

CODEINE IN COMMERCIAL MORPHINE SULPHATE.*

J. B. WILLIAMS, B. SC.

During the course of an examination of some tablets of morphine and atropine sulphates, about eight months ago, the amount of alkaloid other than morphine found greatly exceeded the amount of atropine supposed to be present. This naturally led to the conclusion that either some of the morphine extracted with the atropine, or else some other alkaloid was present. The latter proved to be the case, as is shown by the extraction of tablets of morphine sulphate containing no atropine, codeine being the other alkaloid found.

This led to the examination of a number of tablets and samples of morphine sulphate made by leading pharmaceutical houses and manufacturers, and in every case codeine was found to be present in considerable quantities.

Samples were obtained from five large manufacturers of morphine sulphate, and tested for codeine with the following results:

Sample.	Percentage Codeine Sulphate found.
No. 1.....	1.9 per cent.
No. 2.....	.9 per cent.
No. 3.....	3.6 per cent.
No. 4.....	2.2 per cent.
No. 5.....	7.0 per cent.

Samples of morphine sulphate tablets made by leading pharmaceutical manufacturers were also obtained and tested for codeine:

Sample.	Percentage Codeine Sulphate found.
No. 1. 1/4 gr.....	2.5 per cent.
No. 2. 1/8 gr.....	6.5 per cent.
No. 3. 1/4 gr.....	3.1 per cent.
No. 4. 1/4 gr.....	2.5 per cent.
No. 5. 1/4 gr.....	2.9 per cent.

The method used for determining the codeine was as follows: Dissolve 0.5-1.0 gram of morphine sulphate, or an equivalent number of tablets in a small amount of water (15-20 cc.) and add a solution of sodium or potassium hydrate until the precipitate first formed is redissolved (3-4 cc. 5 per cent NaOH). Shake out with three or four 20 cc. portions of chloroform. Wash the combined chloroform extractions in another separator with 10 cc. water made slightly alkaline with sodium or potassium hydrates. Draw off the chloroform, filtering through cotton well wet with chloroform, into a beaker or flask, and wash the separator with two 10 cc. portions of chloroform, passing the washings through the filter into the flask. Evaporate the chloroform, dissolve the residue in excess of N/10

*Reprinted from Am. Journ. Pharm., Sept., 1912, p. 391.

acid, and titrate back with N/50 alkali, using cochineal as indicator. Each cc. of N/10 acid neutralized by the alkaloid corresponds to 0.0315 gram (0.031483 gram) of codeine alkaloid or 0.039 gram of codeine sulphate U. S. P.

That all of the codeine and practically none of the morphine is extracted by this method was proved in several cases by repeating the extraction of the aqueous residue containing the morphine. The N/50 alkali required in the titration being in every case within 0.1 cc. of the amount required to neutralize the N/10 acid used.

The presence of 0.9 percent. to 7 percent. of codeine in the morphine sulphate being consumed in the United States at the present time is certainly very surprising. This condition of affairs is to be directly attributed to the lack of any test in the United States Pharmacopœia which will show the presence of several percent. of codeine in morphine sulphate. It is a condition of affairs arising from the lack of any test which would show the purity of the product, and not from any desire to market a sophisticated product, this being evident because codeine is a more valuable product, commercially, than morphine, and is readily separated from the latter. Manufacturers would certainly not allow the codeine to remain in their morphine sulphate at a loss to themselves, and at the expense of an inferior product.

In the manufacture of morphine sulphate the morphine is usually precipitated as the alkaloid from a large volume of water, enough to hold in solution several times the amount of codeine present. Some experiments showed that it was not possible to completely separate codeine from morphine in this way, and that part of the codeine is apparently carried down with the crystals of morphine, perhaps being isomorphous with the latter.

In order to avoid the presence of codeine in morphine sulphate in the future, the next edition of the United States Pharmacopœia should include a quantitative test for codeine in morphine. The test outlined above or some suitable modification of this test is suggested. A limit of 1 percent. or 1.5 percent. should also be established as the maximum amount of codeine allowable in morphine sulphate.

ANALYTICAL DEPARTMENT, PARKE, DAVIS & Co., Detroit, Mich., July 17, 1912.

DRUG DETERIORATION.

For years, those interested financially, in cold-storage warehouses and cold-storage products, have been trying to convince the public that, if the keeping of meat, fish, eggs and so forth in cold-storage did not actually improve the quality, it at least had no deleterious effects on the products. Recognizing that products could not be improved by cold-storage but that there was considerable danger of deterioration and believing that the public has a right to know the truth, state legislatures are enacting laws which require that for cold-storage products the duration of such storage be declared on each parcel.

Similarly, while pharmaceutical manufacturers, in general, are attempting to convince us of the permanence of their pharmaceutical products, it is being recognized more and more that there are a considerable number of drug products which are liable to suffer more or less seriously with age. In commenting on ex-