Sample Number.	Assay of ointment, Per cent.	Assay of extract, Per cent.
1	0.843	0.832
2	0.829	0.820
3	0.881	0.835
4	0.857	0.829
5	0.849	0.836
6	0.838	0.822
Average	0.8495	0.829

BIBLIOGRAPHY.

[1] U. S. P. IX, 1916, p. 482.
[2] U. S. P. IX, 1916, p. 161.
[3] U. S. P. IX, 1916, p. 161.
[4] U. S. P. IX, 1916, p. 144.
[5] U. S. P. IX, 1916, p. 178.

FROM THE LABORATORIES OF PHARMACOLOGY OF THE SCHOOL OF MEDICINE OF EMORY UNIVERSITY, ATLANTA, GA.

HOT EXTRACTION OF DRUGS.*

BY WILBUR L. SCOVILLE.

The problem of economical extraction of drugs is serious to the drug manufacturer. The increasing use of standardized preparations calls for a nearly complete extraction of the active or soluble constituents of a drug, and the amount of menstruum needed for this as well as the time involved and cost of concentrating the weaker percolate are all factors in the cost of the product. Any method of procedure which will hasten the exhaustion, or reduce the amount of percolate needed, will be likely to materially reduce the cost of manufacture and also produce a more stable product. For precipitation in galenical preparations depends in large measure upon exposure to light and air, and the less the volume of percolate the less is the exposure, and the smaller the precipitation.

Since heat favors the solution of plant constituents as it does of synthetic or natural chemicals, hot extraction has often been advocated for the more slowly exhausted drugs. But in drugs we have other factors beside the soluble or active constituents. It is desirable to extract the soluble or active constituents with as little of the inert materials as possible so that stability in the finished preparation may be promoted. Moreover, many drugs contain enzymes which act upon other constituents and either produce the desired properties, as in the case of cyanogen products in wild cherry, or of the volatile oil in the case of mustard, or else may destroy the active constituent as in strophanthus. The question of the influence of heat on these enzymes is therefore important. Then there is to be considered the action of heat on both the active constituents and on the inert. Few of the active constituents of drugs are injured by a moderate heat, if not too long continued and if protected, in part, from the action of air while hot. On the other hand, it was shown in the case of licorice[1] that the albuminoid principles of this drug are coagulated by

* Scientific Section, A. Ph. A., Cleveland meeting, 1922.

[1] "The Extraction of Licorice," JOUR. A. PH. A., 10, 688, 1921.

heat and so separated from the desirable glycyrrhizin, which is uninjured by the temperature of boiling water. Here is an instance of a drug which yields a far superior preparation when extracted with boiling water, to that prepared with cold water. The heat rejects undesirable constituents and favors the extraction of the desirable ones.

For experimental purposes, three plans of hot extraction have been tried. In the case of aqueous menstruum, as with licorice, a beaker fitted as a Squibb well-tube percolator, which can be set directly on a steam-bath and kept there during the process of extraction, is a convenient plan. The evaporation is counterbalanced by keeping the drug well covered with water, and renewing it with hot water instead of cold. This keeps the drug and menstruum at a fairly uniform temperature, even with small quantities, during the whole process.

For alcoholic menstrua a special apparatus was made consisting of a copper percolator of the usual form, having a capacity of about 800 cc and provided at the bottom with an extra delivery-tube issuing at one side of the usual delivery. This was enclosed in a larger percolator of corresponding shape, so that there was a space of about 10 mm. between the two percolators. The larger percolator was fitted with a conical top, arranged to be clamped on and connected with a reverse condenser by which the volatilized menstruum would be condensed and dropped on the drug in process of exhaustion. The moistened drug was packed in the inner percolator, saturated with menstruum, and connected tightly to a flask at the lower end by means of a perforated stopper. On connecting the condenser, and applying heat to the flask, the menstruum contained therein was boiled, the hot vapors passing up through the space between the two percolators and into the condenser where it was liquefied and dropped on the drug. The drug was thus kept hot by the heated vapors which also reheated the condensate. The percolate could be collected either in the distilling flask through the straight tubulure, or drawn out through the side tubulure and collected in another flask or bottle. Three drugs were treated in this apparatus, *viz.:*

Cinchona.—250 Gm. of cinchona calisaya assaying 5.3% of total alkaloids were extracted in the usual way (cold) with a menstruum (*a*) 250 cc of 76% alcohol containing 1.75% of hydrochloric acid, followed by (*b*) neutral 76% alcohol. The first 200 cc of percolate obtained assayed 3.02% of alkaloids, indicating 57.0% of exhaustion, and the finished fluidextract assayed 4.6% of alkaloids, indicating 86.8% of exhaustion.

