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CELLULAR UPTAKE OF CHITOSAN-FOLATE-CARBOXYMETHYL 5-FLUOROURACIL CONJUGATE NANOPARTICLES BY MALIGNANT MELANOMA CELLS

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MSc

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

This study examined the effects of folate environment of oligochitosan nanoparticles on their cellular internalization profiles in human melanoma cells. The conjugates and nanoparticles of oligochitosan-folate, oligochitosan-carboxymethyl-5-fluorouracil, and oligochitosan-folate-carboxymethyl-5-fluorouracil were synthesized by carbodiimide chemistry and prepared by nanospray drying technique respectively. The cellular internalization profiles of oligochitosan-folate nanoparticles against the human malignant melanoma cell line (SKMEL-28) were evaluated using confocal scanning electron microscopy technique through fluorescence labelling and endocytic inhibition, as a function of nanoparticulate folate content, size, polydispersity index, zeta potential, shape, surface roughness and folate population density. The cytotoxicity and cell cycle arrest characteristics of oligochitosan-folate-carboxymethyl-5-fluorouracil nanoparticles, prepared with an optimal folate content that promoted cellular internalization, were evaluated against the oligochitosan-folate and oligochitosan-carboxymethyl-5-fluorouracil conjugate nanoparticles. The oligochitosan-folate conjugate nanoparticles were endocytosed by melanoma cells via caveolae- and lipid raft-mediated endocytic pathways following them binding to the cell surface folate receptor. Nanoparticles that were larger and with higher folic acid contents and zeta potentials exhibited a higher degree of cellular internalization. Excessive conjugation of nanoparticles with folate resulted in a high nanoparticulate density of folate which hindered nanoparticles-cell interaction via folate receptor binding and reduced cellular internalization of nanoparticles. Conjugating oligochitosan with 20 %w/w folate was favorable for cellular uptake as supported by in silico models. Conjugating of oligochitosan nanoparticles with carboxymethyl-5-fluorouracil and 20 %w/w of folate promoted nanoparticles-folate receptor binding, cellular internalization and cancer cell death via cell cycle arrest at S phase at a lower drug dose than oligochitosan-carboxymethyl-5-fluorouracil conjugate nanoparticles and neat carboxymethyl-5-fluorouracil.

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