Relationship Between Rate of Dissolution, Disintegration Time, and Physiological Availability of Riboflavin in Sugar-Coated Tablets

By E. J. MIDDLETON, J. M. DAVIES, and A. B. MORRISON

Studies were conducted on the relationship between dissolution rate, disintegration time, and physiological availability of seven sugar-coated multivitamin products. Dissolution rates and disintegration times were determined with the U.S.P. disintegration apparatus. A close relationship was found between *in vitro* disintegration time and the dissolution rate ($T_{50\ per\ cent}$) of riboflavin for the various products. Both procedures correlated reasonably well with physiological availability as measured by urinary riboflavin excretion. It was concluded that either *in vitro* disintegration time or dissolution rate can provide a useful estimate of the availability to the body of riboflavin in sugar-coated tablets.

PREVIOUS STUDIES from this laboratory (1–3) demonstrated that sugar-coated tablets which did not disintegrate in 1 hour by a specified *in vitro* test were not fully available to the body, judged by urinary excretion of riboflavin or *p*-aminosalicylate. Morrison *et al.* (4) concluded that measurement of riboflavin excretion provided a valid indication of physiological availability of vitamin preparations, and that limits for *in vitro* disintegration time based on riboflavin excretion were applicable to other water-soluble vitamins.

The validity of the relationship between disintegration time and physiological availability has been questioned recently. Levy (5) showed that disintegration times for five acetylsalicylic acid tablets were not correlated with the rate of absorption or biological availability of the drug in humans. He noted, however, a direct relationship between the rate at which the tablets went into solution (the dissolution rate) and the amount of salicylate excreted in the urine. Campagna *et al.* (6) reported that the disintegration time for prednisone tablets was not a valid indicator of the availability of this drug to the body. Schroeter *et al.* (7) examined relationships between rate of dissolution and disintegration time for tablets containing an anti-inflammatory steroid, sulfonamide, antidiabetic agent, acetylsalicylic acid-phenacetin-caffeine, or sodium *p*-aminosalicylate. They concluded there was a specificity in the presence or absence of a relationship between rate of dissolution and disintegration time and questioned the validity of uniform disintegration time limits applied to large groups of drugs in compressed tablets.

The experiments described here were conducted to study relationships between *in vitro* disintegration time, dissolution rate, and physiological availability of riboflavin in sugar-coated multivitamin products. The results indicated that either of the two *in vitro* methods can provide a valid indication of availability of riboflavin to the body.

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METHODS

In Vitro Disintegration Times and Dissolution Rates.—The apparatus and fluids described in U.S.P. XVI (8) were used to determine disintegration time. The tablets were immersed for 30 minutes in simulated gastric fluid and the remainder of the time in simulated intestinal fluid. Disintegration times reported were mean values for at least two separate tests on six tablets each.

Without stopping the agitation of the disintegration apparatus, aliquots of the simulated digestive fluids were withdrawn at various time intervals using pipets wound with glass wool at their tips. The aliquots were then analyzed for riboflavin by the U.S.P. XVI fluorometric procedure (8).

Physiological Availability.—The method used to determine physiological availability of riboflavin was essentially that of Melnick *et al.* (9). Seven sugar-coated multivitamin products were tested. Five normal males known to be receiving nutritionally adequate diets were used in the experiment. While on test, they consumed regulated meals containing a relatively constant amount of riboflavin. The subjects were given 6 mg. of riboflavin in a gelatin capsule as the standard and 2–10 mg. of riboflavin as commercial preparations. A single level of standard was chosen because of previous findings that riboflavin excretion expressed as percentage of the dose was linearly related to doses up to 20 mg. (10). The doses were taken at 8:30 a.m. after breakfast. Urine was collected in opaque bottles containing 2 ml. of 3.5 N H_2SO_4 at 2, 4, 6, 8, 14, and 24-hour intervals after dosing. Riboflavin in urine was determined by U.S.P. XVI fluorometric procedure (8). Excretion values were corrected by subtracting the appropriate blank determined on the same individuals without dosing. As in previous studies (1–3), physiological availability was calculated as

$$\% \text{ Physiological Availability} = \frac{\% \text{ Excretion From Preparation}}{\% \text{ Excretion From Standard}} \times 100$$

