CONCLUSIONS.

1. The factors largely responsible for the variation in weight of machine made elastic filled gelatin capsules are (1) the uniformity in thickness and elasticity of the gelatin sheet used as the shell, (2) the accuracy with which the medicament is measured or weighed, (3) the uniformity of the molds, (4) the uniformity with which the medicament is distributed throughout the capsules of one batch, and (5) the uniformity of pressure applied by the machine in sealing.

2. From the data obtained in the tests made it would seem that twice the standard deviation is a reasonable margin of error for machine made elastic filled gelatin capsules. This would include 96.92% of the capsules weighed.

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# A STUDY OF ENTERIC COATINGS.[1]

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INTRODUCTION.

For many years pharmacists have tried to prepare medicines so that they would not be liberated for absorption until they had reached the intestine. Therefore, studies have been made from time to time to determine the value of enteric coatings by various test-tube methods. More recently attempts have been made to trace the disintegration of enteric coatings in the body by means of the X-ray.

The purposes of this investigation were: *First*, to study the physiological processes to which enteric coatings are subjected; *second*, to study the relative merits of the materials now used for enteric coatings; and *third*, to provide a more reliable enteric coating. The study of the passage of coated pills and capsules through the body was made possible by the installation of a General Electric X-ray machine in the Purdue University School of Pharmacy.

It was pointed out as early as 1889 by Bourquelot (1) that there are at least four classes of medicines which should be enterically coated. They are as follows:

(1) Medicines that by prolonged contact cause irritation to the stomach.
(2) Medicine that can injure the digestion by giving insoluble precipitates with pepsin and peptones.
(3) Medicines that are rendered inactive or decomposed by the gastric juice.
(4) Medicines which should arrive in the intestine as concentrated as possible.

In addition to the types of medicines mentioned above, the logic of enteric medication is evidenced by the fact that the intestine is the normal site for absorption. Former investigators have not taken the physiological factors influencing

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disintegration of the coatings into consideration. The importance of enteric medication to the pharmaceutical profession is borne out in a report by Jordan (2) who stated that 3.3 per cent of all prescriptions were orders for enterically coated medicines.

There are no standards in common use for the testing of enteric coatings. The tests which we made *in vitro* were similar to those outlined by Martindale and Westcott (3) and Wruble (4). The resistance to four hours of acid-pepsin solution was used as a basis for estimating the value of our coatings *in vitro*. This, however, is but a reasonable arbitrary limit, being at best no more than an approximation of the average emptying time of the stomach.

For our tests "*in vivo*" extensive use was made of the fluoroscope and the X-ray. The procedures and techniques will be described later in this paper.

## THE PHYSIOLOGICAL FACTORS INFLUENCING THE DISINTEGRATION OF ENTERIC COATINGS.

An understanding of the physiological and chemical reactions of the alimentary tract is necessary before the administration of enteric coatings can be intelligently considered. There are many physiological factors which affect the passage of pills and capsules from the stomach and influence their subsequent disintegration. The most important of these are:

(1) The time required for the pills or capsules to pass from the stomach.

Murlin (5) reported the stomach emptying time to be decidedly an individual matter but that the stomach should empty itself within four hours. We found that the stomach emptying time could not be depended upon as a reliable indication of the time required for the capsules to pass from the stomach. Our fluoroscopic observations revealed that in many cases capsules remained at the pyloric sphincter for a longer time than was required for the food to pass from the stomach. We attributed this to the fact that the passage of the intact capsules was hindered by the smallness of the pyloric opening, while the softened food particles were forced through the opening. We found that capsules when given about one and a half to two hours before a meal, at which time the stomach generally is empty, passed out of the stomach within a more uniform time and also that the stomach passed small capsules more uniformly than large capsules. This is an important observation since in many cases the enteric medicaments are directed to be taken at meal time and in large capsules.

(2) The acidity of the stomach and intestines.

It is well known that the stomach secretions are quite acid, ranging from about 0.2 to 0.4 per cent hydrochloric acid. The reaction of the intestinal tract is of great importance to the solution of this problem of enteric coatings, yet few of the investigators have studied the acid-alkaline condition of the intestine. The theory of enteric medication has depended too much upon the assumption that the intestine is always alkaline. A review of some of the reports on intestinal alkalinity show that this belief has been greatly over estimated. Myers and McClendon (6), McClendon and others (7), Long and Fenger (8) and Okada and Arai (9) all report the intestinal $p_H$ range to be from 3.6 to 7.9. It was their general belief that the extreme range on the acid side was greater than that on the alkaline side.

