Correlation Between the Disintegration Time and the Bioavailability of Vitamin C Tablets

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The goal of this study was to examine if the current USP disintegration standard for vitamin C tablets (max. 30 min in water at 37°C with disks) is adequate or if a tighter disintegration standard (e.g., European compendia max. 15 min) should be recommended based on bioavailability considerations. Four formulations of 500-mg vitamin C tablets ranging in mean disintegration time from 9 to 120 min were compared with a standard vitamin C solution in a double-blind clinical trial with 15 subjects. The products were administered with a standard breakfast. The data show that a solution of vitamin C and a fast-disintegrating tablet (8–9 min) have equal but significantly lower bioavailability than tablets with longer disintegration times (30, 60, 120 min). Tablets with a mean disintegration time of 60 min showed the highest bioavailability. When the disintegration test was performed *without* disks, disintegration times increased so much that only the tablets with the fastest disintegration time (which were also the tablets with the lowest bioavailability) met the current USP disintegration time limit. Based on the results of the study, changes in the USP standard to omit the disks or to shorten the disintegration time will not achieve enhanced bioavailability but will result in reduced vitamin C absorption. *In vitro* dissolution of vitamin C tablets did not show the traditional relationship with bioavailability.

KEY WORDS: vitamin C; ascorbic acid; disintegration; dissolution; bioavailability.

INTRODUCTION

Recent issues concerning quality standards for nutritional supplements led us to examine the relationship of disintegration time (with and without disks) of vitamin C tablets and their dissolution rate on bioavailability in human subjects. Vitamin C was chosen as an example of a water-soluble vitamin, where a compendial disintegration test is thought to be an adequate measure of quality. The current USP disintegration standard for ascorbic acid tablets calls for a maximum of 30 min in water at 37°C using disks. European compendia (e.g., British Pharmacopeia and European Pharmacopeia) allow a maximum of only 15 min.

While there are a few reports in the literature on plasma levels and/or urinary excretion of vitamin C in relation to oral ingestion of plain or sustained-release vitamin C tablets (1–5), there are no studies correlating human bioavailability in terms of plasma vitamin C response with the disintegration time of tablets.

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MATERIALS AND METHODS

Subjects

Fifteen healthy male subjects (20–40 years) were selected for the study. Informed consent was obtained from all the volunteers participating in this study. Exclusion criteria included smoking, alcohol, and drug usage (prescription and OTC including aspirin). Only those subjects having normal fasting plasma vitamin C levels within a narrow range (0.40–0.80 mg/dL) were chosen in order to minimize individual variability.

Vitamin C Formulations

Four formulations of 500-mg vitamin C tablets with disintegration times (with disks) of 8–9, 27–28, 57–60, and 121–124 min (Table I) were prepared by direct compression. All formulations contained the same lot of C-90™ (vitamin C—90% granulation, containing 90% L-ascorbic acid, starch, and lactose; Hoffmann-La Roche) and the same excipients (Avicel PH 102, stearic acid, and magnesium stearate) coming from the same lots. The variation in disintegration time was achieved by varying the amounts of excipients used and the hardness of the tablets (Table II).

The tablets were tested for disintegration time by two independent laboratories using the USP method. The disintegration time was also determined without using disks (Table I). In addition, the formulations were tested for dissolution in the USP dissolution apparatus (using the basket at 100 rpm and the paddle at 50 rpm) in 0.01 *M* phosphate buffer, pH 3.2/37°C, by a spectrophotometric assay with absorbance at 250 nm (Table III).

The tablets were assayed for ascorbic acid content and the results of the four tablet formulations are summarized in Table II.

Bioavailability Study

This was a randomized double-blind crossover study conducted at the New York Medical College, Our Lady of Mercy Medical Center, Bronx. The subjects were randomly assigned to receive one of the four vitamin C formulations listed in Table II or a solution of 500 mg of ascorbic acid in 100 mL of distilled water as a reference standard. Following an overnight fast, the subjects voided their urine first, provided a fasting baseline blood sample, and then ingested 500 mg of one of the five vitamin C products with 100 mL of distilled water. Within 1–2 min following ingestion of vitamin C, the subjects were given a standard FDA breakfast consisting of two fried eggs, two slices of buttered toast, two strips of bacon, and 8 oz of whole milk. Lunch was served to all subjects 6 hr after dosing. The standard lunch consisted of half a fried chicken breast, mashed potatoes with butter, two rolls with butter, and 8 oz of whole milk. Snacking foods (biscuits, coffee/tea or milk, chocolates) were provided to all subjects at 4, 8, and 10 hr after dosing.

