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Clathrin-mediated endocytic uptake of PUFA enriched self-nanoemulsifying lipidic systems (SNELS) of an anticancer drug against triple negative cancer and DMBA induced preclinical tumor model

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ABSTRACT

The current studies envisage unravelling the underlying cellular internalisation mechanism of the systematically developed docetaxel (DTH) polyunsaturated fatty acid (PUFA) enriched self-nanoemulsifying lipidic micellar systems (SNELS). The concentration-, time- and cytotoxicity-related effects of DTH-SNELS on triple negative breast cancer (TNBC) MDA-MB-231 and non-TNBC MCF-7 cell lines were assessed through Presto-blue assay. Subsequently, rhodamine-123 (Rh-123) loaded SNELS were employed for evaluating their internalisation through flow cytometry and fluorescence microscopy, establishing it to be "*clathrin-mediated*" endocytic pathway. Apoptosis assay (65% cell death) and cell cycle distribution (47% inhibition at G2/M phase) further corroborated the cytotoxicity of DTH-SNELS towards cancerous cells. Biodistribution, histopathology and haematology studies indicated insignificant toxicity of the optimized formulation on vital organs. Preclinical anticancer efficacy studies using 7,12-dimethylbenzantracene (DMBA)-induced model construed significant reduction in breast tumor-volume. Overall, extensive in vitro and in vivo studies indicated the intracellular localization and cytotoxicity, suggesting DTH-SNELS as promising delivery systems for breast tumor therapeutics including TNBC.

1. Background

Breast cancer is one of the most commonly diagnosed carcinoma in women throughout the world. Among the subtype of breast cancers, triple negative breast cancer (TNBC) which are tumors that do not express oestrogen, progesterone and human epidermal growth factor receptors, account for almost 20% of breast cancers [1]. Since TNBC does not have the receptors for hormones, they do not benefit from treatment with hormonal therapy and treatment options are limited to chemotherapy and radiotherapy [2]. However being clinically aggressive type of cancer its responsiveness to chemotherapy is very poor [3]. Treating this type of cancer presents a major challenge due to the poor disease prognosis and therefore the need for newer and safer therapies.

The first-line drug currently employed for the management of breast cancer belongs to the group of semi-synthetic taxanes, i.e., docetaxel (DTH), being marketed as intravenous preparation, namely Taxotere® and Docefrez®. DTH, an antimitotic chemotherapeutic drug, promotes the assembly of tubulins into microtubulins, stabilizes microtubules, and thus inhibits cell proliferation [4]. The clinical applications of DTH are hampered by severe side effects such as neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, peripheral neuropathy, musculoskeletal toxicity and hypersensitivity [5]. Besides, DTH, being a biological classification systems (BCS) Class II drug, encounters several physico-chemical challenges, i.e., practically insoluble in water with quite high log P of 2.9, poor oral bioavailability (8%) coupled with high hepatic first-pass metabolism and significant efflux by permeability glycoprotein (P-gp) transporter systems leading to multi-drug resistance [6].

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