Alexandria University
Institute of Graduate Studies and Research
Department of Biotechnology

Biopolymeric Nanovehicular Drug Delivery Systems for Targeted Cancer Therapy

A thesis Submitted to the Department of Biotechnology,
Institute of Graduate Studies and Research,
Alexandria University

In partial fulfillment of the requirements of

PhD Degree

In

Biotechnology

Presented By

Shaimaa Khamis Mohammad Mostafa

Bs.c of Pharmaceutical Sciences-Faculty of Pharmacy, Alexandria University, 2003.
Pharm-D, Faculty of Pharmacy, Alexandria University, 2008

Department of Biotechnology
Institute of Graduate Studies and Research,
Alexandria University

2016

1. ABSTRACT

Several data reveal the beneficial effect of co-administration of celecoxib (CXB) with aromatase inhibitors (AIs) in managing postmenopausal breast cancer. The purpose of this study is to elaborate novel natural protein nanocapsules based on protamine for tumor-targeted co-delivery of letrozole (LTZ) and celecoxib in breast cancer therapy. Polymer coating technique was employed for the preparation of dual drug-loaded protamine nanocapsules (DDLPNCs). Moreover, PEGylated and non-PEGylated CXB-phospholipid complex bilayer enveloping protamine nanocapsules were designed as passive-targeted formulations whereas hyaluronic acid (HA)-coated protamine nanocapsules were prepared for active targeting. The optimal formulations showed high (% EE) of both drugs and sustained drug release. All formulations exhibited a nanometer size range (85–267 nm), spherical shape and were physically stable for three months. Pharmacokinetic studies demonstrated that DDLPNCs exhibit a longer circulation time with markedly delayed blood clearance of both drugs, compared with free dual drug solution. Cytotoxicity studies and biological evaluations of the anti-tumor efficacy revealed the superiority of DDLPNCs over the free dual drug solution. This superiority was manifested as a marked reduction of % cell viability and % change of tumor volume. Mechanistically, the anti-tumor properties were correlated to the ability to activate caspase 3 and marked inhibition of aromatase expression, NF-κB, TNF-α and VEGF. These results were further augmented by the histopathological studies. Conclusively, these results offer a promising method for tailoring tumor-targeted protamine nanocapsules as parenteral, long-circulating nanovehicles of hydrophobic anti-cancer drugs in aqueous vehicles.