CHAPTER I

INTRODUCTION

Dental diseases are recognized as one of the major and most common diseases afflicting mankind throughout the world. Sixty percent of the Thai population aged 35 and above are prone to this disease and some might not even realize it. Periodontitis, or periodontal disease, is caused by bacterial infection, which evades the gum line, thus weakening the gum and destroys the tissue that holds teeth in place. If left untreated, teeth will eventually fall off. Currently the treatments available for periodontitis are scaling and root planing (removing of the plaque), antibiotics, surgery and dentures. Local drug delivery systems that can provide an effective concentration of antibiotics at the periodontal site for the duration of the treatment with minimal side effects such as hypersensitivity, gastrointestinal intolerance and drug interaction with alcohol are more interested. However, because they are costly, they are not popular among patients and dentists unless in extremely severe cases.

Chitosan, a low cost biopolymer, is obtained by deacetylation of chitin, which is abundant polysaccharide next to cellulose. Chitin is the principle component of protective cuticles of crustaceans such as crabs, shrimps, prawns, lobsters and cell walls of some fungi such *as aspergillus* and *mucor*. Chitosan has low toxicity, biocompatible and biodegradable properties. Due to its unique polymeric cationic character, gel and film forming properties, chitosan has been extensively examined in the pharmaceutical industry for its potential use in the development of drug delivery systems. Up to now, drug delivery formulations based on chitosan were usually prepared by chemical-crosslink with glutaraldehyde (Filipović-Grčić et al.1996; Jameela et al., 1998). These formulations were exploited for sustained drug delivery due to the high density of the cross-linking agent. However, the chemical cross-linking agents possibly induce toxicity and other undesirable effects. To overcome this disadvantage, reversible physical cross-linking by electrostatic interactions was recently applied in the formulation preparation. Polyanions such as tripolyphosphate were used as components to prepare chitosan microspheres. For example, Kim et al. (2003) prepared chitosan microspheres loaded

with transforming growth factor-β1 to enhance chondrogenesis in traumatic injury patient.

Due to the damage of periodontal tissue resulting from the direct toxics of subgingival bacteria and the destructive effects of the host inflammatory response, a loss of attachment of periodontal ligament to the tooth root surface and the periodontal pocket is formed. The pocket depths ranging from 4-12 mm are generally observed at diseased sites. To deliver drug into the pocket, liquid dosage forms are easier than solid dosage forms. Liquid crystalline phases offer a number of useful properties which can be injected into the periodontal pocket where would transform into a stiffness gel upon contact with water or gingival crevicular fluid and resulting local drug delivery. Glyceryl monooleate or monoolein is a polar lipid which swells in water and gives rise to different kinds of liquid crystalline phases. The liquid crystalline phases formed by glyceryl monooleate have the potential of acting as an *in situ* forming drug delivery system. Moreover, glyceryl monooleate is also a biodegradable and nontoxic material (Ganem-Quitanar, Quintarnar-Guerrero and Buri, 2000). The use of liquid crystalline phases as drug delivery system has been widely investigated by many researchers such as Norling et al. (1992), Komwachara (1996) and Tan (2004), who added triglyceride into glyceryl monooleate to improve the flow characteristics of the formulations containing metronidazole, *Andrographis paniculata* and *Garcinia mangostana* extract, respectively.

Doxycycline hyclate was origninally used as a broad spectrum antibiotic that affect gram positive, gram negative bacteria including *Chlamydia*, *Ricketsiae*, *Mycoplasma* and some *Spirochetes* species. From the study of Lakhssassi et al. (2005), doxycycline showed highly effective activity against 50 periopathogens isolates from aggressive periodontitis patients. In addition, a further mechanism has been proposed to explain doxycycline efficacy in the treatment of periodontal disease. Doxycycline suppressed collagenase, the protease which degrades collagen in the periodontal tissues. Doxycycline also contributes to increasing collagen production, osteoblast activity and bone formation which confer benefit to patients with periodontitis (Preshaw et al., 2004).

To develop an effective alternative drug delivery system which is inexpensive non-toxic and biodegradable, the present study has been attempted to formulate prolong release of doxycycline hyclate loaded in chitosan microspheres which was resuspended in

glyceryl monooleate-based before injecting into periodontal pocket to promote bioadhesive and slow release the drug. Triglycrides such as sesame oil was also added into glyceryl monooleate-based to improved flow and liquid crystal formation characteristics.

The purposes of this study were as follows:

1. To develop and study physicochemical properties of the formulation of doxycycline hyclate loaded chitosan microspheres for controlled drug release.
2. To prepare and characterize the glyceryl monooleate-based drug delivery systems containing doxycycline hyclate loaded chitosan microspheres.
3. To studying *in vitro* antimicrobial activity of doxycycline hyclate loaded chitosan microspheres in glyceryl monooleate-based drug delivery systems.