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 DRUG EXTRACTION. XVIII. MODIFIED DIACOLATION.\*<sup>1</sup>

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Experiments have been carried out to determine the efficiency of a modified diacolation process in the preparation of fluidextract of belladonna root.

## HISTORICAL REVIEW.

In 1935 and 1936, H. Breddin (1), (2) was granted patents in several countries on an "Apparatus for Extracting Drugs and the Like," commonly called the diacolation apparatus. In this apparatus, the menstruum is forced from a storage bottle, by means of air pressure obtained by pressing on a rubber bulb by hand, through a throttle device and drip chamber arranged for the purpose of controlling the rate of flow of menstruum into the drug. The menstruum is slowly forced through one or more cylindrical glass tubes packed with the drug, the tubes being connected by glass tubing running from the top of one tube to the bottom of the other so that the menstruum flows upward through the drug. The object of the invention is to produce highly concentrated percolates without use of heat, and using only relatively small quantities of extraction fluid (1).

In the preparation of fluidextract of cinchona by diacolation, Breddin (3) used a battery of nine tubes, each tube being 80 cm. long and 1.7 to 1.8 cm. wide. Six hundred grams of cinchona were moistened, macerated and packed in the tubes. By means of the visible drip chamber, the menstruum was allowed to enter the drug at the rate of one and one-half drops per minute and was forced through the drug by air pressure not exceeding one and one-half atmospheres. The receiver was evacuated to facilitate penetration of the drug by the menstruum and to aid in establishing the correct rate of flow. The preparation of 600 Gm. of fluidextract from 600 Gm. of drug was completed in about twenty days.

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<sup>1</sup> This paper is based on part of a dissertation presented to the Graduate Council of the University of Florida by C. L. Huyck, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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*Advantages of Diacolation.*—The advantages of diacolation were stated by Breddin (4) as follows: (a) some drugs, notably cinchona, were not completely extracted by repetition diacolation, but were successfully exhausted by diacolation, (b) diacolation provided for regulation of the rate of penetration and for adjustment of length of drug column and rate of flow of percolate, (c) diacolation provided a quick, efficient and convenient method of preparing tinctures.

F. Gstirner (5) stated that the advantages of diacolation over maceration in the manufacture of tinctures were that less time was required, more total extractive was obtained and less menstruum was used. Tinctures were prepared by six different processes by S. von Bari (6), who concluded that diacolation gave the most promising results. K. Höll (7) found that tinctures of nux vomica, strophanthus, cinchona and ipecac made by diacolation contained a higher percentage of alkaloids than the corresponding tinctures prepared by maceration.

*Disadvantages of Diacolation.*—Considering diacolation from both the theoretical and practical standpoints, R. Kummer (8) outlined the following disadvantages: (a) from a mathematical point of view too much emphasis was placed on the form of the percolator used in the process, (b) from a survey of the literature the value of pressure was questionable, (c) the charging and discharging of the tubes was inconvenient, (d) too much emphasis was placed on uniform packing of the drug.

According to E. Kessler (9), diacolation was not applicable to fine powders, and the use of pressure diminished the efficiency of extraction by causing formation of passages through the drug. C. Koch (10) was of the opinion that the trouble involved in assembling a large diacolation battery for the manufacture of fluidextracts would hinder the adoption of the process. In the manufacture of tinctures of cinchona and valerian by diacolation, K. Höll (7) found that finely powdered drugs could not be used and that the powdered drugs should be mixed with ten per cent of sand before packing. Working on cinchona, Büchi and Feinstein (11) found that finely powdered drug could not be used in the preparation of the fluidextract; they concluded that the apparatus was too complex.