Plasma samples collected at 0, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hr were deproteinized immediately with an equal volume of 10% freshly prepared metaphosphoric acid, and the supernatant was frozen (−70°C) until analyzed for total ascorbate by a spectrophotometric method (6). This

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Table I. Disintegration Time of Vitamin C Tablets

USP test (37°C/water)	Disintegration time (min) for formulation A	B	C	D
With disks				
Lab I	9 (5–11)	27 (24–27)	60 (58–62)	121 (108–134)
Lab II	8 (8–8)	28 (27–29)	57 (57–58)	124 (113–141)
Without disks	9	51	>3.5 hr	>5 hr

method is well accepted and the results obtained are comparable to those generated by HPLC methodology. Urine was also collected during this period (pooled 0–12 hr) for ascorbate analysis and for calculating renal clearance. After each test, a washout period of at least 2 weeks was allowed prior to the next test. This assured each subject receiving all of the five products during the course of the five test periods.

The area under the plasma concentration–time curve (AUC) was calculated from 0 to 12 hr using the trapezoidal rule after subtracting the corresponding baseline values. The values were adjusted, based on actual assay results (Table II), to the standard intake of 500 mg ascorbic acid. The statistical analysis of the data was performed using ANOVA and GLM procedures for crossover measurements in SAS.

RESULTS

The disintegration times (Table I) for the four formulations *with* disks were as follows: A, 8–9 min; B, 27–28 min; C, 57–60 min; and D, 121–124 min. The respective disintegration times without disks were, with the exception of formulation A, considerably longer. The average disintegration times *without* disks were as follows: A, 9 min; B, 51 min; C, >3.5 hr; D, >5 hr (Table I).

From the dissolution data (USP paddle and basket) in Table III, it can be seen that 75% of the vitamin C was dissolved in 8.5 min in Formulation A, in 1.5 hr in Formulation B, in 4.5 hr in Formulation C, and in 6 hr in Formulation D.

Table II. Composition, Hardness and Content of Vitamin C Tablets

	Formulation (mg) A	B	C	D
Ingredients				
C-90™, Roche	583	583	583	583
Avicel PH 102	100	24	24	7
Stearic acid	6	6	75	130
Magnesium stearate	1	1	5	9
Total tablet weight	690	614	687	729
Hardness (SCU)	9 (7–11)	12 (11–14)	25 (23–28)	24 (23–25)
Ascorbic acid content (mg)	524 (517–531)	516 (511–521)	522 (518–526)	516 (511–520)

Table III. Dissolution Time of Vitamin C Tablets

	Dissolution time (0.01 *M* phosphate buffer, pH 3.2/37°C; USP paddle, 50 rpm; USP basket, 100 rpm for formulation A	B	C	D
25% dissolved	4 min (3–5)	15 min (12–25)	30 min (25–40)	30 min (20–40)
50% dissolved	6 min (5–7)	60 min (45–65)	2 hr (1.5–2.2)	2.5 hr (2–3)
75% dissolved	**8.5 min** (7–10)	**1.5 hr** (1.25–1.45)	**4.5 hr** (4–5)	**6 hr** (5.25–6.5)
100% dissolved	11 min (10–12)	2 hr (1.45–2.2)	6 hr (85%) (5.5–6.5)	8 hr (82%) (7.0–8.5)

The results (Table IV) show that the vitamin C solution and the tablet with a disintegration time (with disks) of 8–9 min (Formulation A) have the same bioavailability based on AUC, whereas tablets with disintegration times of 27–28 min (Formulation B), 57–60 min (Formulation C), and 121–124 min (Formulation D) have a significantly higher bioavailability. Vitamin C tablets with a disintegration time of 57–60 min (Formulation C) showed the highest bioavailability.

Figure 1 shows the plasma vitamin C concentration as a function of time for the five products. For both the solution and Formulation A (the tablet with a disintegration time of 8–9 min), the time to peak T_{max} was 1.5 hr. With increasing disintegration time, this peak shifted to the right; T_{max} was 3 hr for Formulation B (27–28 min) and 4 hr for both Formulation C (57–60 min) and Formulation D (121–124 min). The data as well as the corresponding values for maximum plasma concentration (C_{max}) are shown in Table IV.

