Method for Determining *In Vivo* Tablet Disintegration

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To prepare a tablet which disintegrated in about 30 min. in humans, it was necessary to develop a method which would measure disintegration time *in vivo* accurately. A summary is made of unsuccessful procedures which provided unreliable data: X-ray using tablets containing incorporated radiopaque, induction of vomiting at specific time intervals, etc. A method is presented involving X-ray visualization of tablets containing radiopaque pellets which provided reliable data. Results of studies in over 100 patients are reported, correlating *in vivo* with *in vitro* disintegration times. It is concluded that agitation in the stomach is of a low order of magnitude, producing substantially higher disintegration times *in vivo* than obtained using the U.S.P. *in vitro* apparatus.

PHARMACEUTICAL tablet products listed in the official compendia of the United States must disintegrate within certain specified time limits. The official procedure in this country is the U.S.P. XVI method (1). Although this test serves as one of the procedures to confirm that each lot of product replicates the original formula, it also is implied that exceeding the specified disintegration time may interfere substantially with drug availability.

Over the past 5 years, the pharmaceutical industry has made significant progress in the evaluation of drug availability. The skilled pharmaceutical scientist no longer relies on disintegration time as the only test of drug release. Where feasible, initial formulation work is accompanied by *in vitro* dissolution rate studies and confirmed later by *in vivo* blood level studies. These new techniques do not require evaluation of *in vivo* disintegration time since they measure the resultant availability of drug.

This laboratory was assigned development of a prolonged-release antacid tablet. The product concept required a tablet which would disintegrate completely in the stomach at about 30 min. The initial approach was to prepare a tablet, PX-328, which disintegrated in 30 to 40 min. by the U.S.P. method. Since the antacids used in this preparation provide no blood level, it was necessary to determine the *in vivo* disintegration time of this tablet to confirm the *in vitro* findings. The purpose of this paper is to report the studies and to evaluate whether this tablet did, in fact, disintegrate in the stomach at approximately 30 min.

EXPERIMENTAL

Yo-Yo Technique.—Using a high-power drill, a $^1/_{32}$-in. hole was drilled through the center of tablet PX-328, which disintegrated in 30 to 40 min. by the U.S.P. XVI procedure. A 3-ft. No. 50 cotton thread was affixed by knot to two tablets. Under medical supervision, volunteers swallowed the tablets, leaving the end of the string hanging free from the mouth. At varying time intervals, the tablets were pulled back and the degree of disintegration observed. In a total of 250 experiments, the data reported in Table I were obtained. These data would appear to indicate some correlation with the U.S.P. method results, with 26% of the tablets confirmed to be gone completely in 3 to 60 min. Subsequent data will indicate this formulation *did not* disintegrate in 2 hr. in the human stomach. The conclusion was that many tablets were lost from the string substantially before disintegration.

Induced Vomiting.—Under medical supervision, a panel of 12 volunteers were instructed to swallow a four-tablet dose of PX-328. At a specified time after ingestion of tablets, vomiting was induced. Each individual was induced at a different time spaced by 15-min. intervals. Recovered tablets were weighed to determine the extent of tablet dissolution. This method was dropped because most tablets were *not* regurgitated, even at early time intervals.

Direct Visualization.—Lachman *et al.* (2) evaluated the effectiveness of enteric coatings in dogs and humans using direct X-ray visualization of tablets. The tablet under the study reported here did not have sufficient opacity to allow for direct visualization by X-ray.

Weiss *et al.* (3) observed the state of disintegration of aspirin tablets using the gastroscope. The authors considered the fiberscope, which allows for

TABLE I.—DATA FOR PX-328 YO-YO TECHNIQUE

Condition of Tablet	Time, min. 3–7	15	30	45	60	90	Total
All gone	4	15	21	17	8	...	65
10–50% left	...	..	2	4	1	...	7
51–90% left	...	5	12	6	4	1	28
91–100% left	...	10	5	4	2	...	21
Tablet broken	...	4	4	5	6	...	19
Tablet stuck[a]	...	15	26	24	16	...	81
Intact tablet coated with mucus	...	7	5	9	8	...	29

[a] Volunteers were instructed to swallow the tablet and string if the tablet stuck in the throat during removal.