Another portion of 250 Gm. was extracted hot in the apparatus described, using the same menstrua and general process except that heat was employed. The first 200 cc of percolate assayed 2.67% of alkaloids, showing 50.4% of exhaustion, and the finished fluidextract assayed 4.92% of alkaloids, showing 92.4% of exhaustion.

In this experiment a small advantage is shown for the hot method, though less perhaps than might be looked for. But the figures tell only a part of the story. Percolation was at first normal in flow, but it gradually slowed up until at the last the percolator appeared to be clogged and the flow was very reluctant. Repacking the drug did not help materially. Doubtless what happened is that the hot hydrochloric acid acted upon the tannins in the cinchona, changed them into phlobaphenes and clogging resulted. The initial maceration was made in the cold, so that the phlobaphenes were not fully formed until after a considerable portion of the

percolate had been obtained, then clogging became evident. It is highly probable that this effect would be emphasized in operations on a large scale, and render it impracticable. For this reason, further experiments on cinchona by the hot process were not made. The real objection to the hot process on cinchona is the way it acts.

Ipecac.—The stronger alcoholic menstruum which was directed until the last revision gave little trouble in the extraction of ipecac, but it produced a fluidextract which did not mix well with syrup. The weaker menstruum of the last revision makes syrup-making easy, but it does not exhaust the drug well. Therefore, hot extraction in the above apparatus was tried.

A sample of fluidextract was made from a Rio ipecac assaying 2.8% of alkaloids by the U. S. P. process. The first 200 cc of percolate assayed 1.85% of alkaloids, showing 49.3% of exhaustion, and the finished product assayed 1.97% of alkaloids, showing 70.0% of exhaustion.

By the hot process the following results were obtained. The first 200 cc assayed 1.296% of alkaloids, showing 46.3% of exhaustion, and the finished product 1.687% of alkaloids, indicating 60.2% of exhaustion.

Here again the drug clogged in the hot process, and finally refused to run It was impossible to carry the percolation to the usual amount, and, of course, the drug was far from being exhausted.

When the drug was taken from the percolator it was found to be in a gelatinous condition due to the action of the hot menstruum on the starch. This shows another limitation of the hot method. It cannot be applied to starchy drugs with a weakly alcoholic menstruum because the hot fluid cooks the starch and makes it gelatinous and obstructing.

By using a 71% alcoholic menstruum containing 0.8% of hydrochloric acid in the first 250 cc there was obtained 70.3% of exhaustion in the first 200 cc of percolate and 75% in the final product. The stronger alcohol and more acid is undoubtedly the better menstruum for ipecac.

Physostigma.—This is a drug which is difficult to exhaust and also difficult to assay. It may be a question at times whether the assay or the extraction is chiefly at fault, but there is no doubt that extraction is troublesome. This was also tried in the hot extraction apparatus.

The drug used assayed 0.1936% of physostigmine. The menstruum used consisted of 80% alcohol containing in the first portion 0.25% of acetic acid.

By cold percolation, using 250 Gm. of drug, the first 200 cc assayed 0.125% of alkaloid, showing 51.6% of exhaustion, and the finished fluidextract assayed 0.143% of alkaloid, showing 73.8% of exhaustion. By the hot process the figures were for the first 200 cc 0.140% alkaloid equal to 72.3% of exhaustion, and 0.172% alkaloid equal to 89% of total exhaustion.

Using 95% alcohol containing a like amount of acetic acid very similar results were obtained, *viz.:* 51.6% and 76.4% of exhaustion in the cold, and 74.8% and 90.0% of exhaustion by the hot process. Here is shown a marked advantage in the hot process, but the total extraction is yet lower than is desirable.

By the cold percolation, using a menstruum of 80% alcohol containing 0.3% of hydrochloric acid in the first 250 cc, there was obtained 72.3% of exhaustion in the first 200 cc and 89% in the final product. Ninety-five per cent. alcohol containing 2.3% of hydrochloric acid in the first portion gave very similar results. Thus the

more acid menstrua are more efficacious for physostigma, and therefore more economical. The expense of the special apparatus for hot extraction and the cost of operating it are not sufficiently advantageous to warrant it, in view of the fact that more acid menstrua give quite as good results.

Other experiments have been made on the extraction of physostigma which show that the size of powder used is an important factor in the extraction. A drug in No. 40 powder yields 70% of its total alkaloid to 71% alcohol and the same drug in No. 60 powder yields 88% of its activity to the same menstruum. When 1% of salicylic acid was added to the menstruum a yield of 96% of its activity was obtained. With ½% of benzoic acid 83% and with ½% of hydrochloric acid 90% was obtained—using a No. 60 powder in each case. Thus the factors of acid in the menstruum and the fineness of the powder employed are more important than higher temperature in extracting this drug. Furthermore, precipitation is much greater in the fluidextract made by hot percolation than in any of the others.

