NOTES ON THE MORPHIOMETRIC ASSAY OF OPIUM.

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The recent discussions in pharmaceutical journals on the subject of the morphiometric assay of opium have attracted much attention. Inasmuch as the medicinal virtues of opium depend principally upon the percentage of morphine, it is of the utmost importance to the profession to know the exact quantity of morphine in a given specimen of opium or its preparation. Most of the methods for the morphiometric assay of opium may be classified under two general heads. Those using water simply, as a solvent, and those using lime. Each class has merits of its own under certain conditions, but it is an established fact that the two classes will not work equally well on opiums of all grades and varieties. Experience is required to get the best results by any method, and strict adherence to details contributes much to a correct and successful assay.

This paper will be confined principally to the analytical discussion of some of the theoretical and actual errors of the U. S. P. method for the assay of opium adopted in the Pharmacopœia of 1880.

For the benefit of those not familiar with the method, the details are given herewith :

"Opium in any condition to be valued, seven grms. (7), lime, freshly slacked, three grms. (3), ammonium chloride, three grms. (3), alcohol [Sp. Gr. 0.820], stronger ether [Sp. Gr. 0.725], distilled water, each a sufficient quantity. Triturate together the opium, lime and 20 c.c. of distilled water in a mortar, until a uniform mixture results ; then add 50 c.c. of distilled water, and stir occasionally during half an hour. Filter the mixture through a

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plaited filter, three to three and one-half inches in diameter, into a wide-mouthed bottle or stoppered flask (having the capacity of about 120 c.c., and marked at exactly 50 c.c.) until the filtrate reaches this mark. To the filtered liquid (representing 5 grms. of opium) add 5 c.c. of alcohol and 25 c.c. of ether, and shake the mixture, then add the ammonium chloride, shake well and frequently during half an hour, and set it aside for twelve hours. Counterbalance two small filters, place one within the other in a small funnel, and decant the ethereal layer as completely as practicable upon the filter. Add 10 c.c. of stronger ether to the contents of the bottle and rotate it, again decant the ethereal layer upon the filter, and afterward wash the latter with 5 c.c. of stronger ether, added slowly and in portions. Now let the filter dry in the air, and pour upon it the liquid in the bottle, in portions, in such a way as to transfer the greater portion of the crystals to the filter. Wash the bottle and transfer the remaining crystals to the filter with several small portions of distilled water, using not much more than 10 c.c. in all, and distributing the portions evenly upon the filter. Allow the filter to drain, and dry it, first by pressing it between sheets of bibulous paper, and afterward at a temperature between 55° and 60° C. Weigh the crystals in the inner filter, counterbalancing by the outer. The weight of the crystals in grms., multiplied by twenty (20) equals the percentage of morphine in the opium taken."

The queries which suggest themselves concerning this method are :

1. Does the lime treatment extract all the morphine ?
2. Does the aliquot part (50 c.c.) of the filtrate represent the proportional equivalent of 5 grams of opium ?
3. Is all the morphine recovered from the aliquot part taken ?
4. What is the purity and character of the crystals obtained ?

The first of these queries, time did not permit me to investigate sufficiently to present reliable analytical data.

The second query has been subjected to analytical inquiry by a number of careful investigators. The question, however, is still a disputed one. To solve this question the following experiments were undertaken, with results as indicated below.

Theoretically the volume of the solution of the opium assay will

be affected by the quantity of the soluble matter in the opium taken. It is safe to say that each grm. of water in the opium taken will increase the volume of the added water by one (1) c.c., so that opium of different degrees of moisture will, from this source alone, affect the volume of the solution according to the percentage of moisture in the sample taken. Secondly, the volume will be further affected by the quantity of the soluble matter of the opium, other than water. Opium as a rule contains from sixty (60) to sixty-five (65) per cent. of soluble matter, but the solution of much of this is prevented by the lime and the limited quantity of water. The soluble solids of opium which go into solution will have a tendency to increase the volume of the solution by about 60 to 63 per cent. of their weight. It seems therefore, from theoretical deductions, that 50 c.c. of the filtrate will seldom represent exactly 5 grms. of opium.

