CHAPTER II
LITERATURE SURVEY

2.1 CM-chitin Based Material for Drug Delivery Studies

Tokura *et al.* (1992) synthesized the covalently drug –pendanted CM-chitin, in which process the drug was coupled through an enzyme-susceptible bond. In these conjugates, it is expected that the drug will be released through several hydrolysis processes, since the first step is oligomerization of CM-chitin by lysozymic hydrolysis and the release of the parent active drug is followed by the cleavage of spacer-drug linkage with proteolytic hydrolysis as a second step. The main factor to regulate the above hydrolysis is the stabilization of the drug under the physiological conditions that resist the enzymatic attack while the carrier maintained a high molecular weight.

Tokura *et al.* (1990) characterized the sustained release of methamphetamine by using CM-chitin as a drug carrier. After subcutaneous injection of methamphetamine-bound CM-chitin (MAEA-CM-chitin) into rabbits, The MAEA oligosaccharide was released slowly a fter the biodegradation of MAEA-CM-chitin and maintained at a significant level in serum for more than 120 h. As the blood level of MAEA was out of the range of detection within 7 h after the injection, probably owing to rapid metabolism, CM-chitin was revealed to be a suitable drug carrier for controlled release.

Tokura *et al.* (1994) studied biopolymer properties of a water-soluble and biodegradable chitin derivative, CM-chitin. These properties have been investigated to demonstrate the immunological function serving to induce a hapten-specific antibody and the chemotherapeutic function as a drug carrier of controlled release. When CM-chitin was linked by methamphetamine (MA) through a nonbiodegradable spacer, 1-aminobutane (MABA-CM-chitin), MA-specific antibody was produced by the subcutaneous injection of MABA-CM-chitin in combination with Freund's complete adjuvant. When injected without intense immunoadjuvant, MABA-CM-chitin oligomer was secreted into blood for more than 120 h. Two-step hydrolysis of

pendant-type of polymeric drug was also investigated in order to design a more sophisticated drug delivery system.

Nishimura *et al.* (1986) investigated the immunological and biological properties of CM-chitins to seek a fundamental understanding of the charge effect of these compounds, because negatively charged chitin derivatives induce a potent activation of the immune system, as does deacetylated chitin. The activation of mouse peritoneal macrophages by CM-chitin is indicated to depend highly not only on the amount of carboxymethyl groups introduced but also on the site of substitution on the GlcNAc residues in chitin.

Watanabe *et al.* (1992) synthesized the CM-chitin gel containing neocarzinostatin (NCS), a peptidic anticancer drug, in the presence of iron (III) chloride and in the co-presence of calcium chloride. CM-chitin gel containing NCS was digested by lysozyme digestion. The release of NCS from the gel was observed to increase in both a time-and concentration-dependent manner. Furthermore, they studied the potential of CM-chitin gel as a sustained-release dosage form. CM-chitin could prolong the plasma concentration of NCS after subcutaneous injection.

Hata *et al.* (2000) prepared the 30% deacetylated CM-chitin microspheres by complexation with iron (III) in a w/o emulsion system. Theprocedure by sonication for 60 min and subsequent addition of iron (III) enabled the production of the microspheres with a mean diameter of around 1.6 μm and with a narrow size distribution less than several μm. Furthermore, they characterized the microspheres as a drug carrier. The microspheres were preferentially located and retained for long in the liver and spleen after intraveneous injection, and urinary excretion was suppressed compared with polymer aqueous solution.

2.2 Polyvinyl Pyrrolidone Based Material for Drug Delivery Studies

Rao and Diwan (1996) prepared plasticized free films of cellulose acetate (CA) alone and in combination with different concentration of polyvinyl pyrrolidone (PVP) and studied the influence of PVP on the peameability of cellulose acetate (CA) films, used as rate controlling membranes for transdermal drug delivery. The tensile strength of the films was decreased slightly as the proportion of PVP in the

film is increased, but the percentage elongation changes are negligible over the proportion of PVP used. The water vapour transmission (WVT) increased with increase in the proportion of PVP at each relative humidity and decreased with increasing film thickness. The ratio of CA:PVP (2:1) was optimum for the preparation of free films for transdermal use to deliver the drug at controlled rate using a suitable drug reservoir.

Risbud *et al.* (2000) studied a pH sensitive air dried and freeze dried hydrogel of chitosan/polyvinyl pyrrolidone (PVP) based controlled drug release system for antibiotic delivery by using amoxicillin as a model drug. Freeze-dried hydrogels exhibited superior pH-dependent swelling properties over non-porous air-dried hydrogels. Therefore, the releasing of amoxicillin from freeze-dried hydrogels was higher than air-dried hydrogels. Freeze-dried hydrogels could serve as potent candidates for antibiotic delivery in an acidic environment.

