A NOTE ON THE STABILITY OF SOLUTIONS OF PHENYLEPHRINE

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SOLUTIONS containing phenylephrine hydrochloride (10 per cent) are commonly used as eye-drops to produce either a rapid dilatation of the pupil without loss of accommodation or a rapid and temporary reduction in the intraocular pressure in glaucoma. There appears to be no reference in the literature to the stability of such solutions although they may develop a yellow, pink or purple colour on storage.

In 1951, Schou and Rhodes[1] showed that injections of phenylephrine (1 per cent) are stable if made oxygen-free and strongly acidic (pH 1). They stated that sodium metabisulphite (0·1 per cent) must be added to solutions of a higher pH value to prevent coloration and loss of activity on autoclaving. Wahlquist[2] also noted that injections of phenylephrine become yellow on storage if sodium metabisulphite is omitted and oxygen is not totally replaced by nitrogen.

It was noted in hospital practice that solutions of phenylephrine (10 per cent) became yellow or pink within a few weeks of issue in 15 ml. amber-coloured eye-drop bottles, and sodium metabisulphite (0·1 or 0·2 per cent) did not prevent the discoloration. Although colour changes are not necessarily a guide to changes in biological activity attempts have been made to prepare solutions which would remain colourless.

The chelating agent, disodium edetate, was tested as it has been found effective in preventing coloration of solutions of procaine hydrochloride. (Green and Whittet, unpublished).

The solutions prepared, using "Solution for Eye-Drops B.P.C." as solvent, were: phenylephrine (10 per cent) alone, with 0·1 or 0·2 per cent sodium metabisulphite, with 0·1 per cent disodium edetate, or with 0·1 per cent disodium edetate and 0·1 or 0·2 per cent sodium metabisulphite. Samples were placed in 1 ml. ampoules under nitrogen, in corked or screw-capped 30 ml. white glass bottles, and in 15 ml. amber-coloured dropper bottles. All the ampoules were filled with the solutions but only half of the bottles were filled; the remainder were half-filled. All samples were then sterilised by heating with a bactericide at 100° for 30 minutes. They were examined at frequent intervals during nine months' storage at room temperature, and coloured solutions were biologically assayed on the blood pressure of the anaesthetised rat or cat.

The solutions in the ampoules, with the exception of those without added preservative, remained colourless throughout. Those without preservative were a faint yellow. There was no loss of biological activity

in any of these solutions. The solutions in the three types of bottles showed that the appearance of colour was slowest in the full ones stored away from the light, and that disodium edetate exerted a protective action against direct oxidation whereas metabisulphite was unsatisfactory. The

TABLE I

THE EFFECT OF STORAGE AT ROOM TEMPERATURE ON THE COLOUR OF STEAMED SOLUTIONS OF PHENYLEPHRINE (10 PER CENT) IN THE PRESENCE OR THE ABSENCE OF A PRESERVATIVE IN HALF-FULL 15 ML. AMBER-COLOURED EYE-DROP BOTTLES

Preservative added	Storage period (months)			
	1	3	4	6
None	Faint yellow	Yellow, with black specks	Brown, with black deposit	Brown, with black deposit
Sodium metabisulphite 0·1 per cent	Deep pink	Deep brownish-pink	Purplish-red	Brown, with black deposit
Sodium metabisulphite 0·2 per cent	Deep pink	Red, with black specks	Purplish-red with black deposit	Brown, with black deopsit
Disodium edetate 0·1 per cent	Colourless	Colourless	Colourless	Colourless

results in Table I are for the half-filled 15 ml. amber-coloured dropper bottles. The values for the other samples under test followed a similar pattern, although sodium metabisulphite was more effective in preventing coloration in white bottles than in amber-coloured bottles. In amber bottles metabisulphite may even accelerate the coloration. Colourless solutions containing edetate showed no loss of activity when tested

TABLE II

THE EFFECT OF ADDING HYDROGEN PEROXIDE (100 VOL.) TO 10 PER CENT SOLUTION OF PHENYLEPHRINE IN THE PRESENCE OR THE ABSENCE OF PRESERVATIVES IN FULL WHITE GLASS MACARTNEY BOTTLES

Preservative added	Storage period (days)				
	0·2	1	3	10	90
None	Deep red	Black with copious deposit	Black with copious deposit	Black with copious deposit	Black with copious deposit
Sodium metabisulphite 0·1 per cent ..	Colourless	Colourless	Pink	Deep brown	Black with copious deposit
Sodium metabisulphite 0.2 per cent ..	Colourless	Colourless	Pink	Pale brown	Deep brown
Disodium edetate 0·1 per cent	Colourless	Colourless	Colourless	Colourless	Light orange

biologically and the brown solutions with black deposits had lost not more than 10 per cent of total activity.

Further solutions were then prepared and treated with hydrogen peroxide (0·2 ml. 100 vol./15 ml. solution) to accelerate the oxidation processes. The results shown in Table II indicated that disodium edetate exerted a strong protective action against the oxidative property of hydrogen peroxide. Sodium metabisulphite was less effective. The black and brown solutions again showed insignificant losses of activity.

These results confirm the observation that solutions of phenylephrine colour on oxidation but the amount of colour is no indication of the decrease in activity. Sodium metabisulphite delays the colour formation but disodium edetate (0·1 per cent) is better. The protective effect of edetate is generally believed to be due to its chelating power (on metals such as iron and manganese, two constituents of amber glass[3]) but it also exerts an antioxidant effect. Disodium edetate is harmless to the eyes and is therefore recommended as the preservative for solutions of phenylephrine (10 per cent).

REFERENCES

1. Schou and Rhodes, *Dansk. Tiddskr. Farm.*, **1951, 25, 350.**
2. Wahlquist, *Pharm. J.*, 1955, **2**, 364.
3. Dimbleby, *J. Pharm. Pharmacol.*, 1953, **5**, 969.

After Dr. Whittet presented the paper there was a DISCUSSION. The following point was made.

For the treatment of calcium burns in the eye an 11 per cent solution of disodium edetate was now being used without untoward effects.