CHAPTER 1
INTRODUCTION

Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability for ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage rapidly remove foreign substances, including drugs, from the surface of the eye. Moreover, the anatomy, physiology and barrier function of the cornea compromise the rapid absorption of drugs [1-6]. In addition, the relative impermeability of the cornea to both hydrophilic and hydrophobic molecules accounts for the poor ocular bioavailability and also systemic adverse effects.

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The goal of pharmacotherapeutics is to treat a disease in a consistent and predictable fashion. Whenever an ophthalmic drug is applied topically to eyes, only a small amount (<5%) actually penetrates the cornea and reaches the internal anterior tissues of them [5, 7-9]. Nasolacrimal drainage is the major factor for precorneal drug loss, which leads to poor ocular bioavailability [1, 10]. The amount of the drug that ultimately penetrates the cornea is often determined during the first 4-6 minute after topical dosing [11]. Frequent instillation of eye drops is necessary to maintain a therapeutic drug level in the tear film or at the site of action [12-14]. However, the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface. As a result, optimal absorption depends on achieving a satisfactory and rapid penetration rate across the cornea to minimize the competing, but non-absorptive, factor [11].

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Basic research concerning the physiochemical properties of the tears and cornea and their potential impact on ocular drug delivery was performed [15], and the knowledge gained from this is still being used in the development of new ophthalmic delivery systems. Various approaches have been attempted to increase the bioavailability, and the duration of the therapeutic action of ocular drugs can be divided into two categories [1, 11]. The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss (viscosity and penetration enhancers, prodrugs, colloids). Cationic dispersions can provide both advantages simultaneously by interacting with the negatively charged corneal surface components and the epithelium cellular membrane. In addition, their administration via conventional liquid dosage form is an attractive feature for patient acceptability and compliance.

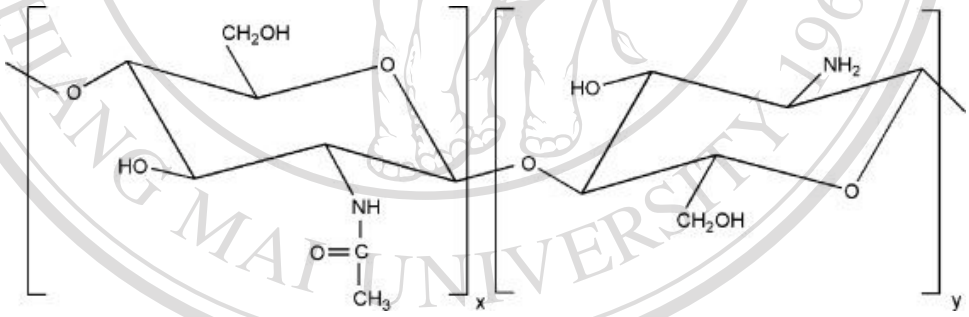

Figure 1.1 Chemical structure of chitosan [16].

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Alonso et al. and Lehr et al. [17, 18] suggested that cationic polymers were probably a superior mucoadhesive, due to their ability to develop molecular attraction forces by electrostatic interactions with the negative charges of the mucus and the polycationic chitosan (see Figure 1.1) was investigated as an ophthalmic vehicle. The polymer is biodegradable, biocompatible and non toxic. It possesses antimicrobial and wound-healing properties. Moreover, chitosan exhibits a pseudoplastic and viscoelastic behavior [17, 19-22]. The mucoadhesive properties of chitosan are determined by the formation of either secondary chemical bonds such as hydrogen

bonds or ionic interactions between the positive charged amino groups of chitosan and the negative charged sialic acid residued of mucins, depending on environmental pH. The mucoadhesive performance of chitosan is significantly high at neutral or slightly alkaline pH in keratitis [23], as in tear film [2]. The rationale for choosing chitosan as a viscosifying agent in artificial tear formulations has been based on its excellent tolerances after topical application, bioadhesive properties, hydrophilicity, and good spreading over the entire cornea [21]. The antibacterial activity of chitosan is an advantage, because in keratoconjuctivitis sicca, secondary infections due to diminished tear secretion, which contains antibacterial lysozyme and lactoferrin, are frequently observed. In rabbits, a radiolabeled chitosan formulation remained at the ocular surface as long as a 5 fold more viscous PVP solution [21]. A 3-fold increase of the precorneal residence time of tobramycin was achieved when adding chitosan to the formulations, compared to the commercial solution of the drug. Only a minimum influence was observed from the concentration and molecular weight of the chitosan employed, indicating a saturable bioadhesive mechanism based on ionic interactions of the cationic polymer with the negative charges of the ocular mucus [22]. Various chitosan derivatives were synthesized to not only improve the mucoadhesion, but also enhance the penetration of drugs and peptides through the mucosa by opening the tight junctions between epithelial cells or by intracellular routes [17]. Felt et al. [22] reported that co-administration of ofloxacin and chitosan in eye drops resulted in increased antibiotic bioavailability, and the time of efficacy in tear fluid compared to commercial eye drops affected the high viscosity of the chitosan solution. These results are relevant to the treatment of external ocular infections. The purpose of this study was to evaluate chitosan in ocular drug delivery for vancomycin.

