UNIVERSITI TEKNOLOGI MARA

DESIGN OF RESISTANT STARCH BASED COMPOSITE NANOPARTICLES AS ORAL COLON-SPECIFIC DRUG VEHICLE FOR COLON CANCER TREATMENT

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ABSTRACT

Starch is constituted of amylose and amylopectin. Debranching of amylopectin converts it into amylose, thereby producing resistant starch which is known to be less digestible by the amylase. This study designed resistant starch using acid hydrolysis and heat-moisture treatment methods with native corn starch as the starting material. Heat-moisture treatment of native corn starch enabled the formation of resistant starch through amylopectin debranching and molecular weight reduction thereby enhancing hydrogen bonding between the starch molecules at the amorphous phase and gelatinization capacity. The nanoparticles prepared from resistant starch demonstrated similar drug release as those of native starch despite the resistant starch had a lower molecular weight. The resistant starch is envisaged to be resistant to the digestive action of amylase in the intestinal tract without the formed nanoparticles exhibiting excessively fast drug release in comparison to native starch. The resistant starch was subsequently used as the main excipient with chitosan as the co-excipient in designing composite nanoparticles as the oral-colon specific 5-fluorouracil carrier for colon cancer treatment. Chitosan-carboxymethyl 5-fluorouracil and chitosan-folate were conjugates and individually prepared via carbodiimide reaction. Resistant starch was introduced to strengthen the assembly of chitosan-carboxymethyl 5-fluorouracil conjugate and chitosan-folate conjugate into nanoparticles, allowing drug, targeting ligand and drug release modulator to co-exist in a single particle. Resistant starch composite nanoparticles were encapsulated into resistant starch/alginate beads and intra-capsular coated with pectin and ethylcellulose in situ. The bead encapsulation and intracapsular coating of resistant starch composite nanoparticles facilitated oral colon-specific drug delivery for local colon cancer treatment. Target delivery of nanoparticles at colon cancer site was envisaged to lead to cell uptake of nanoparticles with resistant starch composite nanoparticles exhibiting a relatively high level of cytotoxicity through inhibiting cell growth via cell cycle arrest at the G1 phase and negating cancer metastasis and drug efflux. The resistant starch composite nanoparticles were endocytosed by HCT 116 colon cancer cells via macropinocytosis. They are a potential carrier for cancer therapeutic delivery in local colon cancer treatment.

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CHAPTER ONE
INTRODUCTION

1.1 Research Background

Colorectal cancer, also known as colon cancer, which is the combined term of colon cancer and rectal cancer (Mayo Clinic, 2019). According to Malaysia National Cancer Registry data reported in 2019, there were 115 238 new cancer cases registered in Malaysia in the period of 2012 to 2016 where 44.7% were males and 55.3% were females. Colorectal cancer was the second most common cancer in Malaysia (13.5%) after breast cancer (19%). National Registration Department reported 82601 cancer deaths where the number had gradually increased from 17.82% to 22.64% from 2012 to 2016, respectively. Out of 58635 cases of reported staging, 15% was in stage I, 20.8% in stage II, 22.8% in stage III, and 40.9% in stage IV. Based on the data, at time of diagnosis, 63.7% had advanced cancer characterized by stage III and IV (Manan et al., 2019). Patient delay can be the main factor behind late diagnosis where it can either be due to unawareness or ignorance of the cancer symptoms. It can also be due to failure to recognise the early cancer signs since it may be non-specific and mistaken for other medical conditions (Lancet, 2010).

There are several types of cancer that can be found in the colon and rectum such as adenocarcinomas, carcinoid tumours, gastrointestinal stromal tumours, lymphomas, and sarcomas (Cancer Treatment Centers of America, 2021). Adenocarcinomas make up 95% of all colorectal cancer cases and they start in cells that form glands which produce mucus to lubricate the colon and rectum. These adenocarcinomas normally start as a growth of tissue called a polyp. Carcinoid tumours start from specialized hormone-making cells in the intestine while gastrointestinal stromal tumours start from specialized cells in the wall of the colon known as interstitial cells of Cajal. Some of these tumours are benign and can be found anywhere in the digestive tract but rarely can be found in the colon. Lymphomas are cancers of immune system cells that usually start in lymph nodes but can also start in the colon, rectum, or other organs. Sarcomas