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TABLE II.—PX-328

Subject	Time, min.	Fiberscopic Observation
1	30 and 60	Tablet not dissolved
2	55	Tablet a homogeneous mass
3	75	No evidence of tablet
4	75	Tablet partially disintegrated
5	30	Tablet not dissolved
6	65	Tablet a homogeneous mass

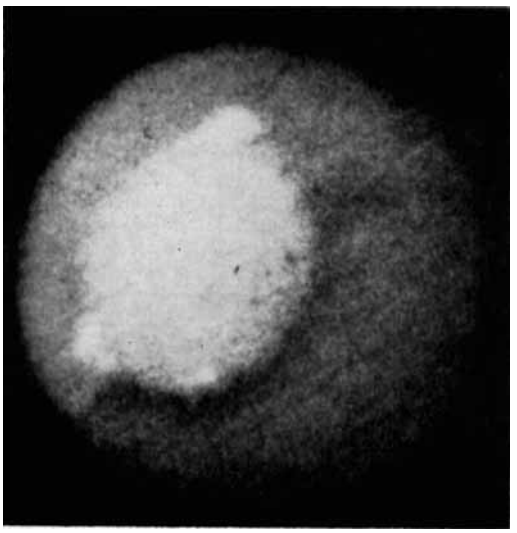

Fig. 1.—Single frame of color cinematographic photograph taken of tablet PX-328 inside the fasting stomach using the fiberscope. This photograph was taken 10 min. after ingestion of the tablet.

better and more complete visualization of the stomach, a more adaptable unit for the purpose. The fiberscope is an instrument devised by Hirschowitz (4), and consists essentially of a flexible tube containing 250,000 individual coated glass fibers which transport the image directly from the distal end to an ocular eye piece at the proximal end. A camera is attached readily to the eye piece, permitting color cinematography.

Six fasting subjects were evaluated by this technique using a one-tablet dose of PX-328. Visualization, using the fiberscope, was made at various time intervals. The data obtained are given in Table II.

Visualization of the tablet using the fiberscope was difficult. A rare example of good visualization is shown in Fig. 1. Because the fiberscope could not be left in place for prolonged periods, it was not possible to follow the tablet during its dissolution. The method requires an empty stomach which can influence the disintegration time. This is especially important because antacids are often taken soon after a meal. It was also concluded that as the tablet became smaller it might not be visualized, providing a false reading of disintegration.

Biosonar.—Biosonar is an instrument designed to measure small anatomical structures by sound wave deflection. This instrument was used in an attempt to follow tablet PX-328 by observing the pattern of sound wave deflection on an oscilloscope. After initial trials, it was concluded that the tablet could not be distinguished from competing sound deflectants (food, muscle, bone, etc.).

Inclusion of Radiopaque.—Lozinski and Diver (5) evaluated the effectiveness of enteric coatings by observing the disintegration of an enteric-coated barium sulfate tablet in humans using the fluoroscope. Bukey and Bliven (6), using barium sulfate tablets, similarly evaluated enteric coatings in humans employing X-ray. Wagner *et al.* (7) reported the use of X-ray in evaluating enteric-coated barium sulfate tablets in dogs. Levy (8) reports the use of barium sulfate tablets in evaluating agitation intensities in the human stomach by X-ray. All of these investigators used tablets made entirely of barium sulfate.

In these studies, amounts of barium sulfate ranging from 15 to 75 mg. per tablet of PX-328 were incorporated. Visualization of these tablets, even initially, was difficult, even for expert radiologists. Each patient swallowed two tablets, and serial roentgenograms were made at 1, 15, 30, 45, 60, 90, and 120 min. A number of tablets could not be visualized, even at 1 min. Tablets lost at early time intervals were often rediscovered at later time periods. The conclusion was that the method was unsatisfactory since it encouraged subjective interpretation of the X-ray films, since good visualiza-

Fig. 2.—X-Ray plate of PX-411 tablet in human stomach at 1 min.

Fig. 3.—X-Ray plate of PX-411 tablet in human stomach at 15 min.

Fig. 4.—X-Ray plate of PX-411 tablet in human stomach at 35 min.

Fig. 5.—X-Ray plate of PX-411 tablet in human stomach at 45 min.

Fig. 6.—X-Ray plate of PX-411 tablet in human stomach at 60 min.

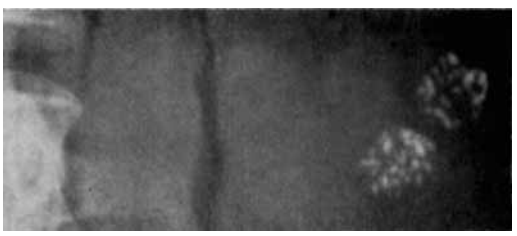

Fig. 7.—X-Ray plate of PX-411 tablet in human stomach at 90 min.

