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The assay of pseudoephedrine hydrochloride in tablets and liquid formulations by two phase acid-base titration

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A novel titration method for the assay of pseudoephedrine hydrochloride in formulations is presented. Pseudoephedrine base is extracted into chloroform and titrated with acid in a two phase system. The method is specific for the drug in tablet and syrup formulations. The precision and speed of assay are comparable with existing spectrometric and titration methods for amine drugs.

The assay of basic drugs present in formulations as their salts, is often non-specific depending on the presence elsewhere in the molecule of a chromophore absorbing in the u.v./visible region of the spectrum.

Those methods which depend on the presence of amino groups use two main principles; formation of ion pairs (Matsui & French 1971; Gfeller & Frey 1978; Carkhuff & Boyd 1954; Pellerin et al 1962) and a back-titration method applicable when the free base can be extracted into an organic solvent then re-extracted into acid solution: examples in the British Pharmacopoeia 1973 are diethylcarbamazine and methadone tablets.

We describe a method for assaying pseudoephedrine hydrochloride in pharmaceuticals. Non-aqueous titration used for the drug substance itself (B.P. 1980) is unsuitable where pseudoephedrine is present in liquid formulations.

The two phase acid–base titration we propose has been used for determining organic solvent/water distribution coefficients (Johansson & Gustavii 1976). One previous application to quantitative analysis (Cantwell & Mohammed 1979) requires specially constructed apparatus and utilizes photometric monitoring. It was used only for pure drugs.

MATERIALS AND METHODS

Materials

Chloroform, sodium sulphate anhydrous, hydrochloric acid, 0·1 M, sulphuric acid, 0·1 M, sulphuric acid, dilute B.P., sodium hydroxide, 5 M, sodium hydroxide, 0·1 M, ethanol, absolute B.P., chlorophenol red, indicator grade (0·3 g) and congo red, indicator grade (0·15 g) dissolved in 50 ml ethanol 12 ml 0·1 M sodium hydroxide and water to 500 ml (protected from light). Reagents were of analytical-reagent grade unless otherwise stated.

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Drugs and formulations

Pseudoephedrine hydrochloride B.P., pseudoephedrine 60 mg tablets, pseudoephedrine elixir, pseudoephedrine and guaiphenesin syrup were used. Both liquid products contain 30 mg of pseudoephedrine hydrochloride per 5 ml.

Assay of pseudoephedrine hydrochloride in tablets

Weigh and powder 20 tablets. Weigh an amount of powder equivalent to 0·48 g of pseudoephedrine hydrochloride into a 250 ml separator. Add 45 ml of water, 1 g of sodium sulphate and 5 ml of dilute sulphuric acid. Shake well. Add 4 ml of 5 M sodium hydroxide solution and extract with four 40 ml quantities of chloroform, washing each extract with the same 10 ml of water. Bulk the chloroform extracts in a 200 ml volumetric flask and dilute to volume with chloroform. To a 100 ml stoppered measuring cylinder add 50·0 ml of the chloroform solution, 50 ml of water and a few drops of mixed indicator. Titrate with 0·1 M hydrochloric acid from a 10 ml burette, shaking well between additions. The colour change in the aqueous layer is red to colourless to yellow, and the end point is taken as the first appearance of a yellow tint. The colour can be assessed without allowing separation of the phases. Each ml of 0·1 M hydrochloric acid is equivalent to 0·02017 g of pseudoephedrine hydrochloride.

Assay of pseudoephedrine hydrochloride in syrups and elixirs

Accurately measure in a volumetric flask an amount of product equivalent to about 0·6 g of pseudoephedrine hydrochloride (100 ml). Transfer quan-

titatively to a 500 ml separator, rinsing with water. Add, in total, 200 ml of water. Add 4 g of sodium sulphate and 4 ml of 5 M sodium hydroxide solution. Extract with four 50 ml quantities of chloroform, washing each extract with the same 10 ml of water. Bulk the chloroform extracts in a 250 ml volumetric flask and dilute to volume with chloroform. Titrate 50·0 ml of chloroform solution following the procedure given for pseudoephedrine tablets.

RESULTS AND DISCUSSION

Linearity of response

The assay response is affected by the efficiency of extraction and the equivalence of the titration. Amounts of pseudoephedrine hydrochloride up to 150% of the assay concentration were passed through the extraction procedures. A linear relation between weight and titre was obtained, and all titres were within 0·7% of the theoretical figures for the weights of drug taken. An extraction omitting the drug gave a negligible titre; no carry over of sodium hydroxide occurs, and it is not necessary to carry out a blank titration.

