

geneous mixture of opium is obtained. Brush the contents of the mortar on a piece of glazed paper and from there into a glass-stoppered Erlenmeyer flask of about 150 Cc. capacity. Add 75 Cc. of distilled water and shake vigorously for fifteen minutes, and then every ten minutes during three hours (or continuously in a mechanical shaker). Filter off 50 Cc. of the solution into a 50 Cc. volumetric flask. This represents approximately 5 Gm. of opium.

Transfer the whole of the filtrate to a separator, washing the flask with a small portion of distilled water. Add 15 Cc. of ether and shake thoroughly. Now add 1 Gm. of ammonium chloride and shake frequently for half an hour; then set it aside in a cool place overnight. Plug the stem of the separator fairly tight with a pledget of purified cotton and allow the liquid to drain off. Wash the funnel and its contents with morphinated water until the drippings are colorless, then wash with two small portions of distilled water to replace the morphinated water. Dislodge the cotton plug in the separator stem by blowing vigorously into the top of the separatory funnel and catch it in a clean Erlenmeyer flask.

Close the stop-cock and add 25 Cc. of tenth-normal sulphuric acid, V. S., replace the stopper and agitate until the crystals in the separator are dissolved. Then dissolve the crystals in the stem of the separator by holding the funnel at an angle, allowing the acid to run out slowly into the Erlenmeyer flask and at the same time rotating the separator. Wash the separator with three 10 Cc. portions of distilled water; also wash the stem of the separator, adding all of these washings to the contents of the Erlenmeyer flask. Agitate the flask until any remaining crystals are dissolved and titrate the excess of acid with fiftieth-normal potassium hydroxide, V. S. Make a correction by adding to the actual number of Cc. of acid consumed one twenty-fifth of this amount. Each mil of tenth-normal sulphuric acid, V. S., consumed corresponds to 0.028516 Gm. of anhydrous morphine.

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TOLU AND SUGAR COATING IN THE DISGUISED OF MEDICINES.

BY BERNARD FANTUS, M.D.

The disguising of disagreeable medicines is, in general, a problem of sneaking the agent past the guardianship of the palate, without changing the substance to such an extent as to impair its medicinal activity. One means of doing this is by some coating insoluble in the saliva but soluble in some of the other digestive juices. Capsules and pills solve this problem for the adult. For children, the problem of coating of medicines is thus far unsolved.

For quite a time I have worked upon the coating of tiny granules of medication with insoluble material: Have tried cacao butter, paraffin of low melting point dissolved in ether, liquid petrolatum, and, though each of these did something in the direction of subduing tastes, none of them was satisfactory. Of late, I experimented with resins, such as mastic and tolu, and believe I have found in the latter an agent that meets the requirements. Mastic does not seem to be more efficient than tolu, and is much inferior to it in flavor.

My aim is to coat each particle of the medicament with a thin layer of resin and then with sugar, which I believe can be accomplished in the following manner: The coarsely powdered (No. 40) or granular drug is stirred up with a suitable amount of a 1 or 2 percent alcoholic solution of tolu. It is then immediately thrown upon powdered sugar on a coarse mesh sieve, say a No. 20 sieve. As the resin-impregnated material is being rubbed through the sieve, it is at one and the same time converted into granules and coated with sugar. By repeating the sifting several times, and then mixing the granules gently and without trituration, a considerable degree of lessening of the taste of substances suitable for this process can be obtained.

It is of advantage to add saccharin to the tolu solution. For, whenever substances of unequal degree of solubility pass through the mouth, the least soluble material is the one that is tasted most, because it is tasted last, and its taste lingers as long as there is a particle of the substance left in the mouth or pharynx. This lingering taste is best subdued by saccharin.

I therefore use the following solution for the saturating of the medicinal powder of granules:

SACCHARINATED SOLUTION OF TOLU.

| | |
|----------------|-------|
| Tolu..... | 2.0 |
| Saccharin..... | 2.0 |
| Alcohol..... | 100.0 |

TOLU-COATED CALCIUM SALICYLATE.