Fig. 8.—X-Ray plate of PX-411 tablet in human stomach at 120 min.

tion of a tablet was rare. It was also apparent that, as the tablet disintegrated, it became harder to visualize.

Barium Sulfate Pellet Technique.—The method that finally proved satisfactory was achieved by the use of barium sulfate pellets included within the tablet to improve visualization. Feinblatt and Ferguson (9) report the use of barium sulfate pellets coated with sustained-release agents to measure the effectiveness of sustained-release capsules.

The pellets used in this work were prepared by the following procedure. Prepare a 2% (w/v) solution of 15 cps. methylcellulose. Place 997.5 Gm. of barium sulfate into a Hobart mixer equipped with a modified wire whip. Add 125 ml. of the methylcellulose solution very slowly while mixing. Mix at moderate speed for 30 to 45 min. Tumble in a warm coating pan for 30 min. Spread thinly on trays, and dry in an oven overnight at 50°. Use only the dry 20- to 30-mesh particles obtained by screening.

The pellets were mixed with the tablet granulation and the final granulation compressed to the hardness specified for the tablet. The tablets used, PX-411, disintegrated in from 29 to 34.5 min. by the U.S.P. XVI method. This formulation represented PX-328 containing 45 mg. of pellets. Serial roentgenograms were taken using a two-tablet dose in 25 patients. Evaluation of the X-ray films showed that all tablets were still present after 2 hr. No diminution in tablet size was noted, indicating that the disintegration time was probably substantially in excess of 2 hr. The subjects used alternately represented full and empty stomachs to evaluate range of disintegration during the day. Visualization was excellent, enabling objective interpretations by trained or untrained observers. A representative sequence of X-ray films for one subject appears in Figs. 2–8.

In an attempt to reduce the disintegration time, a series of three tablet formulations were prepared in which varying amounts of starch and sodium lauryl sulfate were added, as indicated in Table III. Dis-

Table III.—Three Tablet Formulations

Ingredients	Amt., mg. PX-469	PX-472	PX-473
Tablet base	355	355	355
Starch, purity No. 21 National starch	20	25	30
Sodium lauryl sulfate	5	5	5
Barium sulfate pellets	45	45	45
Tablet wt.	425	430	435

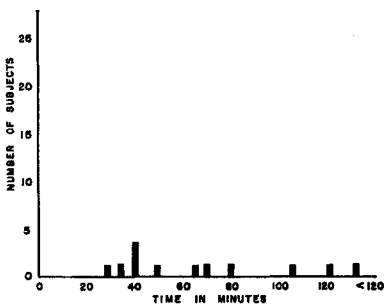

Fig. 9.—PX-469. Distribution pattern of disintegration times for 12 subjects. U.S.P. XVI *in vitro* disintegration = $18^1/_6$ min.; average = 66 min. *in vivo*.

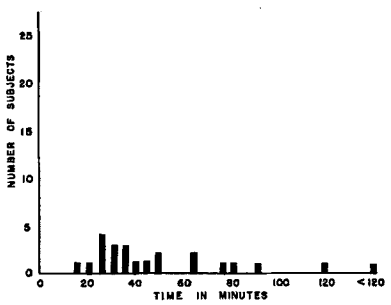

Fig. 10.—PX-472. Distribution pattern of disintegration times for 23 subjects. U.S.P. XVI *in vitro* disintegration = 15 min.; average = 50 min. *in vivo*.

Fig. 11.—X-Ray plate of PX-473 tablet in human stomach at 1 min.

Fig. 12.—X-Ray plate of PX-473 tablet in human stomach at 15 min.

Fig. 13.—X-Ray plate of PX-473 tablet in human stomach at 25 min.

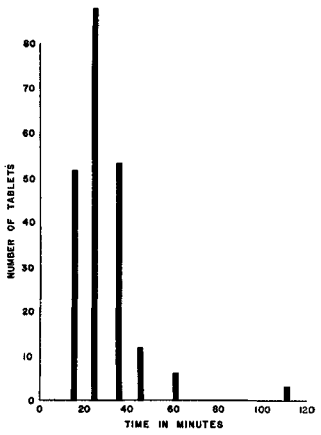

Fig. 14.—PX-473. Distribution pattern of complete disintegration times for both tablets using 216 tablets; average = 29.2 min.

integration times were determined by the U.S.P. XVI method and found to average: PX-469, 18.16 min.; PX-472, 15 min.; PX-473, 10.25 min.