Specificity of the assay

Sodium sulphate is added to minimize emulsion formation during extraction of the free base from the alkaline solution. The initial treatment of the tablets with acid ensures complete dissolution of the drug. Recovery experiments were carried out by adding the drug in solution to mixtures of pharmaceutical excipients in the appropriate quantities used in solid and liquid preparations (per cent recoveries ranged from 98·7–100·5). The following materials were examined for interference: lactose, starch, magnesium stearate, sorbitol, sucrose, glycerol, gelatin, citric acid, methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, sodium benzoate, saccharin, chloroform, ethanol and the dyes FD and C Red No. 2 and Yellow No. 6. No interference was found from these materials or from the drug guaiphenesin, less than 0·2% of the expected titre for the pseudoephedrene being obtained.

Precision of assay

Two operators each carried out four independent assays of a bulk sample of ground tablets or syrup. The results (% of theory) were: tablets mean 98·8, s.d. 0·638, (n = 8); syrup mean 97·5, s.d. 0·432, (n = 8). A single assay of the tablets in this laboratory is expected to give a result within 1·5% of the mean result ($P = 0·95$). A single assay of the syrup is expected to give a result within 1% of the mean result ($P = 0·95$). The low assay result for the syrup was confirmed by h.p.l.c.

Choice of indicator

Of the pH indicators evaluated (methyl red, methyl orange, bromophenol blue, phenol red, bromocresol purple, quinaldine red, bromothymol blue, bromocresol green, metanil yellow, congo red, chlorophenol red) no single indicator gave a sharp end point, but a mixture of two parts chlorophenol red and one part congo red proved satisfactory. The colour change is caused by the chlorophenol red in the aqueous phase. Congo red precipitates at the interface in the red form and does not interfere in the colour evaluation, but appears to sharpen the end point by displacing chlorophenol red from the chloroform–water interface into the bulk of the aqueous phase. The middle tint of the indicator is at pH 5·3 and Fig. 1 shows a typical curve of pH vs titrant volume. It is clear that the indicator will locate the true equivalence point.

Stability of the extract

A chloroform extract of pseudoephedrine base gave a 2% lower titre after standing in sunlight for one day. It is believed that hydrogen chloride is formed by photolysis of the chloroform. The titration and extraction should be completed on the same day.

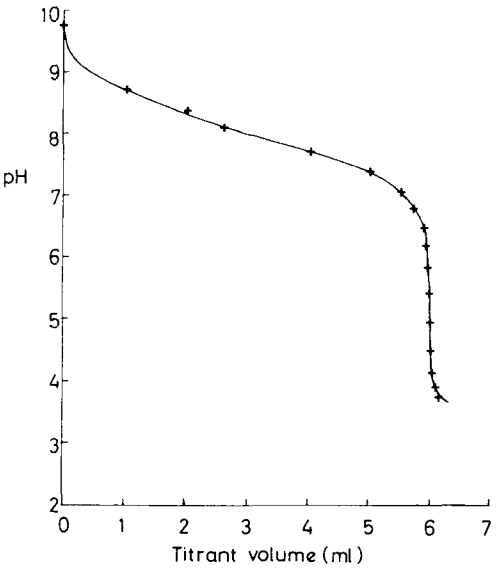

FIG. 1. Graph of pH (in the aqueous phase) vs titrant volume.

Theoretical treatment of the titration

From the equilibrium at the half-neutralization point,

$$pH = \text{apparent } pK_a = pK_a - \log_{10}\left(1 + K_d \cdot \frac{V_{org}}{V_{H_2O}}\right)$$

where

$$K_d = \frac{\text{concentration of base in organic layer}}{\text{concentration of base in aqueous layer}}$$

V_{org} = volume of organic phase at half-neutralization point

V_{H_2O} = volume of aqueous phase at half-neutralization point

The pK_a of pseudoephedrine is reported to be 9·8 (Martindale, The Extra Pharmacopoeia 1977).

The equation predicts a reduction in pK_a which is observed in practice. For pseudoephedrine base in chloroform–water a value of $K_d = 53$ was calculated (mean of 3 results). This equation applies if the free base is the only species which extracts into chloroform. Similar results are obtained with hydrochloric or sulphuric acid as titrant, which confirms that protonated pseudoephedrine does not extract as an ion pair with the chloride ion. A more comprehensive theoretical treatment is given by Johansson & Gustavii (1976).

Conclusion

The method is suitable for the quality control of pseudoephedrine formulations and is probably useful for basic drugs in general. As the desirability on environmental grounds of using mercuric acetate in the non-aqueous titration of amine salts comes under increasing scrutiny, this method will offer an alternative approach.

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