CHAPTER I

INTRODUCTION

The use of polymeric matrix for controlling the release of drugs has been developed over the past few decades. Hydrophilic polymers have played indispensable roles in the preparation of pharmaceutical products as one of the most important materials used in the formulations. A numerous polymers have been modified and used for the controlled release of drugs in a variety of dosage forms. The use of these hydrophilic polymers for the delivery of drug has proven to be advantageous over the conventional drug delivery systems.

Hydrogel is a cross-linked hydrophilic polymer in a three dimensional network form. It consists of ionize groups which can form gel by ionic interaction with the opposite charges, called polyelectrolyte complex (PEC) hydrogel. Because the functional groups of the polymer are able to ionize/deionize depending on the ionic strength and pH of aqueous solution, the PEC hydrogels are useful in designing formulation for the drug controlled release in the gastrointestinal tract (GI tract) which has a variation in 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 from chitin. The properties such as biodegradability, non-toxicity and good biocompatibility make it favorable for using in biomedical and pharmaceutical applications. Moreover, the antacid and anti-ulcer properties are advantageous to 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.

Chitosan/PEG has been developed for controlled release of drug. Wang et al.[6] prepared the chitosan/PEG in the form of films to control the release of ciprofloxacin hydrochloride. The results showed that the amount of drug released increased along with the proportion of PEG.

Poly(ethylene glycol) (PEG) is a biocompatible polymer with excellent biocompatibility and non-toxicity because it exhibits rapid clearance from the body. It has been approved for a wide range of biomedical applications and often blended or compounded with other polymers to be used in the field of drug-controlled release [7].

In addition, to improve chitosan properties for controlled release drug delivery, complexation between oppositely charged molecules such as multivalent counterion tripolyposphate was suggested. Sodium tripolyphosphate (TPP), $Na_5P_3O_{10}$, is a sodium salt of triphosphoric acid. It is a solid inorganic compound which presents multivalent anions and is suitable for interacting with cationic polymers, such as chitosan. In another words, the ionic cross-linking of chitosan and TPP were created for improving the strength of chitosan beads.

Lin et al.[8] investigated the controlled release behavior of ibuprofen from chitosan (CS) polyelectrolyte complex hydrogel microspheres prepared by ionotropic crosslinking with sodium tripolyphosphate (TPP) and dextran sulfate (DS).The results demonstrated that CS/TPP/DS microspheres could successfully deliver a hydrophobic drug to the intestine without losing the drug in the stomach.

Moreover, chitosan crosslinked with glutaraldehyde has been proposed that it is useful to moderate the release of drug from chitosan microspheres. Ida et al.

suggested that chitosan crosslinked with glutaraldehyde can prolong the release of theophylline[9]. Gupta et al.[10] also reported the same result that chitosan microspheres with glutaraldehyde as a crosslinking agent showed significant improvement in releasing cenchroman in controlled manner.

Sodium diclofenac (DFNa, $C_{14}H_{10}Cl_2NO_2Na$) was selected as the model drug for this study to evaluate the potential of polyeclectrolyte complex hydrogel for the oral drug delivery system. DFNa is a non-steroidal anti-inflammatory drug (NSAID) which is widely used in the long-term treatment of 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[11,12] According to the short half-life and adverse effect, DFNa is an ideal candidate for controlled release preparation which aims to reduce the undesirable effects and decrease the frequency of drug administration.

From the literature, the hydrogel based on chitosan and tripolyphosphate in the form of beads should be an excellent delivery device for DFNa. To further reduce the drug release in the stomach and improve their sustained release profiles in the intestine, polyethylene glycol is added to form a polyelectrolyte complex hydrogel with chitosan. In addition, the effect of a co-crosslinking agent is investigated. In this work, glutaraldehyde is selected as a covalent co-crosslinking agent. Chitosan/PEG crosslinked with tripolyphosphate and glutaraldehyde beads should be a good alternative drug delivery system for controlling or sustaining release of the drug in gastric-intestine simulated conditions.

In this study, the chitosan/PEG/DFNa beads were investigated for various proportions of chitosan and polyethylene glycol, DFNa content, types and amount of crosslinking agents, and conditions of sodium tripolyphosphate for preparing

the drug delivery system in GI tract. The drug release behaviors from various formulations were evaluated by *in vitro* dissolution test.

1.1 The Objectives of This Research

The objective of this research is to develop and evaluate a new drug controlled release system consisting of chitosan/polyethylene glycol polyelectrolyte complex beads for sustaining release of diclofenac in the gastrointestinal tract.

1.2 Scope of the Investigation

The stepwise investigation was carried out as follows:

1) Review literatures for related research work.
2) Prepare the hydrogel beads by varying the proportions of chitosan/sodium diclofenac.
3) Evaluate the suitable condition of tripolyphosphate coagulant by varying the concentrations of tripolyphosphate and the pH value of the solutions.
4) Prepare the chitosan/polyethylene glycol beads in various proportions of chitosan/PEG/DFNa.
5) Prepare the crosslinked chitosan/polyethylene glycol beads with glutaraldehyde by varying the amount of the cross-linking.
6) Characterize the morphology of the beads using SEM, FT-IR, DSC and light microscope.
7) Study the swelling behavior of the beads in gastric-intestine simulated conditions by a microscope.
8) Study the release behavior of the beads in gastric-intestine simulated conditions by UV-Vis Spectroscopy.
9) Summarize the results.