Urinary excretion of vitamin C and calculated average renal clearance (Table V) did not reveal any significant difference between any of the five products tested ($P = 0.24$).

DISCUSSION

The results of this study demonstrated that vitamin C tablets with a longer disintegration time (30 min to 2 hr) had a higher bioavailability than the standard solution or a tablet with a rapid disintegration time (8–9 min). This is rather

Table IV. Plasma Pharmakokinetic Parameters of Vitamin C

Formulation	Bioavailability AUC (0–12 hr), mean ± SD (mg/dL) × (hr)	T_{max} (hr)	C_{max} (mg/dL)
Vitamin C solution	3.20 ± 0.75	1.5	1.38
A	2.87 ± 0.55	1.5	1.35
B	4.45 ± 0.90*	3.0	1.41
C	5.86 ± 0.83*	4.0	1.58
D	4.23 ± 0.93*	4.0	1.26

* Significantly different from the solution standard or Formulation A (10-min disintegration time) at $P < 0.0001$.

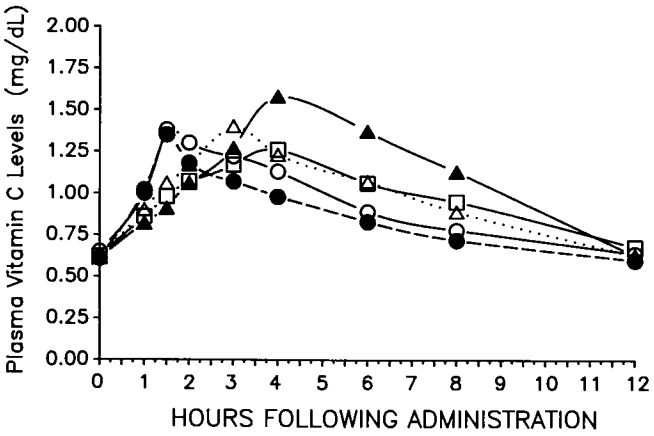

Fig. 1. Mean plasma vitamin C levels following administration of 500 mg of ascorbic acid: (○——○) vitamin C solution; (●——●) Formulation A; (△ · · · · · △) Formulation B; (▲——▲) Formulation C; (□——□) Formulation D.

Table V. Urinary Excretion of Vitamin C

Formulation	Mean ± SD	
	mg/12 hr	Renal clearance[a]
Standard solution	208.95 ± 91.45	69.32 ± 35.69
A	253.54 ± 104.01	91.85 ± 42.28
B	234.17 ± 87.09	53.86 ± 19.18
C	221.65 ± 124.68	38.07 ± 21.28
D	265.83 ± 74.77	64.09 ± 17.32

[a] Urinary vitamin C (mg/12 hr)/plasma AUC in 12 hr

unexpected, since it is generally assumed that a compound in solution is more rapidly absorbed.

Figure 2 shows the relationship between bioavailability as expressed as area under the curve (AUC) and disintegration time with disks. The bell-shaped curve peaks at a disintegration time of 60 min (with disks). At that point the T_{max} for plasma vitamin C levels was 4 hr, as opposed to 1.5 hr for the solution and formulation A (8–9 min DT).

Ascorbic acid is absorbed by a special process, involving both passive diffusion and a saturable active transport at several sites along the small intestine (8). The latter is presumed to involve both sodium-dependent and carrier-mediated processes. The efficiency of absorption depends on the timing of the delivery and the degree of saturation of the transport mechanism. Prolonged contact time at the absorption sites and a lower degree of saturation are known to increase the absorption efficiency of nutrients. For instance, Levy and Jusko (7) have shown that riboflavin was better absorbed with a meal, because of the longer contact with the absorption sites with the slower transit time.

Since vitamin supplements are generally taken with food—approximately 70% of vitamin users take them with food (9)—in this study, all formulations were taken with standard meals. Because of its acidic nature, vitamin C is generally taken with meals in order to minimize gastric discomfort. It is possible that the degree of saturation of the transport mechanism at the absorption sites achieved with the five products may have been different. This would imply that the solution and the fast-disintegrating tablets were not able to maintain the same concentration and contact time at the absorption sites as the longer-disintegrating tablets. It is possible that the formulations with longer disintegration times were able to provide a prolonged contact time with the absorption sites as well as contributing to a lower degree of saturation of the transport mechanism.

