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Development, characterisation and *in vitro* evaluation of disulfiram loaded PEGylated nanoparticles for breast cancer treatment

Disulfiram (DSF), an antialcoholism drug, has shown a selective cytotoxicity towards a wide range of cancer cells. The anti-cancer activity of DSF is copper (Cu+2) dependent as the reaction between both yields cancer-targeting reactive oxygen species (ROS) and diethyldithiocarbamate (DDC) complex with Copper (DDC-Cu) owning a strong NF B-inhibiting activity leading to cancer cell death. However, the clinical use of DSF as an anti-cancer drug is limited by its biological instability in the blood (t1/2 < 4 min). The aim of this study is to design, formulate and characterize PEGylated nanoparticles of DSF to improve stability and provide a proposed long circulation to target cancer cells. Several formulations of PEGylated PLGA/PCL nanoparticles (NPs) loading DSF have been manufactured by direct nanoprecipitation using two water-miscible organic solvents, acetone/methanol (3:1). The resulting NPs were fully characterized; size analysis, zeta potential measurements were performed using Laser Doppler Velocimetry. Drug loading efficiency and stability studies in horse serum were performed and DSF was detected using a validated HPLC method. Freez-dried NPs were also tested using DSC, TGA, FT-IR and SEM. Cytotoxicity *in vitro* on triple negative breast cancer cells MDA-MB 231 and MDA-MB 231pac10 (resistant to paclitaxel 10 nM) was evaluated by MTT assay. All NPs were within a size range of 175-225 nm with narrow PDIs (less than 0.3) and negative zeta potential rang (-25 to -45 mV); loading DS had no impact on these properties. Encapsulation efficiency (EE) was around 55% for all NPs but the none PEGylated PLGA/PCL showing the highest EE% (76%). The NPs provided high stability for DSF in horse serum; (t1/2 > 90 min for all NPs) and the PEGylated NPs demonstrated sustainable release for 96 h. The MTT cytotoxicity assay demonstrated high cytotoxicity of the DSF-NPs on both cell lines. PLGA/PCL PEGylated nanoparticles have a great potential for breast cancer treatment.

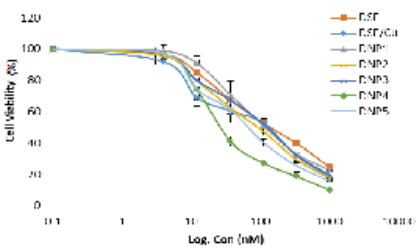

Figure 1: Cytotoxicity of DS-loaded PLGA\PCL NPs (DNP1 to DNP5), DSF and DSF/Cu standards were used as positive controls (MTT assay, mean ± SD; n=3).

Recent Publications

1. Omar, H., Hussein, N., Ferraz, A., Najlah, M., Ahmed, W., Taylor, M. T., Elhissi M. A. 2018. Spray-dried proliposome microparticles for high-performance aerosol delivery using a monodose powder inhaler. AAPS PharmSciTech.
2. Najlah, M.*, Freeman, S., Khoder, M., Attwood, D., D'Emanuele, A. 2018. *In vitro* evaluation of the third generation PAMAM dendrimer conjugates. Molecules, 22(10), 1661.
3. Najlah, M., Ahmed, Z., Iqbal, M., Wang, Z., Tawari, P., Wang, W., McConville, C.*, 2017. Development and characterisation of disulfiram-loaded PLGA nanoparticles for the treatment of non-small cell lung cancer. European Journal of Pharmaceutics and Biopharmaceutics, 112, pp.224-233.
4. Najlah, M.*, Jain, M., Wan K. W., Ahmed, W., Phoenix A. D., Taylor, K. M.G., Elhissi, A.*, 2018. Ethanol-based proliposome delivery systems of paclitaxel for *in vitro* application against brain cancer cells. Journal of Liposome Research, 14, pp.1-12.
5. Najlah, M.*, Kadam A., Wan, K.W., Ahmed, W., Taylor K. M.G., Elhissi, A.*, 2016. Novel paclitaxel formulations solubilized by lipid nanoemulsions for brain tumour therapy. International Journal of Pharmaceutics, 506(1-2), pp. 102-109.

Biography

Mohammad Najlah has an extensive experience in Pharmaceutical and Allied Health Higher Education as a teacher, researcher and manager. He is currently Deputy Head of School of Allied Health at Anglia Ruskin University. Mohammad has an excellent research profile focusing on the development of novel nanomaterials, polymeric prodrugs/conjugates and polymeric nano-particulates for drug delivery. In addition to overcoming mutli-drug resistance by nanoformulations, Mohammad is mainly interested in developing formulations for disulfiram and its metabolites for cancer therapy..

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