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Molecular Modeling for The Interaction between certain drugs with Betacyclodextrin

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Molecular modeling technique has been used in the preliminary screening of certain drugs and to study their interaction with betacyclodextrin (BCD). In the cases of drugs such as norfloxacin, ciprofloxacin, tinidazole, methotrexate and plumbagin, the type and site of interaction between the drug and BCD leading to the formation of an inclusion complex has been established.

MOLECUIAR modeling technique became popular to study the drug-excepient interaction which help to visualize the type and site of interaction on a computer monitor. This technique also helped in the preliminary screening of drugs for their ability to form complexes with betacyclodextrin (BCD).

BCD is a cyclic oligosaccharide in which seven glucose units are linked by alpha 1,4 glycosidic bonds (molecular formula $(C_6H_{10}O_5)_7$)[1]. The structure of the ring is such that all secondary OH groups are located at the wider rim of the cylindrical structure while the primary OH groups are on the narrower rim. The inner lining of the cylindrical cavity is abundant in hydrogen bonding between hydrogen and glucosidic oxygen atom and the cavity environment favours the inclusion of hydrophobic guest molecules of suitable dimension in the formation of drug-BCD inclusion complex. In aqueous solution, this cavity is occupied by seven moles of water, a thermody-namically unstable configuration, which makes it feasible for replacement by hydrophobic drug molecules[1]. Once the dimension of the drug molecule is established and if the length and breadth of the molecule is less than the depth and width of the BCD cavity respectively, there is all possibility of the penetration of the drug molecule into the BCD cavity leading to the formation of drug-BCD inclusion complex. If the length of the drug molecule is more, which portion of it can penetrate and retained inside the BCD cavity and from which direction (wider or narrower rim of BCD) it enters can also be visualized and established. A detailed review on the structure and pharmaceutical applications of BCD in modifying the desired physicochemical properties of various drug molecules has been reported by Rajewski et al, 1996[2]. Other physicochemical properties viz, phase solubility, IR, DSC, XRD, NMR and DTA etc could authenticate the formation of the inclusion complex and the site of interaction[3,4]. Thus the molecular modeling technique has become a popular and versatile tool in the initial selection of the drug molecule which are likely to form complexes with BCD. In the present study, this technique has been used in the initial selection of drugs which include, norfloxacin (NOR), ciprofloxacin (CIP), tinidazole (TIN), methotrexate (MTX), plumbagin (PLB) in the formation of inclusion complex with BCD, leading to the modification of their physicochemical properties, Similar studies of the complexation of salbutamol[5,6], dantrolene[7] and indomethacin[8] with BCD have been reported in the literature.

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EXPERIMENTAL

The computer used in this study was neptune PCAT and the package used was DTMM V 2.0 (supplied by James MCC and Apple Yard JR, Oxford University Press 1991). The BCD molecule was initially built by forming a single molecule of its glucose unit. The dimensions such as bond length and bond angle were compared to the literature value. Then two such molecules were built and conjugated to get energy minimized conformation. This process of conjugation was continued by adding a molecule of glucose moiety each time until seven such molecules were arranged symmetrically to get a well shaped structure having energy minimised conformation. Then the cavity depth, diameter of the wider and narrower rim were calculated and compared to the literature values.

Similarly, the structure of NOR, CIP, TIN, MTX and PLB were built to get energy minimized conformation. The dimensions of each of the molecule were built and made comparable to the literature values. The drug molecule was allowed to penetrate sideways or axially through the depth of the cavity and the probability of its penetration was observed. The portion of the drug molecule and the extent to which penetration into the BCD cavity was also seen on the computer monitor on all the X, Y and Z planes. The drug molecule was rotated inside the cavity and the probable site of interaction was proposed. The molecules were built in various models viz stick, ball and stick, space fill and the three dimensional vision was visualized to realise the dimension of the molecule along the Z axis.

RESULTS AND DISCUSSION

The energy minimised structure of BCD had the following dimensions:Cavity diameters; 9.68 A (wider rim), 6.24 A (narrower rim), average literature value 7.96 A provided by the souviner). Cavity depth 6.9 A (literature value 7.0 to 8.0 A). The success in the formation of inclusion complex with BCD was obtained with NOR, CIP, TIN, MTX and PLB. The BCD molecule was built in stick model and the guest molecules were built in ball and stick model for clarity. The energy minimised conformation of the structure of the inclusion complex formed and the proposed molecular structures are shown in fig 1,2,3,4, and 5 respectively. The figures showed the penetration of the drug through the wider rim and the drug penetrated through the

