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DETERMINATION OF MORPHINE SULPHATE IN TABLETS AND GRANULATIONS.*

BY R. E. SCHOETZOW.

The estimation of morphine has always been of peculiar interest to the pharmaceutical analyst. This alkaloid with its solubilities in the various solvents so different from those of the other alkaloids has required analytical methods especially adapted to it. Probably the average chemist when he first attempts to assay the sulphate of this alkaloid tries the U. S. P. method given under opium. But, if he is working with tablets or granulations that contain, for example, milk sugar, he will not be satisfied with the results obtained. It is the writer's opinion that the presence of sugars render this assay inaccurate.

Quite a number of methods for the determination of morphine sulphate in tablets have been proposed and used, but those most widely employed appear to be of two classes—one based on the chloroform-alcohol separation of the alkaloid from its aqueous solution, made slightly alkaline with ammonia water, and another based on the ammonia precipitation of morphine from aqueous solution. These methods or variations of them have both been used by the writer in the past, but in my hands and by those working with me these methods did not give consistent results. For three or four successive times the methods might work very satisfactorily, then the next time the results would fall far short of theory. So that finally we came to the conclusion that we could not trust either of them. Some time ago H. A. Osborne and the writer, in considering the various methods of estimation, concluded that we could not hope to attain satisfactory results as long as water was present in the separation stage of morphine from the other ingredients of the mixture. We decided that the solubility of morphine in water, the possibility of reversible reactions, the presence at times of morphine salts instead of free morphine in the alkaloid obtained for titration, indicated that we should try to separate morphine in a non-aqueous media. The best way to do this seemed to be as follows:

ASSAY FOR MORPHINE IN GRANULATIONS OR TABLETS CONTAINING MORPHINE SULPHATE AS THE ONLY ALKALOIDAL INGREDIENT.

Place an accurately weighed portion of granulation, theoretically equivalent to 0.260 Gm. Morphine Sulphate, U. S. P., or in the case of tablets, as many tablets as are theoretically equivalent to four grains (0.260 Gm.) of Morphine Sulphate, U. S. P., in a small, glazed, porcelain, evaporating dish. Dissolve in as small a quantity of water as possible. Add sufficient sodium bicarbonate—in about one gram portions—mixing well with a small stirring rod to make a stiff mass. Place

* Scientific Section, A. PH. A., Des Moines meeting, 1925.

in a steam oven and thoroughly dry at a temperature of 75° C. or under, stirring at intervals to prevent the mass from caking on the sides of the dish. Powder the dried mass to a coarse powder—a fine powder is to be avoided. Transfer to a 500-cc. Pyrex Erlenmeyer flask. Add 200 cc. of a mixture (previously mixed and allowed to come to room temperature) of equal volumes of absolute alcohol and chloroform. Stopper and shake thoroughly at intervals for one hour. Let stand four hours. Decant off 100 cc., accurately measured. Filter through barium sulphate paper. Wash, filter and funnel tip with a few cc. of the chloroform-absolute alcohol mixture. Evaporate the solvent almost to dryness on the water-bath. *Note*—The chloroform should be all displaced—one or two cc. of alcohol remaining will aid subsequent solution. Add 5 cc. of tenth normal sulphuric acid to the residue. Aid solution of the residue, if necessary, by adding 2 or 3 cc. of neutral alcohol. When dissolved, dilute with 100 cc. of distilled water and titrate the excess of tenth normal sulphuric acid with fiftieth normal sodium hydroxide, using methyl red as indicator. Run a blank using the same quantities of reagents used throughout. *Note*—This blank with good reagents is almost always negligible. When you are sure of the quality of reagents it may be disregarded.

This method is based on the interaction of sodium bicarbonate and morphine sulphate—morphine being freed; the extraction of the liberated morphine from the dried product of that reaction with a solvent (absolute alcohol and chloroform) which does not dissolve more than a negligible amount of the inorganic alkaline matter. The precautions necessary with this method are, first—to overcome the tendency of the morphine sodium bicarbonate mixture to cake on the sides of the dish in which it is dried by frequent stirring of the drying material, and second—careful handling of the aliquot part method to avoid possible error.

This method has repeatedly and consistently given good results in the hands of the writer and associates for a period of several years, whereas consistent results have not been obtained by many of the more commonly used assays.

ANALYTICAL LABORATORIES,
E. R. SQUIBB & SONS.

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