other sulfanilamide. The sulfanilamide reagent is generally, but not universally, the more sensitive. It usually produces less background color than naphthylamine and the spots are more stable because the background darkens much less rapidly. The sulfanilamide reagent does not have the disagreeable odor of naphthylamine and does not have the carcinogenic action of the latter compound.

Both reagents have been tested against twelve reference acids in four commonly used solvent systems. Sensitivities vary somewhat from one solvent to the next, but the variations are minor and do not prevent use of any solvent tested. Both reagents are much more sensitive than the indicator-permanganate or acridine procedures. The sulfanilamide reagent is notably more sensitive than aniline-xylose or bromcresol green and does not possess the carcinogenicity of aniline-xylose. Both reagents give more reproducible sensitivities than any reagent tested, and neither produces "ghost" spots.

Intense background colors may develop with either sulfanilamide or alphanaphthylamine if chromatograms are exposed to high concentrations of laboratory fumes, but minimal care will prevent this occurrence.

An 8:1:1 propanol-formic acid-water system has been used to develop most of these chromatograms. It has not been extensively studied as a solvent for separating organic acids, but may certainly be used to advantage. It produces excellent separations of many compounds tested, causes little or no tailing, and gives compact spots.

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Protective Coatings XVI

Disintegration of Protective-Coated Tablets as Determined by Urinary Excretion in Humans

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A disintegration test of protective coated preparations in human bodies was carried out by determining the riboflavin amount excreted in urine after administration of the riboflavin tablets coated with the previously reported protective-coating agents. Though the rate of the riboflavin excretion was somewhat slow, there was no indication of unusual disintegration of the coated tablets in human bodies.

IN PRECEDING PAPERS, studies on the protective-coating agents were reported in which the amino derivatives and the amino acid derivatives of cellulose, saccharides and polyhydric alcohols, polyvinylamines, polyvinylaminoacetals, polyvinylpyridines, and others were synthesized and examined (1–12). Polyampholites of the vinylpyridine-methacrylic acid system were also studied for the protective-coating agents which solubilize in both gastric and intestinal juice (13). All preparations coated with these agents showed excellent results in the tests—water-resistance, *in vitro* disintegration, and others.

In this report, the *in vivo* test was examined in human bodies for the disintegration of the preparations. Since riboflavin absorbed in excess is rapidly excreted in urine, disintegration rate was determined by the riboflavin amount in urine excretion after the administration of the coated riboflavin tablets.

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EXPERIMENTAL

Tablets.—The compressed tablets (9.0 mg. of riboflavin each) were used in the experiments. Mean thickness, weight, and diameter of the tablets were 3.5 mm., 120 mg., and 7 mm., respectively. The disintegration time of the tablets in distilled water, artificial gastric juice, and artificial intestinal juice was 2–3 minutes as determined by the method specified in U.S.P. XVI (14).

Protective-Coated Tablets.—By the dipping method, the compressed riboflavin tablets were coated with two different coating solutions: 10% methanol solution of the copolymer, 2-vinyl-5-ethylpyridine-styrene (VEP-St), and 10% ethanol-trichloroethane (1:1) solution of the copolymer, 2-vinyl-5-ethylpyridine-methacrylic acid-methylacrylate (VEP-MAA-MA).

TABLE I.—*In Vitro* DISINTEGRATION TEST OF THE COATED TABLETS

Tablets	Film Thickness, μ	Disintegration Time: Distilled Water, hrs.	Disintegration Time: Artificial Gastric Juice, min.	Disintegration Time: Artificial Intestinal Juice
VEP-St-coated	150	4	5–10	4 hrs.
VEP-MAA-MA-coated	145	4	5–10	10–15 min.

Mean thicknesses of the coating films and disintegration times of the coated tablets are shown in Table I. The mean thicknesses were calculated from the mean weights of coating agents applied to each tablet. The disintegration time of the coated tablets in distilled water, artificial gastric juice, and artificial intestinal juice was determined by the method specified in U.S.P. XVI (14).

Administration test.—Seventy-nine men and 52 women ranging from 18–55 years were divided into three groups, A, B, and C (as shown in Table II), and each person was administered one tablet—uncoated tablets for the A group, VEP-St-coated tablets for the B group and VEP-MAA-MA-coated tablets for the C group. The amounts of riboflavin in total urine excreted in 3 hours prior, 3 hours, and 6 hours after administration were determined individually by the U.S.P. fluorometric procedure (14).

TABLE II.—GROUPS IN ADMINISTRATION

Group	Administered Tablet	Men	Women	Total
A	Uncoated	20	10	30
B	VEP-St-coated	29	21	50
C	VEP-MAA-MA-coated	30	21	51

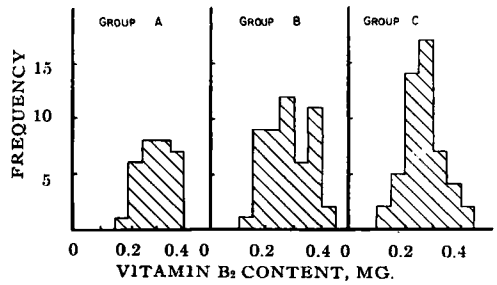

Fig. 1.—Vitamin B_2 content of urine before administration.

