

## THE VALUE OF TOLU COATING, U. S. P. X AND N. F. V.

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The use of tolu as a coating for pills has been recommended for more than seventy-five years. Some of the early investigators even went so far as to employ tolu in forming the mass for phosphorus pills. They made the statement that tolu is soluble in the gastric juice and forms a more plastic pill mass. They also suggested the use of beeswax and tolu as a base for phosphorus pills. Tolu coating is also highly recommended by our present-day textbooks of Pharmacy, as well as being the official coating for Pills of Phosphorus and Pills of Ferrous Iodide.

The authors have found in making enteric coatings that tolu is resistant to the processes of digestion. This leads to the conclusion that possibly tolu coating for these official products is of little value. With this idea in mind, a study was made of tolu-coated pills to determine the percentage of disintegration in the body.

The efficiency of the tolu coating was determined by making some pills, approximately the same size as the official Pills of Phosphorus. The formula for the mass used was as follows:

Methylene Blue	1 Gm.
Althea, powder	12 Gm.
Acacia, powder	6 Gm.
Barium Sulphate	10 Gm.

A mass was made by moistening the ingredients with a sufficient quantity of a mixture of 2 parts of glycerin and one part of water. This mass was then divided and made into 200 pills.

The barium sulphate was added to the mass so that the X-ray could be used to definitely locate the position of the pills in the digestive tract. The methylene blue, by its property of coloring the urine, made possible the determination of the disintegration in cases where the X-ray was not used. The dye was also of value in determining the entirety of the coat. The dried pills were coated with tolu according to the formula given in the U. S. P. The reason for using this coating on Pills of Phosphorus is to form an air-tight seal protecting the phosphorus from the air. If air should come in contact with the mass of either Pills of Phosphorus or Pills of Ferrous Iodide, oxidation would take place in time, which would make the pill of little value. For this reason, it would be necessary to have the tolu coat entire. By placing the pills in water small openings might be detected by the leakage of the methylene blue. This test was made after the application of each coat until no further evidence of blue was noted. Microscopic examinations of the finished pill showed the coating to be on the average of about 0.1 mm. in thickness. These determinations of thickness were made because of the fact that it might be claimed that the pills were coated too heavily. The authors are confident that the coating was no thicker than required to protect the pill. Further microscopic examinations of these coats showed that the tiny depressions in the surface of the pill would not coat as heavy as the smoother surfaces, thus making weak spots in the coat. It is the opinion of the authors that if the coat could be applied uni-

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formly, these pills would be as impervious to water and the digestive fluids as lead shot.

Some of the early investigators made the discovery that old tolu, which had lost most of its volatile oil, was better for a coating than the fresher balsam. The authors agree with this statement as the results of their experiments indicate that there was greater disintegration of pills coated with tolu which was over ten years old. This is believed to be true, because old tolu is more brittle and, therefore, cracks more easily.

In order to be certain that the samples of tolu were not of an inferior grade, the pills were coated with tolu obtained from four different sources: J. L. Hopkins & Co. (4), S. B. Penick & Co. (1), Eimer and Amend (3), Chas. Huisling and Co., Inc. (2).

The coatings were tested in two ways, by the use of the X-ray and by giving an individual one of the pills and then observing the color of the urine for sixty hours. When the X-ray was used, the subject was given six pills. Radiographs were then taken at desired intervals until the pills were excreted from the body or were disintegrated. In most cases, these experiments extended over two days. A small teaspoonful of Bari-o-meal in a glass of water, was given before the first radiograph was taken in order to locate the stomach. The shadow produced by this amount of Bari-o-meal was not heavy enough to mask the pills.

The results obtained by giving the subject a single pill, coated with tolu, purchased from (1) were as follows:

Thirty-seven subjects were used, 23 subjects were used more than once, 8 of the 23 subjects showed no disintegration. In no case where the subject was used more than once was it found that every pill disintegrated; 109 pills were given; 31 pills disintegrated. The percentage of disintegration was 28.44.