The problem of the administration of salicylate in "candy form" was not solved in a perfectly satisfactory manner in my previous publications on "Candy Medication."¹ In the series of salicylates studied, *salophen* (acetylaminosalol) gave the best results, both as far as palatability and clinical usefulness were concerned. Of this substance, 0.06 Gm. (1 grain) can be readily administered in a 0.30 Gm. (5 grain) tablet. *Saloquinine*, of which 0.06 Gm. (1 grain) may also be administered in this form, is somewhat less satisfactory, as far as taste is concerned. There are, however, occasions when it may be undesirable to administer the other agent with which the salicylate is combined in the substance mentioned: the quinine in the case of saloquinine, the phenacetin in the case of salophen. Furthermore, salophen has of late been unobtainable in the market, owing to the European war.

Aspirin (acetylsalicylic acid) is so difficult to disguise that not more than 0.015 Gm. (1/4 grain) can be given in a 0.30 Gm. (5 grain) tablet; and even then the preparation is by no means perfect. *Novaspirin* (methylene-citrylsalicylic acid) is much better from the standpoint of disguising, 0.015 Gm. (1/4 grain) producing practically perfect tablets. Even 0.03 Gm. (1/2 grain) may be given in this form. However, the dose is still rather small. Of *magnesium salicylate*, not more than 0.03 Gm. (1/2 grain) can be given in this form; and even this dose does not make a perfect preparation.

As only perfectly delicious sweet tablets should be used as "candy medica-

¹ "Candy Medication," C. V. Mosby Company, St. Louis. "Candy Medication," *Journ. A. M. A.*, Jan. 1, 1916, LXVI, pp. 25-28.

tion," it is desirable that aspirin and magnesium salicylate be deleted from the "candy materia medica." This can be done all the more readily as we now have in sweet tablets of tolu-coated calcium salicylate, prepared according to the following formula, a satisfactory administration form of salicylate.

SWEET TABLETS OF CALCIUM SALICYLATE.

0.06 Gm. (1 grain).

| | |
|-------------------------------------|-----------|
| Calcium Salicylate (granular)..... | 6.00 Gm. |
| Saccharinated Solution of Tolu..... | 3.00 mils |
| White Fat Sugar ² | 24.00 Gm. |

Pour the tolu solution over the calcium salicylate. Stir without pressure, until the granules have been thoroughly moistened with the fluid. Place the white fat sugar upon a No. 20 sieve. Now add the tolu-coated calcium salicylate to the sugar and pass it through the sieve repeatedly, so as to sugar-coat the granules of calcium salicylate as well as to secure thorough admixture. Compress in a tablet machine, using ³/₈ inch die and punches to make one hundred 0.30 Gm. tablets.

Without the tolu and sugar coating, as described in the above process, calcium salicylate is no better than magnesium salicylate for administration in this form. However, owing to its comparative insolubility in alcohol, it lends itself well to tolu coating. That these tablets liberate the salicylate ion can be readily demonstrated by taking a few of them, whereupon the urine will give the characteristic reaction with ferric chloride within two hours.

Inasmuch as tolu and sugar coating promised to be of help in the administration of other medicaments, further experiments were undertaken with this process. It was soon found that, to be suitable for this purpose, the agent must be sparingly soluble in alcohol and in water. Sodium bromide, for instance, does not lend itself to this method of disguising. On the other hand, there is a host of vegetable powders that may well be disguised by this method.

TOLU-COATED SENNA.

Physic is still the most important agent in the armamentarium of the physician. Phenolphthalein and calomel have thus far been the best cathartics from the standpoint of tastelessness; elaterin, podophyllin and jalap, though easily disguised, being too drastic. Calomel can, of course, not be used frequently; and phenolphthalein is a substance that patients readily become habituated to, so that the dose must be increased from time to time. The senna tablets, containing 0.06 Gm. (1 grain), the formula for which had been previously devised,

² *White Fat Sugar* is prepared as follows:

| | |
|---------------------------|-----------|
| Spirit of Peppermint..... | 2.00 mils |
| Fat Starch*..... | 20.00 Gm. |
| Sugar, Powdered..... | 80.00 Gm. |

To the powdered sugar add the fat starch and the spirit of peppermint. Mix and preserve in a well-stoppered bottle in a dark place.

