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Development and characterization of transferrin modified artemether lipid nanospheres as a potent anticancer delivery system

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Artemether (ART) has been used for a long time in the treatment of malaria as safe and non expensive drug. It is an oil soluble drug that suffers from poor aqueous solubility and hence low bioavailability; and available as oral dosage forms and oily intramuscular injections for the treatment of malaria. The aim of the first part of our study was to prepare and optimize ART lipid nanospheres (ART-LNSs) to enable the i.v. administration. In this study, ART intravenous delivery system was prepared by emulsifying method as lipid nanospheres containing mixture of soya oil and crodamol as the core and soya lecithin and tween 80 as coating layer. According to the physicochemical characterization, the process and formulation variables were optimized by orthogonal design and ANOVA analysis. The *in vitro* characterizations were carried out and ART-LNSs with high entrapment efficiency, small size of about 50 nm and monodispersity were formulated. Recently, ART possessed potent anticancer effects in cancer cell lines. Our aim for the second part of the study was to develop transferrin-modified-ART lipid nanospheres (TR--LNSs) as targeted anticancer drug delivery system. In this study, optimized ART-LNSs were prepared through emulsion formulation and their surface charge was modulated by stearylamine. Based on the electrostatic interaction, TR was physically adsorbed onto the coating layer containing epikuron 200 and tween 80 as surfactants. The effect of medium pH and the charge of the nanocarriers on protein adsorption were investigated. The *in vitro* characterizations were carried out including, the zeta potential, AFM, TEM, FTIR, 1H NMR and gel filtration. Optimized and stable TR-LNSs, a lipoprotein like structure and size, with high entrapment efficiency, small size of about 50 nm and monodispersity were produced. Diverse lines of research show that the cellular response to artemisinin and its derivatives is multi-factorial in nature. The cytotoxicity of ART is specific for cancer cells because most cancer cells over expressed TR-receptors and have high level of intracellular iron; and ART is mainly toxic after interaction with iron ion. Our aim for the third part of the study was to investigate the impact of some formulation characteristics such as surface charge and ligand modification on the anticancer effect of ART in C6 and MCF-7 cancer cells. In this study, ART was loaded in anionic, cationic or neutral, with TR modification, lipid nanospheres to study its cytotoxicity. The cytotoxicity was studied by MTT assay and further confirmed by studying the apoptosis. Quantitative and qualitative characterizations of apoptosis were done by flow cytometer and fluorescence microscope respectively. The effect on the mitochondria and the nucleus was qualitatively characterized by fluorescence microscope after using different types of cell tracker dyes. The cellular uptake, accumulation and distribution of the formulations were characterized by fluorescence microscope after loading a hydrophobic fluorescence probe, coumarin-6 or NIRD-15, instead of ART. The amount of coumarin-6 accumulated in mitochondria, nucleus or cytosol was quantified by flow cytometer after isolation of cell parts through a defined protocol. The relations between the accumulated amount of ART and its cytotoxicity toward cancer cells were defined. Nowadays ART, as an oil soluble compound, is mainly available as oral dosage forms and oily intramuscular injection for the treatment of malaria. Whereas the poor bioavailability and tissue deposition limited the use of these dosage forms of ART as suitable drug carriers for cancer treatment. The cytotoxicity of the anticancer agent toward the tumor tissue must require high bioavailability and long term treatment to achieve high therapeutic efficacy. Lipid nanospheres (LNSs) are excellent carriers for lipophilic drugs. They confer on some lipophilic drugs as prolonged plasma half-life, increased plasma concentration, low uptake by the reticuloendothelial system (RES), and good distribution to inflamed sites such as tumor tissues, through the blood vessels with increased permeability. Furthermore the surface modification of the LNSs by a suitable ligand such as transferrin (TR) will modify and improve the pharmacokinetics and tissue targeting of their loaded drug. The aim of our forth part of the study was to investigate the pharmacokinetics (PK) and tissue deposition of TR-LNSs in rats and the tissue distribution in tumor bearing rats, after intravenous administration. The PK parameters of ART and its metabolite DHA were determined by high performance liquid chromatography- tandem mass spectrometry (LC-MS/MS) method. The tissue distribution was qualitatively studied by the *in vivo* fluorescence imaging after the loading of NIRD15, as a fluorescence probe, in the LNSs instead of ART. Iron plays an important role in the cell growth by involving in the energy metabolism and protein synthesis. Cancer cells are metabolically active more than normal cells and required a higher iron intake. ART, as an endoperoxide containing compound, generates a reactive oxygen species upon reaction with intracellular iron and has a potent and selective cytotoxicity toward the cancer cells. The aim of our final part of the study was to investigate the *in vivo* antitumor activity of ART, loaded in different drug carriers, in heps tumor bearing mice after intravenous administration. ART loaded LNSs and their modification by physical adsorption of TR resulted in efficient tumor growth inhibition and increased survival rate. The results of our entire study showed a method by which stable and an efficient intravenous ART drug carrier, LNS, was prepared and optimized. TR could be physically adsorbed to the surface of the LNS without the need for chemical modification. TR-LNSs exhibited promising anticancer effects on different cancer cell lines with improved pharmacokinetics, tissue distribution, efficient tumor growth inhibition and increased survival rate in animals. We showed a possibility to form a promising targeting carrier of ART with excellent antitumor activity as safe, effective and non expensive anticancer drug delivery systems. Furthermore the study would provide a base for the development of effective drug delivery systems for brain disorders.

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