COMPUTER GRAPHICS AS AN AID FOR PREDICTING DRUG MOLECULE STABILITY IN A CYCLODEXTRIN INCLUSION COMPLEX

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Many drug molecules are capable of residing within the central cavity of a cyclodextrin (CD) molecule, thus forming an inclusion complex. The ability of a guest molecule to penetrate the CD host, thereby determining its position within the complex, may be crucial to the subsequent stability of the guest drug molecule depending upon the degree of inclusion of a labile group (or groups) within the cavity. We have examined the effect of β-CD on the stability of aspirin and benzocaine both in the solid and liquid states, and have related any changes in their stability to the positioning of the guest molecule within the CD cavity by means of computer graphics.

The time taken for half of the available aspirin to degrade ($t_{\frac{1}{2}}$) following incubation of drug (alone) and inclusion complex for 45 days at 50°C/75% RH was 660 days for aspirin alone and 10 days when included within a β-CD cavity. In pH 9.6 buffer at 50°C corresponding values were 0.6 and 0.5 hours. β-CD therefore accelerated aspirin hydrolysis in both the solid and liquid state. Conversely, $t_{\frac{1}{2}}$ values for benzocaine alone and in the presence of β-CD at 50°C in pH 9.6 buffer were 22.5 and 28.8 hours respectively. Benzocaine did not degrade appreciably at 50°C/75% RH over 45 days. However, it can be seen that β-CD does aid the stability of benzocaine in aqueous solution. The difference in stability of these two molecularly similar drugs with β-CD may be explained by the positioning of the guest molecule within the β-CD host.

Using a Chemograf® program (Chemical Design Ltd, Oxford), linked to the SERC Chemical Databank to provide X-ray crystallographic data, it has been possible to display β-CD, aspirin and benzocaine molecules. The program allows the potential guest drug molecules to be moved into the cavity of the CD host molecule.

The labile acetyl moiety of aspirin (with its free hydrogen atoms protruding from the centre of the CD ring) cannot reside within the CD cavity, and is positioned on the rim of the cavity. The molecule is not shielded from hydrolytic attack therefore, and is held in such a position that degradation by hydroxyl groups both in solution and on the CD ring is favoured.

Conversely, the labile ethyl group of benzocaine are included well within the CD cavity, the amino and ethyl groups visible at opposite sides of the cavity. This shields the molecule from hydrolytic attack, and hence increases the aqueous stability of benzocaine.

Thus, computer graphics have illustrated that the positioning of a drug molecule in a β-CD inclusion complex is related to the stability of the drug molecule. This technique should not only enable predictions of drug stabilities to be made prior to their inclusion within a CD molecule, but will assist in determining the ability of a potential guest molecule to penetrate the CD cavity.