By the barium pellet procedure in 12 patients formula PX-469 required an average time of 66 min. to disintegrate *in vivo*, as represented in Fig. 9. Formula PX-472 averaged 50-min. disintegration *in vivo*, as indicated in Fig. 10. Both formulations were considered unsuitable for the purpose because their *in vivo* disintegration was above 30 min.

Formula PX-473 was considered in detail because early roentgenograms indicated an *in vivo* disintegration time near 30 min. This product was evaluated in 108 different normal human volunteers; the 53 males and 55 females ranged in age from 13 to 68 years, with an average age of 31 years. Each subject swallowed a two-tablet dose.

Of the 108 subjects, 89 swallowed the tablets with 1 oz. of water in a nonfasting state. Nonfasting was defined as 0.5 to 3 hr. after the previous meal. The remaining 19 subjects fasted for 4 to 6 hr. prior to the two-tablet administration with 1 oz. of water. Serial roentgenograms were taken of each individual at 1, 15, 25, 35, 45, 60, 90, and 120 min. following ingestion of the tablets. All subjects pursued normal activities during this 2-hr. period. The patients remained in a supine position only for short intervals while being X-rayed. The technique employed is illustrated by the X-rays shown in Figs. 11 to 13. All X-ray films were read in a dry state first by a team of pharmaceutical and clinical research scientists, then independently by a Board Certified Radiologist.

Table IV summarizes all disintegration time data obtained on PX-473 by subject. Since only intermittent serial roentgenograms were taken, it was not possible to pinpoint the exact disintegration time in every case. The end point for complete disintegration was taken as the first plate in which no intact tablet could be seen.

Figure 14 shows the distribution of complete disintegration for all tablets taken; the average disintegration time is 29.2 min.

Figure 15 shows the distribution of complete disintegration for all tablets ingested in a fasting state. The average disintegration time is 26.8 min.

Figure 16 shows the distribution pattern of complete disintegration for all tablets ingested in a nonfasting state; the average disintegration time is 29.9 min.

Figure 17 shows the distribution pattern of complete disintegration for all tablets ingested in a nonfasting state. The average disintegration time is 29.9 min. It also shows the distribution pattern of complete disintegration by subject; the average disintegration time is 28.9 min.

DISCUSSION AND CONCLUSIONS

The majority of tablets listed in U.S.P. XVI have a disintegration time specification of not more than 30 min. *in vitro*. Tablet PX-328 was at the maximum part of this specification. By the barium pellet procedure, this tablet was found actually to be undisintegrated *in vivo* after 2 hr. Although the authors did not evaluate this tablet for longer periods, its size at the end of 2 hr. and the absence of free-flowing barium pellets indicated that complete disintegration was probably markedly in excess of 2 hr. (Table V).

TABLE IV.—TABLET DISINTEGRATION *In Vivo* TIMES OF PX-473 FOR 108 SUBJECTS

Subject	First Tablet Completely Disintegrated, min.	Second Tablet Completely Disintegrated, min.	Av. Disintegration Time of Both Tablets, min.	Subject	First Tablet Completely Disintegrated, min.	Second Tablet Completely Disintegrated, min.	Av. Disintegration Time of Both Tablets, min.
1	35	35	35	55	25	25	25
2	35	45	40	56	15	15	15
3	25	25	25	57	25	25	25
4	35	35	35	58	15	15	15
5	35	35	35	59	25	35	30
6	25	45	35	60	15	15	15
7	15	25	20	61	15	15	15
8	15	25	25	62	25	35	30
9	15	35	25	63	25	35	30
10	15	35	25	64	15	25	20
11	15	25	20	65	25	35	25
12	15	25	20	66	35	60	45
13	15	25	20	67	25	35	30
14	15	25	20	68	15	35	25
15	15	35	25	69	25	35	30
16	35	35	35	70	25	25	25
17	15	60	35	71	15	35	25
18	35	60	45	72	25	45	35
19	35	35	35	73	25	35	30
20	25	35	30	74	25	25	25
21	15	35	25	75	25	25	25
22	15	25	20	76	15	15	15
23	15	60	30	77	25	60	40
24	35	45	40	78	120	120	120
25	15	35	25	79	25	35	30
26	15	15	15	80	25	25	25
27	120	120	120	81	25	35	30
28	25	35	30	82	25	35	30
29	25	25	25	83	15	25	20
30	15	35	25	84	15	45	25
31	15	15	15	85	25	35	30
32	15	15	15	86	35	45	40
33	35	35	35	87	35	35	35
34	25	25	25	88	15	35	25
35	25	25	25	89	15	35	25
36	25	25	25	90	25	25	25
37	25	35	30	91	25	25	25
38	15	25	20	92	25	35	30
39	25	25	25	93	25	35	30
40	15	25	20	94	15	60	35
41	25	35	30	95	15	15	15
42	25	35	30	96	25	25	25
43	25	45	35	97	25	25	25
44	45	45	45	98	25	35	30
45	35	35	35	99	25	60	40
46	25	35	30	100	25	45	35
47	25	25	25	101	25	25	25
48	25	25	25	102	25	25	25
49	15	25	20	103	25	25	25
50	25	25	25	104	25	35	30
51	15	25	20	105	15	25	20
52	15	25	20	106	15	15	15
53	45	45	45	107	15	35	25
54	25	35	30	108	25	25	25

