GI Drug Absorption in Rats Exposed to Cobalt-60 γ-Radiation II: *In Vivo* Rate of Absorption

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Abstract □ The rate of absorption of sulfanilamide, bretylium tosylate, sulfisoxazole acetyl, and riboflavin was studied in rats exposed to 850 rad of cobalt-60 γ-radiation either 1 or 5 days before oral drug administration. Polyethylene glycol 4000 was administered with sulfanilamide; its distribution along the GI tract indicated that the gastric emptying rate was reduced threefold at 1 day postirradiation but returned to normal at 5 days postirradiation; the small intestinal transit rate was not detectably altered by irradiation. At 1 day postirradiation, there was a marked decrease in the absorption rate of sulfanilamide, a smaller, although significant, decrease in the absorption rate of sulfisoxazole acetyl and bretylium, and an increase in the absorption rate of riboflavin. At 5 days postirradiation, the drug absorption rate was normal. The changes in the absorption rate of the drugs were due to a radiation-induced reduction in the gastric emptying rate; the permeability of the GI epithelium did not appear to be affected by radiation. The results indicate that, immediately following irradiation, a marked reduction in the gastric emptying rate causes a pronounced reduction in the absorption rate of rapidly absorbed drugs, a less pronounced reduction in the absorption rate of drugs that are absorbed slowly because of slow dissolution or slow diffusion across the GI epithelium, and an increase in the absorption rate of drugs that are absorbed by a saturable mechanism provided the mechanism is not impaired by irradiation.

Keyphrases □ Absorption, GI—various drugs, effect of cobalt-60 γ-radiation, rats □ Radiation, gamma—effect on GI absorption of various drugs, rats □ Sulfanilamide—GI absorption, effect of cobalt-60 γ-radiation, rats □ Bretylium tosylate—GI absorption, effect of cobalt-60 γ-radiation, rats □ Sulfisoxazole acetyl—GI absorption, effect of cobalt-60 γ-radiation, rats □ Riboflavin—GI absorption, effect of cobalt-60 γ-radiation, rats

The results of a previous study (1) showed that prior exposure of rats to cobalt-60 γ-radiation may significantly alter the absorption pattern of orally administered drugs. In irradiated animals, the extent of absorption of sulfisoxazole acetyl and riboflavin was increased compared to control animals. Irradiation did not have a detectable effect on the extent of absorption of bretylium tosylate or sulfanilamide, although the extent of metabolism of sulfanilamide was significantly increased in irradiated animals.

While the previous study dealt with the effects of ionizing radiation on the extent of drug absorption, radiation-induced changes in GI structure and motility may also affect the rate of drug absorption. To explore this possibility, the *in vivo* absorption rate of sulfanilamide, bretylium tosylate, sulfisoxazole acetyl, and riboflavin was studied in irradiated and sham-irradiated rats.

EXPERIMENTAL

Materials—The drugs and reagents used were described previously (*1*). 1,2-^{14}C-Polyethylene glycol 4000[1] (specific activity 0.3 mCi/g) was dissolved in water and stored at 5° in an opaque container.

Absorption Rate—Male Sprague–Dawley rats, 170–250 g, were irradiated or sham irradiated as described previously (1). At 1 or 5 days postirradiation, 8.0 ml/kg of a water–propylene glycol (1:1) solution of sulfanilamide (200 mg/kg) and ^{14}C-polyethylene glycol (4.0 mg/kg) was administered by gastric intubation (2) to animals that had been fasted overnight. Equal numbers of irradiated and sham-irradiated animals were used each time an experiment was performed.

At 0.5, 1.0, 2.0, and 6.0 hr after dosing, the animals were sacrificed by exposing the head to microwave radiation[2] for 15 sec (3, 4). Blood was immediately removed by cardiac puncture, and the GI tract was excised and separated into five portions: stomach, small intestine divided into three segments of equal length, and the caecum and colon. The intestinal segments and serum separated by centrifugation from clotted blood were frozen until assayed.