*Drugs upon Which Diacolation Was Tested and Results Obtained.*—Breddin (3) reported that he successfully prepared fluidextract of cinchona by diacolation; he also described methods of making fluidextracts of ergot, condurango, orange, frangula, hydrastis, thyme, senega, ipecac and valerian by diacolation (12). Szentgale (13) found that diacolation with a weaker alcoholic menstruum produced a better fluidextract of hydrastis than percolation, but percolation with a menstruum of the same alcoholic strength was better than diacolation in the manufacture of fluidextracts of belladonna leaves, hyoscyamus and ipecac, the conclusions being based on the content of alkaloids and total extractive matter. In preparing fluidextract of cinchona, Büchi and Feinstein (11) obtained no better results by diacolation than by ordinary percolation but declined to draw any conclusions as to the efficiency of the process until after making further tests.

#### EXPERIMENTAL PART.

From an examination of the patent and journal literature on diacolation it appeared that any favorable results obtained with the apparatus were due primarily to the length of the drug column. The complicated arrangements for regulating the flow of menstruum into the percolator tubes seemed unnecessary. It could hardly be expected that upward flow of the percolate against the force of gravity would add anything to the efficiency of extraction. The use of water to dis-

place the alcoholic menstruum from the exhausted drug could only replace other methods of alcohol recovery and would in no way affect the rate of extraction.

In the present study, therefore, an apparatus was constructed with the object of determining the efficiency of extraction under conditions of forced flow of menstruum through a long column of drug. As shown in the photograph, a long drug column was obtained by using flanged pipe made of Pyrex glass. Eight sections of glass pipe were joined together by means of U-shaped fittings made of Pyrex glass pipe. Interface joint gaskets made of sulfur-free gum rubber were used at the joints, which were held together by metal joint flanges. The menstruum was forced through the drug by use of compressed air. The dimensions of the tubes were as follows: Length, 91 cm.; internal diameter, 2.5 cm.; thickness of wall, 5 mm.

The apparatus had a capacity of 2400 Gm. of drug, the drug used being moderately coarsely powdered belladonna root from a 100-lb. shipment previously described (14). To determine the

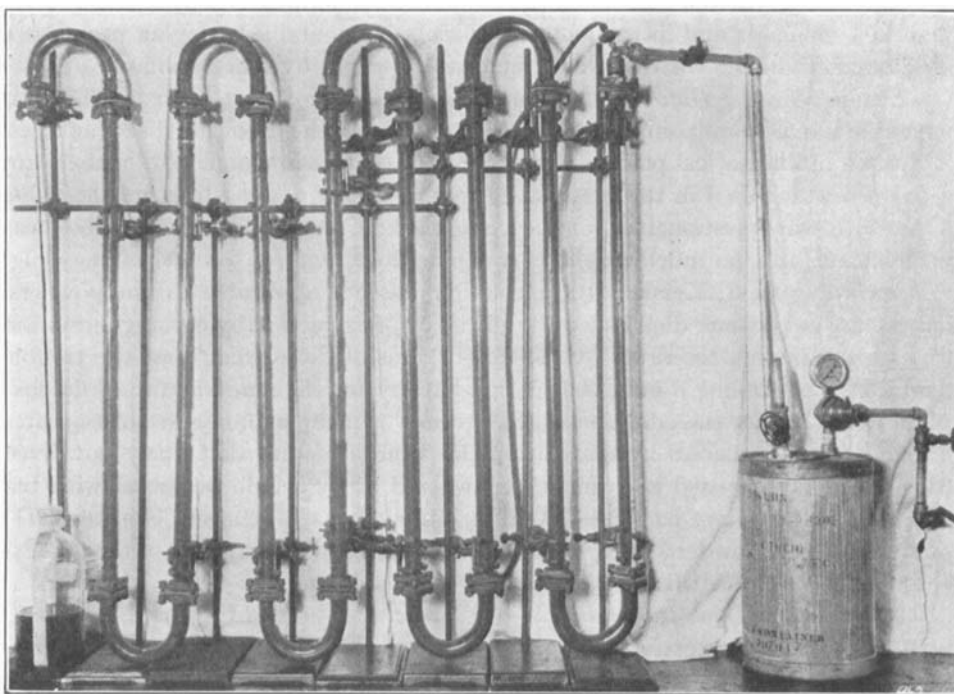


Fig. 1.—Extraction apparatus used in present study.

efficiency of the apparatus, 2400 cc. of fluidextract of belladonna root were prepared from 2400 Gm. of drug, using a menstruum of four volumes of alcohol and one volume of distilled water. In order to determine the rate of extraction at different stages the fluidextract was collected in two portions of 1200 cc. each and in addition a 1200-cc. portion of weak percolate was collected. After the experiment had been carried through once a duplicate experiment was carried out to verify the results obtained.

