Table II.—Solubility of Ephedrine in Light and Heavy Liquid Petrolatum at 25° C.

Number of Hours of Contact	Light Liquid Petrolatum: Hemihydrated Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.	Light Liquid Petrolatum: Anhydrous Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.
36	1.240	3.137
	1.248	3.111
60	1.237	3.149
	1.243	3.134
Av.	1.242	3.133

Number of Hours of Contact	Heavy Liquid Petrolatum: Hemihydrated Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.	Heavy Liquid Petrolatum: Anhydrous Ephedrine, Gm. of Anhydrous Ephedrine per 100 Cc. of Soln.
36	1.092	2.842
	1.118	2.855
60	1.110	2.876
	1.119	2.920
Av.	1.110	2.873

with fiftieth-normal sodium hydroxide using methyl red indicator.

In the determinations at 25° C., and also the one marked 24° in Table I, the acid solution from the extraction of the oil was saturated with sodium chloride and alkalinized with an excess of 10% ammonia water instead of sodium hydroxide. By saturating the solution with sodium chloride the complete extraction of the alkaloid was attained with four portions of ether. Also, the use of ammonia water eliminated the necessity of washing the ether with water. Any ammonia retained in the ether solution was removed by gentle suction.

The results reveal a striking effect of the 5% of water in the hydrated ephedrine on its solubility in liquid petrolatum. The ratio of the solubility of the hydrated ephedrine to the anhydrous is 1:2.67 at 20° C., and 1:2.52 at 25° C. in light liquid petrolatum. For the heavy liquid petrolatum the ratio is 1:2.58 at 25° C. At the temperatures of 20° and 25° C. substantially anhydrous ephedrine is, in round numbers, $2^1/_2$ times as soluble as the hemihydrate.

It is interesting to call attention to another curious distinction in the properties of hydrated and anhydrous ephedrine. Whereas anhydrous ephedrine melts at about 34° C., the hemihydrate melts at about 40° C.

The difference in the degree of solubility between 20° and 25° is also noteworthy. At 20°, 100 cc. of the solution hold 0.84 Gm. of ephedrine calculated as anhydrous, and at 25° 1.24 Gm.—a difference of 0.40 Gm. or a little over 30%. The difference in solubility of the anhydrous at 20° and 25° is 0.64 Gm. or a little over 20%. We observed crystallization of ephedrine to take place from a saturated solution in light liquid petrolatum prepared at 25° after the solution has stood over night during which the temperature was only a few degrees below 25° C.

The results presented in Table II indicate that the difference in the solubility at 25° C. between the light and the heavy liquid petrolatum used is only about 10%.

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Enteric Coating*

By Paul V. Maney† and Ruldoph A. Kuever‡

INTRODUCTION

Interest in the mode of administering medicine in individual doses, protected by enteric coating, is on the increase. The purpose is to deliver the medication to the intestinal tract for optimum disintegration in the duodenum or jejunum. Drugs delivered in such a manner are of value because:

1. Prolonged contact of highly irritating concentrations with the mucous membrane of the stomach is eliminated.
2. Possible interference with the digestive processes of the stomach by forming precipitates with pepsin and peptones is avoided.
3. Those that are otherwise rendered inactive by the secretions of the stomach, are delivered to the intestinal tract in their therapeutically active form.
4. Delivery of a high concentration to the desired portion of the intestinal tract is possible.
5. Recently it has been disclosed that it may be possible, by means of administering medicine with delayed action, to avoid sleep interruption.

Many drugs are at present administered in enteric form. A common list follows: sodium and potassium chloride; magnesium sulfate; potassium nitrate; ammonium nitrate; ammonium chloride; ferrous sulfate; salts of salicylic acid; methenamine, sodium biphosphate combinations; mandelic acid, ammonium chloride combinations; emetine, and bismuth compounds; aminophyllin;

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theobromine; sodium acetate; phenobarbital combinations; sulfanilamide; pancreatin; bile salts and extract of bile; ovarian substance; thyroid; digitalis; and gentian violet. In addition a number of proprietary antiseptics and anthelmintics are so administered. A number of European products so coated, for the purpose of eliminating excessive intestinal fermentation, are also available.