In similar studies, 8.0 ml/kg of an aqueous sulfisoxazole acetyl suspension (100 mg/kg), a bretylium tosylate solution (30 mg/kg), or 12 ml/kg of an aqueous riboflavin solution (0.80 mg/kg, 0.12 μCi/ml) was administered by gastric intubation; polyethylene glycol 4000 was not present. At 0.5 or 2.0 hr after dosing, the animals were sacrificed; the GI tract and a sample of serum were removed and frozen until analysis.

Analytical Methods—Each portion of the GI tract was homogenized[3], and the amount of drug or radioactivity in the homogenate and serum was assayed by methods described previously (1). Radioactivity was not detected in serum following administration of ^{14}C-polyethylene glycol or ^{14}C-riboflavin. Recovery of radioactivity from homogenates containing ^{14}C-riboflavin or ^{14}C-polyethylene glycol was greater than 94%; chemiluminescence was not a problem since homogenate blanks were negligible.

Mean recoveries of bretylium tosylate, free sulfanilamide, and total sulfisoxazole acetyl from GI homogenates were 96, 96, and 101%, respectively. Blank values of free sulfanilamide from homogenates of the stomach, small intestine, and caecum and colon were 0.32, 0.22, and 0.64 mg, respectively. Blank values of total sulfisoxazole acetyl from stomach and intestinal homogenates were 0.10 and 0.56 mg, respectively; bretylium blank values were negligible. Recovery of free sulfanilamide and sulfisoxazole acetyl from serum was nearly 100% with serum blanks of 8.6 and 6.1 μg/ml, respectively.

RESULTS AND DISCUSSION

At 1 day postirradiation, the distribution of orally administered polyethylene glycol, a nonabsorbable marker (5), along the GI tract of irradiated animals was quite different from that of the controls (Figs. 1 and 2, respectively). The most notable difference in distribution was the increased level of polyethylene glycol in the stomachs of irradiated animals, indicating that prior irradiation reduced the gastric emptying rate as reported by others (6, 7). In both irradiated and control animals, the gastric emptying of polyethylene glycol followed apparent first-order kinetics with half-lives of 3.4 and 0.8 hr, respectively. At 5 days postirradiation, the GI distribution of polyethylene glycol was not altered appreciably by irradiation. Since the distribution appeared similar to that in Fig. 2 for both groups of animals, it is not shown.

Small intestinal transit times for polyethylene glycol were calculated by a method described previously (8). No radiation-induced change in the motility of the small intestine was detected. This finding agrees with previous studies in which a nonabsorbable marker was administered to the stomach (6, 9). However, when the marker was administered intraduodenally, the small intestinal transit rate was increased in irradiated rats (10). Since this latter study was not complicated by the effects of radiation on gastric emptying, it may be a more sensitive measure of the effects of radiation on intestinal motility than studies that involved gastric administration of the marker.

The recovery of polyethylene glycol from the GI tract of both irradiated and control animals was nearly complete (>90%) at all times up to 6 hr following its administration (Table I). Thus, the very low permeability of the GI epithelium to large, polar molecules is not altered by prior irradiation of the epithelium, even though marked anatomical and phys-

[1] New England Nuclear, Boston, Mass.

[2] Toshiba electronic oven model ER-625BT, Toshiba American, Inc., Flushing, N.Y.

[3] Sorvall Omni-Mixer, Ivan Sorvall, Inc., Newtown, Conn.

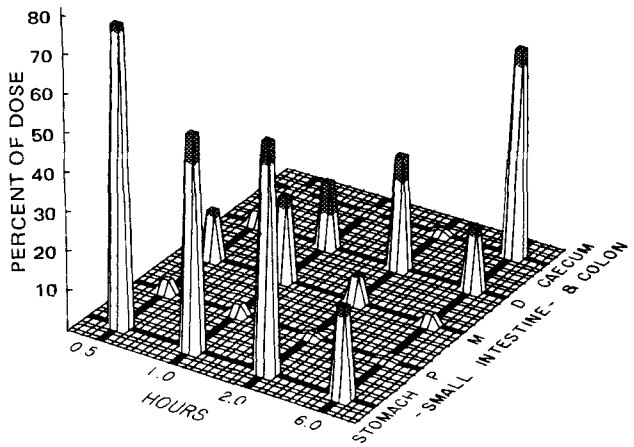

Figure 1—*Distribution of polyethylene glycol 4000 along the GI tract following its oral administration to rats exposed to 850 rad of cobalt-60 γ-radiation 1 day previously. Each bar represents the mean of six animals; stippling represents 1* SE. *P, M, and D are the proximal, middle, and distal thirds of the small intestine, respectively.*