It is conceivable that many U.S.P. tablets meeting official requirements would similarly not disintegrate in humans for hours. Evaluation of thousands of X-rays in this study left the authors with the impression that agitation conditions in the stomach are of a very low order of magnitude—substantially less than the vigorous action obtained using the current official *in vitro* disintegration procedure. It was apparent in the majority of X-rays that the two tablets ingested remained close together most of the time. It was also noted that the position of the tablets remained often unchanged for long periods.

The conclusions regarding the low degree of agitation in the stomach are in agreement with Levy (8). Similarly, the authors agree with Levy (8) that mild agitation conditions should be employed for predictive *in vitro* dissolution tests.

It is interesting that the PX-328 formula which took 30 to 40 min. to disintegrate with disks by the current official U.S.P. XVI procedure required 4.5 hr. to disintegrate by the U.S.P. XV method (10) without disks. Although the use of disks increases the reproducibility of the disintegration time method, it also increases the disintegration of the tablet, providing data which the authors found were

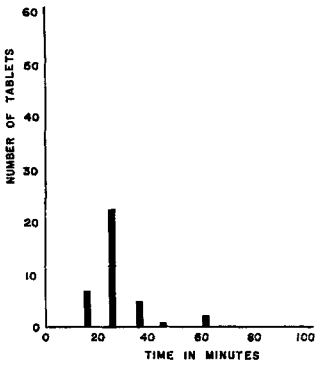

Fig. 15.—PX-473. Distribution pattern of complete disintegration times of both tablets in fasting state using 38 tablets; average = 26.8 min.

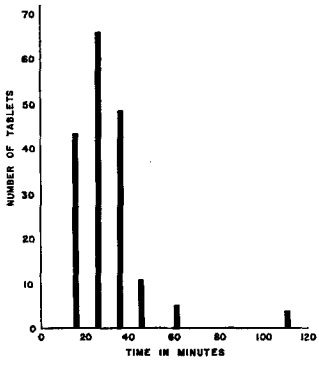

Fig. 16.—PX-473. Distribution pattern of complete disintegration times of both tablets in a nonfasting state using 178 tablets; average = 29.9 min.

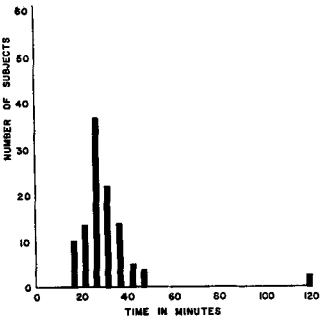

Fig. 17.—PX-473. Distribution pattern of average disintegration time of both tablets using 108 subjects; average = 28.9 min.

TABLE V.—AVERAGE DISINTEGRATION TIMES FOR FORMULATIONS

Formulation	Av. Disintegration Time, min. U.S.P. XVI *In Vitro*	Barium Pellet Method *In Vivo*
PX-328 (411)	30–40	More than 120
PX-469	18.1625	66
PX-472	15	50
PX-473	10.25	28.9

not in agreement with actual disintegration times *in vivo*.

The barium sulfate pellet procedure provides a method of correlating the *in vitro* disintegration time as determined by the official procedure with the actual disintegration time in humans. The technique is simple and should be adaptable to most compressed tablets. Using this procedure, the authors were able to gain insight into gastric agitation conditions and to complete the assignment to prepare a tablet which disintegrated in 30 min. in humans.

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