Increase in the number of drugs thus administered coupled with the generally unsatisfactory results obtained from coatings commonly employed led to the selection of this problem for investigation.

HISTORY

The problem of enteric coating dates back many years. A large variety of coatings has been applied with varying degrees of success. However, as pharmaceutical chemistry has progressed, the value of many of these older coatings has been disproved. At the same time new materials have been made available, but equally important is the new method of testing these coatings in the human body.

In reviewing the previous methods and types of coatings, it was found that as far back as 1884 Unna (1) published reports on the use of keratin. Scoville (2) found that formalin-gelatin possessed enteric properties of limited value. In 1915 Toplis (3) suggested stearic acid and in 1928 a report by Freeman (4) supported this work. Also in 1915, Peacock (5) reported experience with salol in the coating of pills. Wruble (6) and Hilton (7) used ammoniated solutions of shellac, with variations by the latter with combinations of salol. In 1932 Husa and Magid (8) investigated a mixture of salol, stearic acid and shellac.

The use of cetyl alcohol by Mills (9) was reported in 1937. In 1938 Worton, Kempf, Burrin and Bibbins (10) published a paper on the use of a compound coating composed of stearic acid, carnauba wax, petrolatum, powdered agar and powdered elm bark,[1] in which the agar and elm bark were incorporated as mechanical agents to effect timed disintegration. The work of Bukey and Klemme (11) in 1939 reviewed the possibilities of mastic and mastic magnesium stearic combinations.

The progress that has been made in testing their efficiency has made possible the development of more satisfactory enteric coatings.

In 1915 Toplis (3) reported a testing method consisting of applying the enteric coating to an individual dose of ipecac, the resulting delayed action being the measure by which the coating was evaluated. In 1932 Husa and Magid (8) prepared coated capsules composed of methylene blue and calcium sulfide. The effectiveness of the coating was determined as follows: If the capsule dissolved in the stomach, regurgitation of hydrogen sulfide followed. If disintegration occurred in the intestines the urine was colored blue, and there was no regurgitation. If neither occurred it was evident that the capsule did not dissolve. In 1930 Wruble (6) reported the use of a mechanical device, using artificial gastric and intestinal fluids, to test the solubility of a coating.

Recently the roentgen ray has been of great value in determining the behavior of the enteric-coated products in the gastro-intestinal tract. After radiographical experimentation Bukey and Rhodes (12), in 1935, reported wide variation in the efficiency of the commercial coatings. Testing enteric coating by means of roentgen rays was applied by Worton, Kempf, Burrin and Bibbins (10) and is now generally considered the most accurate method.

EXPERIMENTAL

After a review of literature the experimental work to be undertaken was divided as outlined below:

1. Construction of a mechanical device for testing enteric coatings.
2. Correlating results of the mechanical laboratory method with those of roentgen rays.
3. Conducting a series of tests to determine to what extent tablets, now on the market, vary in respect to the disintegrating time.
4. A study of the physiological conditions in the gastro-intestinal tract, to create a type of coating which will resist the fluids of the stomach, but disintegrate in the fluids of the intestines.
5. Development of a new enteric coating.

[1] Patent numbers 2,011,586 and 2,011,587.

Construction of a Mechanical Device for Testing Enteric Coatings.—In the construction of the mechanical apparatus for laboratory testing (Figs. 1, 2 and 3), the objective was to simulate, as nearly as possible, the condition found within the gastro-intestinal tract. A brief outline of the course the tablet took when tested will describe the function of the apparatus.