The disintegration time was as follows:

One to 5 hours, 1 pill; 6 to 10 hours, 1; 11 to 15 hours, 7; 16 to 20 hours, 3; 21 to 25 hours, 5; 26 to 30 hours, 6; 31 to 35 hours, 5; 36 to 40 hours, 1; 41 to 45 hours, none; 45 to 50 hours, 2 pills.

The X-ray experiments with (1) tolu gave the following results, with the four subjects that were used:

Subject 1, pills disintegrated, 1; excreted, 4; undetermined, 1. Subject 2, disintegrated, 3; excreted, 3; undetermined, none. Subject 3, disintegrated, 2; excreted, 4; undetermined, none. Subject 4, disintegrated, none; excreted, 5; undetermined, 1.

The following table gives the number of pills with their time and location of disintegration and the time of excretion:

TABLE I.

Time in Hours.	5.	10.	15.	20.	25.	30.	35.	40.	45.	50.
Stomach	18	13-2D <sup>1</sup>	5							
Small intestine	6	2	1							
Ascending colon		1D	1	12	10	3	3			
Transverse colon			1D	2D		4	1	2	2	
Descending colon						2	2	4	4	
Pelvic colon			3	3		2	5			1
Excreted				3	2	1		3		7

<sup>1</sup> The letter D is used to designate disintegration. The number preceding the D is used to designate the number of pills disintegrating and the number in front of the dash is the total number of pills, inclusive of the ones disintegrating in the given location, for example, stomach 5-2D.

The results obtained by giving the subject a single pill coated with tolu purchased from (2) were as follows:

Twenty-seven subjects were used; 10 subjects were used more than once, 5 out of the 10 subjects showed no disintegration. In the case of one subject, who was used more than once, it was found that every pill disintegrated; 49 pills were given; 14 pills disintegrated. The percentage of disintegration was 28.57.

The disintegration time was as follows:

One to 5 hours, 1 pill; 6 to 10 hours, none; 11 to 15 hours, 2; 16 to 20 hours, none; 21 to 25 hours, 4; 26 to 30 hours, 3; 31 to 35 hours, none; 36 to 40 hours, 2; 41 to 45 hours, 2; 46 to 50 hours, none.

In the X-ray experiments using (2) tolu, seven subjects were used and the results were as follows:

Subject 1, pills disintegrated, none; excreted, 2; undetermined, 4. Subject 2, disintegrated, 3; excreted, 1; undetermined, 2. Subject 3, disintegrated, 3; excreted, none; undetermined, 3. Subject 4, disintegrated, 1; excreted, 4; undetermined, one. Subject 5, disintegrated, none; excreted, 6; undetermined, none. Subject 6, disintegrated, 1; excreted, 4; undetermined, 1. Subject 7, disintegrated, 3; excreted, 3; undetermined, none.

The following table gives the number of pills with their time and location of disintegration and the time of excretion.

TABLE II.

Time in Hours.	5.	10.	15.	20.	25.	30.	35.	40.	45.
Stomach	22	17-3D	6						
Small intestine	19	9-1D	1						
Ascending colon	1	13	14-1D	4	10-1D	5-1D			
Transverse colon		1	4	2	4-3D		2	1D	
Descending colon		2	1		1				
Pelvic colon			1	11	9	9	6		
Excreted					13	2	2	3	

The results obtained by giving the subject a single pill coated with tolu purchased from (3) were as follows:

Twenty-two subjects were used; 16 subjects were used more than once; 3 of the 16 subjects showed no disintegration. In the case of three subjects who were used more than once, it was found that every pill disintegrated; 67 pills were given; 35 pills disintegrated. The percentage of disintegration was 52.23.

The disintegration time was as follows:

One to 5 hours, 1 pill; 6 to 10 hours, 4; 11 to 15 hours, 3; 16 to 20 hours, 5; 21 to 25 hours, 11; 26 to 30 hours, 4; 31 to 35 hours, 1; 36 to 40 hours, 1; 41 to 45 hours, 5; 46 to 50 hours, none.

