CHAPTER I

INTRODUCTION

Polymers have played indispensable roles in the preparation of pharmaceutical products. They are one of the most important materials used in the pharmaceutical formulations. A large number of polymers have been modified and used for the controlled release of drugs in a variety of dosage forms. This leads to a reduction of toxic and undesirable effects of drugs, a decrease in frequency of drug administration and improvement in treatment efficiency.

Hydrogels are cross-linked hydrophilic polymers in a three-dimension network form. It consists of ionize groups, which can form gel by ionic interaction with opposite charges. This kind of polymer is called polyelectrolyte complex (PEC). The functional groups of this polymer can ionize or deionize depending on their ionic strength and pH of the dissolution medium. Thus, the PEC hydrogel is useful in designing the polymeric matrice for controlled release drug in the gastrointestinal tract (GI tract), which has a variation of pH from the stomach to the intestine.

Chitosan is a copolymer of β-(1-4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. It is a polycationic biopolymer which is generally obtained by alkaline deacetylation of chitin. Some of its important properties are biodegradability, non-toxicity and good biocompatibility that make it suitable for biomedical and pharmaceutical applications. Moreover, its antacid and anti-ulcer properties can prevent or weaken drug irritation in the stomach [1].

According to previous studies, drugs released from chitosan beads or microspheres could be controlled by anionic polymer. Anionic polymers used to form a PEC with chitosan in those studies were, for example, alginate [2],

cellulose[3], pectin [4] and poly(acrylic acid) [5]. All of the studies suggested that the ability of drug release was related to the pH of the dissolution medium.

Carrageenan is an anionic polymer extracted from the marine red algae. Its structure is a linear heteropolysaccharides with ester sulfate groups. The main chain consists of alternating copolymer of 1,4-α and 1,3-β-D-galactopyranose and 3,6-anhydro-D-galactopyranose. Due to its gelling and viscosity enhancing properties along with proven safety [6], there has been an interest in the use of carrageenan in a sustained-release composition. Moreover, a PEC gel prepared by mixing chitosan and κ-carrageenan solution shows no swelling at pH below 9 [7]. It exhibits a potential for sustaining the drug in the GI tract.

Chitosan/carrageenan PEC has been developed for the drug controlled-release. Tomida et al. [8] prepared the suspension coating of the ionotropically gelled κ-carrageenan beads with chitosan powder followed by the incubation in low pH to create a capsule outerlayer. The model drug (theophylline) released from the capsules followed zero-order kinetics, suggesting that the κ-carrageenan/chitosan PEC could be useful for controlled-release drug delivery.

Thereafter, Tapia et al. [9] evaluated the possibility of using mixtures and/or PEC of chitosan-carrageenan in a tablet form as prolonged drug release systems, using diltiazem hydrochloride as a drug model. The release of the drug was controlled by the capacity of carrageenan to promote the entry of water into the matrices.

Sodium diclofenac (DFNa, $C_{14}H_{10}Cl_2NO_2Na$), was selected as the model drug for this study to evaluate the potential of PEC hydrogel for the oral drug delivery system. DFNa is a widely used non-steroidal anti-inflammatory drug (NSAID) which exhibits antirheumatic, analgesic, osteoarthritis and antipyretic activity. It has a short half-life in plasma (1-2 hours). The daily dose varies

between 75 to 200 mg/person, given in three or four divided portions depending on the route of administration. The most common adverse effects of drug are gastritis, peptic ulceration, and depression of renal function [10, 11].

In this study, the chitosan/carrageenan beads were prepared with various proportions of chitosan and carrageenan, DFNa content, and types and amounts of crosslinking agents for drug delivery in the GI tract. The drug release behavior from various formulations were evaluated by a in vitro dissolution test.

1.1 Research Objective

The objective is to develop and evaluate a new drug controlled release system consisting of chitosan/carrageenan PEC beads for sustained release of NSAID drugs in the gastrointestinal tract.

1.2 Scope of the Investigation

The stepwise investigation was carried out as follow:

1) Review literatures for related research work.
2) Prepare the hydrogel beads by varying the proportions of chitosan and carrageenan.
3) Determine DFNa content in the chitosan/carrageenan beads.
4) Prepare the crosslinked chitosan/carrageenan beads by varying the crosslinking method, types and amounts of crosslinking agent.
5) Characterize and study the morphology of the beads using SEM, FT-IR, DSC, TGA and microscope.
6) Study the swelling behavior of the beads in gastric-intestine simulated conditions by a microscope.
7) Study the release behavior of the beads in gastric-intestine simulated conditions by UV-Vis Spectroscopy.
8) Summarize the results.