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Solubility and stability of diazepam in sodium salicylate solution

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Diazepam is practically insoluble in water and hence, the injection is formulated with propylene glycol as the main solvent (Reilly, 1978). The reported undesirable clinical effects following the i.m. and i.v. diazepam injection have been attributed to the failure of the vehicle to maintain complete solubilization of the drug and the direct action of propylene glycol on the tissues (Jusko et al., 1973; Kanto, 1974; Graham et al., 1977). Consequently, attempts were made to reduce the amount of propylene glycol (Korttila et al., 1976) or to change the solvent system (Siebke et al., 1976).

In this study, we investigated the effect of a hydrotropic salt, sodium salicylate, on the solubility of diazepam since hydrotropes have been used to increase the solubility of water-insoluble drugs of various chemical structures (Ueda, 1966a; Poochikian and Cradock, 1979). The effect of sodium salicylate on the stability and dissolution rate of diazepam was also studied.

The solubility study was carried out by adding excess diazepam to sodium salicylate solutions of different concentrations (ranging from 0 to 30%). The mixtures were shaken mechanically in a constant temperature water bath at 37 ± 1°C for 24 h. The mixtures were then equilibrated at the same temperature for another period of 24 h. Aliquots of the filtered solutions were suitably diluted with 0.1 N HCl and assayed spectrophotometrically at 365 nm for diazepam content.

The effect of sodium salicylate on the dissolution rate of diazepam was studied by adding 40 mg of diazepam to 400 ml of water or sodium salicylate solutions of different concentrations in a constant temperature water bath at 37 ± 1°C. The mixtures were stirred mechanically at a speed of 60 rpm. The amount of diazepam dissoluted at different time intervals was assayed spectrophotometrically.

The stability of diazepam in sodium salicylate solution against photodecomposition was studied by placing the diazepam solution, 5 mg/ml, in 30% sodium salicylate, at a distance of 50 cm from a light source (100 W tungsten lamp). Samples were removed at different time intervals and assayed spectrophotometrically.

Fig. 1 shows that the solubility of diazepam is increased progressively with sodium salicylate concentration and the relationship is a typical hydrotropic solubility curve. It could also be shown that the solubility of diazepam is increased from 8 mg% to 1718 mg% by the addition of 30% sodium salicylate. Various mechanisms were postulated for the solubilization by hydrotropic salts. Ueda (1966b) suggested the formation of 1 : 1

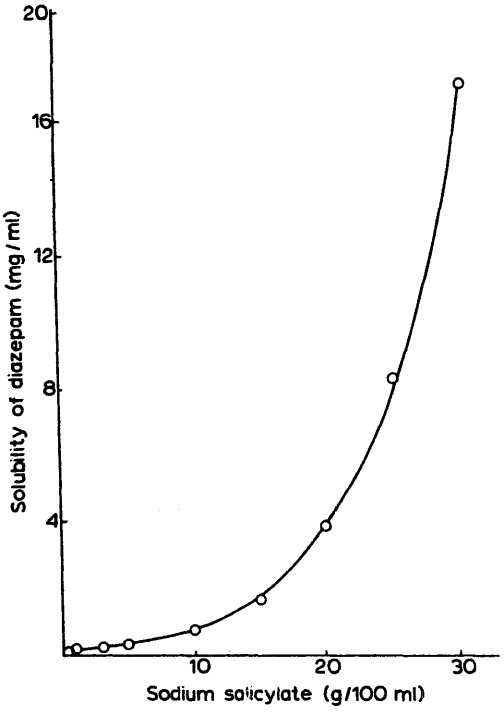

Fig. 1. Effect of sodium salicylate on the solubility of diazepam in water at 37°C.

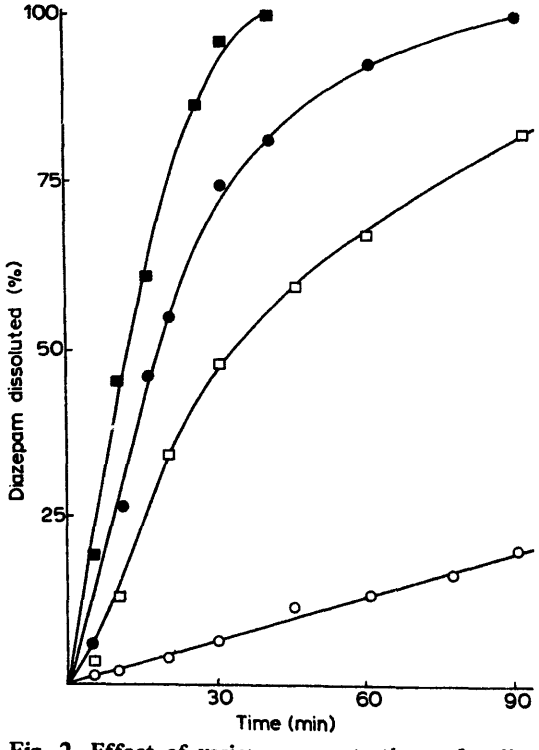

Fig. 2. Effect of various concentrations of sodium salicylate on the dissolution rate of diazepam in water at 37°C. Key: water, ○; and 4%, □, 8%, ●; and 12%, ■; sodium salicylate.

TABLE 1

PHOTODECOMPOSITION OF DIAZEPAM, 5 MG/ML, IN 30% SODIUM SALICYLATE SOLUTION; THE LIGHT SOURCE IS A 100 W TUNGSTEN LAMP

Time (days)	Remaining concentration (%)
0	100.0
1	100.0
3	100.2
6	99.6
12	99.4
17	100.0
20	100.4

molecular complex and salting-in mechanisms and Poochikian and Cradock (1979) postulated plane-to-plane orientation of the substrate and the ligand molecules favoring intermolecular interaction. However, we believe that the mechanism of solubilization by hydrotropic salts may involve change in water structure. The dissolution rate of diazepam is increased by increasing sodium salicylate concentration (Fig. 2). This effect could be attributed to the lowering of surface tension by sodium salicylate (Saleh and York, 1978). Table 1 shows that diazepam in sodium salicylate solution is completely stable against photodecomposition over a period of 20 days. A slight yellow discolouration was observed after autoclaving the diazepam solution 5 mg/ml in 30% sodium salicylate, but the concentration of diazepam remained unchanged.

In conclusion we suggest the use of 30% sodium salicylate solution as a suitable vehicle for diazepam injection. This will overcome the problems encountered when using other vehicles for the preparation of commercial diazepam injection.

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