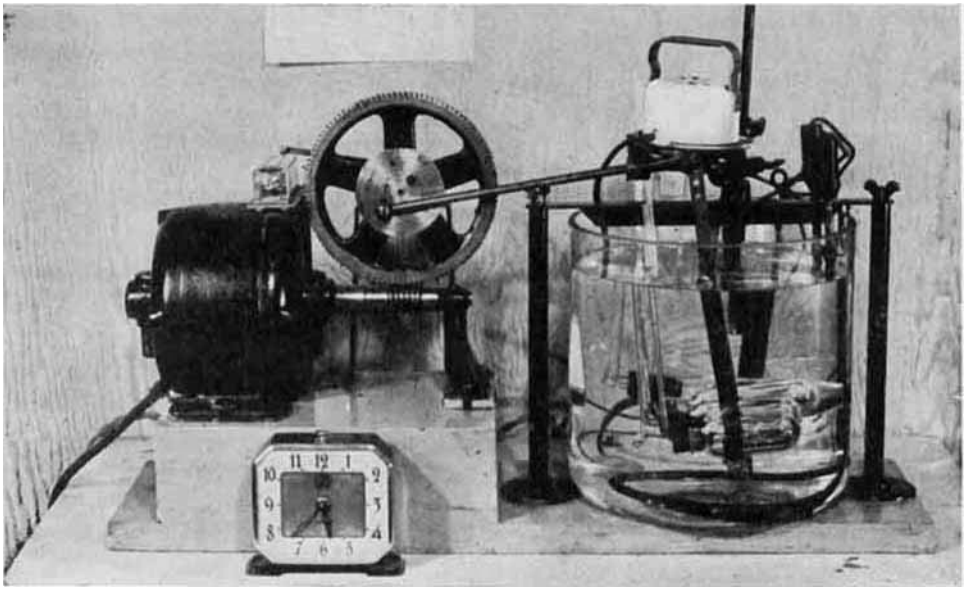

Fig. 1.—Mechanical Laboratory Apparatus for Testing Enteric Coatings.

The tablets tested were placed within an elongated tube containing the digestive fluids. The tube, having an outlet for gas escape, was placed in a rack that could swing through an arc of one hundred and twenty degrees. The motion was timed to approximately sixteen oscillations per minute. The exact number of oscillations was recorded on an automatic counter. The tablets were moved slightly by the motion and gently washed by the digestive fluids. The entire rack, containing the tubes, was immersed in a constant temperature bath maintained at 37° C. The gastric fluid employed was that recommended by Toplis and later used by Wruble (6), and Worton, Kempf, Burrin and Bibbins (10).

Artificial Gastric Fluid

Sodium chloride	1.400 Gm.
Potassium chloride	0.500 Gm.
Calcium chloride	0.060 Gm.
Hydrochloric acid 36%	6.944 Gm.
Pepsin, U. S. P.	3.200 Gm.
Distilled water, to make	1000.000 cc.

Gastric fluid made by this formula has a pH index of 1.6 which corresponds to that outlined in the text of Best and Taylor (13). To substantiate the action of the artificial gastric fluid, several tests were conducted in which the gastric juice of freshly killed hogs was used. The gastric juice from the hog, with a pH index 3, was found to have identical effects on the coating with that of the artificial gastric fluid.

In selecting an artificial intestinal fluid, the formula previously used by other workers was studied. It consists of the following and was previously used in the Pharmacopœia as a test for pancreatin:

Pancreatin, U. S. P.	2.8 Gm.
Sodium bicarbonate	15.0 Gm.
Distilled water, to make	1000.0 cc.

Fig. 2.—Tablets with New Enteric Coating after Ten Hours in Artificial Gastric Fluid. No Evidence of Disintegration Visible.

Fig. 3.—The Same Tablets as in Fig. 2, Thirty Minutes after Being Placed in Artificial Intestinal Fluid. Disintegration Is Taking Place.

Verźar and Kúthy (14), Bodansky (15), as well as others, have demonstrated that the small intestinal tract is not always alkaline even in normal cases. Karr and Abbott (16) carried out a series of experiments in this connection finding that in fasting men a gradient of pH from slight acidity in the duodenum to a slight alkalinity in the ilium was observed. With this evidence it was not felt that the alkalinity alone of the intestines would suffice. Artificial intestinal fluids were therefore made by the following formulas:

Artificial Intestinal Fluid—Alkaline

Pancreatin, U. S. P.	2.8 Gm.
Sodium bicarbonate	15.0 Gm.
Distilled water, to make	1000.0 cc.

Artificial Intestinal Fluid—Neutral

Pancreatin, U. S. P.	2.8 Gm.
Distilled water, to make	1000.0 cc.

Artificial Intestinal Fluid—Acid

Pancreatin, U. S. P.	2.8 Gm.
Hydrochloric acid to a pH index of	6.8
Distilled water, to make	1000.0 cc.