In describing the procedure, any differences in the rates of flow, etc., in Exps. I and II will be pointed out. In both experiments the total length of the drug column was 936 cm. and the volume of packed drug was 5120 cc. The time required for packing the drug in the tubes was about seven hours. In each case the drug was moistened with 25 cc. of menstruum per 100 Gm. of drug before packing. After packing the system was allowed to stand for 39½ hours in Exp. I and 18 hours in Exp. II. In each case the menstruum was run in at a pressure of 25 to 35 pounds per square inch. In Exp. I the menstruum had penetrated the drug in six of the tubes in 107 hours and at this point it was necessary to shut off the pressure for 48 hours, after which the pressure was again applied and after 47 additional hours the liquid had progressed through all the tubes

and had begun to drop into the receiver. In Exp. II there was no interruption and the liquid reached the end of the last tube in 164 hours or about 7 days. Data as to the time required are given in Table I and analytical data on the fluidextracts appear in Table II.

TABLE I.—PREPARATION OF FLUIDEXTRACTS OF BELLADONNA ROOT BY FORCED PERCOLATION THROUGH A LONG COLUMN OF DRUG.

	Time of Operator Required in Hours.	Total Elapsed Time in Hours.	Time Required for Collection of Percolates in Hours.		
			First Reserve.	Second Reserve.	Weak Percolate.
Exp. I	10	317 $\frac{1}{2}$	74 $\frac{1}{2}$	80 $\frac{1}{2}$	48 $\frac{1}{2}$
Exp. II	10	405	72	101	43

TABLE II.—ANALYTICAL DATA ON FLUIDEXTRACTS OF BELLADONNA ROOT.

	Gm. Alkaloids in Percolates.		Gm. Total Extractive in Percolates.	
	Exp. I.	Exp. II.	Exp. I.	Exp. II.
First reserve 1200 cc.	13.8	14.1	168.8	173.8
Second reserve 1200 cc.	0.8	0.7	167.4	173.1
Weak percolate 1200 cc.	0.4	0.5	92.6	92.6
Total 3600 cc.	15.0	15.3	428.8	439.5
Total of first and second reserves calculated on 1000 cc.	6.1	6.2	140.1	144.5

#### DISCUSSION OF RESULTS.

The data in Table II show that a very high proportion of the total alkaloids is contained in the first reserve, with a much lower concentration in the second reserve and still less in the weak percolate. By collecting 2400 cc. of fluidextract from 2400 Gm. of drug, a product containing 6.1 to 6.2 Gm. of alkaloids per L. was obtained. These results show that it is possible to prepare a full strength fluidextract without concentration of weak percolates as in ordinary percolation and without collecting numerous fractions of percolates as in fractional percolation.

In comparing the alkaloidal content of the fluidextracts with that of fluidextracts made from the same shipment of drug in earlier studies (14), (15) it is seen that the apparatus and method described in the present paper gave results as good as those obtained by modified repetition diacolation and better than those obtained by the U. S. P. Processes A and C for fluidextracts. The content of alkaloids in Gm. per L. in the fluidextracts prepared in the present study was 6.1 to 6.2 as compared with an average of about 6.2 by modified repetition diacolation and about 5.8 by Processes A and C of the U. S. P. XI and N. F. VI.

In a previous study by the present authors (16) comparisons were made of the efficiencies of funnels, Oldberg percolators and cylindrical tubes; the different lengths of drug column obtained with these different percolators did not affect the final results of extraction to any great extent in ordinary percolation. However, the present study shows that when the drug column is greatly increased in length there is a marked increase in efficiency of extraction of alkaloids.

