Enhanced Intestinal Absorption of Riboflavin from Sodium Alginate Solution in Man

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Abstract □ The absorption of orally administered riboflavin-5′-phosphate by healthy male subjects was increased significantly when the vitamin was administered in 50 ml. of 2% sodium alginate solution rather than in the aqueous vehicle without sodium alginate. It is proposed that the highly viscous and thixotropic sodium alginate solution moves through the GI tract relatively slowly and thereby causes prolonged retention of the vitamin at specialized absorption sites in the small intestine.

Keyphrases □ Riboflavin, enhanced intestinal absorption—using sodium alginate solutions, man □ Viscosity effect—enhanced riboflavin absorption using sodium alginate solutions, man □ Absorption, riboflavin—enhanced with use of sodium alginate solutions for administration □ Sodium alginate solutions—role in promoting intestinal absorption of riboflavin, man □ Intestinal transit, riboflavin—decreased by use of sodium alginate solutions, increased vitamin absorption

The purpose of the investigation described here was to extend previous studies in this laboratory of the effect of viscosity on drug absorption (1, 2) and of factors affecting the intestinal absorption of riboflavin in man (3–5). Drug absorption and the GI transit rate of a drug solution are decreased in rats when the viscosity of the solution is increased by addition of methylcellulose (1). On the other hand, the rate and extent of thiamine and riboflavin absorption were not affected significantly in man when these vitamins were administered orally in highly viscous methylcellulose solution rather than in simple aqueous solution (2). The question arose, therefore, whether any reasonable change in the rheologic characteristics of aqueous solutions could modify the GI absorption of substances dissolved in these vehicles. In view of the negative finding with methylcellulose, a nonionic polymer with pseudoplastic characteristics in aqueous solution, it was decided to explore the effect of an anionic viscosity-enhancing agent, sodium alginate, which yields thixotropic solutions particularly when exposed to acidic gastric fluids.

Riboflavin, the test substance employed in this investigation, is absorbed in man by a specialized, readily saturable process located in the proximal region of the small intestine (3). Therefore, the extent of absorption of relatively large doses of the vitamin should be affected by the length of time it is in contact with intestinal absorption sites. This has been part of the rationale for using riboflavin to study aspects of GI physiology as a function of age and disease (6–8). Provided that absorption itself rather than diffusion to the site of absorption is rate limiting regardless of the vehicle used, the extent of riboflavin absorption should be increased if the vitamin is administered in a vehicle that is emptied from the stomach and moved through the small intestine rather slowly. This should be true also for drugs that are absorbed very slowly by passive diffusion.

Table I—Apparent Viscosity of Riboflavin–Sodium Alginate Solutions at Several Shear Rates[a]

Shear Rate, sec.$^{-1}$	Shear Stress, dynes/cm.^{2}	Viscosity, cps.
5.14	313 ± 81[b]	6090
30.4	964 ± 260	3170
137.	1772 ± 190	1290

[a] Average of five solutions at 37°. [b] Standard deviation.

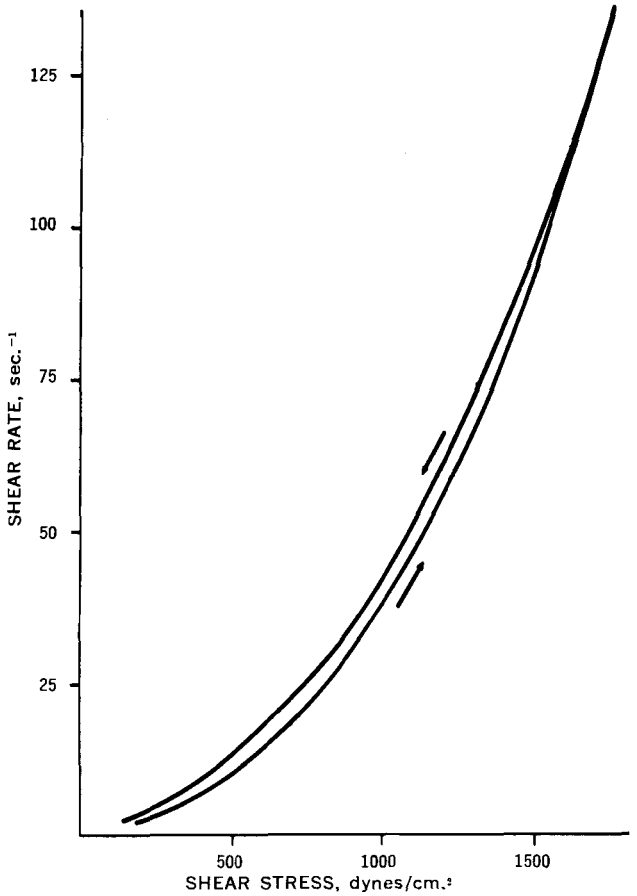

Figure 1—*Representative rheogram at 37° of the riboflavin–sodium alginate solution used in this study.*

EXPERIMENTAL

Five healthy male volunteers, 26–34 years old, weighing 63–77 kg., served as test subjects. They received about 41 mg. riboflavin-5′-phosphate·$2H_2O$ (equivalent to 30 mg. riboflavin) in the morning on an empty stomach. The vitamin was dissolved in 50 ml. flavored sodium alginate solution consisting of 2% sodium alginate[1], 1% citric acid, 0.1% sodium saccharin, and about 0.01% sweet orange oil in distilled water, or in the same vehicle but without sodium

[1] Sodium alginate XRD-1000, Marine Colloids, Inc., New York, N. Y.