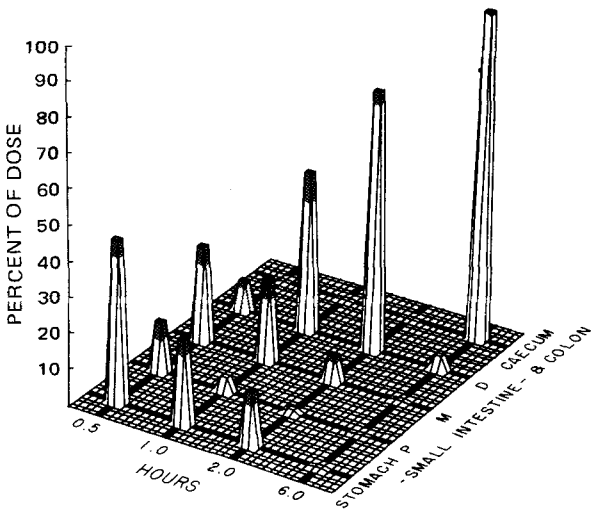

Figure 2—*Same as Fig. 1 except that the rats were sham irradiated.*

iological changes are manifest for several days following irradiation (11, 12).

Sulfanilamide was administered simultaneously with polyethylene glycol; its distribution along the GI tract at 1 day postirradiation is shown in Figs. 3 and 4 for irradiated and control animals, respectively. In both groups, less than 10% of the administered drug was recovered below the level of the stomach at any time. In addition, sulfanilamide disappeared from the stomach at the same rate as polyethylene glycol 4000 (Fig. 5). Since polyethylene glycol 4000 was not absorbed, sulfanilamide apparently was not absorbed from the stomach. The intestine is the primary site for absorption of sulfanilamide, and gastric emptying is the rate-controlling step in the absorption of this drug.

Table I—Recovery of Polyethylene Glycol from GI Tract following Oral Administration to Irradiated and Sham-Irradiated Rats

Time after Dosing, hr	Percent of Dose Recovered[a]			
	1 Day Postirradiation		5 Days Postirradiation	
	Sham	850 rad	Sham	850 rad
0.5	94.4 ± 2.23	96.0 ± 4.46	102.3 ± 7.72	91.7 ± 4.35
1.0	92.9 ± 5.22	94.6 ± 2.28	94.2 ± 3.38	104.4 ± 11.25
2.0	94.6 ± 1.62	96.7 ± 4.40	94.1 ± 2.00	103.2 ± 4.28
6.0	94.0 ± 2.81	91.7 ± 2.57	100.5 ± 5.18	92.7 ± 2.42
Mean	94.0 ± 0.76	94.8 ± 2.22	97.8 ± 4.25	98.2 ± 6.73

[a] Mean of six animals ± *SD*.

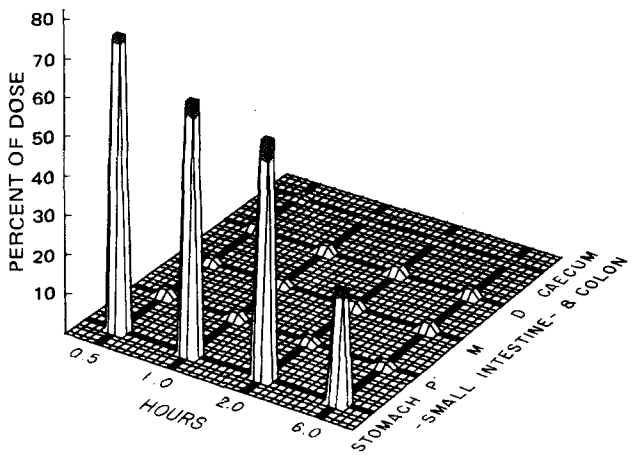

Figure 3—*Distribution of sulfanilamide along the GI tract following oral administration of 200 mg/kg to rats exposed to 850 rad of cobalt-60 γ-radiation 1 day previously. Each bar represents the mean of six animals; stippling represents 1* SE. *P, M, and D are proximal, middle, and distal thirds of the small intestine, respectively.*

