

Determination of Salicylamide in Compound Medicinal Tablets

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Salicylamide is a common ingredient in tablets for the relief of coughs and colds. Several methods have been described for its determination in such preparations but usually require prior separation from other ingredients, or fairly involved techniques.

The 4-aminophenazone coupling reaction does not seem to have been applied to salicylamide in tablets although it gives a strong colour with this reagent, unlike salicylic acid, which gives no reaction. The present investigation assesses the use of 4-aminophenazone for the rapid determination of salicylamide when present with other drugs.

Salicylamide can be determined by several methods^{1,2,3,4}. The conditions for the 4-aminophenazone coupling reaction outlined by Johnson and Savidge⁵ for dyes insoluble in chloroform gave excellent results with salicylamide but the developed colour was unstable on standing, necessitating immediate measurement. The procedure finally adopted was that used in the B.P.C. 1968 for phenylephrine eye drops⁶, but modified as below.

Reagents

1. *4-Aminophenazone solution*: A 0.5 per cent. solution in water.
2. *Potassium ferricyanide solution*: A 2.0 per cent. solution in water.
3. *Sodium bicarbonate buffer solution*: A 8.4 per cent. solution in water.

These solutions should be freshly prepared.

Method

Take a known weight of powdered tablets, not exceeding 0.5 g, and transfer it to a 100 ml beaker. Add 10 ml of 0.5 N NaOH solution.

Stir thoroughly for a few minutes until dissolved. Do NOT heat. Transfer the solution to a suitable volumetric flask and dilute to produce a solution containing about 0.05 mg of salicylamide per ml. Filter, rejecting the first few millilitres of the filtrate and titrate 10 ml of the clear solution with 0.1 N HCl solution, using phenolphthalein indicator (X ml.)

Pipette a further 10 ml filtrate into a 100-ml volumetric flask and dilute to about 50 ml. If X is greater than 0.1 ml, add $X - 0.1$ ml of 0.1 N HCl solution to the flask and mix the contents. Add 5 ml of reagent (1) and 1 ml of reagent (3). Mix well; add 5 ml of reagent (2), make up to the mark with distilled water and mix again. Allow the mixture to stand for 30 minutes. Measure the extinction in a 1 cm cell at 510 nm using as blank, a solution

prepared as above with 10 ml of distilled water in place of the sample filtrate. The value of $E_{1\text{ cm.}}^{1\text{ per cent.}}$ of salicylamide under these conditions is 1650.

Results

Following the method of the British Pharmaceutical Codex as printed, resulted in poor linearity in the graph of the extinction plotted against the salicylamide concentration, and results were not reproducible.

However, by adding the sodium bicarbonate buffer solution and mixing *before* adding the potassium ferricyanide solution, a truly linear relationship was obtained, passing through the origin with a constant $E_{1\text{ cm.}}^{1\text{ per cent.}}$ over the usable range of 0.1–0.6 mg salicylamide per 100 ml. In addition, the sensitivity was increased and the transient red colour produced by interaction of the reagents was practically eliminated. The developed colour was very stable, identical readings being obtained after allowing it to stand for a further 30 minutes. A cold alkaline solution of salicylamide was allowed to stand for 24 hours before estimation. The result, only slightly lower than an immediate determination, indicated that hydrolysis would be insignificant during the period of the test.

Discussion

The method showed itself to be remarkably free from interference by other drugs commonly found in "cold" tablets. Aspirin, caffeine, salicylic acid, and phenacetin caused no interference, even when mixed in a ratio of 10 to 1 with salicylamide. Paracetamol, when present in this proportion, caused a slight raising of the true salicylamide content (8 per cent. above the true figure) but interference became negligible when the ratio was reduced to 5 to 1, a higher proportion than is found in most tablets. Several proprietary brands were tested containing, in addition to salicylamide, various combinations of paracetamol, aspirin, and caffeine, the results being excellent.

Certain drugs containing phenolic groups such as phenylephrine would interfere. In this case salicylamide could be separated from phenylephrine by shaking an acid aqueous solution of the two with chloroform, the phenylephrine remaining in the aqueous layer. Indeed, this separation has been used by Cottam⁷ to determine phenylephrine itself in cold relief preparations, using the 4-aminophenazone reaction.

References

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