TABLE I.—DESCRIPTION OF TABLETS STUDIED

Sample	Medication	Labelled Riboflavin Content/Unit, mg.	Riboflavin Unit Found, mg.	*In Vitro* Disintegration Time, Min.	*In Vitro* Dissolution Rate $T_{50\%}$, Min.	Physiological Availability, %
A	Multivitamin and minerals	3	3	151	114	58 ± 10[a]
B	Multivitamin and minerals	10	10	45	25	87 ± 4
C	Multivitamin	6	6	101	83	36 ± 10
D	Multivitamin and minerals	3	3	45	38	88 ± 11
E	Multivitamin	10	11	20	11	94 ± 7
F	Multivitamin and minerals	3	3	98	124	12 ± 5
G	Multivitamin	2	2	20	11	98 ± 5

[a] Standard error of the mean.

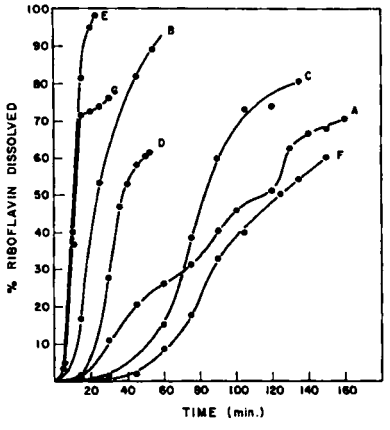

Fig. 1.—*In vitro* dissolution curves of products A to G plotted as per cent riboflavin dissolved in simulated gastrointestinal fluids against time in minutes.

RESULTS

Data describing the products used are shown in Table I. All products contained vitamins; products A, B, D, and F also contained minerals. *In vitro* disintegration times varied from 20 minutes (products E and G) to 151 minutes (product A). *In vitro* dissolution rates were expressed as the time for 50% of the riboflavin to be dissolved in simulated digestive fluids ($T_{50\%}$). Dissolution curves are given in Fig. 1. The $T_{50\%}$ values varied from 11 minutes (products E and G) to 124 minutes (product F).

The relationship between dissolution rate ($T_{50\%}$) and disintegration time is shown in Fig. 2. A significant relationship was found (r = 0.923). Product F, which was only partially available to the body, had a longer dissolution rate than would have been predicted from the disintegration time, suggesting that the product disintegrated but did not go into solution.

Results of the physiological availability studies also are summarized in Table I, and the relationship between disintegration time and physiological availability is illustrated in Fig. 3. Products A, C, and F, which did not disintegrate within 60 minutes *in vitro*, were not fully available to the body.

Products C and F gave lower physiological availability values than predicted from their *in vitro* disintegration times.

A significant relationship (r = 0.906) was observed between dissolution rate ($T_{50\%}$) and physiological availability (Fig. 4). Tablets F and C, however, which displayed abnormal disintegration times gave results quite different from those of the other products tested.

DISCUSSION

The results of these studies confirm the previously established relationship between *in vitro* disintegration time and physiological availability. Tablets which did not disintegrate within 60 minutes (30 minutes in simulated gastric juice and 30 minutes in simulated intestinal juice) were not fully available to the body. Similarly, tablets with $T_{50\%}$ values of greater than 60 minutes were not fully available.