2.3 Polyvinyl Pyrrolidone Based Blend Films

Sakurai *et al.* (2000) prepared chitosan which was blended with poly(*N*-vinyl pyrrolidone) (PVP) in acetic solution and this solution was cast to prepare the blend film. They studied the miscibility and the phase structure in the binary blend films by using DSC measurement and the wide-angle X-ray diffraction (WAXD) method. The glass transition temperature of the binary blend films decreased with increase of PVP content. This implies that the blend system of chitosan and PVP is able to form a miscible phase.

Cheryl Lau and Yongli Mi (2002) prepared and characterized polymer complex and blends of poly(acrylic acid) (PAA) and poly(vinyl pyrrolidone) (PVP). Both miscible blends and complex can be made due to the strong hydrogen bonding interaction between PAA and PVP which was supported by the significant chemical shifts in the FTIR and solid NMR spectra. As a result, more intimate association between the two polymers exists in the polymer complex than in the blends that was supported by the higher T_g and T_d of complex than those of the blends. The blends are soluble and the complex is insoluble. Such insoluble property might be used in the encapsulation applications that are processed in water solution.

2.4 PVA Based Material for Drug Delivery Studies

Kim et al. (1992) prepared the PVA/chitosan membrane and studied the permeation of riboflavin and insulin through this membrane. The results show that the permeation were dependent on both pH and glucose concentration. Riboflavin and insulin were presumed to permeate through the free water region in the swollen blend membrane. The greater permeation rate of solutes in acidic solution rather than in neutral solution was due to an increase in both water content and the amount of free water and freezing bound water.

Nakatasuka and Andrady (1992) studied the permeability and diffusion of vitamin B-12 in chitosan, crosslinked chitosan, and chitosan/PVA blend membrane by using 'lag time' technique. The diffusion coefficient of vitamin B-12 in the hydrogels depended on the degree of hydration of the membrane which was measured by swelling ratio. The degree of crosslinking and the presence of PVA in the blends affected the diffusion coefficient.On the other hand, the partition coefficient was unaffected by the crosslinking and blending with PVA. The results are shown to be consistence with the 'pore type' transport mechanism for vitamin B-12 in these chitosan membranes.

2.5 Chitosan Based Material for Drug Delivery Studies

Khoo et al. (2003) investigated chitosan blend with hydrophilic polymers including poly(vinyl alcohol) (PVA), poly(ethylene oxide) (PEO) and poly(vinyl pyrrolidone) (PVP) as candidates for oral gingival delivery system. The study indicated that PEO and PVP gave the most miscible blends with chitosan in all blend ratios studied; PVA was significantly less miscible. However, the film properties of phase-seperated chitosan/PVA blends appeared to be interesting and exploitable. The study also indicated that chitosan blends were superior in other properties compare to chitosan alone. Blends of chitosan with hydrophilic polymers could be promising condedater for formulation in oral mucosal delivery system.

Shiraishi et al. (1993) prepared chitosan gel beads containing indomethacin which used as an acidic model drug, by a polyelectrolyte complexation of sodium

tripolyphosphate and chitosan. It was found that the release rate of indometha cin decreased with increasing of molecular weight and drug content. The release of indomethacin depended upon the dispersion of the indomethacin solid particle in the beads, as well as the porosity, tortuosity and surface area of the matrix. In addition, the plasma concentrations of indemrthacin after oral administration of chitosan gel beads to beagle dogs exhibited the sustained-release pattern.

Gupta et al. (2000a) investigated the in vitro release kinetics of diclofenac sodium (DFS) from chitosan beads and microgranules. It was found that the release rate of DFS from chitosan beads was slower that of chitosan microgranules. The total amount of DFS released was found to be more from the highly loaded beads in comparison to the beads loaded with low concentrations. However, the percentage of drug released has decreased with increasing DFS concentration.The percent and amount of the drug release were much higher in acidic solution than in basic solution, probably dur to the swelling properties of the matrix at acidic pH.

Thacharodi et al. (1996) studied membrane permeation-controlled transdermal delivery devices for controlled delivery of nifedipine by using collagen and chitosan membranes as rate-controlling membrane. It was found that drug release depended on the type of membrane used to control the drug delivery, suggesting that drug delivery is efficiently controlled by the rate-controlling membranes