Vancomycin, as shown in Figure 1.2, is an antibiotic produced by *Streptococcus orientalis* [24-26]. Vancomycin is a glycopeptide of 1,447 molecular weight [25], and it inhibits cell wall synthesis by binding firmly to the D-Ala-D-Ala terminus of the nascent peptidoglycan pentapeptide. This inhibits the transglycosylase, thus preventing further elongation of peptidoglycan and cross-linking. The peptidoglycan is thus weakened and the cell becomes susceptible to lysis. The cell membrane is also damaged, which contributes to antibacterial effect [27, 28].

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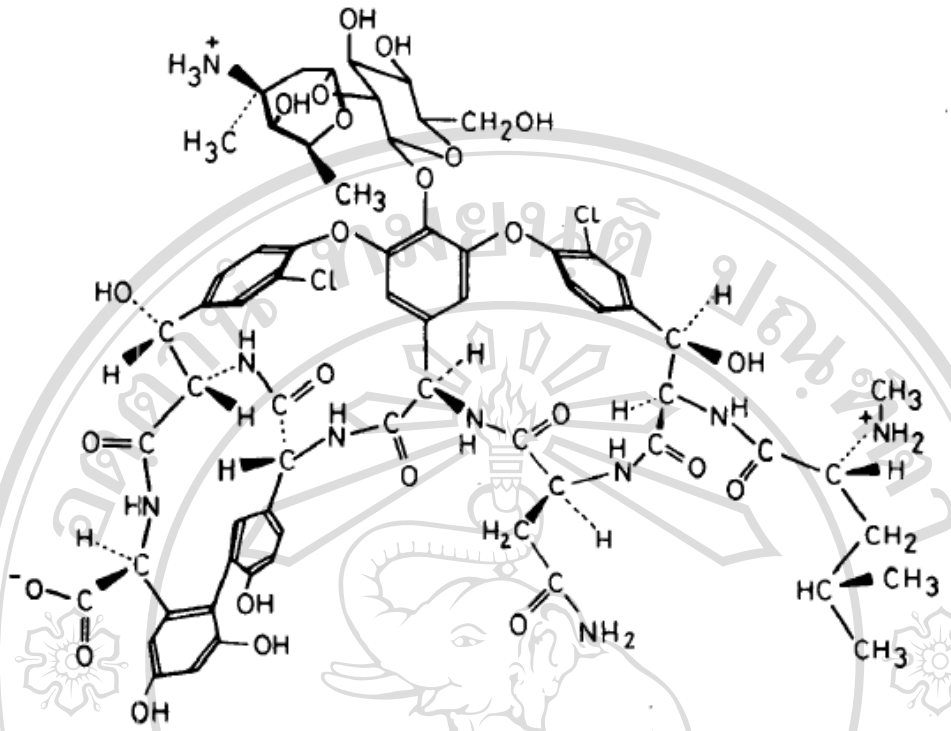

Figure 1.2 Chemical structure of vancomycin [29].

Vancomycin eye drops (25-50 mg/ml) are used for the treatment of certain eye infections [28, 30]. Ophthalmic infection by *Staphylococcus aureus* and *Staphylococcus epidermidis* causes conjunctivitis and blepharoconjuctivitis. Over time, these pathogens have become resistant to cephalosporin therapy. Furthermore, strains of methicillin-resistant *S. aureus* (MRSA) are infectious pathogens that have become prevalent in many hospitals and long term facilities. Conventional therapy for MRSA and methicillin-resistant *S. epidermidis* includes the use of vancomycin [31]. Fleischer et al. [30] successfully treated two patients with severe *Staphylococcus epidermidis* blepharoconjuctivitis using topical vancomycin solution (50 mg/ml) prepared with sterile water. However, this preparation also caused significant ocular irritation, probably because of its low pH and osmolality values. The seriousness of the condition and bacterial combinations implicate the need for strengthened eye drops containing a high concentration of antibiotics [32]. As these are not commercially available, they are dispersed by the pharmacist for treatment of eye infections caused by sensitive bacterial combinations after isolation. The vancomycin

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eye drops at 50 mg/ml were prepared by adding 10 ml of Tears Naturale II^{TM} to vancomycin at 500 mg injection [31, 33]. In this study, chitosan solution was used as a vehicle for vancomycin and the evaluation of chitosan in ocular drug delivery for vancomycin eye drops.

This study, used chitosan in ocular delivery for vancomycin, a polysaccharide that had not been tested for its vancomycin delivery. The rationale for choosing chitosan for ocular delivery of vancomycin was based on its excellent tolerance after topical application, bioadhesive properties, prolonged retention and good spreading over the entire cornea [17, 19].

This study be determined:

- Physicochemical characteristics of chitosan and chitosan solution stabilities.
- Evaluation of the use of chitosan in ocular drug delivery of vancomycin.
- Pharmacokinetics of topically applied vancomycin in the eyes of rabbits.

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