Nux Vomica.—A number of experiments have been made on the extraction of whole nux vomica beans by digestion with aqueous acid. The process consisted in simply digesting the whole beans in a beaker with sufficiently acidulated water to cover them and after 24 hours pouring off the liquid and repeating the process. The beans usually had about eight hours of heating and sixteen hours more of maceration in a warm place. A 1% sulphuric acid was found to extract the alkaloids more rapidly than a 2% acetic acid. The rate of extraction with one-half to one per cent. sulphuric acid is shown in the following results obtained by treating 250 Gm. of the beans. The figures show the proportion of alkaloids contained in the beans extracted in each treatment.

	Per cent.
First portion	31.71
Second portion	31.14
Third portion	16.23
Fourth portion	13.41
Fifth portion	3.90
Sixth portion	2.04
Seventh portion	0.11
Eighth portion	0.03
Total extracted	98.57

The first four portions extracted 92.5% of all the alkaloids in the drug. Cold water softens and penetrates the whole beans so slowly that the process without heat would be impracticable. So for aqueous extraction heat has a decided advantage in treating nux vomica.

Vanilla.—Vanilla beans are notoriously slow in yielding up their virtues, and are especially difficult to percolate because they contain so much albuminoid material. Most of the manufacturers of vanilla preparations extract the beans by long-continued macerations. One large dealer in vanilla extract has a series of vats in which the chopped beans are macerated in the menstruum and the tanks are used in sequence and so regulated that no extract is less than six months old when it is drawn off from the macerated beans. This is an expensive method of aging and extracting but he considers that it is worth while.

Other manufacturers are reported to hasten the process by digesting the beans in the menstruum, instead of macerating them.

For experimental purposes the following simple method was employed:

The ground or chopped beans were placed in a flask of suitable size, and 200 cc of menstruum poured on for each 100 Gm. of beans used. This is just enough to cover the beans well after they are thoroughly swollen in the menstruum. The flask is then fitted with a reflux condenser and placed in a sand-bath where it is heated to a little below the boiling point of the menstruum, or to about 60° C. After digesting 48 hours the liquid is poured off and enough fresh menstruum added to cover the beans. The process is repeated until the required volume of extract is obtained—usually four or five digestions.

Preparations so made compare well in strength and quality of flavor with others made from the same beans by longer processes of maceration and percolation.

But an added advantage in this heat treatment of vanilla lies in the fact that the heat coagulates some of the albuminous bodies in vanilla and produces a clearer preparation. It is well known that clear preparations of vanilla are difficult to get when a menstruum of 49% of alcohol or less is used, and that filtration of the cloudy extract is slow and tedious in all cases and almost impossible in some. The heat coagulates some of the viscid and slimy pseudo-solutions and enables the liquid to be filtered. Thus a practically clear extract is obtained in a menstruum containing less than 49% of alcohol, and without special difficultv in filtration or the need of a clarifying agent.

SUMMARY.

Hot extraction has been tried on six drugs of different types, with the following results:

1. Drugs containing a considerable proportion of albuminous matter which is coagulated by heat, and which are extracted with an aqueous or weakly alcoholic menstruum are better extracted by the hot menstruum. Licorice, vanilla and nux vomica are examples—the latter two when extracted with weakly alcoholic menstrua or with water.

2. Drugs containing a material proportion of starch are not helped by hot extraction because the heat gelatinizes the starch and makes the drug impermeable. This was proved especially on ipecac.

3. Cinchona, a drug which contains much tannoid matter and a drug which needs hydrochloric acid for the rapid extraction of its alkaloids, has its tannoid bodies changed to phlobaphenes by the action of the hot hydrochloric acid solution, and the drug then clogs and refuses to allow the menstruum to pass through it. Heat hinders rather than favors extraction in this case.

4. Physostigma, which needs a highly alcoholic menstruum, is helped some by hot extraction. But quite as good results are obtained in this case by cold percolation through a finer powder, and by the use of more acid menstrua. For strongly alcoholic menstrua finer powders are needed in all cases than for aqueous menstrua and the heat is likely to induce loss of menstruum which will offset economy in percolate.

5. In general hot extraction is better applied when aqueous menstrua are used and coarser powders employed. It is likely to be inapplicable to starchy drugs because of the gelatinizing of the starch and the hindrance to penetration of the drug by the hot menstruum by this action. Drugs containing albuminous matters give clearer and more stable preparations by hot extraction.

LABORATORY OF
PARKE, DAVIS & COMPANY,
DETROIT, MICHIGAN.