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CYCLODEXTRIN-SPIRONOLACTONE COMPLEXES - IN-VITRO DISSOLUTION AND IN-VIVO BIOAVAILABILITY

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Spironolactone (SP), a sparingly aqueous soluble diuretic, exhibits poor bioperformance which has been partly improved by particle size reduction (McInnes et al, 1982). We have previously reported on the structure and improved aqueous solubility of solid-state complexes of spironolactone with cyclodextrins (CD) (Yusuff & York, 1988, 1989). This report considers the in vitro dissolution and in vivo bioavailabilty of hard gelatin capsule formulations containing SP and SP:CD complexes. Drug: CD complexes have been reported to give products of improved bioavailability (Seo et al, 1983).

In vitro dissolution tests on capsules containing 25mg of SP in powder form (surface area = 1.4 m^2/g) or equivalent complexed with beta-CD and gamma-CD were carried out using the BP(1980) basket apparatus at 100 r.p.m., 37°C with distilled deionised water as the dissolution medium. The solid state complexes studied had drug:CD molar stoichiometrias of 1:3 and 1:2 for the beta - and gamma - cycodextrins respectively. Figure 1 shows the improvements in dissolution achieved for the complexed forms of SP compared with the uncomplexed form.

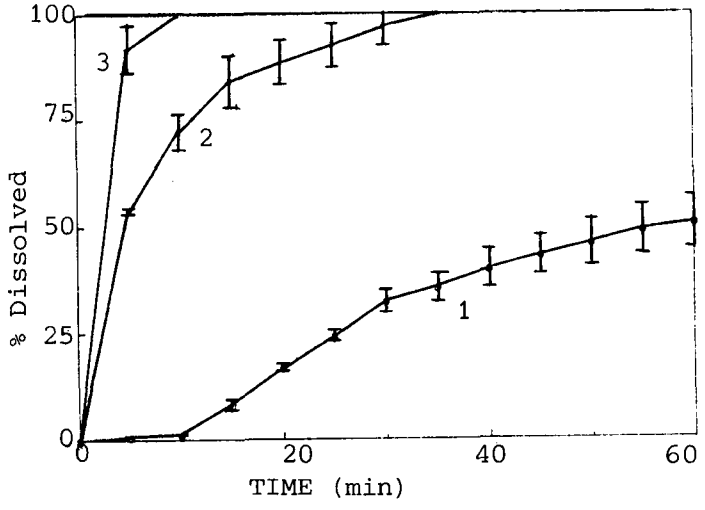

Fig. 1 In vitro dissolution profiles

Key:
1 = SP powder
2 = SP: beta-CD complex
3 = SP: gamma-CD complex

The hypothesis that poor in vitro solubility and dissolution compromise the bioavailability of SP was tested by carrying out a double blind crossover bioavailability study, approved by the ethical committee at St. James's Hospital, with 8 healthy volunteers. The two formulations compared were 4 x 25mg of SP and the equivalent of 100mg of SP (4x25mg) as the beta-CD complex in opaque, hard gelatin capsules. A washout period of 7 days was used and volunteers' diet and exercise on study days was controlled. Venous blood samples were collected at defined times from indwelling heporinised cannulae for 8 hours, then at 24 hours by venepuncture. A specific HPLC assay was developed to measure canrenone, the major metabolite, concentrations in serum samples. Data analysis revealed that differences in t_{max}, C_{max} and AUC of the two products were significant at $p<0.05$, (Wilcoxon signed rank test), with shorter t_{max}, higher C_{max} and a relative bioavailability of 233% $\pm$ 76% for the complex. Thus, the dramatically improved bioperformance of the complex due to the increased solubility and dissolution is demonstrated, highlighting the clinical potential of drug:cyclodextrin complexes.

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