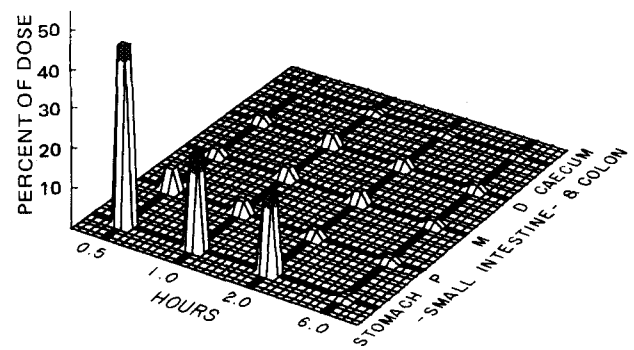

Figure 4—*Same as Fig. 3 except that the rats were sham irradiated.*

The reduced rate of absorption of sulfanilamide in irradiated animals at 1 day postirradiation is apparent in Figs. 3 and 4. The relatively slow absorption of sulfanilamide is also evident in the serum concentration–time curve of sulfanilamide; the serum level was threefold higher in control animals than in the irradiated group (Fig. 6). The linear relationship between serum concentrations of sulfanilamide and the amount of drug absorbed for both irradiated and control animals indicates that

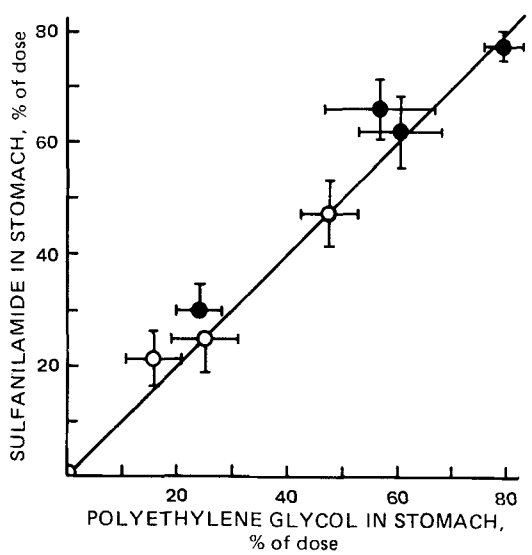

Figure 5—*Relationship between the recoveries of sulfanilamide and polyethylene glycol from the rat stomach at various times following their oral administration 1 day postirradiation. Key: ●, irradiated (850 rad); and ○, sham irradiated. Each point represents the mean of six animals, and lines indicate ± 1* SE.

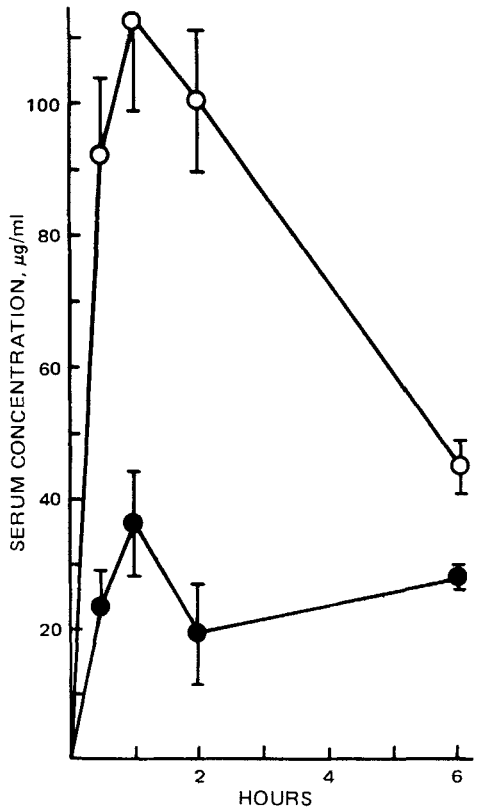

Figure 6—*Serum levels of sulfanilamide in rats following oral administration of 200 mg/kg 1 day postirradiation. Key: ●, irradiated (850 rad); and ○, sham irradiated. Each point represents the mean of six animals; bars indicate ± 1 SE.*