* *Fat Starch* has the following composition:

| | |
|--|------------|
| Alcoholic Solution of Saccharin, 3%..... | 15.00 mils |
| Liquid Petrolatum..... | 25.00 Gm. |
| Starch..... | 75.00 Gm. |

Mix the starch with the solution of saccharin, and permit the alcohol to evaporate completely. Then incorporate the liquid petrolatum.

were not absolutely perfect. By means of tolu-coating a perfect tablet can be obtained, as the result of the following formula:

SWEET TABLETS OF SENNA (IMPROVED FORMULA).

0.06 Gm. (1 grain).

| | |
|-------------------------------------|-----------|
| Senna, No. 40 Powder..... | 6.00 Gm. |
| Saccharinated Solution of Tolu..... | 6.00 mils |
| Red Fat Sugar ³ | 24.00 Gm. |

Doubt might be entertained regarding the efficiency of the tolu-coated drug. I therefore experimented upon myself, and found that 0.50 Gm. of senna in form of these tablets gave me violent purgation within eight hours. Even 0.30 Gm. of senna in form of these tablets proved unpleasantly strong in purgative effect after ten hours. I must confess than I am rather sensitive to cathartics. However, there is no doubt in my mind that these tablets are an efficient physic.

TOLU-COATED IPECAC.

In view of the importance of ipecac as an emetic and expectorant, I did considerable experimenting with it; but was unable to subdue its taste sufficiently to administer useful doses of it in perfectly pleasant form. Tolu-coating, as proposed, solves the problem of the administration of ipecac in "candy form." As much as 0.03 Gm. of powdered ipecac can be given, which is practically equal in strength to 1/2 mil of syrup of ipecac, so that two of these tablets would represent the average expectorant dose for adults. A few of these tablets ought to be sufficient to produce vomiting in a child. I felt distinctly nauseated an hour after taking five of them.

The following formula for 0.03 Gm. (1/2 grain) ipecac tablets might, therefore, be considered emetic for children, expectorant for adults. Tablets of 1/10 the strength would give a sufficient dose for expectorant action in children, 3 years of age.

SWEET TABLETS OF IPECAC.

0.03 Gm. (1/2 grain).

| | |
|-------------------------------------|-----------|
| Ipecac, No. 40 Powder..... | 3.00 Gm. |
| Saccharinated Solution of Tolu..... | 3.00 mils |
| Cacao Sugar ⁴ | 27.00 Gm. |

Process of preparation same as specified in first formula.

³ Red Fat Sugar is prepared as follows:

| | |
|-------------------------------------|-----------|
| Solution of Carmine, N. F..... | 6.00 mils |
| Spirit of Cinnamon, 10 percent..... | 1.00 mils |
| Fat Starch..... | 20.00 Gm. |
| Sugar, Powdered..... | 80.00 Gm. |

Mix the carmine solution with the sugar and permit the powder to dry. Then add the spirit of cinnamon. Preserve in well-stoppered bottle in a dark place.

⁴ Cacao Sugar:

| | |
|-------------------------------------|-----------|
| Spirit of Cinnamon, 10 percent..... | 0.50 mil |
| Cacao Powder..... | 10.00 Gm. |
| Dextrose..... | 10.00 Gm. |
| Sugar, Powdered..... | 80.00 Gm. |

Mix thoroughly by trituration in a mortar, and preserve in a well-stoppered bottle.

To ascertain the relative effects of tolu-coated ipecac and of the drug without coating, one dog was given by stomach tube 0.2 Gm. of ipecac No. 40 powder per Kg. Another dog was given the same relative amount of the same drug, previously coated with tolu and sugar, as described above. Care was taken to permit the tolu-coating to dry before administration. In both cases the drug was mixed with 50 mls of water and injected into the stomach through the stomach tube by means of a large syringe. The results are shown in Table I, from which

TABLE I.