Correlation of Results of the Mechanical Laboratory Method with Those of Roentgen Rays.—To compare the results of the tests *in vitro* with those *in vivo*, 185 mechanical, roentgenogram, roentgenoscopic observations were recorded. The coating was developed and tested *in vitro* before being tested *in vivo*.

To determine the position of the stomach a portion of barium meal was administered and a roentgenogram taken. Discrepancies were disclosed in the two methods, the difficulty arising from the many variables in the gastro-intestinal tract. However, generally speaking, the data obtained from tests *in vitro* made possible a dependable predication of the results *in vivo*.

In vivo experiments proved that an efficient coating must be capable of withstanding artificial gastric fluid for at least ten hours *in vitro*. When transferred to the artificial intestinal fluid disintegration should take place within three hours whether it be alkaline, neutral or slightly acidic.

A Series of Tests to Determine to What Extent Enterically Coated Tablets Now on the Market Vary in Respect to the Disintegrating Time.—To determine the variation in the disintegrating time of enteric coatings now on the market, 31 tablet specimens were tested. The tabulation of results is shown in Table I.

Table I.—Variation in Disintegrating Time of Tablets

	Artificial Gastric Fluid								Artificial Intestinal Fluid					
Specimen	½	1	2	3	4	5	6	←Hours→	½	1	1½	2	3	24
1	5	5	5	0	0	0	0		0	0	0	0	0	0
2	5	5	5	5	5	5	5		5	5	5	4	3	0
3	5	5	3	0	0	0	0		0	0	0	0	0	0
4	5	5	4	3	3	3	0		0	0	0	0	0	0
5	5	5	5	4	0	0	0		0	0	0	0	0	0
6	5	5	5	4	2	2	2		2	2	2	1	1	0
7	5	5	5	5	4	0	0		0	0	0	0	0	0
8	5	5	5	5	5	4	0		0	0	0	0	0	0
9	5	5	5	5	5	5	5		5	0	0	0	0	0
10	5	5	5	5	5	5	5		5	4	1	0	0	0
11	5	5	5	5	5	5	5		5	4	3	0	0	0
12	5	5	5	5	5	4	0		0	0	0	0	0	0
13	5	5	5	5	5	5	4		3	0	0	0	0	0
14	5	5	5	0	0	0	0		0	0	0	0	0	0
15	5	5	5	5	5	5	5		5	0	0	0	0	0
16	5	5	5	5	5	5	4		4	4	3	2	2	2
17	5	5	4	0	0	0	0		0	0	0	0	0	0
18	5	5	5	4	3	3	3		3	2	1	1	1	1
19	5	4	1	0	0	0	0		0	0	0	0	0	0
20	5	5	4	0	0	0	0		0	0	0	0	0	0
21	5	5	5	4	0	0	0		0	0	0	0	0	0
22	5	5	5	4	3	0	0		0	0	0	0	0	0
23	5	5	5	4	0	0	0		0	0	0	0	0	0
24	5	5	5	5	5	5	5		5	4	0	0	0	0
25	5	5	3	2	0	0	0		0	0	0	0	0	0
26	5	5	5	5	5	5	5		5	5	5	5	5	5
27	5	5	4	0	0	0	0		0	0	0	0	0	0
28	5	5	5	5	5	5	4		4	0	0	0	0	0
29	5	5	5	4	0	0	0		0	0	0	0	0	0
30	5	5	5	3	3	3	3		3	1	0	0	0	0
31	5	5	5	5	5	4	0		0	0	0	0	0	0

Five tablets were used in each test. The figures indicate the number of tablets *not* disintegrated at the time designated. Specimen No. 19 was nearly disintegrated in the gastric fluid in one and one-half hours, while in contrast specimen No. 16 remained in the gastric fluid and likewise in the artificial intestinal fluid for twenty-four hours with only three disintegrating.

Artificial intestinal fluids, made according to the formula in Table II, were found to be more effective in disintegrating the enteric coating when one-half of one per cent of bile salts, a natural intestinal tract constituent, was added.

