SOLID DISPERSIONS OF DRUGS IN POLYOXYETHYLENE 40 STEARATE: DISSOLUTION RATES AND PHYSICO-CHEMICAL INTERACTIONS

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Solid dispersions of drugs in water-soluble matrix materials, such as polyethylene glycol (PEG), are potentially useful dosage forms (e.g. Chiou and Riegelman, 1971). The PEG ester, polyoxyethylene 40 stearate (P40S), may offer the following advantages over PEG itself: the hydrocarbon chain, by enhancing surface activity, might subject lipophilic drug molecules to aqueous micellar solubilization and thereby promote drug dissolution (Elworthy and Lipscomb, 1968); the reduced polarity might increase the solubility of lipophilic drugs in liquid excipient and perhaps also in the solid excipient and thereby improve drug dispersion. These hypotheses are being tested by comparing solid dispersions of tolbutamide, griseofulvin and frusemide in P40S with those in PEG 2000, prepared by physical mixing, fusion or co-precipitation from ethanol. PEG 2000 and P40S have approximately the same mean molecular weight. Daily intakes of up to 25 mg of P40S per kg body weight are acceptable in food (WHO, 1974).

The solubility and dissolution rate of non-disintegrating discs of each pure drug in water increased only slightly in the presence of PEG, but increased considerably with increasing concentration of P40S in water, being an order of magnitude higher in 5% w/v P40S than in 5% w/v PEG. This difference is due to micellar solubilization of the drugs by P40S. The critical micelle concentration of P40S is 0.014% w/v at 37°C; that of PEG is >5% w/v, if it exists.

Complete solid-liquid phase diagrams for each type of dispersion of each drug in each excipient were determined by differential thermal analysis and hot stage microscopy. These diagrams, which were of the monotectic type for PEG and mostly of the eutectic type for P40S, showed greater solubility of each drug in liquid P40S than in PEG. Microscopic examination of the solid dispersions revealed micro-crystals of each drug even when present at less than 1% w/w.

Solid discs, 13 mm in diameter, of certain of the solid dispersions were prepared by compression at 75.1 MN m^{-2}. Upon exposure to aqueous buffers at pH 1 or 7 in a simple beaker-stirrer dissolution test (Levy and Hayes, 1960), the compacts disintegrated by progressive erosion releasing floccules of micro-crystals of the drug. The size distribution of the drug particles released from fused dispersions in P40S, were determined by Coulter counter in drug-saturated electrolyte. The mean particle size of tolbutamide decreased from >30 μm to 10 or 3 μm, whereas that of griseofulvin (micronised) was virtually unchanged.

The rate and extent of release of each drug from P40S dispersions were greater than from PEG dispersions of the same composition by weight. For example, co-precipitates containing 60% w/w of each drug disintegrated completely and the concentration of drug dissolved levelled off after less than 30 minutes from P40S dispersions but after more than 120 minutes from the corresponding PEG compacts.

Although no solid solutions of the drugs in the excipients were detected, the results support the original hypothesis in all other respects. P40S is superior to PEG 2000 in promoting dispersion in the solid, disintegration of the compacts and solubilization of the drugs. Drug bioavailability from the dispersion systems and the effects of added disintegrants are also being studied.

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