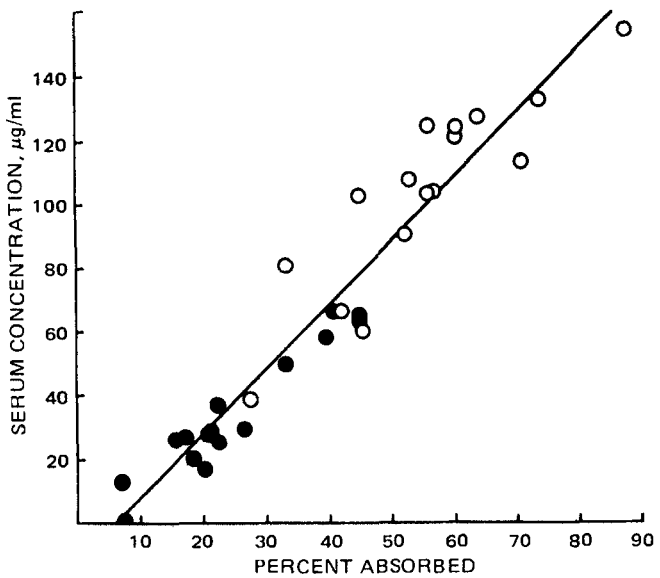

Figure 7—*Serum levels of sulfanilamide in rats and corresponding percent of dose absorbed at 0.5 and 1.0 hr following oral administration of 200 mg/kg 1 day postirradiation. Key: ●, irradiated (850 rad); and ○, sham irradiated.*

differences in serum levels were due solely to differences in the absorption rate (Fig. 7); distribution and elimination of the drug following absorption were apparently not affected by irradiation with 850 rad.

Immediately following irradiation, irradiated animals consume considerably more food than sham-irradiated animals (1). The stomachs of irradiated animals were greatly distended at 1 day postirradiation, even following an overnight fast. To determine whether food in the stomachs of irradiated animals caused the reduced absorption rate of sulfanilamide, the experiment was performed with animals that were not permitted food following irradiation. The sulfanilamide absorption rate remained significantly lower in the irradiated animals (Table II), indicating that these differences between irradiated and sham-irradiated animals were not due to differences in food consumption.

In agreement with the studies on polyethylene glycol 4000 and sulfanilamide, the gastric emptying rate of bretylium tosylate in irradiated animals was significantly reduced at 1 day postirradiation compared to sham-irradiated animals (Table III). This difference was not apparent at 5 days postirradiation. High levels of bretylium in the intestine indicate that the rate-controlling step in the absorption of this drug is diffusion across the GI mucosa to the blood rather than gastric emptying. Radiation-induced slowing of the gastric emptying rate, therefore, did not markedly reduce the bretylium absorption rate (Table III) as it did for sulfanilamide. The tendency for the absorption rate of bretylium to be reduced in irradiated animals is probably due both to a reduced rate of gastric emptying and a reduced mucosal permeability. The absorption rate of bretylium is probably more rapid from the intestine than the stomach, and both *in vitro* and *in situ* studies indicate that irradiation may cause a subsequent reduction in the permeability of the GI mucosa (13–15). Bretylium concentrations in serum were below the sensitivity of the analytical procedure, 5 μg/0.5 ml of serum.

The gastric emptying rate and the absorption rate of sulfisoxazole acetyl were reduced significantly in irradiated animals compared to the sham-irradiated group at 1 day postirradiation, but no detectable difference between the two groups was observed at 5 days postirradiation (Table IV). The reduced rate of drug absorption in irradiated animals compared to controls was also apparent from the significantly lower concentration of the drug in serum at 1 day postirradiation (Table IV).

