

Impurity profiles of pharmaceutical colourants

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Regulations governing the use of colourants in foods and in pharmaceuticals vary throughout the world with many differences from country to country in the dyes permitted. Hard gelatin capsules are marketed on a world-wide basis and a problem arises in the selection of colouring materials of international acceptability. In view of the nature of the compounds and the manufacturing procedures commercial dye materials are inevitably contaminated with impurities. These subsidiary impurities are usually closely related to the main component and are sometimes excluded dyes in their own right.

The aim of the present investigation was to examine a range of the commercial dye products available as a standard colour with the dual objects of assessing the quantities of subsidiaries present and of obtaining a qualitative 'impurity profile' for identification purposes. Amaranth (trisodium salt of 1-(4-sulpho-1-naphthylazo)-2-naphthol-3,6-disulphonic acid) and Sunset Yellow FCF (disodium salt of 1-p-sulphophenylazo-2-naphthol-6-sulphonic acid) were selected and thirteen different commercial samples of the former and twelve of the latter were chromatographed on prespread films of cellulose (Macherey Nagel CEL 300 0.2 mm) using the solvent systems specified in the appropriate British Standard. The light absorption of the dried chromatograms at 525 nm was measured by scanning the films by transmission in a Vitatron TLD 100 flying spot densitometer in the log mode at a scanning speed of 1 cm/min using a 0.25 mm aperture and a strike length of 14 mm. Peak areas were estimated directly by means of a Vitatron integrating recorder and related to the concentrations of components by reference to standards.

The Amaranth samples showed between 78.4 and 99.7% of the total absorption in the major peak with some variation in the subsidiaries. Of the subsidiaries Fast Red E is permitted in Britain but not in the E.E.C. (although the French National Standard contains it). The Sunset Yellow samples had a lower range of major peak absorption of 93.6 to 98.6 per cent but the distribution of the subsidiaries was more varied. The subsidiary Orange II is no longer permitted in any country. Each sample showed a characteristic impurity profile which enabled the manufacturing source to be identified.

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The soda lime pyrolysis of saccharin

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We have repeatedly observed that a primary aromatic amine, detected by the Stenhouse reaction (Stenhouse, 1870), is formed when saccharin, or its sodium salt, is subjected to soda lime pyrolysis. In an effort to characterize the products formed in this common, semi-micro qualitative test, the pyrolysis was carried out on a larger, test-tube scale and the distillate was collected and dried. The distillate was then subjected to gas-liquid chromatography using a column packed with 10% polyethylene glycol adipate on celite, and to column chromatography on neutral alumina. The products were identified by comparison of their physical characteristics with authentic samples, and, in some cases, by the preparation of suitable derivatives. In this way saccharin was found to give rise to benzene, aniline, benzonitrile, biphenyl, diphenyl sulphide, carbazole and ammonia. Examination of the carbonized residue remaining after pyrolysis showed that it contained some benzenesulphonamide, together with the anions S^- , SO_3^- and a trace of SO_4^- .

A similar soda lime fusion of benzenesulphonamide resulted in the formation of the same products, with the exception of benzonitrile.

The formation of this complicated mixture of products under the drastic conditions of the

test makes the assignment of clear reaction pathways impossible. However, a number of suggestions can be made concerning the mode of formation of some of the products.

(i) Benzenesulphonamide, but not benzoic acid, is formed indicating that decarboxylation of saccharin (or decarboxylation of a derivative of it) takes place.

(ii) Benzonitrile may be formed either by dehydration of the imide group, or by attack of some aromatic species by CN^- formed *in situ*. The former is favoured since no CN^- was detected in the residue, and both benzamide and nicotinamide were converted into their nitriles by soda lime pyrolysis.

(iii) It is possible that aniline is formed through attack by NH_2^- on an aryne intermediate (i.e. by elimination-addition) but more probable that direct nucleophilic displacement of a sulphonate (or related) group occurs. Jackson & Wing (1886) have shown that the fusion of sodium amide with salts of aromatic sulphonic acids produces primary aromatic amines in low yield.

(iv) Carbazole is probably formed from aniline via the intermediate diphenylamine, since Braun & Grieff (1872) showed that distillation of either of these with lime gave carbazole.

(v) Under the reductive conditions of the test it is likely that benzene-sulphonamide is deaminated and converted into thiophenol, which may dimerize to form diphenyl disulphide. The latter would readily decompose on heating to diphenyl sulphide in a manner similar to that described by Heldt (1965) for *p*-tolyl disulphide.

(vi) The formation of benzene and biphenyl can be accounted for by assuming that phenyl radicals or ions are liberated which either combine with hydrogen or couple together. Reasonably good yields of *p*-bitolyl were obtained by Heldt (1965) from *p*-tolyl sulphide upon pyrolysis over metal oxide catalysts.

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Effect of sodium carboxymethylcellulose and compound tragacanth powder on the sedimentation and redispersal of sulphadimidine mixture, paediatric B.P.C. 1968

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This communication is a report on the physical stability of Sulphadimidine Mixture, Paediatric B.P.C. 1968, when prepared with sodium carboxymethylcellulose 50 or, contemporaneously, with compound tragacanth powder. Previous studies on the evaluation of factors controlling the physical stability of sulphonamide suspensions were conducted mainly on model systems (Haines & Martin, 1961; Wilson & Ecanow, 1963; Ecanow, Grundman & Wilson, 1966; Jones, Matthews & Rhodes, 1970).

Sulphadimidine Mixture, Paediatric B.P.C. 1968 was prepared using 1% sodium carboxymethylcellulose 50 or 4% compound tragacanth powder, as described in the British Pharmaceutical Codex (1968). Care was taken to minimize air entrainment into mixtures. Sedimentation heights were recorded as suggested by Martin (1961). Samples for particle size analysis were withdrawn at a fixed depth at the midpoint of settling mixtures, diluted 1:50 with filtered 1% sodium chloride solution and assayed using a Coulter Counter "Model B" Industrial, fitted with a 400 μm orifice tube (Coulter Electronics Limited, Dunstable). Redispersibility was measured as described by Matthews & Rhodes (1968). Mixtures were stored for periods up to 21 days in a constant temperature room at $20^\circ \pm 1^\circ$.

The initial sedimentation rate of the mixture containing 4% compound tragacanth powder was more rapid than for the mixture containing 1% sodium carboxymethylcellulose 50. However, as the period of storage was extended beyond 8 h the reverse effect occurred. Falling sphere viscosity measurements indicated that during this storage period constituents of the compound tragacanth powder settled, gradually forming a viscous sol. The latter initially produced a viscosity gradient in the mixture which increased progressively with depth. These findings would contribute to an explanation of the observed sedimentation rates. Size