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INFLUENCES OF MICROWAVE ON DRUG DISSOLUTION PROFILES OF MANNURONIC ACID-RICH ALGINATE SPHEROIDS

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AUTHOR'S DECLARATION

I declare that the work in this thesis/dissertation 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

Since the last decade, various formulation and processing approaches have been introduced in drug delivery system design to negate the propensity of drug release from dosage form in the acidic gastric region. Extrusion-spheronization is one of the processing approaches that is extensively used in the production of multi-particulate system for oral controlled drug delivery. Polysaccharides have been employed in the formulation of pharmaceutical drug delivery system for small molecule drug. Nevertheless, the formed matrix frequently is found to have a porous structure. Consequently, this results in an uncontrollably fast release rate of small molecule drug. Such rate of drug release is undesirable in the case of the need to target the drugs to the lower part of gastrointestinal tract, particularly, the colon. Alginate is a type of polysaccharide that has been employed in the formulation of pharmaceutical drug delivery system for small molecule drug. It is produced from brown seaweeds, and is biocompatible, non-toxic, non-immunogenic and biodegradable. The present study investigates small molecule drug release from spheroids prepared from mannuronic acid-rich alginate. The drug release property of these spheroids was examined with reference to additive and microwave effects as formulation and processing variables respectively. The spheroids were prepared by extrusion-spheronization technique using microcrystalline cellulose as spheronization aid, zinc chloride as crosslinking agent, chlorpheniramine maleate as model water-soluble drug, stearic acid and 12-hydroxystearic acid as additives. The formed spheroids were subjected to size, shape, drug content, drug release, zinc release, Fourier Transform Infrared spectroscopy, Differential Scanning Calorimetry and surface morphology analysis. They were treated by microwave at 80 W for 5 to 40 min when required. Alginate spheroids demonstrated a fast drug release characteristics and such fast release attribute can be reduced through zinc alginate crosslinkage formation. The zinc alginate spheroids exhibited a lower level of drug release despite the matrix was disintegrated into fines particles which had a larger specific surface area for drug dissolution. Loading of stearic acid or 12-hydroxystearic acid into alginate or zinc alginate spheroids did not substantially retard drug release though these fatty acids were relatively hydrophobic. Overall, the treatment of alginate-based spheroids by microwave tended to bring minor changes in drug release property except that of zinc alginate-12-hydroxystearic acid spheroids where O-H moiety of fatty acid and alginate increasingly responded to the influence of microwave.

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CHAPTER ONE
INTRODUCTION

1.1 OVERVIEW

1.1.1 Anatomy and Physiology Factors of Gastrointestinal Tract

Generally, digestive tract or gastrointestinal tract is the system of organs within multicellular animals that takes in food, digests it to extract energy and nutrients, and excretes the remaining waste or in other terms, responsible for the process of ingestion, digestion, absorption and defecation or secretion of various foods and liquids needed in order to sustain life. Gastrointestinal tract is anatomically described as approximately 6.5 meters long tube and comprises of three major regions that are the stomach, the small intestine and the large intestine but the actual sequences basically starts with the mouth and proceeds to the esophagus, stomach, small intestine (duodenum, jejunum, ileum), large intestine (colon), rectum, and terminates at the anus (Figure 1.1). Gastrointestinal tract is also essentially defined as a hollow muscular tube composed of four concentric layers of tissue named from the internal to the external layer as mucosa, submucosa, muscularis externa (or external muscle layer) and adventitia or serosa. Another reference identifies gastrointestinal tract as an important part of immune system due to several factors involving large pH variations, biliary salts and enzymes along the gastrointestinal tract. Since pH of the gastrointestinal fluids varies significantly along the length of the tract, drugs may encounter the stomach at pH range of 1-3.5, duodenum at pH 6, jejunum at pH range 5.5-6.8 and caecum at pH range 6.8-7.3 before admitting in the local or undergoing systemic absorption (Aulton, 1996). The unique properties in the gastrointestinal tract that helps with immune function are gastric fluid that is known to be highly acidic and is fatal for many microorganisms that enter it, enzymes in the saliva, bile and also mucus that contains IgA antibodies which help to neutralize many of these microorganisms.