

TINCTURE OPIUM.*¹

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Tincture of opium that was made according to directions given in the United States Pharmacopœia (1) contained a very large amount of precipitate in a short time. This precipitate continued to form even after aging and subsequent filtration. A sample of such a product that had been aged and filtered several times during its manufacture was still so turbid that one could not see through a column of the liquid which was 20 millimeters in diameter. This sediment does not seem to adhere to the sides or the bottom of the bottle, but remains thoroughly suspended for a long time. The unsightly appearance of such a product will immediately suggest the desirability of a more elegant tincture.

The United States Dispensatory has the following statement regarding tincture of opium which has precipitated:

"Laudanum when long kept with an occasional exposure to air becomes thick from evaporation of a portion of the alcohol and the deposition of solid matter. If given in this state, it often acts with unexpected energy, and death has resulted in infants from doses which would have been entirely safe if the tincture had been clear" (2).

The method of preparing tincture of opium as outlined in the French Codex (1908) is somewhat different than the U. S. P. X method. The French tincture is manufactured by dissolving an aqueous solid extract of opium in 70 per cent alcohol. The solid extract of opium is prepared as follows: Opium is cut in fine pieces and macerated in distilled water. This is expressed, and a second extraction made. The two liquids are then combined and reduced to a soft extract on a water-bath. This extract is then dissolved in distilled water and filtered. The filtrate is again reduced to its former consistency (3).

In order to develop a method whereby the objectionable precipitate in tincture of opium might be eliminated, several experiments were tried. The results of quite a number of experiments can be reduced to three, which will properly illustrate the procedure.

The following formula was used:

Granulated opium	100 Gm.
Paraffin	50 Gm.
Alcohol	200 cc.
Water, distilled, a sufficient quantity to make	1000 cc.

The tincture was prepared by dissolving the proper amount of opium in hot water. We allowed this mixture to stand over night; filtered the liquid, and added water distilled *q. s.* to make 250 cc. This aqueous mixture was heated on the water-bath until it was reduced to about 150 cc. This concentrate was cooled, and paraffin added. The mixture was then heated just sufficiently to melt the paraffin, and the whole was thoroughly mixed. After the paraffin had solidified, the product was allowed to stand twenty-four hours. The pellicle of paraffin was pierced, and the liquid poured off. The paraffin was washed with sufficient dis-

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¹ From the Control Laboratories, Eli Lilly and Company.

tilled water to make a total of 800 cc. This liquid was filtered, and 200 cc. of 95 per cent alcohol added. This resulted in a fairly clear product.

Tincture of opium made by this method after aging thirty days was clear. One can easily see through 20 millimeters of the liquid.

Sixty days' aging, with subsequent filtration, further improved the clarity of the product, and gave us a brilliant tincture.

This procedure does not entirely inhibit the formation of the precipitate. However, the precipitate that forms on the sides and bottom of the bottle was more or less of a scaly nature, and while it will flake off and mix with the contents of the bottle, yet it does not produce a turbid and unsightly tincture. A product made by this method could be used in dispensing very easily, merely by decanting the clear portion.

A further improvement on this formula can be made by changing the procedure slightly. An example of such a formula follows:

Granulated opium	100 Gm.
Paraffin	50 Gm.
Alcohol	200 cc.
Water, distilled, a sufficient quantity to make	1000 cc.

The granulated opium was dissolved in about 200 cc. of hot water, and allowed to stand overnight; filtered, and the filter paper washed with water *q. s.* to make about 250 cc.

This aqueous mixture was then heated to 77–80° C., and kept at this temperature until it was evaporated to about one-half volume. The paraffin was added to this, and allowed to melt. The mixture was then thoroughly beaten and allowed to cool.

After the paraffin had solidified, the pellicle was punctured and the liquid drained off. The paraffin was washed with enough distilled water to make a total of 800 cc. This was then filtered, and 200 cc. of alcohol mixed with the filtrate.

A portion was assayed, and the product diluted according to this assay. A sample of this mixture after aging 7 days and then filtering had much less precipitate in it than one made by the regular U. S. P. X method.

A sample that was aged 30 days and then filtered showed improvement in the amount of precipitate thrown down upon longer aging.

Sixty days' aging was found to further reduce this quantity of final precipitate.

A sample of tincture that had been made by this method and aged sixty days showed only a very small amount of precipitate. This precipitate adhered to the bottom and sides of the bottle as a hard scale, which could be shaken loose, but immediately settled to the bottom. Therefore, such a tincture could be used for dispensing very conveniently, as the clear product could be decanted readily from any dispensing bottle.

A tincture that was made according to the U. S. P. X method contained a very thoroughly suspended and muddy precipitate which, even after long aging, did not allow a clear portion to be decanted.

These two groups of experiments were followed by a third one, in which the same procedure was followed, except with a change at only one point. At the

stage where the aqueous mixture of opium was reduced, the liquid was boiled for 15 minutes, and allowed to stand overnight, instead of being maintained at a temperature of 77° to 80° C. The result of this procedure was even better than the previous experiments. The amount of precipitate in this tincture was materially reduced, and at the end of eighteen months had not shown any further sedimentation. An assay on the clear supernatant liquid showed no loss in potency during this period.

This experiment was repeated with opium from several different shipments in order to be sure that such a formula would be adaptable to the material usually obtained in commerce.

It has been suggested by some that caramel should be added to tincture of opium as a coloring agent. In order to prove that this might have some effect on the resulting precipitate, samples of all experiments were colored with a small amount of caramel. The results of all such experiments performed were the same; namely, a small amount of additional caramel to any of these tinctures increases the amount of precipitate, or at least the character of its formation. In all cases in which caramel had been added to the tincture, these products showed a fine, well-suspended precipitate which had no tendency to coagulate, and was very easily mixed by shaking. It is interesting to note that the samples colored with caramel showed the same easily suspended, and muddy precipitate that is characteristic of the U. S. P. product. Therefore, the addition of caramel is objectionable.

CONCLUSIONS.

Since a tincture of opium made by the method outlined above is free from this large amount of light, muddy precipitate that is characteristic of the U. S. P. product, we suggest that the formula for tincture opium U. S. P. be modified slightly so that a product can be made which will remain clear for a considerable period of time. Furthermore, the use of caramel as a coloring agent causes an additional precipitate, which is undesirable.

REFERENCES.

- (1) The Pharmacopœia of the United States, Tenth Decennial Revision, 400 (1926).
- (2) The United States Dispensatory, Nineteenth Edition, 1280 (1907).
- (3) French Codex, 438 (1908).

A STUDY OF COMPOUND CRESOL SOLUTION.*

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Compound Solution of Cresol was first made official in the U. S. Pharmacopœia VIII. It has been continued in the succeeding revisions with but slight changes in the formula and procedure.

As a germicide the use of cresol is attributed to German workers (1). The fact that it is soluble in a soap solution has led to its wide use in such preparations which are well known by the official titles and various trade names.

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