A COMPARISON OF INDOMETHACIN/CYCLODEXTRIN COMPLEXES

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It is well established that complexation with beta cyclodextrin (βcd) can favourably alter various physico-chemical properties of drug molecules. Owing to the poor aqueous solubility of bcd there is interest in the more freely soluble modified derivatives.

In this work we have used phase solubility and NMR studies to investigate the interaction of βcd and the (2,6-di-o-methyl) [DM βcd] and hydroxypropyl (HP βcd) derivatives with the drug indomethacin (ind). The results obtained have been interpreted at a molecular level by modelling the 3D structures of the complexes using interactive computer graphics.

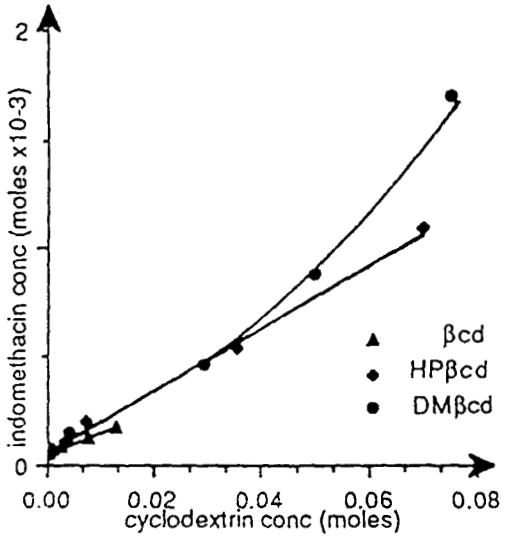

Figure 1
Phase solubility plots for indomethacin in the presence of beta, hydroxypropyl and dimethyl beta cyclodextrins

The linear response observed for the βcd and HP βcd systems has been assigned as a Type A_L profile demonstrating the predominance of one complex species in solution (Higuchi & Connors 1965), Figure 1. The upward curve observed in the presence of DM βcd can be assigned as a Type A_P curve and indicates that with increasing cd concentration complexes of differing stoichiometries are formed.
For the linear solubility profiles, assuming a host:guest stoichiometry of 1:1 the apparent stability constants for the complexes are determined as $99M^{-1}$ and $245M^{-1}$ for the βcd and HP βcd systems respectively. The nature of the DM βcd diagram precludes the determination of a stability constant.

The ^1H NMR spectra were recorded for each complex using a Bruker 250 MHz NMR with DSS/D_2O as an external reference. The influence of ind on the NMR spectrum for the cd protons was consistent with complex formation. The NMR spectra for ind in the presence of each cd, shows changes to the chemical shift for the protons associated with the chlorphenyl group and those of the indole aromatic ring, indicating that both of these moieties are substrates for the cd cavities.

In order to interpret these results at a molecular level the structures of the complexes have been modelled by graphics. We have shown previously that the interaction between ind and βcd can be modelled as a 2:1 host:guest complex (Myles et al 1988). The effect of chemical modification to the βcd molecule has been to extend the length of the cavity. The overall length of the DM βcd has not been increased sufficiently to prevent the formation of a dimer so that the complex may be modelled with either a 2:1 or 1:1 stoichiometry. In contrast the hydroxypropyl group hinders dimer formation, thus 1:1 complexes have been modelled.

Higuchi, T. & Connors, K. A. (1965) Adv. Anal. Chem. Instr. **4**: 117-212
Myles, A. M. C., et. al. (1988) J. Pharm. Pharmacol. Supp. **40**: 125P

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