UNIVERSITI TEKNOLOGI MARA

DESIGN OF FOLATE-CONJUGATED CHITOSAN-PECTIN NANOPARTICLES AS ORAL COLON-SPECIFIC 5- FLUOROURACIL DELIVERY SYSTEM FOR COLON CANCER TREATMENT

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Thesis submitted in fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Pharmaceutics)

Faculty of Pharmacy

March 2021

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

Microencapsulation of polysaccharidic nanoparticles is met with nanoscale and biological performance changes. This study designs soft agglomerates as nanoparticle vehicle to delay the drug release of nanoparticles without them undergoing physical processes that alter their geometry. The nanoparticles were made of high molecular weight chitosan/pectin with covalent 5-fluorouracil/folate. Nanoparticle aggregation vehicle was prepared from low molecular weight chitosan. The nanoparticles and aggregation vehicle were blended in specific weight ratios to produce soft agglomerates. Nanoparticles alone are unable to agglomerate. Adding aggregation vehicle (< 2 μm) promoted soft agglomeration with nanoparticles deposited onto its surfaces with minimal binary coalescence. The large and rough-surfaced aggregation vehicle promoted nanoparticles deposition and agglomeration. A rounder vehicle allowed assembly of nanoparticles-on-aggregation vehicle into agglomerates through interspersing smaller between larger populations.

Soft agglomerates alone appeared to retard drug release in the upper gastrointestinal tract, but not able to meet the colon-specific requirement. This study probed into intracapsular-coating of soft agglomerates. *In vitro* drug content, drug release, *in vivo* pharmacokinetics including local colonic drug content, *in vivo* pharmacodynamics including tumour, aberrant crypt foci and clinical chemistry profiles of intracapsular-coated and uncoated soft agglomerates as well as cytotoxicity of nanoparticles were examined against the unprocessed drug. Intracapsular-coated soft agglomerates of chitosan-folate-carboxymethyl-5-FU conjugate/pectin nanoparticles with nanoparticle aggregation vehicle by means of a mix of sodium alginate and 2:1 weight ratio of calcium phosphate to calcium acetate mediated oral colon-specific drug release *in vitro*. The intracapsular-coated soft agglomerates were characterized to reduced drug bioavailability and enhanced drug accumulation at colon. They reduced tumor number and size (ANOVA: $p < 0.05$), through reforming tubular epithelium with basement membrane and restricting expression of cancer from adenoma to adenocarcinoma. Unlike intracapsular-coated soft agglomerates of chitosan-carboxymethyl-5-FU conjugate/pectin nanoparticles with nanoparticle aggregation vehicle and unprocessed drug, the intracapsular-coated soft agglomerates of chitosan-folate-carboxymethyl-5-FU conjugate/pectin nanoparticles with nanoparticle aggregation vehicle eliminated aberrant crypt foci which represented a putative preneoplastic lesion in colon cancer. They did not inflict additional systemic toxicity. MTT assay showed that covalent conjugation of drug onto the polymeric backbone, polyelectrolyte coacervation and nanoparticulation reduced the drug cytotoxicity against the HCT 116 human colon cancer cells. Soft agglomeration and intracapsular coating of chitosan-folate/pectin coacervate nanoparticles enable orally targeting 5-fluorouracil at the cancerous colon.

ACKNOWLEDGEMENT

Alhamdulillah, thanks to ALLAH S.W.T for his mercy and guidance in giving me full strength to complete this thesis.

First and for most, I would like to express my deepest thanks to my supervisor, Professor Dr Wong Tin Wui for his guidance and encouragement throughout my study. I wish to express my sincere gratitude to iPROMISE and Faculty of Pharmacy, Universiti Teknologi MARA, Ministry of Science and Technology (MOSTI) and Ministry of Higher Education for financial and facility support given throughout this research project.

Deepest thanks and appreciation to my husband, Mohamad Yusof bin Hassanusi and my parents, Musa bin Haron and Jamaliah binti Zainal for their encouragement and full support for the PhD study, from the beginning till the end. I love all of you so much.

Special thanks to all friends in Particle Design Research Group and Non-Destructive Biomedical and Pharmaceutical Research Center (NDBPRC) for their warm friendship, knowledge sharing, constructive suggestion and understanding as well as great moments we share together along this journey.

Finally, I offer my regards and blessings to all of those who supported me in any aspect during the completion of the research project.

Alhamdulillahirabbilalamin

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