PREPARATION AND CHARACTERIZATION OF DISULFIRAM β-CYCLODEXTRIN INCLUSION COMPLEXES FOR THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

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Background: Breast cancer (BC) is the most frequently diagnosed cancer in women and the second major cause for cancer related death, and Triple Negative Breast Cancer (TNBC) accounts for an estimated 10-20% of all BCs and is characterised by its clinical implications and lack of prognosis(1). Disulfiram (DS), an anti-alcoholism drug, proven to have an excellent anti-cancer activity, remains a focus point in pharmaceutical research because of its low water-solubility and rapid metabolism (1,2). Cyclodextrins (CDs), cyclic oligosaccharides, are biocompatible macromolecules used to improve the solubility of drugs. CDs have a hydrophilic surface and a lipophilic center being able to interact with hydrophobic drug molecules to form inclusion complexes soluble in water (2).

Methods: In order to enhance the solubility of DS, two types β-cyclodextrins, Hydroxypropyl β-Cyclodextrin (HP) and Sulfobutyl Ether β-Cyclodextrin (SBE), were used to form inclusion complexes. Formulations were prepared by mixing DS with five different concentrations of both cyclodextrins (1%, 5%, 10%, 15% and 20% w/w). Solubility of DS was assessed using spectrophotometric analytical method. DS-CD solutions were freeze dried to study the interaction between DS and CD using DSC, TGA, FT-IR and XRD. Finally, the cytotoxic effect of DS-CD inclusion complexes of chemoresistant TNBC cell lines was evaluated using MTT assay.

Results: The solubility of disulfiram increased significantly when combined with β-cyclodextrins, reaching more than 10 mg/mL at 20% w/w. The phase solubility of DS SBE-β-CD showed the aqueous solubility of disulfiram to be a linear function of the CD concentration (A_L type), suggesting that the total amount of drug increases as a function of the CD concentration. Whereas the solubility of DS had a polynomial relationship with the increase of HP-β-CD, deviating negatively from linearity (N_A type). All lyophilized formulations were easily reconstituted indicating instant water solubility of the resulting freeze-dried formulations. DSC studies confirmed the inclusion of the amorphous of the drug in the CD-DS complexes. Finally, CD-DS inclusion complexes reserved the cytotoxic effect of DS on chemoresistant TNBC cell lines. Combined with Cu^{2+}, both CD formulations were of the similar cytotoxic effect to that of DS.

Conclusions: Our results report that the cyclodextrin inclusion complexes are a very practical approach for the enhancement of DS solubility and have a great potential for further in vivo studies against triple negative breast cancer.

References:

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2- Suliman, A. S. *et al.* (2021) 'Cyclodextrin diethyldithiocarbamate copper ii inclusion complexes: A promising chemotherapeutic delivery system against chemoresistant triple negative breast cancer cell lines', *Pharmaceutics*, 13(1), pp. 1–12.