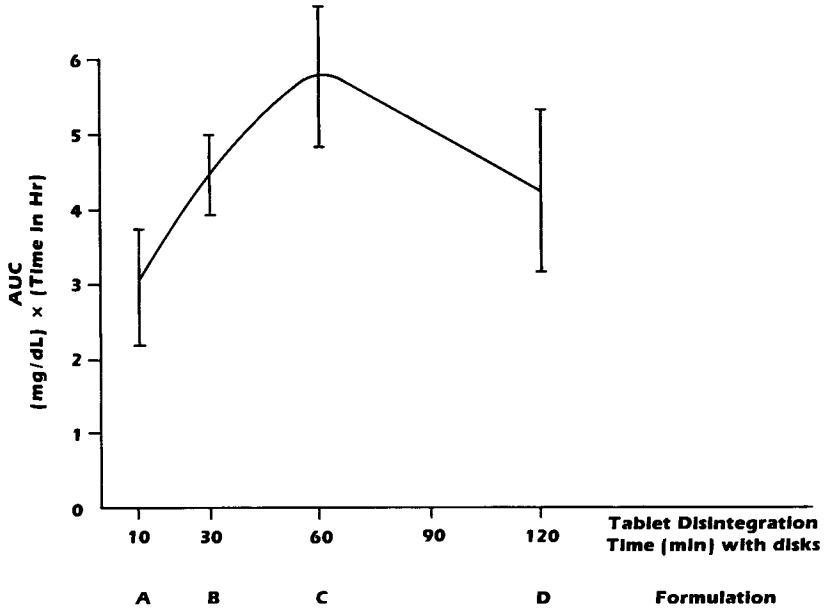

Fig. 2. Disintegration time of vitamin C tablets (500 mg) with disks vs bioavailability.

In this study each subject served as his own control. Subjects were selected on the basis of their vitamin C status (within a narrow range of normal plasma values) so as to minimize individual variability. This is reflected in the small standard deviation at each data point.

Although urinary excretion data have been employed in previous studies to assess bioavailability, we have found no correlation between disintegration or dissolution of vitamin C tablets and 0- to 12-hr urinary excretion. Despite carefully controlling for various factors influencing bioavailability, urinary excretion was found to be highly variable as evidenced by the standard deviations. Since the urinary collection was not extended to 24 hr, we cannot draw a firm conclusion as to the usefulness of urinary vitamin C data to assess bioavailability of vitamin C.

The data suggest that the current USP disintegration standard for vitamin C tablets (max. 30 min in water, 37°C, with disks—Formulation B) is not optimal, since it allows only a maximum of 76% relative bioavailability compared to Formulation C (Fig. 3). Omission of the disks would further decrease this value. The European standard of a 15-min disintegration time limits the bioavailability even more (max. 49% relative bioavailability; Fig. 3). A disintegration specification of 30–90 min with disks would optimize bioavailability.

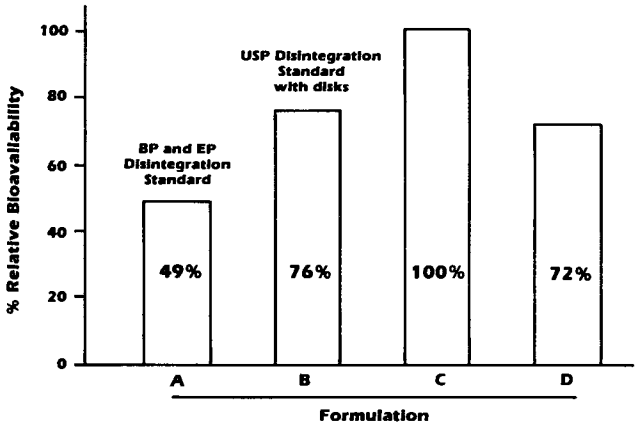

Fig. 3. Relative bioavailability of Formulations A, B, and D compared to Formulation C (100%).

The study suggests that a meaningful disintegration/dissolution standard for vitamin C tablets has to be based on bioavailability data and not on the assumption that a fast dissolution rate assures good absorption. The observation that a slower disintegration time and slower rate of dissolution optimize the bioavailability of vitamin C tablets may also apply to other water-soluble vitamins. Additional studies are needed to confirm and extend these findings.

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