The effect of cosolvents on the sensitivity of benzocaine in aqueous solution to ionizing radiation

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Pharmaceuticals in aqueous solution are more susceptible to irradiation than in non-aqueous systems, because the highly radiolytic products of water (H·, e^-_{aq}, OH·, H_2 and H_2O_2) are capable of inducing chemical changes. Because of the decreased amount of water in such topical preparations as creams and the desirability of presenting them sterile we have begun an investigation into the feasibility of sterilizing creams by ionizing radiation, recognizing that the association of the drug with the surfacant micelles and the presence of stabilizers, cosolvents or other adjuvants may afford protection to the drug. This communication reports the effect of cosolvents on the sensitivity of benzocaine to gamma radiation.

2 ml of 1.25×10^{-1} M benzocaine in water-cosolvent mixtures were irradiated in a ^{60}Co source. The water-cosolvent mixtures investigated were ethanol in water (10, 20, 40% w/v) glycerol in water (5, 20% w/v) and polyethylene glycol 200 in water (5, 10, 40 % v/v) and the distilled water used was saturated with oxygen by bubbling O_2 through the water for 1 h before use. Following irradiation, 1 ml of each of the solutions was subjected to a modified Bratton-Marshall reaction and the absorbances of the resulting solutions were measured spectrophotometrically at 536 nm (Meakin, Tansey & Davies, 1971). Plots of percentage residual concentration of benzocaine against dose of radiation (M rad) for the water cosolvent mixtures are shown in Figs 1a and 1b, along with a control for 1.25×10^{-4}M solution of benzocaine in water.
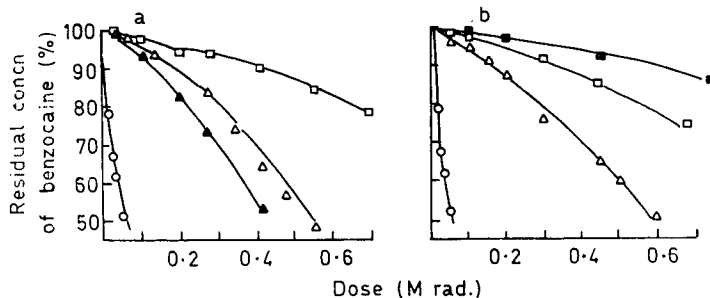

FIG. 1. Plots of % residual concentration of benzociane against dose of radiation for the water cosolvent mixtures. 1.25×10^{-4}M, benzocaine in (a) ethanol (○—0% ▲—10% △—20% □—40% w/v) and in (b) PEG (○—0% △—5% □—10% ■—40 % v/v).

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Investigations of solid dispersions of primidone in citric acid

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Sekiguchi & Obi (1961) suggested that solid dispersion systems could be used to increase the rate of solution of sparingly soluble drugs, and subsequently, much work has been carried out on this concept (see Chiou & Riegelman, 1971).

The purpose of the present investigation was to produce solid dispersions of primidone (solubility in water 1 in 2000 at 20°) as part of a project concerned with the formulation, dissolution and absorption of such systems.

Organic glass-forming compounds have been proposed as suitable water-soluble carriers, and citric acid (solubility in water 1 in less than 1 at 20°) has been used by Chiou & Riegelman (1969) to form glass solutions with griseofulvin.

Thus glasses containing from 1 to 30% w/w primidone (m.p. 295° approximately) were prepared by fusing the drug with citric acid (m.p. 153°) followed by rapidly cooling.

The glasses were metastable and devitrified over a period of time. Thus, before determination of the phase diagram of the system, devitrification was aided by storing the glasses in an oven at 60° for up to 3 days. The phase diagram was constructed by determining the onset and completion of melting of the various dispersions by hot stage microscopy and differential scanning calorimetry.

X-ray powder diffraction was also used to assess the nature of the solid dispersions present. For example, it was found that the 30% w/w glass was amorphous in nature, and this suggested that in the glass state primidone was molecularly dispersed. Devitrified samples containing 5 to 15% w/w primidone exhibited diffraction lines typical of the drug, suggesting that a eutectic mixture had crystallized out. This correlated with the phase diagram obtained from the melting point data. The primidone recrystallized from the glass as the Form II polymorph whereas the starting material (commercial material) was the Form I polymorph (Daley, 1973). X-ray diffraction data of devitrified samples containing from 1 to 3% w/w of the drug were inconclusive, but melting point data suggested that at these low concentrations the drug was present in molecular dispersion.

The influence of citric acid on the solubility of primidone was assessed by equilibrating commercially available drug, and the two prepared polymorphic forms, with distilled water and citric acid solutions of varying concentrations overnight at 37°. A $0.5 g ml^{-1}$ citric acid solution increased the solubility of the commercially available drug from 56.4 mg per 100 ml to 172.2 mg per 100 ml.

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Some effects of polyvinylpyrrolidone on the solubility and dissolution rate of allopurinol

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There is considerable interest in the use of water soluble polymers in the modification of drug solubility and dissolution rate. Various theories have been put forward to account for the observed modifications in individual systems. However, theoretical dissolution rates calculated for other systems using these theories are often not consistent with experimentally determined ones. This is a preliminary report of work aimed at determining the mechanism controlling the dissolution of allopurinol from polymer/drug mixtures.

Solubilities of allopurinol in P.V.P. of different molecular weight (K15, 10,000, K30, 40,000, K90, 100,000, Plasdone 30,000, G.A.F. Ltd.) were measured at 15, 25, 35 and 40°. In all cases solubilities increased with temperature and concentration of polymer. Thermodynamic parameters were calculated using standard equations. Differential heats of solution ΔH ranged from 25.2 to 33.6 K Joules mol^{-1}, the value decreasing with increasing polymer concentration, suggesting possible complex formation between drug and polymer. Free energies of partitioning ΔFp were negative and small 0.3 to 1.8 K Joules mol^{-1} and increased with polymer concentration at any one temperature, indicative of a more favourable environment for the drug. In contrast a decrease in value was noted at constant P.V.P. concentration with increase in temperature, probably due to a decreasing affinity of polymer for solvent with temperature increase. These thermodynamic parameters are all consistent with binding between polymer and drug. The binding is a composite one involving the polymer and drug in a hydrated form and will be considered in terms of ordering of water molecules around the solute (Frank & Evans, 1945).