with starch than in other media. Since the addition of polysorbate 80 to the borate buffer does not alter the dissolution time, polysorbate 80 appears in this instance to function as a wetting agent to hasten disintegration.

SUMMARY

1. The disintegration times of hydrochlorothiazide tablets granulated with acacia, polyvinylpyrrolidone, or starch were measured in distilled water, 0.1 *N* hydrochloric acid, simulated intestinal fluid, and a borate buffer at pH 10.

2. The addition of 0.03% polysorbate 80 to the dissolution media did not alter the disintegration time of the tablets, except for a more rapid disintegration in the borate buffer of the tablet granulated with starch.

3. The dissolution times of the three tablet formulations were the same in distilled water, 0.1 *N* hydrochloric acid, and simulated intestinal fluid, and they were faster in the borate buffer.

4. The addition of 0.03% polysorbate 80 to the dissolution media did not significantly alter the dissolution times of the tablets.

5. There was no correlation between the disintegration and dissolution times.

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