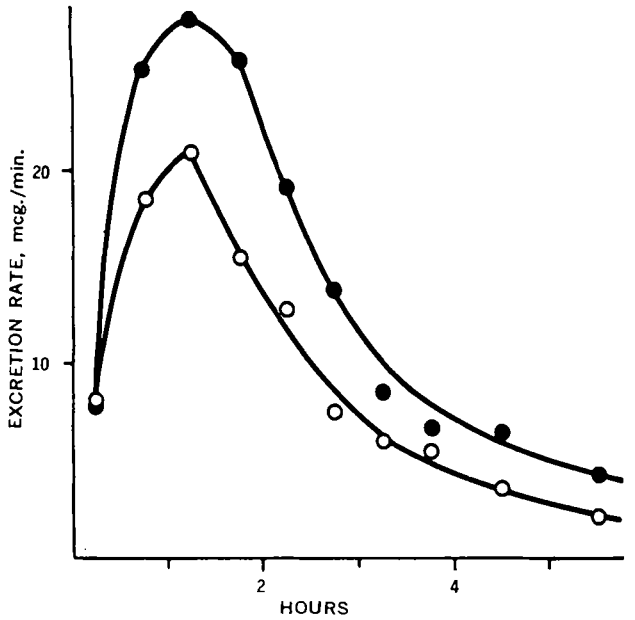

Figure 2—*Urinary excretion rate of riboflavin as a function of time after oral administration of 41 mg. riboflavin-5′-phosphate in aqueous solution* (○) *and in aqueous solution with sodium alginate* (●). *Average of five subjects.*

alginate. The two preparations and the alginate solution without riboflavin were taken in random order, at least 1 week apart, and urine was collected for 36 hr. thereafter. The clinical protocol, the analytical procedures, and the rheological determinations were identical to those used previously (2).

The excretion of apparent riboflavin without vitamin administration was 0.57–1.69 mg./day in five subjects; three of the subjects who received the sodium alginate vehicle without riboflavin had apparent excretion rates of 0.44–0.97 mg./day (uncorrected). The riboflavin solutions were prepared individually, separate rheograms were obtained for each solution containing sodium alignate, and an aliquot of every solution was assayed together with the urines from the subject who received the solution. The urinary recoveries were calculated on the basis of these assays after correcting for blank values.

RESULTS AND DISCUSSION

The sodium alginate solution used in this study has definite thixotropic characteristics, as shown by the thixotropic "loop" in the rheogram (Fig. 1). The apparent viscosity at several shear rates on the "up" curve is listed in Table I for comparison with similar information on the methylcellulose solutions used in a previous study (2). It is impossible, in principle, to match exactly the rheologic characteristics of two different non-Newtonian fluids, particularly if one is pseudoplastic and the other has thixotropic characteristics. However, an attempt was made to prepare the sodium alginate solution so that its flow characteristics were at least grossly similar to those of the previously used methylcellulose solution which had an apparent viscosity of 3410, 2680, and 1560 cps., respectively, at the three shear rates listed in Table I. The major difference between the two solutions was in the very low shear rate range where the sodium alginate solution becomes very viscous and presumably shows a yield value, although this is not apparent in the rheogram.

The average urinary excretion rates of riboflavin in five normal subjects as a function of time after oral administration of riboflavin-5′-phosphate in aqueous solution and in aqueous solution with sodium alginate are shown in Fig. 2. The time courses of excretion are quite similar, but excretion rates from the riboflavin–

Table II—Effect of Sodium Alginate on Riboflavin Absorption in Man

Subject	Percent of Dose Recovered in Urine	
	Control	Sodium Alginate
KR	19.2	24.2
BK	16.2	23.1
WH	9.8	13.8
TT	18.4	32.2
SO	13.3	22.4
Mean	15.4	23.1[a]

[a] Significantly different from control ($p < 0.02$).

sodium alginate solution are considerably higher than those obtained after administration of the aqueous solution without alginate.

The extent of absorption of riboflavin by the five subjects from the two solutions is summarized in Table II. Fifty percent more riboflavin was absorbed from the sodium alginate solution than from the aqueous solution without alginate, a statistically significant difference ($p < 0.02$ by paired t-test). The excretion rate and bioavailability[2] for the aqueous control are quite similar to data obtained previously in four subjects (2, 5), only one of which (WH) also participated in the present study. Interestingly, that subject was an unusually poor absorber in both of these studies.

The results of this investigation demonstrate the feasibility of increasing the bioavailability of a substance given orally in solution by modifying the pharmaceutical formulation of that solution. It is suggested that the observed effect is due to the very high apparent viscosity of the sodium alginate solution at low shear rates and its consequent poor mixing in GI fluids and lower GI transit rate. This may result in prolonged retention of the vitamin at its site of absorption in the upper small intestine. If such a mechanism is indeed operative, then it should be possible to use the same technique to enhance the bioavailability from solution of certain very slowly and therefore incompletely absorbed drugs, provided that they do not complex extensively with alginate. It is planned to extend the study described here to certain poorly absorbed drugs and to other thixotropic systems.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 26, 1971, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214*

Accepted for publication October 27, 1971.

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[2] At least 90% of an injected dose of riboflavin is usually recovered as such in the urine (7, 9), so urinary excretion is a useful index of the bioavailability of orally administered forms of this vitamin.