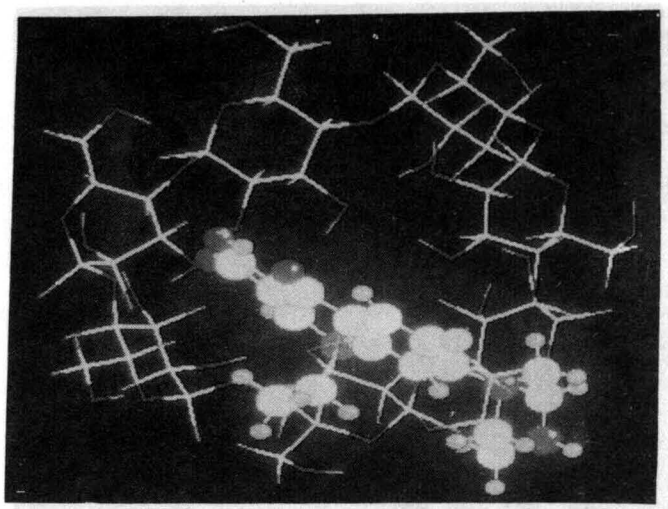

Fig. 1a. Molecular model of norfloxacin-betacyclodextrin inclusion complex

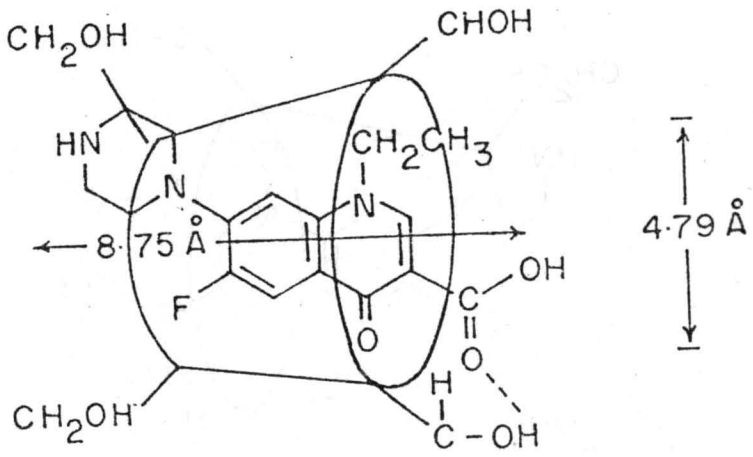

Fig. 1b. Proposed structural formula of norfloxacin-betacyclodextrin inclusion complex

axis of BCD cavity along its depth. In the case of NOR and CIP the width of the molecule (4.79 A) was lesser than the diameter of the BCD cavity facilitating the molecule to penetrate into BCD cavity, but the length (8.75 A) was more than the cavity depth. Hence the piperazine moiety was protruding out. The probable site of interaction was the carbonyl function of the carboxylic acid with the secondary hydroxyl function of BCD (Fig 1,2). In the case of TIN,