To demonstrate this, two samples of opium, A and B, containing respectively 8.0 per cent. and 7.13 per cent. of moisture, were submitted to assay under the following conditions: Into a tared Erlenmayer flask containing a weighed, rubber-tipped glass rod, 7 grms. of opium were placed, followed by 3 grms. of freshly slaked lime (3 pts. lime to 1 pt. of water) and 70 c.c. of water. The weight of the whole was accurately noted. The contents of the flask were then thoroughly mixed and stirred during one hour. This is somewhat longer than the U. S. P. method directs. It is not always practical to stop the maceration at the end of half an hour, so that this deviation, though slight, must be taken into account, although it may not cause any practical difference in the results. The maceration in the flask was adopted to avoid loss by evaporation, which from an open mortar is often quite considerable, as was verified by direct weighings. On completion of the maceration, the magma was filtered through a filter paper, the weight of which, with the funnel, was previously noted. Precautions were taken to avoid evaporation during the filtration. A little over fifty c.c. were collected in a tared flask and the weight of the whole immediately taken. The residuum on the filter, with the filter, funnel, flask and glass rod, was dried at 100° C., and the increase in weight noted. A portion of the collected filtrate was evaporated, the residue dried at 100° C., and the quan-

tity of solids and water determined, from which data the relative volumes were calculated.

The following are the analytical data:

Opium A, containing 8 per cent., moisture.

Flask + rod = 43.385 g.
Funnel = 41.050 g.
Dried filter = .884 g.
+ residuum dried at 100° C = 93.330
tare = 85.319

Total tare .85.319 Solids in residuum = 8.011

Total weight of filtrate collected=52.841 grms. of Sp. Gr. 1.0173 at 15.5° C. Hence volume of collected filtrate=51.942 c. c.

Total weight of material taken, 7 grms. of opium+3 grms. slaked lime+70 c.c. water=80 grms., 80.000 grms.—52.841= 27.159 grms., total weight of residuum on filter.

27.159 grms. residuum on filter—8.011 grms. solids=19.148 grms. water in same.

Of the collected filtrate 8.6027 grms. evaporated and dried at 100° C. gave .3077 grms. solids, whence the difference=8.295 grms. water. The weight of water in the 52.841 grms. (=51.942 c.c.) of collected filtrate is therefore 50.9509 grms. water. From these data the total volume of the liquid may be calculated by the equation $a : b :: (a+d) : x$, in which a is the weight of the water in the collected filtrate, b the volume of the same, and d the weight of water in the residuum. $50.9509 : 51.942 :: (50.9509 + 19.148) : x = 71.46$ c.c., total volume of the solution.

Opium B=7.13 per cent. moisture.

Flask, funnel, rod, paper=85.064 grms.,+residuum dried at 100° C=93.120 grms.=8.056 grms. solids in residuum.

Weight of filtrate collected=52.540 grms., Sp. Gr. at 15.5° C. 1.0178 =51.629 c.c., volume of collected filtrate. 80.000—52.549 =27.451 total residuum on filter—8.056 grms. solids=19.395 grms. water.

9.1125 grms. filtrate dried at 100° C.=.3385 grms. solids, hence difference = 8.7740 grms. water, whence 50.596 grms. water in filtrate collected.

$50.596 : 51.629 :: (50.596 + 19.395) : x = 71.419$ c.c. total volume of solution.

It is thus seen that the 70 c.c. of added water were increased in

volume to 71.46 and 71.41 c.c. respectively in the two assays. It will be noticed that in the above calculation it is taken for granted that the character of the filtrate is the same as the liquid portion remaining in the residuum on the filter, that is, equal volumes of each will contain the same quantity of soluble solids. This point is disputed by some. I have, however, not seen any data which will support the objection, and which are not open to criticism. Further, no account is taken of any decomposition during drying. What these experimental errors would amount to it is difficult to say. They would, however, not materially alter the conclusion to be drawn from the above data, which are given in sufficient detail to be available for correction in case any error appears in the modus operandi adopted.

It is shown, therefore, that in these assays 50 c.c. of filtrate represented less than 5 grms. of opium, the actual quantities being 4.897 and 4.9 grms., causing a loss in the assay of .25 and .24 per cent. morphine respectively, in an opium assaying 12 per cent. morphine.

The third of the above queries is readily answered. It is not to be supposed that all the morphine can be recovered in a pure state by a single crystallization from such a complex solution as the concentrated infusion of opium. The object, therefore, is to produce the morphine in as pure a condition as possible, so as to avoid unnecessary after treatment, and it becomes a question whether the impurities contained in the weighed morphine counterbalance the morphine lost in the crystallization and subsequent treatment. Some of the older methods weighed morphine of a notoriously impure character.