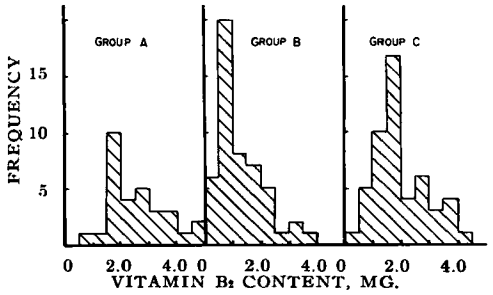

Fig. 2.—Vitamin B_2 content of urine 0–3 hours after administration.

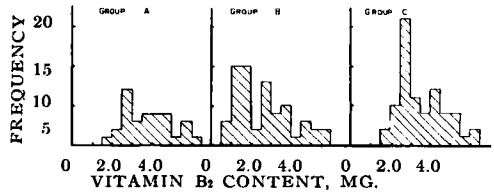

Fig. 3.—Vitamin B_2 content of urine 0–6 hours after administration.

RESULTS AND DISCUSSION

Riboflavin Contents of Urine Before Administration.—Figure 1 shows the riboflavin content of urine before administration. All individuals showed almost similar values, and no particular difference was observed between men and women.

Amounts of Riboflavin Excreted in Urine After Administration.—Figures 2 and 3 show the total amounts of riboflavin excreted in urine during 3- and 6-hour periods after administration, and Table III shows the mean values of riboflavin in the three groups after 6 hours.

As shown in Table III, the B group excreted less riboflavin than the other two groups, and women excreted less than men. Analysis of the variances by Snedecor's method (15) shows that these differences are statistically significant at the 5% level, but

TABLE III.—MEAN AMOUNT OF RIBOFLAVIN EXCRETED IN URINE IN 0–6 HOURS

Tablets	Men: Administered Number	Men: Mean Value of Excreted Riboflavin, mg.	Women: Administered Number	Women: Mean Value of Excreted Riboflavin, mg.	Mean: Administered Number	Mean: Mean Value of Excreted Riboflavin, mg.
A	20	3.95	10	3.49	30	3.797
B	29	2.87	21	2.26	50	2.614
C	30	3.60	21	3.24	51	3.447
Total	79	3.40	52	2.89	131	3.211

the lower excretion of women might result from some errors in urine collection.

Variation of Riboflavin Amounts Excreted in Urine With the Lapse of Time.—Table IV shows the mean values of riboflavin excreted in both 3-hour periods. X_1 and X_2 indicate milligrams of riboflavin excreted in 3 hours and the next 3 hours, respectively.

TABLE IV.—MEAN VALUES OF RIBOFLAVIN EXCRETED IN 0–3 (X_1) AND 3–6 (X_2) HOURS

Tablet Group	X_1, mg.	X_2, mg.
A	2.512	1.285
B	1.251	1.363
C	1.951	1.496

The B and C groups showed lower values of X_1 as compared with the A group. But the C group showed the highest X_2 value of the three, and the total for 6 hours was nearly the same as the A group.

The B group (as described above) showed the lowest total value of the three, but the X_2 value was greater than the X_1. It can be seen that the excretion gradually increased with the lapse of time, and further increase of the value might be expected in the following period.

These differences of riboflavin excretion between the groups were statistically significant at the 5% level in the result of analysis of dispersion.

The results show that the excretion of riboflavin with the coated tablets was slightly slower than the uncoated tablets. This was expected as the disintegration rate of the coated tablets was somewhat retarded.

Disintegration of Coating Films in Humans.—Variances of the amounts of excreted riboflavin in each group were calculated in order to see whether an unusual disintegration of the coated tablets occurred.

TABLE V.—VARIANCES OF RIBOFLAVIN EXCRETED IN 0–3 AND 0–6 HOURS

Tablet Group	0–3 Hours	0–6 Hours
A	1.0220	1.3257
B	0.7204	1.9221
C	0.8080	1.6065

As can be seen in Table V, amounts of the excretions showed no significant difference between three groups and, it can be considered that there were no unusual disintegrations in humans with both coated tablets.

It may be concluded from these results that the coated tablets must disintegrate to release medicaments in humans.

SUMMARY

1. Riboflavin tablets were coated with the copolymers 2-vinyl-5-ethylpyridine-styrene (VEP-St), and 2-vinyl-5-ethylpyridine-methacrylic acid-methyl acrylate (VEP-MAA-MA). The disintegration of the coated tablets was tested by determining the riboflavin amount excreted in human urine after administration of the tablets.

2. The group administered VEP-St-coated tablets showed lower excretion of riboflavin in 6 hours after administration than the group administered uncoated tablets. The group administered VEP-MAA-MA coated tablets showed nearly the same as the control in the excretion.

3. Both groups administered the coated tablets showed lower excretions of riboflavin in 3 hours after administration, and higher excretions in the following 3 hours than the control.

4. The coated tablets disintegrated in humans to release medicaments. Any unusual disintegration did not occur.

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