Sulfisoxazole acetyl is absorbed more rapidly than sulfanilamide from solution by the rat small intestine (15). The relatively high level of sulfisoxazole acetyl in the intestine following its oral administration as a suspension indicates that the rate-controlling step in the absorption of this drug is dissolution. Although the absorption rate of sulfisoxazole acetyl is reduced in irradiated animals, the extent of absorption is increased (1), apparently because the reduced rate of GI transit allows more time for the drug to dissolve.

The gastric emptying rate of riboflavin was decreased in irradiated animals at 1 day postirradiation. In accord with previous studies, it appeared normal by 5 days postirradiation (Table V). The riboflavin level in the intestine was quite high. Since the vitamin was administered in solution, the rate-controlling step in the absorption process is apparently transport across the intestinal epithelium, in a manner similar to bretylium absorption. In contrast to the absorption of bretylium, however, the absorption rate of riboflavin was significantly *greater* in irradiated than in sham-irradiated animals. A possible explanation for this difference is that riboflavin is absorbed by a saturable process at a specific site in the proximal small intestine (16 and references cited therein) while the

Table II—Sulfanilamide in Serum and GI Tract following Oral Administration[a] of 200 mg/kg to Rats Fasted Postirradiation

Time after Dosing, hr	Treatment[b]	Serum Concentration[c,d], μg/ml	Percent of Dose Recovered[c]		Percent Absorbed[c,e]
			Stomach	Intestine	
0.5	Sham	105.0 ± 23.7	40.3 ± 10.9	6.33 ± 2.11	53.2 ± 12.9
0.5	850 rad	44.1 ± 23.8[f]	67.4 ± 15.3[f]	4.69 ± 1.95	27.9 ± 16.9[f]
2.0	Sham	117.0 ± 12.0	14.4 ± 9.12	5.29 ± 1.81	80.3 ± 8.01
2.0	850 rad	51.7 ± 14.9[f]	49.2 ± 11.7[f]	3.27 ± 0.99	47.5 ± 11.2[f]

[a] Administered as a solution in water–propylene glycol (1:1). [b] Rats were exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated 1 day before administration of sulfanilamide. [c] Mean of five animals ± *SD*. [d] Non-N^4-conjugated. [e] Difference between dose and recovery from the stomach and intestine. [f] Significantly different ($p < 0.05$) from corresponding sham-irradiated animals.

Table III—Bretylium Tosylate in GI Tract following Oral Administration[a] of 30 mg/kg to Rats

Time after Treatment, days	Time after Dosing, hr	Treatment[b]	Percent of Dose Recovered[c]		Percent Absorbed[c,d]
			Stomach	Intestine	
1	0.5	Sham	38.8 ± 4.43	55.8 ± 13.4	8.7 ± 9.4
1	0.5	850 rad	69.6 ± 6.02[e]	25.4 ± 2.64[e]	5.0 ± 4.0
1	2.0	Sham	2.13 ± 1.46	85.5 ± 4.65	12.3 ± 4.40
1	2.0	850 rad	39.9 ± 7.37[e]	54.2 ± 8.03[e]	6.0 ± 3.4[e]
5	0.5	Sham	42.0 ± 12.0	47.5 ± 13.2	10.5 ± 8.22
5	0.5	850 rad	44.4 ± 10.8	46.5 ± 8.03	9.1 ± 6.6
5	2.0	Sham	1.63 ± 1.24	81.4 ± 6.20	16.8 ± 6.11
5	2.0	850 rad	4.73 ± 0.47[e]	84.8 ± 4.38	10.4 ± 4.38

[a] Administered as a solution in water. [b] Rats were exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated 1 or 5 days before administration of bretylium tosylate. [c] Mean of five animals ± *SD*. [d] Difference between dose and recovery from the stomach and intestine. [e] Significantly different ($p < 0.05$) from corresponding sham-irradiated animals.

