A MODIFIED PROCEDURE FOR THE DETERMINATION OF ISONIAZID IN MIXTURES WITH SODIUM *p*-AMINOSALICYLATE

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A modification of a routine method for the determination of isoniazid in mixtures with sodium *p*-aminosalicylate in tablet form is described. After the removal of interfering tablet excipients with hydrochloric acid the isoniazid is determined by reduction of the hydrazine group with a zinc-copper couple in potassium hydroxide to ammonia which is absorbed in standard acid the excess of which is titrated with standard alkali.

MITCHELL, Haugas and McRoe (1957) described a method for the determination of isoniazid based on the reduction of the hydrazine group with zinc-copper couple in potassium hydroxide solution to give ammonia which is determined after distillation into standard acid solution. It was claimed that excess *p*-aminosalicylate did not interfere with the determination of isoniazid. This method was studied and it was found that when the conditions described were strictly adhered to, particularly the volume of distillate to be collected, this method gave satisfactory results when applied to mixtures of pure drugs. But when applied to tablets erratic results were obtained. Considerable frothing occurred making it very difficult to control the rate of distillation. The frothing was caused by the presence of starch and magnesium stearate.

The simplicity of the method described by Mitchell, Haugas and McRoe (1957) makes it very attractive as a routine method, provided the substances that cause frothing can be removed.

It was found that treatment with concentrated hydrochloric acid hydrolysed the starch and the magnesium stearate was removed with the *p*-aminosalicylate hydrochloride by filtration. The isoniazid could be determined in the filtrate by a slight modification of the procedure described by Mitchell, Haugas and McRoe (1957). No frothing was encountered during the distillation. The results were independent of the volume of the distillate so long as it is not less than 100 ml.

EXPERIMENTAL

Reagents

Zinc powder, 25 per cent w/v aqueous copper sulphate solution, potassium hydroxide pellets, 0·02N sulphuric acid, 0·02N sodium hydroxide, and 15 per cent sodium chloride solution.

Preparation of Zinc-Copper Couple

About 2 g. of zinc powder and 5 ml. of the copper sulphate solution are shaken in a 50 ml. flask until the supernatant liquid is nearly colourless. This liquid is decanted and the residue washed three times with 10 to 15 ml.

portions of water, decanting each washing. The zinc-copper couple is then ready for use.

Procedure

Twenty tablets are weighed and powdered. About 0·6 g., accurately weighed, of the sample, containing 15–30 mg. of isoniazid, is placed in a 50 ml. beaker together with 10 ml. of water and 1 ml. of concentrated hydrochloric acid. The solution is cooled in ice for 15 min. and filtered through a Whatman No. 1 filter paper. The residue is washed three times with 10 ml. portions of 15 per cent sodium chloride solution. The combined filtrate is placed in a 1 litre flask together with 10 g. of potassium hydroxide, zinc-copper couple and 350 ml. water. This mixture is distilled into 25 ml. of 0·02N sulphuric acid until not less than 100 ml. has been collected. The excess acid is titrated with 0·02N sodium hydroxide solution using methyl red–methylene blue as an indicator.

Each ml. of 0·02N sulphuric acid used is equivalent to 0·00137 mg. of isoniazid.

Recoveries from synthetic mixtures of isoniazid with sodium *p*-aminosalicylate were 100·9 per cent (range +1·2–0·9) and 100·2 per cent (range +1·0–0·7). The figures of analyses of seven commercial samples indicated that the isoniazid contents of some of the commercial samples were lower than the amounts claimed. To ensure that true values had been obtained, recovery experiments were conducted and the results are shown in Table I.

TABLE I

RECOVERY OF ISONIAZID ADDED TO COMMERCIAL SAMPLES CONTAINING ISONIAZID AND SODIUM *p*-AMINOSALICYLATE

Weight of isoniazid per tablet (mg.)		Weight of isoniazid (mg.)		
Stated	Found previously	Added	Total	Amount recovered
15·0	13·8	10	25·0	10·2
15·0	14·5	10	24·4	9·9
15·0	15·1	10	25·0	9·9
25·0*	23·7	10	33·4	9·7
25·0*	25·0	10	34·9	9·9

* The ammonia from these samples was distilled into 30 ml. of Standard 0·02N H_2SO_4.

Calcium phosphate, alginic acid, sugar, starch, magnesium stearate and lactose have been added and do not interfere with the modified procedure of analysis for isoniazid.

REFERENCE

Mitchell, B. W., Haugas, E. A. and McRoe, C. S. (1957). *J. Pharm. Pharmacol.*, **9**, 42–45.