The method of testing was the same as that described under mechanical testing apparatus. The tablets were placed in the artificial gastric fluid and

permitted to remain there, with the machine in motion, for six hours. They were then treated in like manner with the alkaline intestinal fluid. Five tablets were used in each test. Tablets of the same source but of different composition were treated simultaneously to test the same coating on different tablets under identical conditions. Two separate tests were made on each specimen. Little variation was found; therefore, only one result was tabulated.

A Study of the Physiological Conditions in the Gastro-Intestinal Tract, to Determine the Proper Type of Coating Which Will Resist the Fluids of the Stomach, but Disintegrate with the Fluids of the Intestines.—The selection of suitable material for enteric coating necessitated a study of the physiological aspect of the gastro-intestinal tract.

Bukey and Brew (17) observed that human stomachs emptied quickly on high carbohydrates, more slowly on high protein and still more slowly on high fat content diets.

The time of day when tablets are administered has an influence on the rate of discharge from the stomach, the tablets remaining in the stomach longer as the day progresses. However, roentgenoscopic examinations show that tablets administered on an empty stomach early in the morning may remain there for as long as nine hours.

The individual who exercises regularly was, as a rule, found to discharge the stomach contents more rapidly than the individual who does not (18).

Bukey and Brew (17) found that the size of tablet did not alter the rate with which the stomach emptied. But the work of Crane and Wruble (19) indicated that capsules, as a rule, passed more rapidly from the stomach than did tablets.

An interesting observation is that when several tablets are swallowed simultaneously some may pass into the intestines while others may remain in the stomach for several hours (Fig. 4).

Worton, Kempf, Burrin and Bibbins (10), citing Bukey and Brew (17) and Briggs (20), pointed out that an efficient enteric coating should be stable for about six hours and then disintegrate quickly, regardless of the pH of the body fluid surrounding it. However, the recent work of Crane and Wruble (19), after investigating enteric coatings by means of 1000 roentgenograms and roentgenoscopic observations, indicated that approximately 15 per cent of the tablets and capsules remained in the stomach for nine to ten hours.

The optimum position for disintegration, as outlined by Bodansky (15), is in the duodenum or jejunum. As these portions of the small intestines are best adapted for absorption it can be seen that the most satisfactory coating should disintegrate immediately after passing from the stomach.

The pH index of the duodenal contents varies after the ingestion of certain types of food substances according to McClure, Montague and Campbell (21). Duodenal contents were acid after ingestion of high protein diets, and alkaline after ingestion of high fat and carbohydrate food substances. No relation was found between the pH of the duodenal contents and the stimulation of the flow of bile and pancreatic juice.

The gastric juice is the first principal medium to which the coating is exposed, and according to Best and Taylor (13) the gastric juice is composed essentially of lipase, pepsin and hydrochloric acid with rennin in cases of infancy. According to Harrow and Sherwin (22) acid chyme ejected from the stomach comes in contact with the intestinal juice, bile and pancreatic juice.

The work of Verźar and Kúthy (23) indicates that very little digestive action on fatty acids takes place in the gastric juice under normal conditions. This work is supported by Harrow and Sherwin (22). However, Verźar and Kúthy reported that the alkaline soaps of the fatty acids are soluble at a pH index higher than is normally found in the human intestine. They also demonstrated that fatty acids,

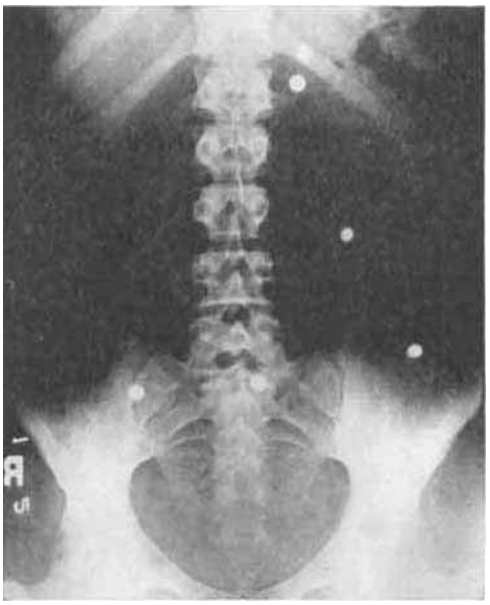

Fig. 4.—A Photograph of a Roentgenogram Two Hours after Administration of Six Tablets. Two Tablets Are in the Stomach, and Four Have Passed into the Intestines.

