48th Annual Meeting of the Brazilian Biophysical Society
2 - 5th October, 2024, USP, São Paulo

MOLECULAR INCLUSION COMPLEX WITH GAMA-CYCLODEXTRIN: AN ALTERNATIVE PHARMACEUTICAL FORM TO DELIVER DOCETAXEL

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

[1]Department of Biochemistry and Tissue Biology, Institute of Biology, University of Campinas (UNICAMP), Campinas/SP, Brazil (email: thiagostevanatto@gmail.com)
[2]Faculty of Pharm. Sciences, Federal Univ. of Amazonas (UFAM), Manaus/AM, 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) is a semi-synthetic derivative of 10-deacetyl-baccatin III, a non-cytotoxic compound extracted from yew leaves (Taxus baccata L). DTX use for the treatment of anthracycline-refractory metastatic breast cancer (1996) was then expanded for skin, lung, prostate, gastric, head/neck and other neoplasias. However, as a class IV BCS drug, the clinical application of docetaxel is limited by its low water solubility (5 mg/L or 6 μM), intestinal permeability and fast elimination. Also, the use of commercially available DTX formulations is associated to adverse effects such as neutropenia, hypersensitivity reactions, peripheral neuropathy, musculoskeletal toxicity and nasolacrimal duct stenosis. To overcome such adverse effects and increase DTX anticancer potential we investigated the inclusion complexation of DTX with cyclodextrins (CD). CD are known to accommodate molecules of proper size and polarity into their macrocyclic ring, forming host-guest inclusion complexes. Complexation in CD may improve the aqueous solubility, increase the stability and prolong the release kinetics of the guest molecule. In here we report results on the characterization of a DTX:gama-cyclodextrin complex. The DTX:γCD inclusion complex was prepared by the co-solubilization method, lyophilized, and characterized regarding the equilibrium time (5 h) and stoichiometry of complexation (1:2). As expected, complexation significantly increased (20-fold) the aqueous solubility of DTX and biophysical techniques (DSC and X-ray) provided evidence of DTX:γCD complex formation. *In vitro* release kinetics tests were conducted to compare the release of DTX from the complex with that of the commercial DTX formulation (Taxotere®). Finally, cytotoxic effects against breast cancer cells (4T1) and normal fibroblasts (NIH-3T3) had been evaluated. Both DTX:γ-CD and Taxotere® caused significant reduction in the cell viability of breast cancer cells, even at the lowest concentration tested ($5x10^{-11}$M). Interestingly, DTX:γ-CD complex was found to be less toxic to NIH-3T3 non-tumor cells than Taxotere® (cell viability was reduced to 48.5 ± 2.4% with DTX:γ-CD and to 20.2 ± 0.8% with Taxotere® at the concentration of 5mM). These preliminary results suggest that DTX:γCD may represent a new drug delivery system, capable of reducing the toxicity and enhancing the effectiveness of DTX in cancer treatment.

This work was supported by FAPESP (#19/17784-0).