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COMPLEXATION OF THE CHEMOTHERAPEUTIC DOCETAXEL WITH HYDROXYPROPYL-γ-CYCLODEXTRIN: A STRATEGY TO INCREASE DRUG'S SOLUBILITY

Natália S. Mendonça[1]; Thiago S. Sampaio[2]; Fabíola V. Carvalho[2]; Fabiano Yokaichiya[3]; Margareth K.K.D. Franco[4]; Eneida de Paula[2] and Tatiane P. de Souza[1]

[1]Faculty of Pharmaceutical Science, Federal University of Amazonas (UFAM), Manaus, AM, Brazil (email: ndsmendonca@gmail.com).
[2]Department of Biochemistry and Tissue Biology, Institute of Biology, University of Campinas (UNICAMP), Campinas, SP, Brazil.
[3]Department of Physical, Federal University of Paraná (UFPR), Curitiba, PR, Brazil.
[4]Nuclear and Energy Research Institute, IPEN, - CNEN/SP, São Paulo, SP, Brazil.

Docetaxel (DTX) a chemotherapy drug of the taxane class is recognized as an essential medicine by the World Health Organization (WHO) for treating various cancers, including breast cancer. Classified under class IV of the biopharmaceutical classification system, DTX has low water solubility (6 μM) and limited bioavailability. Commercial DTX formulations employ a non-ionic surfactant (polysorbate 80) and ethanol to enhance solubility which exacerbates the side effects of chemotherapy. Forming inclusion complexes with cyclodextrins (CDs) presents a promising strategy to improve drug solubility. CDs are cyclic oligosaccharides derived from starch degradation by the bacterial enzyme cyclodextrin glucosyltransferase. α-, β- and γ-cyclodextrins are the most abundant natural CDs, but their applications are limited due to poor drug-binding capacity and toxicity concerns, especially in parenteral administration. To address these issues, chemically modified CDs such as hydroxypropyl-γ-CD (HP-γ-CD) have been developed. In this study, a DTX:HP-γ-CD inclusion complex was prepared by the co-solubilization method followed by freeze-drying, in a 1:2 stoichiometric ratio and an equilibration time of 6 hours. Characterization techniques such as scanning electron microscopy (SEM) and X-ray diffraction were employed. The complexation markedly increased the aqueous solubility of DTX by up to 25 times (150 μM). SEM micrographs indicated that DTX loses its crystalline structure upon complexation, resulting in an amorphous arrangement similar to HP-γ-CD. X-ray diffraction confirmed the loss of DTX's crystalline pattern in the inclusion complex, a phenomenon not observed in the physical mixture of excipients. The dimensions of the $DTX_{HP\text{-}\gamma\text{-}CD}$ complex (D=18.09, d= 10.13 and h= 8.07 angstroms) compared to pure HP-γ-CD (D=17.57, d= 10.56 and h= 8.96 angstroms) suggest that docetaxel slightly enlarges the size of the external ring and internal cavities (D and d, respectively) of HP-γ-CD and decreases the height of its cone (h); additionally, there was a decrease in peak intensity from the physical mixture

to the complex. These results provide compelling evidence of the complexation between DTX and modified γ-cyclodextrin. This complex holds the potential to become a new formulation with reduced side effects and enhanced therapeutic efficacy against cancer.