COMPARISON OF EFFECTS OF IPECAC AND TOLU-COATED IPECAC UPON DOGS WITH EMPTY STOMACH. STOMACH TUBE ADMINISTRATION.

| Time | Hour | 10: | | 11: | | 12: | | 1: | | 2: | | | | |
|--------|----------------------------------|-----|-----|-----|-----|-----|-----|----|----|-------|----|----|----|---------|
| | | 10: | 10: | 11: | 11: | 12: | 12: | 1: | 1: | 2: | 2: | | | |
| | Minutes | 15 | 30 | 45 | 15 | 30 | 45 | 15 | 30 | 45 | 15 | 30 | 45 | |
| Dog 1 | Dose Ipecac 0.2 X Kg. | | | | X | X | X | X | X | X | XX | X | X | b. m. |
| Dog 2. | Dose Tolu ipecac 0.2 X Kg. | | | | | | | X | | b. m. | X | | | b. m. X |

X means emesis; b. m., bowel movement.

It will be seen that the effect of tolu-coated ipecac sets in a little later and is milder.

it is evident that some of the emetic action of ipecac is still obtainable from the tolu-coated drug. The action is merely delayed and milder. That drying of the tolu-coating is necessary for reliable results was shown by another experiment in which such care was not exercised, and which resulted in the dog that obtained the tolu-coated drug, vomiting 15 minutes after the administration, while the control animal did not vomit until 48 minutes had elapsed. The emesis was equally frequent in both doses, both dogs vomiting about seven times within the next few hours.

TOLU- AND SUGAR-COATED DIGITALIS.

In view of the importance of digitalis as a medicament, experiments were next undertaken to determine the suitability of this substance and it can be positively asserted that tolu-coating gives a much better product than the form previously developed.

SWEET TABLETS OF DIGITALIS.

(Improved formula.)

0.008 Gm. (1/8 grain).

| | |
|-------------------------------------|-----------|
| Digitalis, 40 Powder..... | 0.80 Gm. |
| Saccharinated Solution of Tolu..... | 1.60 mls |
| Cacao Sugar ⁵ | 29.20 Gm. |

Preparation same as before described.

Twice the dose, that is, 0.016 Gm. (1/4 grain) and even more could be administered in perfectly delicious form by means of this process.

Of course, the most important question is whether the tolu-coated digitalis does or does not have the same action as the native drug; for activity is of much greater importance than palatability. A study was therefore undertaken to compare the toxicity of the two forms of digitalis. At first, an attempt was made to

⁵ Formula in footnote on previous page.

use rabbits for this purpose. It was found almost impossible to kill rabbits with digitalis. As much as 4 Gm. per Kg. did not have uniform effects, some animals surviving and some dying a few days later. The administration of digitalis to dogs leads to vomiting. It therefore became necessary to administer morphine previously, to prevent the emesis. In the experiments about to be reported, 4 Mg. of morphine sulphate per Kg. were given hypodermically one hour before administration of the dose. During this time, the dogs vomited and purged freely. They were then given, by means of the stomach tube, the tolu- and sugar-coated digitalis prepared according to the formula given and permitted to dry, while control dogs were given equivalent doses of the same drug in its native form.

The results are shown in Table II, from which it is evident that tolu-coating does not greatly lessen the toxicity of digitalis to dogs.

TABLE II.

COMPARISON OF EFFECT OF DIGITALIS WITH TOLU-COATED DIGITALIS ADMINISTERED TO MORPHINIZED DOGS BY MEANS OF STOMACH TUBE.