(3) The enzyme activity of the digestive tract.

The pancreatic juice contains enzymes which are both specific and powerful in their action. These enzymes are normally present and can be depended upon to distintegrate an enteric coating composed of the substrate of one or more of these enzymes in an alkaline or acid medium. Of the three main classes of foods, fats, proteins, and carbohydrates, only fats reach the intestine unaffected by the saliva or gastric juice. From a physiological viewpoint fats should make an ideal enteric coating but when used alone they are not hard enough to withstand body temperature and peristaltic pressure.

MATERIALS STUDIED FOR THEIR ENTERIC PROPERTIES.

Keratin was the first substance proposed as an enteric coating (10). Unna reported using it in 1884 at a meeting of the Berlin Medical Society. It was used because it belongs to a class of proteins which are insoluble in acid-pepsin solution and soluble in alkali solutions. It is interesting to note that keratin was first used as a pill mass and later used as a coating. Mylius (11), Puckner (12) and several others have pointed out the failure of keratin-coated medicines to withstand acid-pepsin digestion for more than a very short time. We studied the digestibility of a sample of commercial keratin in an acid-pepsin solution using the method of Puckner and found it to be 69 per cent soluble.

SALOL.

The method of applying salol as a pill coating is described in the National Formulary III, IV and V. There are several objections to the use of salol which render it unsuitable for enteric coatings. They are: (1) Salol upon hydrolysis yields phenol (36 per cent) and salicylic acid (64 per cent) which upon prolonged use may be objectionable, for regardless of the amount taken, its physiological action cannot be ignored; (2) The minimum amount of salol required to coat pills by the National Formulary V method is about 25 per cent of the weight of the coated pill; (3) Salol is not suited for the coating of hard gelatin capsules or tablets not of a spherical shape.

The solubility of salol in buffer solutions corresponding to the $p_H$ range of the intestine was undertaken. The procedure was as follows: To a tube containing 50 cc. of the buffer solution 0.080 Gm. of salol was added, placed in a water-bath maintained at 38° C. and stirred continuously for three hours. The contents of the tube were then filtered. The salol which remained upon the filter, the sides of the tube, and the stirrer was dissolved in chloroform. The chloroform was evaporated and the residue heated with ten cc. of 2.5% solution of sodium hydroxide on a steam-bath for five minutes. This solution was transferred to a 500-cc. iodine flask, and diluted with about 200 cc. of water. Fifty cubic centimeters of a 0.1*N* bromide-bromate solution were added together with 10 cc. of concentrated hydrochloric acid and the flask was shaken for one minute. Shaking was continued at intervals for thirty minutes, at the end of which time 10 cc. of a 15% solution of potassium iodide were added and shaking continued at intervals for 15 minutes. The free iodine was titrated with 0.1*N* thiosulfate, one cc. of 0.1*N* $Br.BrO_3$ being equivalent to 1.784 mg. of salol. The results of our analyses are shown in Table I.

TABTE I.—HYDROLYSIS OF SALOL WITH BUFFER MIXTURES.

| $p_H$. | Cc. of Buffer. | Cc. *N*/10 $Br.BrO_3$. | Cc. *N*/10 $Na_2S_2O_3$. | Gm. Salol. | Gm. Undissolved Salol. | Per Cent Hydrolyzed Salol. |
|---|---|---|---|---|---|---|
| 7.0 | 50 | 54.84 | 11.64 | 0.080 | 0.07282 | 8.90 |
| 7.4 | 50 | 53.12 | 9.05 | 0.080 | 0.07618 | 4.80 |
| 7.8 | 50 | 53.69 | 11.23 | 0.080 | 0.07604 | 4.90 |
| 8.0 | 50 | 52.87 | 14.70 | 0.080 | 0.06843 | 14.40 |
| 8.4 | 50 | 53.81 | 11.32 | 0.080 | 0.078016 | 2.40 |
| Distilled Water | 50 | 53.66 | 11.14 | 0.080 | 0.07586 | 5.10 |

Each of the above determinations is an average of four trials. The buffer mixtures for $p_H$ 7:0 and 7.4 were $Na_2HPO_4$ and $NaH_2PO_4$, respectively. Those for $p_H$ 7.8, 8.0 and 8.4 were $H_3BO_3$, KCl and NaOH.