finely emulsified, form a diffusible suspension with paired salts of sodium taurocholate and sodium glycocholate. Such suspensions are formed in neutral or slightly acidic medium and have a low surface tension. They postulate the formation of fatty acid suspensions by means of bile salts complexes. This leads to a new principle of enteric coating which has been developed and demonstrated. It was possible to prepare a coating of suitable fatty acids, properly modified, which will resist the action of the gastric juice for a period of ten hours. Tablets coated with this material will

not disintegrate while they remain in the stomach. Upon passing into the intestinal tract disintegration will occur quickly irrespective of whether the fluid is alkaline, slightly acidic or neutral.

Development of a New Enteric Coating.—The use of shellac and shellac combinations has been recommended. A series of tests revealed that over a period of two years tablets so coated increased their disintegrating time materially. Salol and karatin used for a long time were found unreliable, thus supporting the information in "Remington's Practice of Pharmacy" (24) and Scoville's "The Art of Compounding" (25). Good results were obtained in some cases with cetyl alcohol. These coatings were tested *in vitro*.

The fatty acids investigated were lauric, myristic, stearic and eutectic mixtures of palmitic and stearic. The individual acids as well as many mixtures were investigated. It was found desirable to produce a coating with greater firmness and elasticity than the acids themselves could supply. The addition of opal wax[1] and castor oil was found to be of value. A small quantity of cholesterol increased the ease with which the coating would emulsify. When tested *in vitro* and by roentgen rays, this coating gave favorable results. However, in some cases disintegration did not take place until the tablets reached the colon. To overcome this, sodium taurocholate, a timing factor, was included. The formula of the completed coating follows:

New Enteric Coating

Myristic acid	68%
Opal Wax	25%
Castor Oil	2%
Cholesterol	1%
Sodium taurocholate	4%

For test purposes barium sulfate tablets, which would readily disintegrate when brought in contact with the digestive fluids, were used. The coating is applied as follows: Melt the myristic acid, opal wax, castor oil and cholesterol and dilute these with an equal volume of a mixture of equal parts of ethylene dichloride and benzin. To this mixture add the sodium taurocholate previously dissolved in ten times its own weight of absolute ethyl alcohol.

This coating, kept warm at 50° C., may be applied in the ordinary manner using special precaution to build a coating of uniform thickness. No dusting powder is necessary. Hot and cold air are desirable to evaporate the solvent and harden the application. A number of applications are necessary to bring the coating up to the desired thickness.

Tablets so coated were found to remain in the stomach in certain individuals for six hours, but disintegrated within two hours after entering the duodenum. In other cases, the tablets left the stomach in two hours and disintegrated within thirty minutes in the small intestines. All tests indicated that the coating possessed highly efficient enteric properties.

For results of tests conducted in the mechanical laboratory apparatus see Table II. For roentgeno-

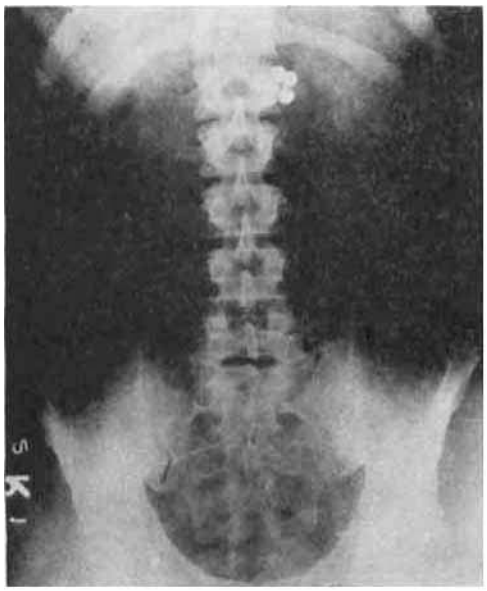

Fig. 5.—Photograph of a Roentgenogram, Five Minutes after Administration of Six Tablets Protected by the Developed Enteric Coating. All Tablets Are in the Stomach.