In the U. S. P. method, the yield of the morphine is affected by the quantity of alcohol and calcium and ammonium chloride contained in the crystallizing liquid. To decrease the solvent power of these, ether is added as an anti-solvent, as well as for facilitating a pure precipitation of morphine.

To illustrate how different quantities of lime and ammonium chloride affect the results, the following two assays were conducted by the U. S. P. method, using .600 grms. of pure, crystallized (finely pulverized) morphine in place of opium.

ASSAY A.

.600 grms. morphine with lime and NH_4Cl by U. S. P. method. Yield of morphine=.360 grms. ÷ .4285 (equivalent for 50 c. c.) =84.01 per cent. morphine recovered by assay.

ASSAY B.

.600 grms. morphine, 1.5 grms. slaked lime, and .8 grms. NH_4Cl by U. S. P. method. Yield of morphine =.3935 grms.=91.83 per cent. recovered.

Hence in A the loss of morphine was 15.99 per cent., while in B, with lime and NH_4Cl decreased, the loss amounted to only—8.17 per cent.

In opium, however, this vast loss of morphine is, to a considerable extent, decreased by the presence of the soluble matter extracted from the opium.

The principal loss of morphine is that in the mother liquors, as will futher be seen from the assays of an opium which gave exceptionally low results by the U. S. P. method.

Opium "O"=5.35 per cent. moisture.

No. 43. U. S. P. method. a. 10.48 per cent. morphine } average 10.525
No. 44. U. S. P. " b. 10.57 " " " } per cent.
No. 40. U. S. P. modified c. 11.38 " " "
No. 41. U. S. P. " d. 11.14 " " "

The modification in 40 and 41 consisted in using only 1.5 g. lime and .8 g. NH_4Cl with the quantity of alcohol also decreased to 3 c.c. in No. 40 and 4 c.c. in No. 41. The influence in the quantity of alcohol used is quite perceptible here, a difference of 1 c.c. alcohol having caused a difference of .24 per cent. morphine in the assays, while the influence of the smaller quantities of lime and NH_4Cl is still more marked, the percentage of morphine having been increased .62 and .86 per cent. over the U. S. P. average. The crystals in each of these four assays were exceptionally pure and white, dissolving completely to a clear solution in officinal lime water. The filtrates of the U. S. P. assays No. 43 and No. 44, with the ether and other washings from the assays, were combined, the whole therefore representing 10 grms. opium.

The combined solutions, after acidulating, were concentrated on

the water-bath to remove the alcohol and ether, and finally exhausted with ether, as long as the same removed coloring and other matter. The ether washings were reserved. The water solution was then futher treated with several washings of amyl alcohol the latter with the reserved ether washings thoroughly washed with acidulated water, and the water washings concentrated and added to the main bulk. Amyl alcohol was again added, the solution made alkaline with an excess of ammonium hydrate, and the extraction continued to exhaustion. The amyl alcohol extracts were first washed with water, and then with water containing a slight excess of hydrochloric acid, so that the water washings were acid in reaction. This acid water solution containing all the alkaloid was evaporated twice on the water-bath to remove the amyl alcohol and excess of hydrochloric acid. It was then transferred to a crystallizing flask and diluted to 7 c.c., 5 c.c. of alcohol were now added, together with 20 c.c.; of ether, followed by 1.25 c.c. of 10 per cent. ammonia. The whole was thoroughly shaken and allowed to crystallize for 48 hours. The resulting crystals were washed with "morphiated spirit," "morphiated water," and finally benzol, and were comparatively pure. The crystals weighed .1033 grms., indicating 1.033 per cent. morphine which was lost in the U. S. P. assays, No. 43 and 44. All the morphine, however, was not recovered by the above treatment, for the percentage of morphine in opium "O" as determined by three other methods of assay, each performed in duplicate, and all agreeing very closely, was found to be 12.32 per cent., so that in this opium the U. S. P. method yielded 1.795 per cent. less than the true quantity of morphine contained therein. The opium, it will be observed, was quite dry, and it is possible that this may have influenced the results; but for all the confirmatory assays the opium was used in the same condition as to percentage of moisture. The yield and purity of crystals is affected decidedly if the crystals on the filters are not first thoroughly dried between bibulous papers. To accomplish this readily it is expedient to compress the filter papers containing the crystals, places them between two pieces of blotting or filter paper, and then press thoroughly between toweling until all excess of moisture has been expressed, as determined by observing whether the filters when compressed be-

tween fresh blotting or filter paper, dampen the same. This also facilitates the drying.