Salol has been used as an enteric coating for sometime. However, it is not very reliable inasmuch as pills coated with it have been known to pass through the body intact. On the other hand, many salol coatings have been known to break in the stomach due, perhaps, to the fact that the temperature of the body is but a few degrees below that of the melting point of salol.

We have shown that salol is not hydrolyzed to any great extent in buffer solutions having ranges of $p_H$ comparable to those of the intestine. Our observations are about the same as those reported by other workers.

A limited number of pills, which had been carefully coated with salol, were given to several subjects and their density determined by means of the X-ray. The story is as follows: 10% of them disintegrated in the intestine, 20% in the stomach, 30% failed to disintegrate and the site of disintegration of the remaining 40% was uncertain.

### STEARIC ACID MIXTURES.

Stearic acid and stearic acid mixtures have long been used or suggested for use as enteric coatings. Many experiments were undertaken using combinations of stearic acid with salol, paraffin, wax, ceresin, glycosterin, lauric acid, palmitic acid, myristic acid, and stearic acid alone. The results of these experiments indicated that such substances possess the disadvantage of not forming a hard, tough coating and, because of their low melting point, cannot withstand peristaltic pressure. It might be well to note here that coatings which could be made hard with wax were so brittle that they invariably cracked on handling. Coatings containing sufficient paraffin to withstand body temperature formed a mixture which was not acted upon by the digestive juices.

### SANDARAC.

Sandarac has at various times been suggested as a coating. It is interesting to note that the earlier workers used it to mask the taste of bitter pills and not for an enteric purpose. The advantage of sandarac over most resins is its ease of application. It is not nearly as sticky as shellac and can be sprayed upon the pills very conveniently. Sandarac was unsuited for our use because it does not withstand stomach acid-pepsin or stomach digestion. Observations showed that invariably some pin-point sized holes existed in the coating and that the resin did not form a varnish-like film but rather a granular surface.

### SHELLAC.

Shellac has been used as a coating by the British Pharmaceutical Codex, Lascoff (13), Hilton (14) and Wruble (4). There are several disadvantages to its use. One is that it is inconvenient to apply as a coating because of its stickiness or tackiness and another is the uncertainty as to whether it is acted upon by the enzymes of the intestine.

Shellac has some properties which make it well suited for enteric purposes. It is insoluble in acid or neutral aqueous solutions and soluble in alkali solutions and alcohol. In an alcoholic solution it can be sprayed on the pills or capsules in a coating drum and the solvent quickly evaporated by means of a current of air, leaving a thin, smooth, tough film of coating on the capsules.

Tschirch (15) has shown that shellac is composed chiefly of oxygenated aliphatic acids.

### MISCELLANEOUS SUBSTANCES TESTED FOR ENTERIC PROPERTIES.

The following substances were mentioned in the literature as being suitable for use as enteric coatings. The results of our studies upon them may be briefly stated as follows:

1. Collodion formed a tough film which proved to be insoluble in both stomach and intestinal fluids.
2. Tolu and benzoin. These substances failed to dry properly and showed poor enteric properties.
3. Lacquers. The samples tested were insoluble in acid and alkaline solutions.
4. Albuminoids were digested in an acid-pepsin solution.
5. Waxes. When waxes were used alone and in combination with fats, a heavy coating was formed which fissured badly upon standing.
6. Formaldehyde-gelatin. Capsules treated with formaldehyde become insoluble upon aging and are, therefore, unreliable for enteric uses.

### SHELLAC AND CASTOR OIL COATINGS.

Since it was found that the intestine is not always alkaline, that a successful enteric coating must depend upon some factor other than alkalinity, and that fats are not digested until they reach the intestine, we attempted to find a coating that would possess the proper physical properties and yet be disintegrated in the intestine. Morel and Terroine (16) showed that the rate of digestibility of a series of triglycerides was influenced by the amount of unsaturated fatty acids in them. Of the fats and oils, castor oil was well suited for our purpose, containing as its chief glyceride the unsaturated ricinoleic acid. It is soluble in alcohol and mixes well with an alcoholic solution of shellac which upon evaporation leaves a thin, tough film. We found that a mixture of 20 parts of castor oil and 100 parts (by weight) of shellac in dissolved alcohol to be a satisfactory enteric mixture. In mixtures with the proportion of oil greater than this the coating was soft and would not withstand handling. The greater part of X-ray work was done upon capsules coated with this formula.