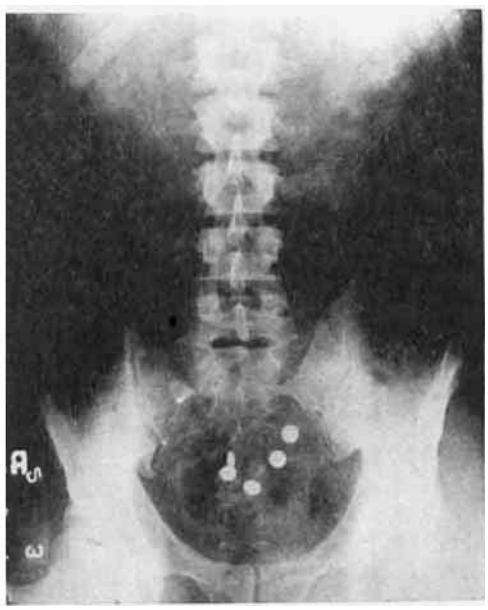

Fig. 6.—A Photograph of a Roentgenogram of the Same Individual as Is Shown in Fig. 5, but Taken Four Hours Later. All of the Tablets Are Now in the Intestines.

[1] Commercial name for hydrogenated castor oil, E. I. du Pont de Nemours & Co.

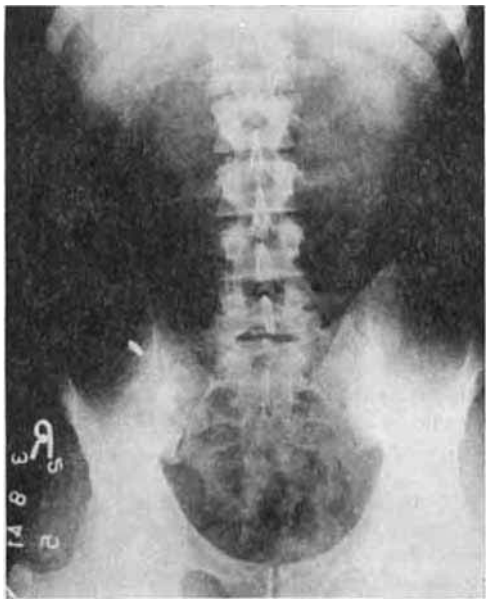

Fig. 7.—A Photograph of a Roentgenogram of the Same Individual as Is Shown in Figs. 5 and 6, but Taken Six Hours Later. All Tablets Have Disintegrated or Are in That Process.

grams showing results of the same coating see Figs. 5, 6 and 7.

Table II.—Tests in Mechanical Laboratory Apparatus

Five Tablets in Artificial Gastric Fluid Without Disintegration	Time Required for Disintegration in Artificial Intestinal Fluid
2 hours	4 hours in intestinal, neutral[a]
2 hours	5 hours in intestinal, acid[a]
2 hours	1/2 hour in intestinal, alkaline[a]
4 hours	3 hours in intestinal, neutral
4 hours	4 hours in intestinal, acid
4 hours	1/2 hour in intestinal, alkaline
6 hours	2 hours in intestinal, neutral
6 hours	3 hours in intestinal, acid
6 hours	1/2 hour in intestinal, alkaline
8 hours	2 hours in intestinal, neutral
8 hours	2 hours in intestinal, acid
8 hours	1/3 hour in intestinal, alkaline
10 hours	1 1/2 hours in intestinal, neutral
10 hours	2 hours in intestinal, acid
10 hours	1/3 hour in intestinal, alkaline

[a] See formulas for artificial intestinal fluid.

SUMMARY

A satisfactory method to determine the efficiency of enteric coatings, *in vitro*, has been developed.

In vitro results of tablets tested compare favorably with those obtained by roentgen rays *in vivo*.

Wide variation with respect to the disintegrating time was found in those tablets now on the market.

The rate with which the stomach empties and the fact that the alkalinity of the intestinal fluid cannot be relied on are important factors.

An enteric coating has been developed that demonstrated a high degree of efficiency.

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"The success of a discovery depends upon the time of its appearance."—Weir Mitchell