COMPLEX FORMATION BETWEEN DIGOXIN AND BETA CYCLODEXTRIN

H Jones, Pharmaceutical Development Laboratories, Wellcome Foundation Ltd., Dartford, Kent, DA1 5AH

Beta cyclodextrin (β C.D.) is a macrocylic polymer of glucose containing 7 gluco pyranose units. Spatially it resembles a toroid with a cavity of 8 A° diameter and this allows it to form inclusion complexes in aqueous solution with molecules of a suitable size. Numerous papers have been published on the interaction in solution between cycloamyloses particularly β C.D. and drug molecules, together with their isolation and evaluation in the solid state (e.g. Cohen and Lach (1963)). A recent review was carried out by Saenger (1980).

Digoxin is a cardiac glycoside of very low aqueous solubility (approx. 50 mg litre^{-1}) and absorption from the gastrointestinal tract is dissolution rate limited. This investigation examines the effect of β C.D. on the aqueous solubility and dissolution rate of digoxin.

The solubility of digoxin in the presence of aqueous solutions of β C.D. (0-0.02M) was determined following addition of excess solid drug and shaking for 24 hours at R.T. Filtrates were assayed for digoxin content by a reversed phase H.P.L.C. technique. The figure shows a recti-linear increase in solubility from 46 (0.59. 10^{-4}M) to 9,600 (123. 10^{-4}M) mg litre^{-1} (i.e. approx. 200 fold increase in solubility). The slope of the interaction isotherm was calculated to be 0.60.

A β C.D. -digoxin "complex" (3 : 1 molar basis) was prepared by dissolving the two components in water at R.T. and removing the solvent in a rotary evaporator. The resultant material was removed, dried and coarsely ground (5-500μm). Dissolution rate was determined on neat powder using 50 mg samples in (i) the Sartorius solubility simulator in 100 ml water at 37°C and, (ii) the B.P. rotating basket apparatus at 100 r.p.m. in 1,000 ml water at 37°C. Samples were removed at 1 minute intervals and assayed by H.P.L.C. The table shows times to release 50 and 80%.

Fig.1 Solubility of digoxin in aqueous β C.D. solution

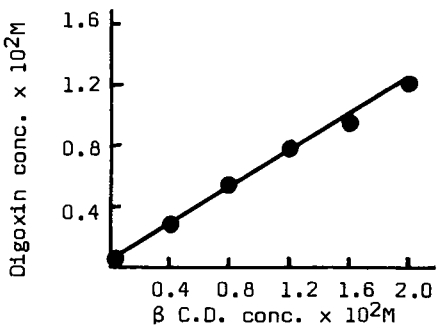

Table 1 Release of digoxin from "complex"

	T50	T80
Solubility simulator	< 2min	< 5
B.P. apparatus	< 2	< 5

(For 0.25 mg digoxin tablets, the B.P. stipulates that not less than 75% drug should be in solution after 60 minutes)

It has been shown that β cyclodextrin does significantly increase the solubility of digoxin in water and that a powder with very rapid dissolution characteristics can be prepared.

Cohen, J., Lach, J. (1963) J.Pharm.Sci. 52, 137-142
Saenger, W. (1980) Chem.Inst.Ed., Eng., 19, 344-362

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