The results of the X-ray experiments using seven subjects may be tabulated as follows:

Subject 1, pills disintegrated, 4; excreted, 1; undetermined, 1. Subject 2, disintegrated, 2; excreted, 4; undetermined, none. Subject 3, disintegrated, 6; excreted, none; undetermined, none; Subject 4, disintegrated, 2; excreted, 4; undetermined, none; Subject 5, disintegrated, 2; excreted, 4; undetermined, none. Subject 6, disintegrated, 4; excreted, none; undetermined, 2. Subject 7, disintegrated, 3; excreted, 1; undetermined, 2.

The following table gives the number of pills with their time and location of disintegration and the time of excretion:

TABLE III.

Time in Hours.	5.	10.	15.	20.	25.	30.	35.	40.	45.	50.
Stomach	17-1D	8	4							
Small intestine	19-1D	6-4D	7-1D							
Ascending colon	3	11	10-1D	6	9-1D	5				
Transverse colon	2	2	3-1D	3	7-3D	4-1D				
Descending colon	1	1	2-1D	2	4-3D			3-3D		
Pelvic colon			3	1	4					
Excreted			3	4	1	6				

The results obtained by giving the subject a single pill coated with tolu, purchased from (4) were as follows:

Twenty-six subjects were used; 19 subjects were used more than once; 5 subjects out of 19 showed no disintegration; 1 subject out of the 19 showed total disintegration; 61 pills were given; 22 pills disintegrated. The percentage of disintegration was 36.65.

The disintegration time was as follows:

One to 5 hours, none; 6 to 10 hours, none; 11 to 15 hours, none; 16 to 20 hours, 4 pills; 21 to 25 hours, 7; 26 to 30 hours, 8; 31 to 35 hours, 1; 36 to 40 hours, none; 41 to 45 hours, 2; 46 to 50 hours, none.

The results of the X-ray experiments using four subjects may be tabulated as follows:

Subject 1, pills disintegrated, 3; excreted, 1; undetermined, 2. Subject 2, disintegrated, 4; excreted, 2; undetermined, none. Subject 3, disintegrated, 2; excreted, 4; undetermined none; Subject 4, disintegrated, 2; excreted, 4; undetermined, none.

The following table gives the number of pills with their time and location of disintegration and the time of excretion.

TABLE IV.

Time in Hours.	5.	10.	15.	20.	25.	30.	35.	40.	45.	50.
Stomach	18	6	6							
Small intestine	3		4-2D							
Ascending colon	2		7-1D	11-2D	7-1D	6	1D	2-1D		
Transverse colon			2	5	3	2-1D		1-D		
Descending colon			3		1	2		1		
Pelvic colon			2	1-D	2	2	2	2	2	
Excreted				4	1			2	2	2

By summarizing all the experiments, the following results were found:

Two hundred eighty-six pills were given; 112 subjects were used; 102 pills disintegrated. The percentage disintegration was 35.66.

The average for the disintegration time is shown in the following table, which gives the number of pills disintegrated at five-hour intervals. It will be noticed that the highest number of pills disintegrated in 21 to 30 hours, which would indicate that most of them were in the colon before disintegration took place. For proper medication, disintegration should take place before the pills reach that part of the alimentary canal:

One to 5 hours, 3 pills; 6 to 10 hours, 5; 11 to 15 hours, 12; 16 to 20 hours, 12; 21 to 25 hours, 27; 26 to 30 hours, 21; 31 to 35 hours, 7; 36 to 40 hours, 4; 41 to 45 hours, 9; 46 to 50 hours, 2.

It is evident, from this data, that the further use of tolu as a coating should be discontinued, since in 64.34 per cent of the cases no medication whatever was obtained and in many cases where disintegration was obtained, it probably occurred too late for proper absorption. It is therefore recommended to the U. S. P. and N. F. Revision Committees that gelatin coating be substituted for tolu coating in the forthcoming revisions.

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