UNIVERSITI TEKNOLOGI MARA

DESIGN OF PECTIN-CHITOSAN NANOPARTICLES AS ORAL INSULIN CARRIER

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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 result 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 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

Polymeric nanoparticles are characterized by high risks of premature drug dissolution and low drug encapsulation efficiency. The latter is aggravated by slow nanoparticle formation from large molecular weight polymers due to their slow diffusion kinetics in the reaction medium. This study investigated large molecular weight pectin-chitosan coacervate in insulin encapsulation and sustained release. The nanoparticles were prepared through coacervation of pectin-insulin and chitosan with tripolyphosphate anions in pectin-insulin mixture, or calcium cations in chitosan solution. The formed particles were nanospray-dried when required. The size, zeta potential, morphology, drug content, drug association efficiency, drug release, polymer-polymer and drug-polymer interaction in particulate matrix were examined. Both non-crosslinked and crosslinked pectin-chitosan nanoparticles failed to encapsulate insulin substantially, unless nanoparticles were formed with rapid particle aggregation into micromatrices during coacervation. The aggregation level of nanoparticles can be reduced via spray drying and disaggregation of the particle clusters. These nanoparticles demonstrated fast drug release and chitosan dissolution. The chitosan dissolves readily in intestinal medium and can be utilised to increase mucosal permeability of the promptly released insulin in future endeavour.

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In the name of God, Most Gracious, Most Merciful.
Read! In the name of your Lord and Cherisher, Who created. Created man, out of a mere clot of congealed blood. Read! And your Lord is Most Bountiful. He Who taught the use of the Pen. Taught man that which he knew not. Nay, but man does transgress all bounds. In that he looks upon himself as self-sufficient. Verily, to your Lord is the return of all (Surah Al-Alaq: 1-8).

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CHAPTER ONE
INTRODUCTION

1.1 OVERVIEW

Pectin is an anionic heteropolysaccharide made of 1,4 linked α-D-galactosyluronic acid residues and a range of neutral sugars [1, 2]. Chitosan is a cationic binary heteropolysaccharide consisting of β(1-4) linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glycopyranose units [3]. Both pectin and chitosan are biodegradable, biocompatible, safe and non-toxic. They have received a widespread application in oral drug delivery system design.

Diabetes mellitus is an endocrine disease which is related to the disorders of carbohydrate metabolism brought about by deficiency in insulin secretion, insulin resistance or both [4]. Epidemiology study indicates that hyperglycemia is the primary cause of diabetes. The global burden of diabetes is estimated to increase from about 171 million in 2000 to 366 million people in 2030. The primary mode of treatment of type 1 diabetes is subcutaneous exogenous insulin administration. Most patients need to self-administer at least two injections of insulin daily or three to four injections for best control of blood glucose levels. The diabetes patients regard the injection needle as a bothering necessity and consider it to be a stigma of their disease.

Oral route has been explored by researchers as the alternative insulin administration pathways [4]. Chitosan has been intensively examined as potential oral insulin carrier in the forms of either single-unit or multi-particulate system, tripolyphosphate crosslinked or alginate- and dextran sulphate-coacervated matrices, and microparticles or nanoparticles [4–7]. The matrix polymers are required to protect the insulin from pH or enzymatic degradation, promote intestinal mucoadhesion and sustain drug release of matrix. Chitosan is found to interact weakly with insulin and the formed matrix exhibit fast insulin release [8, 9]. Pectin is well known for its ability to withstand degradation in upper gastrointestinal tract [10]. Nonetheless, for a water-soluble polymer