# Stability of hyoscyamine in some B.P.C. mixtures

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A number of mixtures containing either belladonna or hyoscyamus tincture are official in the B.P.C. Although it is stated that such mixtures should be recently prepared, no detailed studies appeared to have been made concerning the stability of hyoscyamine in these mixtures. A report from the Pharmaceutical Society Laboratory (Pharm. Soc. Lab. Report No. P/71/9, 1971) attempted to predict the shelf-lives of some B.P.C. mixtures containing belladonna and hyoscyamus tinctures. The derivations made were based on previously reported values of the rate constant (k) for atropine in buffered solutions at various pH values (Zvirblis, Socholitsky & Kondritzer, 1956; Kondritzer & Zvirblis, 1957). It was assumed that similar rates of decomposition to those known for atropine in buffered solutions would occur in the B.P.C. mixtures. However, this assumption was not validated by experimental evidence. In some B.P.C. mixtures, factors such as viscosity, adsorption and electrolyte concentration may influence the rate of decomposition of hyoscyamine. The objective of the present work has been to examine the accelerated decomposition of hyoscyamine in the following B.P.C. mixtures: aluminium hydroxide and belladonna; magnesium trisilicate and belladonna; potassium citrate and hyoscyamus. Stability testing of hyoscyamine in the mixtures was carried out on samples stored at either 40 or 60 ± 0·2°. For the magnesium trisilicate and belladonna mixture stability was also monitored at room temperature (18–22°) over 8 weeks. At specified intervals, a sample of the mixture (5–10 ml) was assayed for hyoscyamine content. Duplicate runs were made for each time interval. The assay method adopted is based on the acid dye technique using bromocresol purple at pH 6·6 (El-Masry & Khalil, 1973). Details of the procedure used for extraction of hyoscyamine from the samples have been previously published (Khalil & El-Masry, 1976). Under the conditions of the assay no interference occurred from either hyoscine or tropine (a hydrolytic product of hyoscyamine).

To test whether the stability of hyoscyamine was influenced by the viscosity of aluminium hydroxide gel or adsorption of the alkaloid by magnesium trisilicate (El-Masry & Khalil, 1974), the following experiment was carried out. Belladonna tincture was added to the clear supernatants of either aluminium hydroxide gel, B.P. or magnesium trisilicate mixture, B.P.C. obtained by centrifugation and the stability of hyoscyamine in the supernatants was determined as described above.

* Correspondence.

Figs 1 and 2 show the first-order plots for stability of hyoscyamine in the mixtures and supernatants. The calculated values of the rate constant (k) and t10% (time for 10% decomposition) are shown in Tables 1

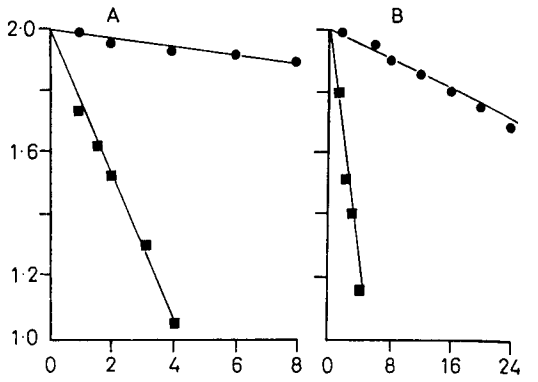


FIG. 1. First-order plots showing the stability of hyoscyamine in (●) magnesium trisilicate and belladonna mixture, B.P.C.; (■) belladonna tincture added to the supernatant of magnesium trisilicate mixture. (A) at room temperature, 18–22°; (B) at 40 ± 0·2°. Ordinate: % hyoscyamine remaining (Log scale). Abscissae A: Time (weeks); B: Time (days).

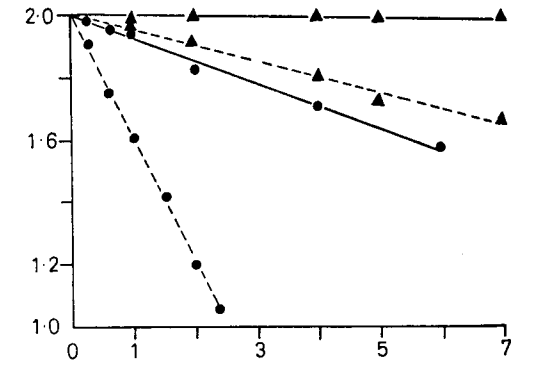


FIG. 2. First order plots showing the stability of hyoscyamine at 60 ± 0·2° in (▲——▲) potassium citrate and hyoscyamus mixture, pH 6·1 (▲- - -▲) hyoscyamus tincture added to the phosphate buffer pH 6·1; (●——● aluminium hydroxide and belladonna mixture; (●- - -●) belladonna tincture added to the supernatant of aluminium hydroxide gel. Ordinate: as for Fig. 1. Abscissa: Time (weeks).