### X-RAY AND FLUOROSCOPIC EXAMINATIONS.

Because we had no previous methods to follow we had to find the most suitable physiological conditions for enteric medication. At first the capsules were taken immediately after the noon meal and the individuals examined during the remainder of the day. Results from this procedure were very inconsistent even after we had developed the coating where it would hold up six hours or more in the stomach. It was commonly observed that the stomach would be empty, or nearly so, and the capsule still unbroken in the stomach.

### GIVING ENTERIC CAPSULES BEFORE MEALS.

Having formulated a coating with good enteric properties, it was assumed that there should be a most favorable time for giving such medication for maximum results. An attempt was made to study the passage of capsules from the stomach when given one hour and a half to two hours before meal time.

In many cases it was observed that capsules left the stomach within 30 minutes, and in a high percentage of the cases before the next ingestion of food. Once in a while capsules would remain in the stomach from one meal to the next. However, our results indicated that enterically coated medicaments should be given one to two hours before meals. This claim is well borne out in Table II which shows what happened to 168 capsules taken by 85 subjects. Each was observed by means of the fluoroscope frequently enough to determine the path of the capsules.

These studies were made upon local townspeople who were unable, in some cases, to remain in the X-ray laboratory for the length of time necessary to complete the study. 137 of the capsules are accounted for in Table II. The remaining 31 were not successfully followed. We feel that complete observations were made upon 93 of these capsules.

The 44 capsules which are reported as "not disintegrated" are incomplete observations for reasons just stated above. However, it does show that the coatings were resistant to the gastric secretions. The capsules under this heading, as observed in the stomach, were made upon individual subjects. Furthermore, those capsules which failed to leave the stomach within three hours after ingestion are considered as unsuccessful in these observations. We feel that 89 capsules in this study proved to be reliable as far as the factors of time and disintegration are concerned.

TABLE II.—CAPSULES TAKEN BETWEEN MEALS.

Number of subjects—85
Number of capsules given—168
Number of capsules traced—137
Coating: Castor oil, shellac and alcohol mixture.

| Location. | Time after Ingestion. | Capsules Disintegrated. | Capsules Not Disintegrated. |
|---|---|---|---|
| A. In Stomach | 1 hour after taking | .. | 2 |
| | 1¼ hours after taking | .. | 2 |
| | 1½ " " " | .. | 3 |
| | 2 " " " | .. | 2 |
| | 3 " " " | .. | 3 |
| | 3½ " " " | .. | 5 |
| | 4 " " " | .. | 2 |
| | 4½ " " " | .. | 4 |
| | 5½ " " " | .. | 2 |
| | 6½ " " " | 4 | 1 |
| B. In Intestine | ½ hour " " | .. | 16 |
| | 1 " " " | 89 | .. |
| | 1½ hours " " | .. | 2 |
| | Total | 93 | 44 |

Observations: In three cases during the fluoroscopic observations necessary for the data in Table II capsules were observed at the moment they passed the pyloric sphincter into the duodenum. They were observed to move in a series of jerks, across the body and the length of the duodenum in about twenty seconds. This caused us to wonder whether intestinal digestion takes place in the jejunum and ileum rather than in the duodenum.

Another observation was that sodium tetraiodophenolphthalein is superior to that of barium sulfate as an opaque for this work. It dissolved readily as soon as the enteric coating broke, whereas barium sulfate, being insoluble, seemed to remain intact for some time in the broken capsule.

Tests were made upon two coatings, one much thicker and the other thinner than the one reported in Table II. The results were unsatisfactory. The thin coats broke down in the stomach and the heavier ones failed to disintegrate.

## CONCLUSIONS.

1. Of the coating materials studied only shellac and shellac-castor oil mixture gave evidence of disintegrating in the intestine within a reasonable time and of not being damaged by stomach conditions.

2. The best results were obtained when the capsules were taken on an empty stomach about one to two hours before meals.

3. An enteric coating, to be successful, must be dependent upon some factor other than alkalinity. The coating of shellac and castor oil has been found to digest in the intestinal fluids whether neutral or slightly acid, and is a reliable coating.

4. There was evidence that small capsules passed out of the stomach much more uniformly and within a shorter period of time than did the large capsules.

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