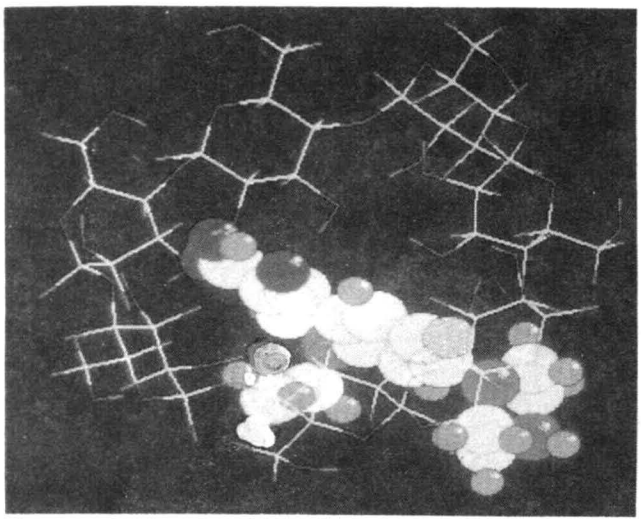

Fig. 2a. Molecular model of ciprofloxacin-betacyclodextrin inclusion complex

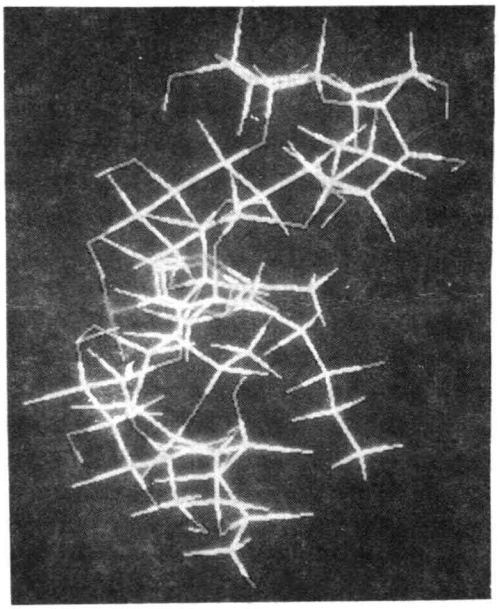

Fig. 3a. Molecular model of tinidazole-betacyclodextrin inclusion complex

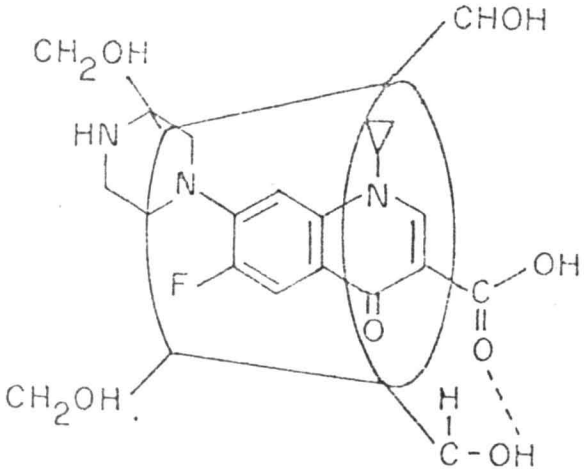

Fig. 2b. Proposed structural formula of ciprofloxacin-beta cyclodextrin inclusion complex

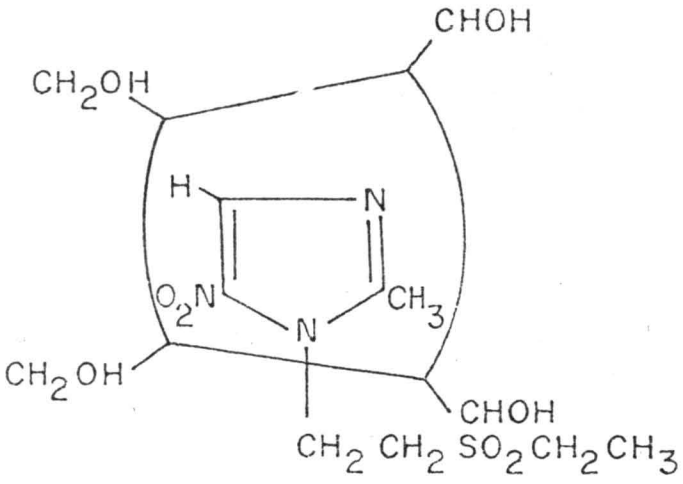

Fig. 3b. Proposed structural formula of tinidazole-beta cyclodextrin inclusion complex

the length and breadth of the molecule were less than the cavity dimension. Hence the whole molecule could penetrate into the BCD cavity. However, there was least possibility of interaction between the two molecules through hydrogen bonding as the favorable groups, such as NH_2, C=O or OH were absent in the TIN molecule (Fig 3). In the case of PLB, the length of the molecule (8.5 A) was slightly more than the depth of the BCD cavity (6.9 A), but its breadth (6.02 A) was less than the BCD cavity diameters (6.24 / 9.68 A). Hence the drug could penetrate into the BCD cavity through its axis only length-wise leaving the aliphatic side chain CH_3 protruding out. The OH function in PLB could interact with the OH function of BCD through hydrogen bonding (Fig 4). In the case of MTX, which was

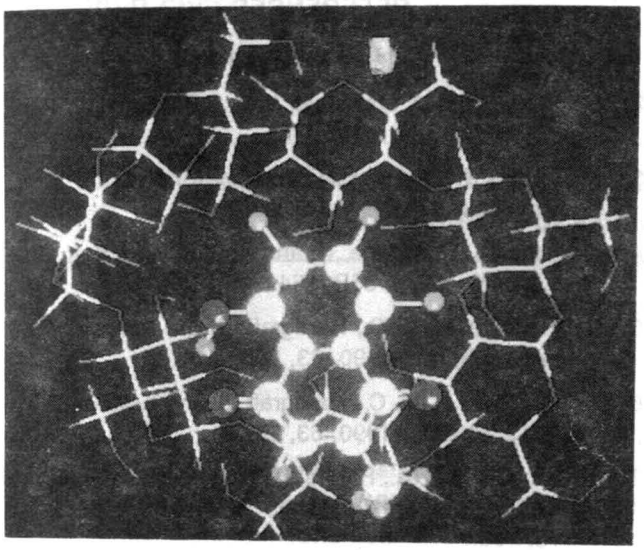

Fig. 4a. Molecular model of plumbazin-betacyclodextrin inclusion complex

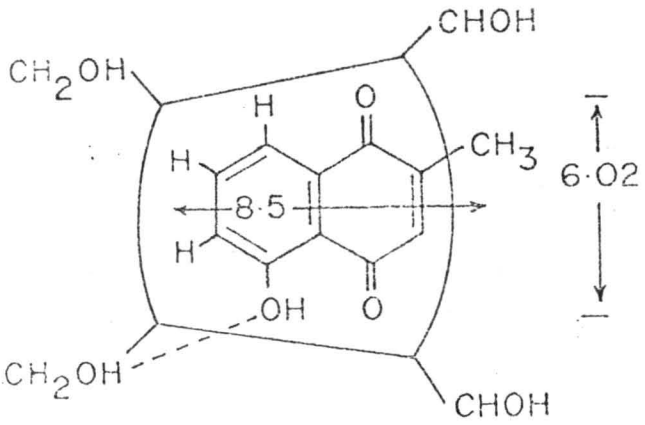

Fig. 4b. Proposed structural formula of plumbazin-beta cyclodextrin inclusion complex

