THE EFFECT OF SUGARS ON THE STABILITY OF SALBUTAMOL SULPHATE SOLUTIONS

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We have previously described a stability-indicating HPLC assay for salbutamol and have shown that at pH9 the BPC indoaniline colorimetric assay overestimates the salbutamol content of degraded solutions (Hakes and others 1979). Further work at pH7 and pH3.5 has confirmed that the colorimetric method is unsuitable for stability studies. The HPLC assay has therefore been used to generate a complete pH-stability profile (pH 1-10) which has confirmed previous studies (Winterborn 1972) which indicated that salbutamol is most stable in the pH range 3-4. For this reason the injections and syrup are formulated at a pH of 3.5.

Although the syrup has an adequate shelf-life, its stability is inferior to that of the simple injection solutions, indicating that the syrup adjuvants may accelerate breakdown of the drug. We have therefore studied the influence of some sugars on the stability of salbutamol solutions. Initially, experiments were carried out at pH7 and 70° in order to give a rate of breakdown that could be followed in a reasonable time period. Figure 1 shows that although glucose accelerated the breakdown of salbutamol by a factor of two, sucrose surprisingly had no effect. The experiments were therefore repeated at the formulation pH of 3.5 when both sugars were found to accelerate the reaction to a similar extent (Fig. 2). These effects were also found to be concentration dependent, degradation increasing with sugar concentration.

Sucrose is a *non-reducing* disaccharide, each molecule arising from a fructose and a glucose unit joined through their anomeric centres. It is subject to acid catalysed hydrolysis to its constituent monosaccharides and at pH3.5 and 70°C. degradation is extensive, with a half-life of about 23 hours (Vukov 1965). However, at pH7, hydrolysis is minimal and there is less than 0.1% degradation under the experimental conditions (250 hours at 70°C). Further studies have revealed that fructose is as effective as glucose at causing salbutamol breakdown.

The inference to be drawn from these results is that the interaction of the drug with sugar molecules requires the latter to exist in an acyclic form, with a free carbonyl group. This condition cannot be met by the unhydrolysed sucrose solutions at pH7 and so the rate of salbutamol breakdown is unaffected.

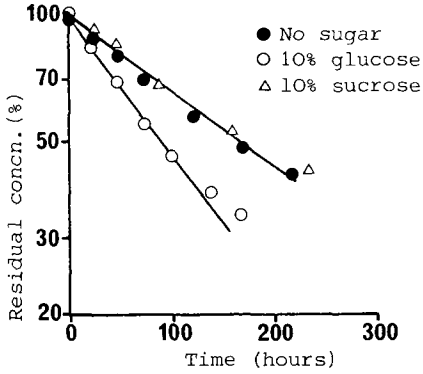

Fig.1. Degradation of 0.5% Salbutamol Sulphate at pH7 and 70° under oxygen

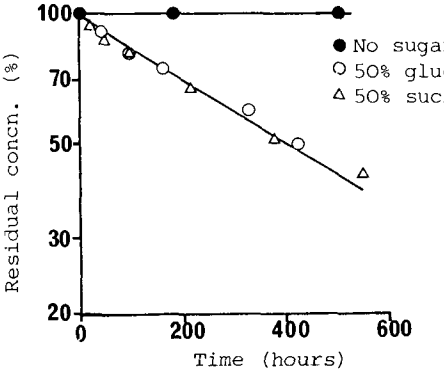

Fig.2. Degradation of 0.5% Salbutamol Sulphate at pH 3.5 and 70° under oxygen

Hakes, L.B., Corby, T.C. and Meakin B.J.(1979) J.Pharm.Pharmacol 31 Suppl. 25P
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Winterborn I.K. (1972) unpublished industrial data