Table IV—Sulfisoxazole Acetyl in Serum and GI Tract following Oral Administration[a] of 100 mg/kg to Rats

Time after Treatment, days	Time after Dosing, hr	Treatment[b]	Serum Concentration[c,d], μg/ml	Percent of Dose Recovered[c,e]		Percent Absorbed[c,f]
				Stomach	Intestine	
1	0.5	Sham	62.9 ± 10.8	40.0 ± 9.94	35.3 ± 8.41	26.0 ± 9.39
1	0.5	850 rad	48.7 ± 7.58[g]	74.4 ± 5.93[g]	22.5 ± 6.31[g]	4.1 ± 4.9[g]
1	2.0	Sham	163.0 ± 19.8	16.0 ± 5.73	47.4 ± 7.67	36.6 ± 2.80
1	2.0	850 rad	97.5 ± 13.3[g]	70.7 ± 7.63[g]	11.8 ± 4.01[g]	17.4 ± 4.31[g]
5	0.5	Sham	58.7 ± 25.6	43.8 ± 8.31	39.3 ± 12.4	16.8 ± 13.0
5	0.5	850 rad	46.4 ± 21.4	48.1 ± 4.24	30.7 ± 12.6	21.2 ± 10.9
5	2.0	Sham	161.0 ± 11.4	10.9 ± 3.37	54.4 ± 3.88	34.8 ± 4.87
5	2.0	850 rad	155.0 ± 20.3	19.4 ± 7.56[g]	43.0 ± 7.55[g]	37.6 ± 7.58

[a] Administered as a suspension in water containing 0.5% methylcellulose. [b] Rats were exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated 1 or 5 days before administration of sulfisoxazole acetyl. [c] Mean of five animals ± *SD*. [d] Non-N^4-conjugated sulfisoxazole acetyl. [e] Total sulfisoxazole acetyl and sulfisoxazole. [f] Difference between dose and recovery from the stomach and intestine. [g] Significantly different ($p < 0.05$) from corresponding sham-irradiated animals.

Table V—Riboflavin in GI Tract following Oral Administration[a] of 0.8 mg/kg to Rats

Time after Treatment, days	Time after Dosing, hr	Treatment[b]	Percent of Dose Recovered[c]		Percent Absorbed[c,d]
			Stomach	Intestine	
1	0.5	Sham	44.1 ± 14.9	51.2 ± 11.8	4.6 ± 4.5
1	0.5	850 rad	67.3 ± 10.7[e]	26.8 ± 18.7[e]	8.9 ± 5.4
1	2.0	Sham	0.69 ± 0.26	93.3 ± 7.44	7.3 ± 5.0
1	2.0	850 rad	39.0 ± 22.8[e]	45.0 ± 28.9[e]	16.0 ± 6.49[e]
5	0.5	Sham	29.4 ± 13.1	64.1 ± 9.60	6.5 ± 6.2
5	0.5	850 rad	36.7 ± 16.4	66.5 ± 24.2	2.4 ± 2.4
5	2.0	Sham	2.54 ± 2.98	88.2 ± 4.93	9.3 ± 3.1
5	2.0	850 rad	2.76 ± 3.28	85.0 ± 5.13	12.1 ± 5.33

[a] Administered as a solution in water. [b] Rats were exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated 1 or 5 days before administration of riboflavin. [c] Mean of five animals ± *SD*. [d] Difference between dose and recovery from the stomach and intestine. [e] Significantly different ($p < 0.05$) from corresponding sham-irradiated animals.

absorption of bretylium is not saturable. Slow release of riboflavin from the stomach of irradiated animals at 1 day postirradiation presents the vitamin to the absorption site at a relatively low concentration for a relatively long time. This increased time of contact allows a greater fraction of the dose to be absorbed. The *in vivo* extent of riboflavin absorption was also increased in irradiated rats at 1 day postirradiation (1).

An alternative explanation for the radiation-induced increase in riboflavin absorption is that riboflavin is absorbed more rapidly from the stomach than from the intestine, and slowed gastric emptying thereby increases the absorption rate. In view of the very slow absorption of practically all drugs from the stomach compared to the intestine, this latter mechanism is not likely.

With regard to the drug absorption rate, the primary effect of irradiation is the marked reduction in the gastric emptying rate immediately following irradiation. The slowed gastric emptying appears to be a normal response to intestinal injury in the rat (17). By 5 days postirradiation, the gastric emptying rate had returned to normal.

