UNIVERSITI TEKNOLOGI MARA

COLON-SPECIFIC DELIVERY OF 5-FLUOROURACIL FROM ZINC PECTINATE SPHEROIDS THROUGH *IN SITU* INTRA-CAPSULAR ETHYLCELLULOSE-PECTIN PLUG FORMATION

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AUTHOR'S DECLARATION

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

Conventional fluid-bed and immersion film coating of hydrophilic zinc pectinate spheroids using ethylcellulose-pectin mixture is met with fast drug release due to hydrophobic ethylcellulose coat detachment. This study explored *in situ* intra-capsular spheroid coating for colon-specific delivery of 5-fluorouracil. The solid coating powder was constituted of ethylcellulose and pectin in weight ratios of 11:0 to 2:9. Its weight ratio to spheroids was varied between 2:3 and 3:2. Delayed 5-fluorouracil release was obtained when the weight ratio of ethylcellulose and pectin in coating powder was kept at 8:3, and weight ratio of solid coating powder to spheroids was kept at 3:2 with particle size of ethylcellulose reduced to 22 μm. *In situ* intra-capsular wetting of pectin coat by dissolution medium resulted in the formation of ethylcellulose plug interconnecting with spheroids through the binding action of pectin. The majority of drug was released in the colon region and complete drug release was obtained through digestion of core spheroids by pectinase. Through *in vivo* pharmacokinetic and pharmacodynamic studies, the intra-capsular coated spheroids were found to be able to reduce the drug bioavailability, enhance its accumulation at colon and reduce both number and size of tumor through reforming the tubular epithelium with basement membrane and restricting the expression of cancer from adenoma to adenocarcinoma. Given a dosage regimen of 15 mg/kg/day for 5 days in rats, the intra-capsular coated spheroids also eliminated the formation of aberrant crypt foci which represented a putative preneoplastic lesion in colon cancer, unlike other treatment modes. Inferring from blood levels of hemoglobin, red blood cell, white blood cell, hematocrit, mean corpuscular hemoglobin, platelet, urea, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and bilirubin, intra-capsular spheroid coating to target 5-fluorouracil delivery at cancerous colon is concluded as a feasible colon cancer formulation approach with reduced risks of systemic adversity.

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CHAPTER ONE

INTRODUCTION

1.1 OVERREVIEW

The occurrence of cancer could rise by 50 % to 15 million new cases in the year of 2020, in accordance to World Cancer Report of which represents the most comprehensive global examination outcome to date [1]. Colon cancer refers to cancerous growth in colon, rectum or cecum [2]. It accounts for 940,000 new cases annually, following lung and breast cancers with annual 1.2 million and just over 1 million new cases respectively [1]. Colon cancer is reckoned to be a disease of affluence and occurs most frequently in North America, Australia, New Zealand, Japan and Western Europe [3-7]. A total of 639,000 deaths related to colon cancer are reported worldwide each year.

Surgery remains the primary mode of colon cancer treatment with chemotherapy and/or radiotherapy recommended upon the nature and extent of severity of disease [2]. Chemotherapy can be provided after surgery as adjuvant, before surgery as neo-adjuvant or as primary therapy to reduce tumor size and growth as well as the likelihood or propensity of metastasis. 5-fluorouracil (5-FU) is one of the common drugs used as colon cancer chemotherapeutic [8,9]. It is a thymidylate synthase inhibitor which primarily interrupts the synthesis of pyrimidine thymidine, a nucleoside required for deoxyribonucleic acid replication, through depleting thymidine monophosphate. This then results in rapidly dividing cancerous cells undergoing thymine less cell death.

Oral colon-specific drug delivery can be mediated by means of prodrugs, azo-polymers, time-, pH- and pressure-sensitive, as well as, microbial-activated approaches [10-15]. To succeed in colon targeting, it is imperative to deliver drugs at an adequate local concentration and without premature drug release/loss in the upper gastrointestinal tract. The spheroids and microparticles are preferred oral dosage forms for delivery of chemotherapeutic agents to the target sites of colon cancer [2]. Unlike gastric transit, small dosage forms show a slower colon transit than large dosage forms [10]. Prolonged colonic retention of dosage form and/or consistent local colonic exposure to anti-cancer