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Increasing Tamoxifen bioavailibilty using Tam:HPβCD inclusion complex

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Tamoxifen (Tam), a synthetic a synthetic estrogen-like hormone ($C_{32}H_{37}NO_8$), binds to the estrogen receptors and acts as a competitor of natural estrogen to inhibit the growth of malignant mammary and other estrogen receptor positive tumors. Tamoxifen antagonize estrogen (E2)-regulated gene expression, promote the re-expression of E2-repressed genes and regulate the expression of E2-independent genes. Cyclodextrins are used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility, improve chemical and physical stability. Cyclodextrins consist of 6, 7, or 8 (α, β and γ respectively) D-glucopyranosyl units connected by alpha-(1,4) glycosidic linkages. The most stable three dimensional molecular configurations for these non-reducing cyclic oligosaccharides take the form of a toroid with hydrophilic exterior and hydrophobic interior cavity. Insoluble drugs (guest) associates with the hydrophobic cavity of the cyclodextrin. Hydroxypropyl cyclodextrin (HPβCD) has been widely accepted for oral and parentral use because of high aqueous solubility and the most extensive collection of safety data.

Tamoxifen inclusion formulation (Tam:HPβCD) was prepared by mixing Tam in aqueous solution of HPβCD in 1:2 molar ratio. The complex was characterized by differential scanning calorimetery (DSC), and ^{1}H-NMR spectroscopy. The cytoxic effect of Tam:HPβCD on breast (MCF-7) and ovarian cancer cells (OAW-42) was studied by MTT assay.

HPβCD demonstrated overlapping signals due to repeated glucopyranosyl units which were connected by alpha-(1,4) glycosidic linkages. The incorporation of Tam into the HPβCD cavity led to de-shielding of the hydrogen atoms located in the interior of the cavity (H-3, H-5) of HPβCD whereas hydrogen atoms on the outer surface (H-1,H-2,H-4) either remained unaffected or experienced only marginal shift. ^{1}H-NMR studies showed a clear distinction between inclusion and other possible interaction processes. The clear and pronounced downfield shift of the signals of H-3 and H-5 protons of HPβCD have been attributed to magnetic anisotropy effects in the HPβCD cavity, due to the inclusion of phenyl groups rich in π-electrons. Further, the observation of NOE connectivities between protons of HPβCD and Tam demonstrated the inclusion of Tam into the cavity of HPβCD. The observation of a single peak and absence of new peaks for protons of HPβCD and Tam in nanotamoxifen indicated that Tam was in fast exchange between free and included forms. A downfield displacement in 3 and 5 protons of phenyl ring B of the drug protons indicated that they were close to an electronegative atom, like oxygen, in the HPβCD cavity. An upfield shift in 4,5 protons of ring B of Tam indicated a location at some distance from the oxygen atoms and close to a hydrogen atom. The shift may also arise due to van der Waals interactions between the drug and carbohydrate chains or due to variation in local polarity when the protons were inside the HPβCD cavity. The magnitude of the shift difference for these aromatic protons is dependent on the relative strength of interactions with electron-rich or hydrogen atoms of the HPβCD cavity. Thus, ^{1}H-NMR spectra demonstrated the inclusion of Tam in HPβCD cavity and intermolecular cross peaks observed in ROESY, NOESY spectra confirmed the formation of inclusion complex. The inner hollow space of HPβCD toroid was occupied by Tam molecule.

The survival of breast cancer (MCF-7) cells and ovarian cancer cells (OAW-42) with Tam concentration between 5-25 μg/ml was decreased from 96% to 5%. But with Tam:HPβCD complex, the survival was significantly decreased to ~ 7% with the lowest dose i.e. 3μg/ml Tam concentration. However, the HPβCD did not show any anticancer activity. These results demonstrated the increased cytotoxic effect of Tam:HPβCD complex on breast and ovarian cancer cells (MCF-7 and OAW-42). The Increased antiestrogenic effect with lower dose is possible only if the bioavailability of Tam in Tam:HPβCD complex is increased and resulted in the increased cytotoxic effect on ER positive cancer cells.

The excellent cytotoxicity can be achieved by antiestrogenic effect of Tam on ER positive cells using Tam:HPβCD inclusion complex.

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