and 2. The results obtained suggest that hyoscyamine was relatively more stable in the mixtures than in their corresponding supernatants. Also, values of (k) found for the mixtures were much less than the values for atropine in buffered solutions at comparable pH values (Tables 1 and 2). The apparent increased stability of hyoscyamine in the mixtures examined is attributed to some properties in the mixtures tested; namely viscosity due to aluminium hydroxide gel, high electrolyte concentration in potassium citrate and hyoscyamus mixture and adsorption of the alkaloid in magnesium trisilicate and belladonna mixture. In the latter, where about 93% of the alkaloid was adsorbed (El-Masry & Khalil, 1974), only a low percentage of 'free' hyoscyamine would be available for decomposition in the alkaline medium. That adsorption can protect drugs from decomposition was reported for ascorbic acid. Adsorption onto silicic acid yielded a product which was relatively more thermally stable than unadsorbed ascorbic acid (Wu, Chin & Lach, 1970). Since adsorption of hyoscyamine was not detected in aluminium hydroxide and belladonna mixture it follows, therefore, that the observed stabilization might be due to the viscosity and gel structure of this mixture. In the supernatants of both aluminium hydroxide gel and magnesium trisilicate mixture hyoscyamine (present in the belladonna tincture added) was much less stable than in the corresponding mixtures (Table 1 and 2) hence confirming the suggestions mentioned above. The presence of 30% potassium citrate and 5% citric acid in potassium citrate and hyoscyamus mixture produced a significant stabilizing effect. About 14-fold variation in the value of (k) was found when stability of hyoscyamine was determined in the mixture and in 0·1M Sørensen phosphate buffer solution of similar pH value (6·10).

From the foregoing it is evident that the shelf-lives of the B.P.C. mixtures examined were relatively longer than the values predicted from stability data of atropine in buffered solutions. For magnesium trisilicate and belladonna mixture the time for 10% decomposition of hyoscyamine at room temperature (18–22°) was 21·2 days. The t10% predicted from Zvirblis data was 1·3 days (Table 1). The results obtained in the present work emphasize the importance of monitoring stability in the finished product.

Table 1. *Values of the rate constant (k, day$^{-1}$) and time for 10% decomposition (t10%, day) for hyoscyamine in magnesium trisilicate and belladonna mixture B.P.C. (I) and in belladonna tincture added to the supernatant of magnesium trisilicate, B.P.C. (II). The calculated k values for atropine in buffered solutions are also shown (III)*. (n = 4).*

| | At 18–20 °C | | At 40 °C | |
|---|---|---|---|---|
| | k(±s.e.) | t10% (±95% conf. lim.) | k(±s.e.) | t10% (±95% conf. lim.) |
| I, pH 8·60 | 0·005 (0·0002) | 21·19 (3·05) | 0·029 (0·0011) | 3·65 (0·45) |
| II, pH 8·65 | 0·081 (0·0031) | 1·31 (0·16) | 0·461 (0·0069) | 0·23 (0·01) |
| III, pH 8·60* | 0·079 | 1·34 | 0·491 | 0·22 |

* Calculated from the data of Zvirblis & others (1956).

Table 2. *Values of the rate constant (k, day$^{-1}$) and times for 10% decomposition (t10%, day) for hyoscyamine at 60 ± 0·2° in potassium citrate and hyoscyamus mixture (I), aluminium hydroxide and belladonna mixture (II) and in belladonna tincture added to the supernatant of aluminium hydroxide gel, B.P. (III). (n = 4)*

| | k(±s.e.) | t10% (±95% conf. lim.) | k* | t10%* |
|---|---|---|---|---|
| I, pH 6·10 | 0·001 (0·0001) | 105·94 (15·93) | 0·014 | 7·57 |
| II, pH 7·00 | 0·023 (0·0015) | 4·61 (0·91) | 0·131 | 0·81 |
| III, pH 6·95 | 0·135 (0·0025) | 0·78 (0·04) | — | — |

* Calculated from the data of Zvirblis & others (1956) for atropine in buffered solutions at 60°.

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