# Dissolution of solid dispersions: the glutethimide-Renex 650 melt system

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Solid dispersions, prepared by fusing poorly soluble drugs with water soluble carriers have been shown to increase the dissolution of many drugs (Chiou & Riegelman, 1971; Hajratwala, 1974). The carriers used have included polyethylene glycol (Chiou & Riegelman, 1969; El-Gindy, Karara & El-Khalek, 1977) sugars (Allen, 1972), urea (Goldberg, Gibaldi & Kanig, 1966a; Goldberg, Gibaldi & others, 1966b; Ford & Rubinstein, 1977) and surfactants (Hoelgaard & Møller, 1975). Usually only the release of the drug and not the carrier has been monitored and consequently information concerning the dissolution of solid dispersions is incomplete. This communication reports dissolution from solid dispersions of glutethimide and Renex 650 (a polyoxyethylene nonylphenyl ether), prepared by the melt method.

Constant surface area discs were prepared by the melt method of Ford & Rubinstein (1977). Molten mixtures of glutethimide and Renex 650 were poured into aluminium vial covers (2 cm internal diameter) and allowed to cool. Immediately before a dissolution rate measurement the excess was sliced away with a razor blade to produce a smooth uniform surface. 1 h old melts were used for dissolution studies. The discs were rotated at 100 rev $min^{-1}$, 3 cm above a magnetic stirrer 2 cm long, rotating at 200 rev $min^{-1}$ in a counter direction to the disc. 1 litre of freshly distilled water was used as the dissolution medium, maintained at 30°, in a Quickfit FV-IL, 1 litre flask (Ford & Rubinstein, 1977). At suitable intervals 4 $cm^3$ samples were withdrawn and undiluted, assayed spectroscopically at 258 and 278 nm. At 278 nm the absorbance of glutethimide was zero and Renex was assayed without interference. Glutethimide was assayed at 258 nm, after subtraction of the absorbance contributed by Renex. After assay the samples were returned to the dissolution medium.

The phase diagram of Glutethimide-Renex 650 was determined by hot stage microscopy (Ford & Rubinstein, 1978). A simple eutectic was formed (21% glutethimide 79% Renex 650) with a eutectic temperature of 35°. Consequently dissolution studies were performed at 30°, and not 37° to avoid melting the eutectic. Solid solutions of glutethimide in Renex 650, and Renex 650 in glutethimide also existed.

The dissolution profiles of some melts are shown in Fig. 1 (a–e). Intrinsic dissolution rates (mg $min^{-1}$ $cm^{-2}$) were calculated from the slopes (Fig. 1a, b) or the initial linear portion (Fig. 1d, e) or the best straight line through the points by linear regression (Fig. 1c). The initial portions were used since they arbitrarily corresponded to an equilibrium dissolution rate. The intrinsic dissolution rate was plotted against the disc composition

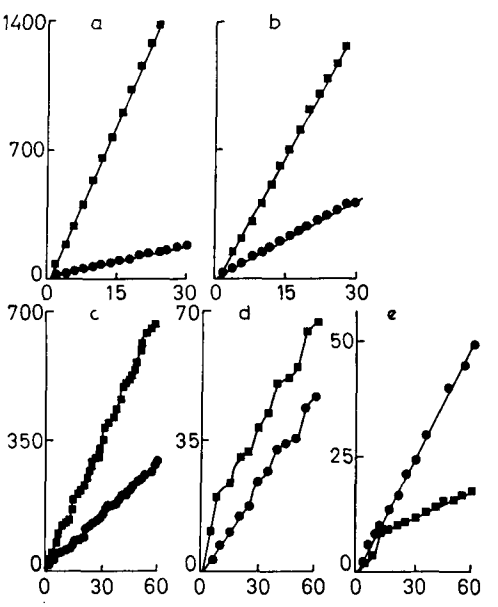


FIG. 1. Dissolution profiles of some 1 h old glutethimide-Renex 650 resolidified melts into distilled water at 30°. Glutethimide : Renex mixes %: (a) 10 : 90; (b) 25 : 75; (c) 30 : 70; (d) 70 : 30; (e) 90 : 10.
Ordinate: mg of drugs or carrier released. Abscissa: time (min). ■ Renex 650. ● Glutethimide.

to give a dissolution rate-composition profile (Fig. 2).