It is of interest that two products gave results for disintegration time and dissolution rate which did not correlate closely with physiological availability. This discrepancy may be related, in part, to the fact that these tablets formed a viscous mass in the simulated digestive fluids, making it difficult to determine disintegration time accurately. It is possible also that the *in vivo* availability of riboflavin in these products may have been lower than expected be-

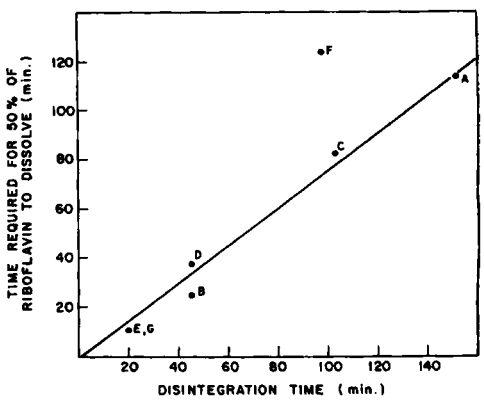

Fig. 2.—Correlation of time required for 50% of riboflavin to dissolve in simulated gastrointestinal fluids with disintegration time for products A to G.

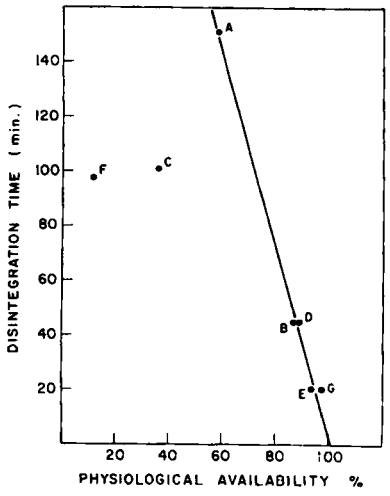

Fig. 3.—Relationship between disintegration time for products A to G and physiological availability of the products measured by urinary riboflavin excretion data.

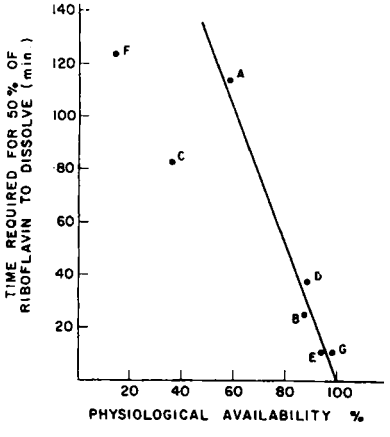

Fig. 4.—Correlation between time required for 50% of the riboflavin from products A to G to dissolve in simulated gastrointestinal fluids with physiological availability of the products measured by urinary riboflavin excretion data.

cause the vitamin was bound or adsorbed to tablet excipients and hence rendered partially unavailable. For example, it is well known that thiamine bound to Fuller's earth is only partially available to man (11).

A close relationship was found between *in vitro* disintegration time and dissolution rate ($T_{50\%}$) values. Results obtained by both *in vitro* procedures correlated reasonably well with those for physiological availability. The relationship between $T_{50\%}$ values and physiological availability was particularly good. This finding indicates that the rate of solution of riboflavin from sugar-coated tablets is an important factor in determining *in vivo* availability of the vitamin. From other studies (12) it is known that riboflavin is absorbed mainly from the upper part of the small intestine. Therefore, it would appear likely that tablets from which riboflavin dissolves only slowly may be beyond the portion of the gut in which efficient absorption can take place before dissolution occurs, and hence show reduced availability of riboflavin.

The results indicate that *in vitro* disintegration time provides a valid indication of the rate at which riboflavin goes into solution from sugar-coated tablets. Thus, either *in vitro* disintegration time or dissolution rate can provide a useful estimate of the availability to the body of riboflavin in sugar-coated tablets. For other drugs disintegration time and dissolution rate may not be so closely related (5, 6). There is a need for further studies on methods for determining dissolution rate and on the relationship between dissolution rate and physiological availability.

Previous studies have shown that limits for *in vitro* disintegration time based on riboflavin also are applicable to other water-soluble vitamins. Therefore, it would be expected that the rate of solution of riboflavin would provide useful information about the availability of other water soluble vitamins to the body. Studies now are underway to investigate this possibility. Relationships between *in vitro* disintegration time and dissolution rate for enteric coated tablets with varying degrees of *in vivo* availability also are being investigated.

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