The losses of morphine in the U. S. P. assays of opium "O" were exceptionally large. Two other varieties of gum opium gave much better results.

	Opium A.	B.
U. S. P. method	11.60 per cent. morph.	12.94 per cent. morph.
U. S. P. modified	11.35 " " "	13.12 " " "

	Opium C.—8.0 per cent. moist.	D.—7.13 per cent. moist.
U. S. P. method	11.82 per cent. morph.	13.89 per cent. morph.
U. S. P. modified	12.30 " " "	14.36 " " "

The opium C and D, assayed by Stillwell's modification of Squibb's method, yielded 12.31 per cent. and 14.70 per cent. morphine respectively, so that in C the deficiency amounted to .49 per cent. and in D to .81 per cent. by the U. S. P. method, while in the modification (see assays No. 40 and 41 of opium "O" above) the results were much closer, C. showing a deficiency of only .01 per cent. and D a loss of .24 per cent. These assays are certainly instructive in demonstrating how differently different varieties of opium work with the U. S. P. method.

PURITY AND CHARACTER OF THE CRYSTALS.

In a properly conducted assay the U. S. P. crystals are certainly exceptionally pure. An average lot of morphine, yielded by the U. S. P. method from different varieties of opium and laudanum, gave but little residue when treated with lime water, and by titration with oxalic acid, standardized on pure morphine, the purity of the crystals was found to be 96.94 per cent. As a rule the crystals are purer than this. I have frequently found them 98.0 to 99.8 per cent. pure, as indicated by titration with standardized oxalic acid.

Several investigators have lately called attention to the loss of water of crystallization of morphine when dried at 100° C. The U. S. P. directs the crystals to be dried at not over 60° C. Experience teaches that that temperature should not be much exceeded. In methods directing the crystals to be dried at 100° C. it frequently happens that partly dehydrated crystals are

weighed. Pure crystallized morphine, $C_{17}H_{19}NO_3H_2O$ contains 5.94 per cent. of water of crystallization.

Some pure morphine was prepared from commercial "pure morphine" by subjectiong the latter to the following treatment: ½ oz. of crytals were finely pulverized, washed with "morphiated spirits," dried, then washed with repeated portions of benzol, the crystals then dissolved in water (q.s.,) acidulated with hydrochloric acid, the whole diluted to 100 c.c., and 5 c.c. of alcohol and finally 5 c.c. of water of ammonia added, the whole shaken and allowed to crystallize, transferred to a filter, and washed with water until free from chlorine and ammonia; the crystals were then compressed between bibulous paper and finally dried at 56° C. to constant weight. 92.3 per cent. of the quantity taken were recovered.

The crystals thus prepared, when dried in an open air bath at 100° C., lost all their water of crystallization in four hours. The loss amounted to 6.081 per cent. or .141 per cent. in excess of 5.94 per cent., the true amount of pure crystals.

The U. S. P. crystals of morphine contain rather more water than this, as will be seen from the following nine determinations, representing morphine from as many different U. S. P. assays. The crystals in each case were dried at 100° C. to constant weight. Most of the crystals lost all their water of crystallization in 4 hours, while a few suffered a slight further loss by 5 to 8 hours longer drying at the above temperature. The total loss in weight for the respective lots was 6.83 per cent., 6.88 per cent., 6.75 per cent., 6.73 per cent., 6.51 per cent., 6.83 per cent,, 6.93 per cent., 6.86 per cent., 6.81 per cent., which is an average of 6.79 per cent. water in the U. S. P. crystals. Neither any of these crystals, nor the sample of pure morphine, suffered any further loss by drying at 120° C. for 3 hours, thus demonstrating that all the water of crystallization is lost at 100° C., by from 4 to 12 hours drying.

When the U. S. P. assay is properly conducted, the crystals seldom contain over 4 per cent. of impurities.

It is evident from the data obtained, that with some opiums the U. S. P. method gives results considerably below the truth, and although the results are uniform, duplicates agreeing well with each other, the results cannot always be relied upon as giving the true percentage of morphine in an opium.