The pressure used in our experiments was obtained from the service compressed air line, the high pressure in the line being reduced to the desired figure by a reducing valve and gage. The success of this arrangement verified our previous opinion that the complicated arrangement of throttle device, drip valve, etc., as used by Breddin is superfluous; possibly some of Breddin's devices are necessary when the pressure is supplied by a rubber hand bulb but all this inconvenience is eliminated in our apparatus.

Instead of packing the drug in separate tubes and connecting these by glass tubing as was done by Breddin, our tubes were connected to each other by glass U-tubes of the same diameter. The U-tubes were packed with drug, thus forming one long continuous drug column. In this respect our apparatus differs from that of Breddin and other previous workers.

In Breddin's apparatus the flow of menstruum was upward in each tube packed with drug, and downward in the connecting glass tubes which contained none of the drug. There appears to be no special merit in this arrangement, since good results were obtained in our apparatus in which the flow was downward in four of the tubes and upward in the other four. As outlined in a previous paper (15) the use of water to displace an alcoholic menstruum from the marc is not applicable to drugs which swell and clog the percolator when water is added.

Many features of Breddin's diaculation apparatus have been known and used for many years. The method of passing the menstruum through a series of containers without collecting reserve percolates is very old, this procedure having been employed by Boullay (17) in 1833. Laliou (18) in 1862 used a series of tubes arranged on an incline so that the liquid would flow continuously from one to the other. A series of extraction tubes connected by smaller glass tubing was employed by Catford (19) in 1898. Pressure has been used in percolation in a number of ways for more than one hundred years. Displacement of an alcoholic menstruum by water was employed many years ago by Squibb (20). Considering all these things it is difficult to see anything original or patentable in Breddin's claims (1) with the exception of the complicated arrangements for a visual drip chamber, etc., for regulating the inflow of the menstruum and our results show that this feature is by no means necessary for successful extraction.

While the use of a series of tubes is not new, our results show that the use of a long drug column leads to very efficient extraction, since a fluidextract considerably above U. S. P. strength was prepared by straight percolation without concentration of weak percolate. Naturally a long column of drug offers such resistance to flow of the liquid that pressure is necessary to force the percolation.

The forced flow of menstruum through a series of tubes may be considered as a fractional percolation process in which the menstruum flows from one percolator to the other without separating the percolate into fractions or collecting reserve percolate from the individual tubes. In using a battery of tubes, more time is required for packing and assembling and the total elapsed time is greater than in ordinary percolation or fractional percolation.

#### SUMMARY.

Full strength fluidextracts of belladonna root were made by slow percolation under pressure through an extremely long column of drug without resorting to collection of various fractions of weak percolate as in fractional percolation and without use of heat to concentrate weak percolate as in Process A of the U. S. P.

The apparatus devised and assembled in the present study consisted of a series of tubes of Pyrex glass pipe, connected by glass U-tubes of the same diameter. The drug was packed in one long continuous column and the menstruum forced through by compressed air.

A discussion is given of the patented extraction apparatus which is used in the process of diacolation as carried out by Breddin.

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## ALCOHOL CONTENT OF EXTRACTIVE PREPARATIONS.\*

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## INTRODUCTORY.

It is required by law that the content of alcohol be stated on the label of each package of every item containing alcohol and offered for sale in interstate commerce. Manufacturers and distributors generally state this alcohol content as a single figure.

In the National Formulary the alcohol content of each preparation containing one per cent or more of alcohol is given in the monograph of such preparation with a minimum and a maximum limit. Alcohol content means the volume of  $C_2H_5OH$  present in one hundred volumes of the liquid preparation.

The official method for the determination of absolute alcohol, first introduced into U. S. P. IX, has been subject in recent years to considerable criticism, as is noted in the following papers: "Determination of Alcohol in Pharmaceutical Liquids I, Study of the U. S. P. X and U. S. P. XI Method," *Jour. A. Ph. A.*, 25, 313-316 (1936); "Determination of Alcohol in Pharmaceutical Liquids II, a New Method," *Jour. A. Ph. A.*, 25, 982-985 (1936). Both papers are by Karl Bambach and T. H. Rider.

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