The net effect on the drug absorption rate of a reduction in the gastric emptying rate depends partly on the drug. Irradiation markedly slows the absorption rate of drugs that are rapidly absorbed from the intestine; it causes a less pronounced reduction in the absorption rate of drugs that are slowly absorbed from the intestine, whether slow absorption is due to low mucosal permeability or low dissolution rate. The drug absorption rate may be increased for drugs that are absorbed by a saturable, relatively low capacity mechanism.

In this study, the effect of radiation on the permeability of the GI mucosa appeared to be negligible, although the large reduction in the rate of gastric emptying may have masked a change in mucosal permeability. To explore further the possible effects of radiation on the permeability of the intestinal mucosa, the effects of radiation on the rate of drug absorption from solution by the *in situ* rat intestine were determined and will be reported elsewhere (15).

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Application of Gluconolactone in Direct Tablet Compression

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Abstract □ Gluconolactone was evaluated as an excipient for tablets prepared by direct compression using various drugs known to be difficult to compress. The physical properties of the tablets were evaluated after compression and after storage and were satisfactory. Comparative studies were conducted between gluconolactone and anhydrous lactose, a common direct compression diluent, for development of static charges during blending, flow, drug distribution, drug stratification, color distribution, compressibility, and preservation against mold growth. Gluconolactone possesses those properties necessary to produce high quality tablets by the direct compression process. Separate powdered mixtures of aspirin USP with gluconolactone, anhydrous lactose, spray-dried lactose, mannitol, and sorbitol were stored at various humidities and temperatures for specified periods and tested for the integrity of aspirin. Gluconolactone contributed least to the degradation of the drug as compared to other excipients studied. A preliminary *in vivo* study also was conducted on the bioavailability of aspirin from separate and similar mixtures with gluconolactone, anhydrous lactose, and starch. Gluconolactone did not show any inhibitory effect on aspirin absorption.

Keyphrases □ Gluconolactone—excipient in directly compressed tablets of various drugs, effect on physical characteristics □ Excipients—gluconolactone in directly compressed tablets of various drugs, effect on physical characteristics □ Tablets, direct compression—various drugs, gluconolactone as excipient, effect on physical characteristics □ Dosage forms—directly compressed tablets of various drugs, gluconolactone as excipient, effect on physical characteristics

In terms of economics and stability, the direct compression process offers distinct advantages over other methods used in the manufacture of compressed tablets. During the last decade, considerable interest has been shown in this process. Excipients such as spray-dried lactose (1), microcrystalline cellulose (2), fused mannitol (3), calcium phosphate (4), dextrose (5), amylose (6), anhydrous lactose (7), and directly compressible starch (8) have been studied for their ability to aid in the preparation of compressed tablets. The use of these materials had certain limitations including the difference in particle size and bulk density leading to stratification, the excipients to drug ratio necessary to effect compression, the requirement of an optimum amount of moisture, incompatibility with the drugs, the development of static charges during processing, and cost.

Table I—Properties of Gluconolactone (I) and Anhydrous Lactose

Property	I	Anhydrous Lactose
Solubility in water at 25°, g/ml	0.59	0.2
Particle-size distribution[a] of commercial powders used, % retained		
20 mesh	0.0010	0.00257
30 mesh	0.0450	0.02318
40 mesh	3.4000	0.21894
60 mesh	3.8975	4.6623
80 mesh	4.0525	11.9391
100 mesh	4.250	14.90907
Flow properties, angle of repose		
Plain	26° 23′	22° 43′
With 1% magnesium stearate	23° 50′	20° 12′

[a] A total of 84.354% of I and 64.246% of anhydrous lactose passed through the 100-mesh sieve.

Due to these factors, evaluation of new excipients is warranted. Preliminary experiments with gluconolactone (D-glucono-1,5-lactone, I) indicated considerable potential as an excipient in direct compression; therefore, a thorough study was undertaken.

Compound I was used previously in pharmaceuticals as a stabilizer for multivitamins (9) and tetracycline (10). It is prepared by the oxidation of glucose with bromine water (11) or by oxidation of glucose in *Acetobacter suboxydans* (12). Compound I has a sweet taste and is highly soluble in water (59 g/100 ml); it is slowly hydrolyzed by water to gluconic acid. The calcium and ferrous salts of this acid are