IN VITRO RELEASE OF COMPLEXED AND FREE OESTRADIOL FROM PESSARIES

E.G. Salole, A. Pearson, Department of Pharmacy, University of Strathclyde, Glasgow G1 1XW.

The complexation of drugs with cyclodextrins with a view to improving dissolution and bioavailability has received much attention recently (Saenger 1980). As complexation improves the solubility of steroidal compounds also (Uekama et al 1982), it was of interest to examine the effects of β-cyclodextrin on 17β-oestradiol, a poorly soluble steroid susceptible to solvation and other manipulations in the solid state (Florence & Salole 1976).

Using the data from the type-B_S phase solubility diagram (Higuchi & Connors 1965) exhibited by oestradiol and β-cyclodextrin, a solid complex was eventually obtained by interfacial crystallisation. The dry powdered (< 90μm) complex, substrate:ligand in 1:3.6 molar ratio, exhibited the anticipated higher solubility and faster dissolution rate compared with plain, micronized oestradiol (Fig. 1). In view of the preference for natural oestrogen for the treatment of menopausal symptoms requiring replacement therapy (Harrison & Bonnar 1981), the apparent superiority of the vaginal route in terms of avoiding first-pass metabolism of oestradiol and minimising the risk of high systemic levels of exogenous oestrogen (Deutsch et al 1981), and patient incompliance with creams, it was considered worthwhile to investigate the possibilities of a low-dose pessary formulation of highly-soluble oestradiol. A polyethylene glycol mixture (PEG 600/6000/water: 20/60/20) and Witepsol H15 were chosen as representative bases for 1g pessaries (prepared by fusion) containing 0.5mg oestradiol as complex or free drug. On testing single pessaries for dissolution it was found that the release of complexed oestradiol was indeed rapid but, surprisingly, no more so than that of plain drug (Fig. 2; the curves for Witepsol H15 were similar, except that 100% release was achieved in 10 min). It appeared that the pessary bases enhanced the dissolution of otherwise slowly soluble steroid. With the water-soluble formulation, this effect may have been due to the well recognised solubilizing action of PEG in boundary layers around the eroding pessary. However, considering also the similarities in release rates from the water-insoluble melting base, solid-solution formation would seem to be a more likely cause of the fast dissolution.

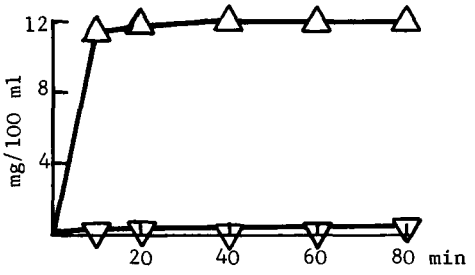

Fig. 1 Dissolution rate of 25mg oestradiol as complex (△) and micronized powder (▽) in 150ml water at 25°.

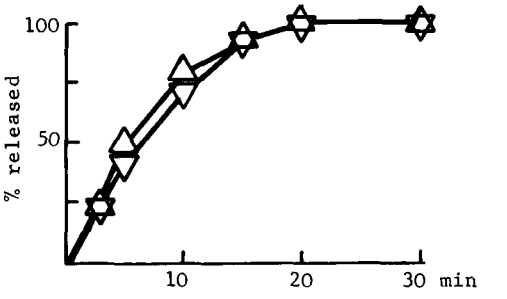

Fig. 2 Dissolution rate of complexed (△) and free (▽) oestradiol from PEG pessaries in 150ml water at 37°.

Deutsch, S. et al (1981) Am. J. Obst. Gyn. 139:967-8
Florence, A.T., Salole, E.G. (1976) J. Pharm. Pharmac. 28: 637-642
Harrison, R.F., Bonnar, J. (1981) Pharmacol. Ther. (Supp. 4): 95-111
Higuchi, T., Connors, K.A. (1965) Adv. Anal. Chem. Instr. 4: 117-212
Saenger, W. (1980) Angew. Chem. Int. Ed. Eng . 19: 344-362
Uekama, K. et al (1982) Int. J. Pharm. 10: 1-15

0022-3573/82/120004P-01$02.50/0