| Dog. | Weight, Kg. | Dose per Kg. | Total dose. | Lived. | Necropsy. |
|------|-------------|-----------------|-------------|--------|---|
| | | Tolu Digitalis. | | | |
| 1. | 8.70 | 2 Gm. | 17.4 | 1 day | Much digitalis in stomach. Submucous hemorrhages in stomach. Urine contains albumin |
| 2. | 10.00 | 1.5 | 15.00 | 1 day | Much digitalis in stomach. Some gastric irritation |
| 3. | 7.00 | 1.0 | 7.00 | Lived | |
| 4. | 6.00 | 1.0 | 6.00 | 2 days | Stomach almost empty. No albumin in urine |
| 5. | 5.00 | 1.0 | 5.00 | 1 day | Much digitalis in stomach. Upper part of intestine hemorrhagic in spots |
| 6. | 3.60 | 1.0 | 3.60 | 2 days | No necropsy performed |
| 7. | 5.9 | 1.0 | 5.9 | 1 day | Stomach contains moderate amount of digitalis. No albumin in urine |
| | | Digitalis. | | | |
| 10. | 6.50 | 2 Gm. | 13.00 | 1 day | No necropsy performed |
| 11. | 8.00 | 1 Gm. | 8.00 | 1 day | No necropsy performed |
| 12. | 8.60 | 1 Gm. | 8.60 | 2 days | No necropsy performed |
| 16. | 11.40 | 1 Gm. | 11.40 | 1 day | No necropsy performed |
| 13. | 10.00 | 0.5 Gm. | 5.00 | 1 day | Much digitalis in inflamed stomach |
| 14. | 9.50 | 0.5 Gm. | 4.75 | Lived | |
| 15. | 10.00 | 0.25 Gm. | 2.50 | Lived | |

SUMMARY OF ABOVE DETAILED EXPERIMENTS.

| Dose per Kg. | No. of experiments. | Tolu-Coated Digitalis. Result. | No. of experiments. | Digitalis. Result. |
|--------------|---------------------|-----------------------------------|---------------------|-----------------------|
| 2 Gm. | 1 | Died | 1 | Died |
| 1.5 Gm. | 1 | Died | | |
| 1 Gm. | 5 | 4 died | 3 | All died |
| 0.5 Gm. | | | 2 | 1 died |
| 0.25 Gm. | | | 1 | Recovered |

It will be seen that there is not much difference in the toxicity of digitalis and of tolu-coated digitalis.

It is interesting to note, in this connection, that morphinized dogs dying within 24 hours of the administration of the poison still hold a large amount of digitalis in their stomach, while dogs dying within 2 days had an almost empty stomach. Inasmuch as the death, in either case, was due to the digitalis, one is led to suspect that the gastric juice is capable of extracting the active principles even from tolu-coated digitalis. It seems fair to infer that tolu-coated digitalis will exert its action in the human being.

CONCLUSIONS.

1. Tolu and sugar coating of granulated medicaments of slight degree of solubility in alcohol and water is distinctly advantageous from the standpoint of disguising.
2. This coating does not interfere with the activity of digitalis, senna and of calcium salicylate. It may lessen somewhat the effect of ipecac upon the stomach.
3. Tolu and sugar coating can easily be carried out by any pharmacist, provided with a set of sieves.
4. The medication, thus disguised, might be administered in the form of powder or preferably in form of compressed tablets.

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SOME COLOR CHANGES IN SOLUTIONS CONTAINING FERRIC CITRO-CHLORIDE.*

BY WILLIAM R. WHITE.

In making a stock solution of ferric citro-chloride, the same strength as the Tincture Ferric Citro-Chloride, N. F., for use in making elixirs, I have frequently noticed a difference in the shade of the green color produced. Seeking to obtain the same shade each time, I proceeded along the lines suggested by Prof. Otto Raubenheimer in his article published in the *JOURNAL OF THE A. PH. A.*, Vol. IV, p. 351. By adding sodium bicarbonate I succeeded in getting the desired apple-green color. The process was tedious and the effervescence annoying, and induced me to make other experiments.

I soon found that not only would alkali carbonates and bicarbonates change the color of the solution from an olive-green to an apple-green but also that the alkali hydroxides would produce the same results; an excess, however, destroys the green color, which changes to a reddish brown.

I next tried the effect of the mineral acids, hydrochloric, sulphuric and nitric, and found that when they were added in excess to a green solution, the green color was entirely destroyed and like with the excessive addition of alkali a reddish brown color produced. Also if the acid is added gradually to a reddish brown solution, produced by the addition of excess alkali, the solution again assumes a green color; continued addition of acid causes the green color to disappear and the solution again becomes reddish brown. By adding alkali to a reddish brown solution, due to excess of acid, the green color is again developed and gives place to the reddish brown color when the alkali is in excess.

These experiments proved that the green color does not persist in a ferric citro-chloride solution unless the acidity or alkalinity is within certain degrees

* Read before Scientific Section, A. Ph. A., Indianapolis meeting.