

An impurity in polyethylene glycol 300

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DURING routine examination of a non-aqueous formulation containing 1% tripeleannamine hydrochloride in a vehicle composed principally of polyethylene glycol 300 (liquid macrogol BPC), large losses (up to 40%) of active agent were noted in some instances. Such losses were occasioned only by some batches of polyethylene glycol 300 and occurred after autoclaving for 30 min at 15 psi, or after several days at room temperature.

Gas chromatography of available batches revealed that all contained ethylene oxide (0.01-0.2%); loss of tripeleannamine was associated with batches containing more than about 0.1% of this impurity. The ethylene oxide content of polyethylene glycol 300 was determined by direct addition of the sample (3 μ l) to a column (9 ft) of Carbowax 20M (20%) on Gas Chrom P: gas flow rate 45 ml/min (N_2), temperature 30° (injection block 80°); retention time 2 min. Tripeleannamine may normally be recovered from formulations of this kind by basifying then extracting with chloroform. In batches containing ethylene oxide, only a proportion of added tripeleannamine may be recovered. Examination of the residual aqueous phase revealed a substance with a modified ultraviolet spectrum (Fig. 1). Windmueller, Ackerman & others (1959) have

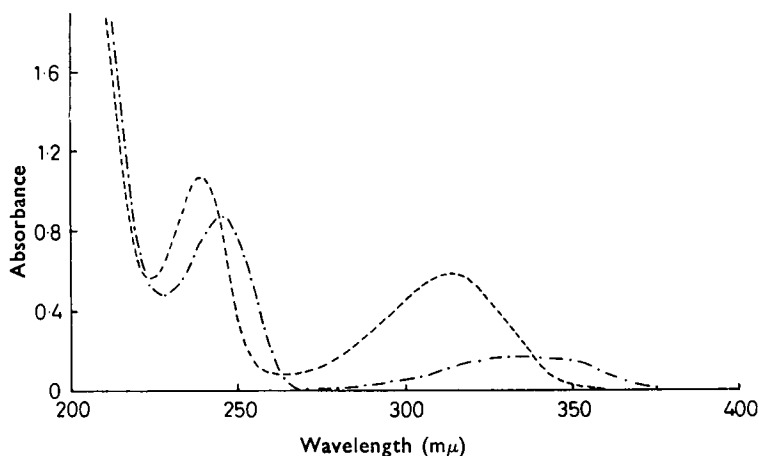


FIG. 1. Ultraviolet absorption spectra in 0.01N-hydrochloric acid of ----- 0.002% tripeleannamine hydrochloride - - - - - 0.002% tripeleannamine hydrochloride-ethylene oxide reaction product.

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shown that ethylene oxide reacts with nicotinamide to form a quaternary ammonium compound and a similar reaction would seem indicated in the present instance. This is supported by our inability to extract the reaction product with chloroform from the formulation.

Analysis of the dipicrate (m.p. 147°, tripeleennamine dipicrate 192°) formed by the reaction product gave C, 46.7; H, 4.15; N, 16.4%. The dipicrate of a product formed by addition of one molecule of ethylene oxide to one molecule of tripeleennamine would contain C, 46.5; H, 4.3; N, 16.3%.

The high reactivity of ethylene oxide raises the possibility of interaction with other drugs and we have observed a bathochromic shift (268 to 260 m μ) in the spectrum (in 3N HCl) of clioquinol after autoclaving a 0.1% solution in polyethylene glycol containing 0.1% ethylene oxide. O'Leary & Guess (1968) have shown ethylene oxide to be cytotoxic, in addition the reaction of ethylene oxide with inorganic chloride to give the toxic ethylene chlorohydrin has been reported (Wesley, Rourke & Darbishire, 1965). Deficiencies of inorganic chloride in our degraded samples support the belief that chlorohydrin formation proceeds simultaneously with quaternization.

References

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