Fig. 2 shows that the dissolution optimum for the drug occurs from discs containing 25% glutethimide. Similar profiles have been obtained from chlorpropamide-urea melts (Ford & Rubinstein, 1977) and indomethacin-PEG-6000 melts (Ford & Rubinstein, 1978) with optima containing 40 and 15% drug respectively.

The dissolution rate-composition profile (Fig. 2) can be related to the individual dissolution profiles (Fig. 1) and can be subdivided into four portions. The linear portion between 0 and 25% glutethimide represents unhindered dissolution of both drug and carrier. The carrier rapidly dissolved and a fine deposit of drug was formed which immediately redissolved. A similar precipitation-redissolving phenomenon has been reported previously for indomethacin-polyethylene glycol (Ford & Rubinstein, 1978). Fig. 1a and b are typical of profiles obtained in this region: both drug and carrier dissolve at rates directly dependent on their concentration.

The second portion, represented between 25 and 30% glutethimide, produced a marked drop in dissolution

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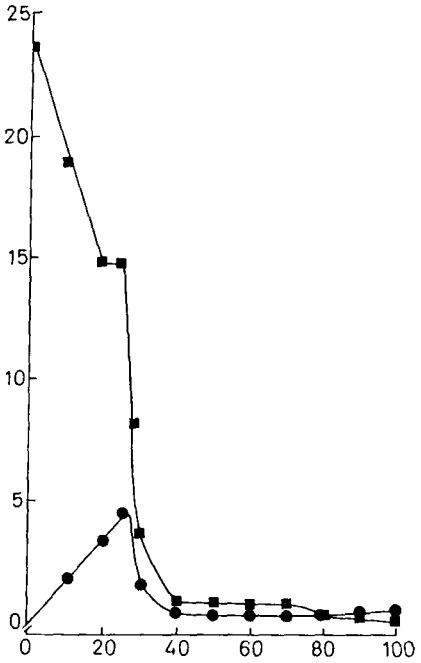


FIG. 2. Dissolution rate—composition profile: Effect of glutethimide renex composition on the intrinsic dissolution rates of 1 h old resolidified melts into distilled water at 30°. Abscissa: % glutethimide in disc. Ordinate: Intrinsic dissolution rate mg $min^{-1} cm^{-2}$. ■ Renex 650. ● Glutethimide.

rate. The drug and carrier did not dissolve at rates directly proportional to their concentration; it is thought that dissolution of glutethimide was retarded by generation of excess precipitate. This system corresponds to the regions of sphere formation in chlorpropamide-urea (Ford & Rubinstein, 1977) and indomethacin-PEG6000 systems (Ford & Rubinstein, 1978).

The third portion between 30 and 70% gave staggered dissolution profiles (Fig. 1c, d). There is a further decrease in dissolution rate of drug and carrier, the carrier dissolved rapidly leaving surface deposits of pure glutethimide (confirmed by infrared analysis). An excess of drug was deposited at the surface which periodically flaked away producing fresh disc surface from which increased dissolution rates are obtained; the flakes sank to the bottom of the flask. With higher glutethimide-containing discs the thickness of the drug deposit is increased, flaking occurs less often since the disc surface is more stable, and slower dissolution rates were obtained (Fig. 1d).

The final portion, 80–100% represents regions of biphasic profiles (Fig. 1e). Initial solubilization of the surfactant at the surface rapidly produced a glutethimide-rich surface. Slower dissolution rates of glutethimide were obtained and it is thought the glutethimide rich surface acts as a barrier for Renex dissolution. Biphasic profiles were obtained for chlorpropamide-urea melts containing 80 and 90% chlorpropamide (Ford & Rubinstein, 1977). The dissolution of 90% glutethimide discs is slower than the pure drug since the pure drug forms a glass solid (Brandstatter, 1971) and incorporation of Renex induced crystallization in the melt. The dissolution profile of glutethimide was linear.

The position of the optimum alters with agitation rates, the age of the melt and the physical properties of drug and carrier. It is proposed that similar dissolution rate-composition profiles can be obtained from other solid dispersions prepared by this melt method, unless solid–solid complexes are formed during the production of the melt (El-Gindy & others, 1977).

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