a U shaped skeletal structure with the aromatic ring at one end in one plane and aliphatic glutamic acid tail at the other end which was perpendicular to the plane of the aromatic ring. The length of the aliphatic side chain was more than the depth of the cavity. Hence the aromatic moiety only could penetrate into the BCD cavity on its either openings as the breadth of the ring (6.06 A) was less than the cavity diameter. Thus only the aromatic part of the drug could make a deep penetration into the BCD molecule as its

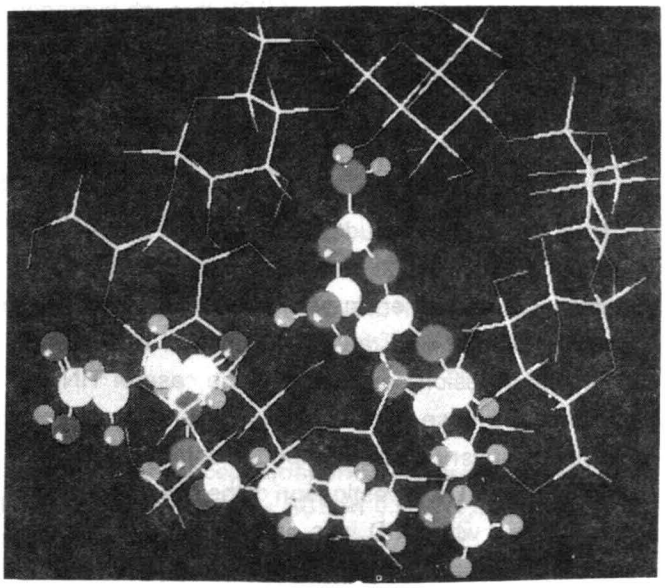

Fig. 5a. Molecular model of methotrixate-betacyclodextrin inclusion complex

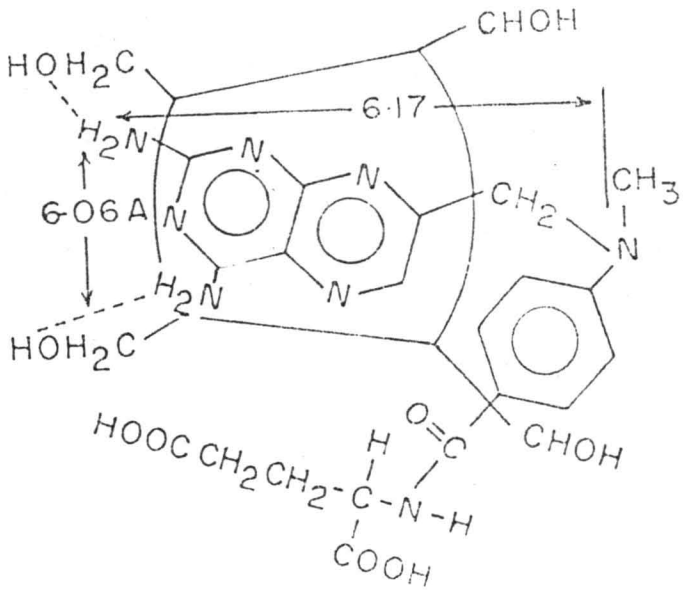

Fig. 5b. Proposed structural formula of methotrixate-beta cyclodextrin inclusion complex

length (6.17 A) was less than the depth of the cavity, leaving the glutamic acid part protruding out wrapping the BCD molecule from outside. The primary NH_2 function of MTX

could interact with OH function of BCD through hydrogen bonding. Even though MTX molecule contains C=O function, a potential group for hydrogen bonding, it was projecting outside the BCD cavity and could not interact with the OH function of BCD (Fig 5).

Thus, it can be concluded that all these drugs evaluated could form inclusion complexes with BCD. However, excepting TIN, the other drugs under investigation could chemically interact with the OH function of BCD to produce stable inclusion complexes. In the case of TIN, the inclusion was a loose fitting configuration and the complex could not be a very stable compound compared to other drugs evaluated. The investigation of the site of interaction of these drugs with BCD was authenticated by spectral methods. From the IR and NMR data and formation of hydrogen bond was further confirmed(4).

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