CHAPTER I
INTRODUCTION

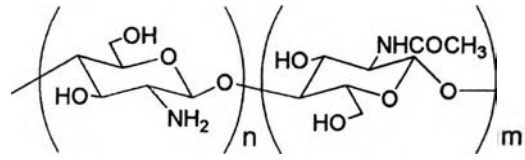
Amphiphilic copolymers consisting of hydrophilic and hydrophobic segments form micelles with the hydrophobic inner core and hydrophilic outer shell vice versa in media. These polymers can be used for a wide range of applications, such as drug carriers, matrices in tissue engineering, and stabilizers for food and drugs.

The present work focuses on polymeric micelles in form of nanoparticles/ nanospheres for drug delivery applications. Nanoparticles give colloidal phenomena, possessing diameters ranging between 1 and 1000 nm. One of the ultimate goal applications is that the nano-size range of this delivery system allows the possibility of circulation in blood without the risk of blocking blood vessels. In addition, the opsonization including its subsequent recognition and the phagocytosis by macrophages is strongly correlated with the size of the particle. Moreover, the charge on sphere surface is also important to be considered as a drug targeting. In order to achieve active targeting, specific ligands must be attached to nanoparticles surface to enable molecular recognition (Gu *et al.*, 2007). The internalization of drug-loaded nanoparticles is beneficial for more efficient drug therapy since the drug can be delivered directly to the target cells.

Various types of polymeric nanoparticles were studied such as poly-ϵ-carpolactone (PCL) (Chawla *et al.*, 2002), polylactide (PLA) (Riley *et al.*, 2003), poly (lactide-co-glycolide) (PLGA) (Csaba *et al.*, 2005), and poly (γ-glutamic acid) (γ-PGA) (Matsusaki *et al.*, 2004) due to their biocompatibility, biodegradability, and ability to prolong drug release behavior.

Chitosan, poly-(1→4)-2-amino-2-deoxy-β-D-glucose, is a deacetylated form of chitin.

Scheme 1.1 Chemical structure of chitin-chitosan



Chitin-chitosan has unique properties such as biocompatibility (Hirano *et al.*, 1988), biodegradability (Värum *et al,* 1997), bioactivity (Dumitriu *et al.*, 1989), and non-toxicity (Sugano *et al.*, 1978). Moreover, the carbon atom at the 2nd and the 6th positions has reactive alcohol group and amino group, respectively. These groups assign the advantages to chitosan to be possibly modified with other functional groups. The high electron density at amino group enables chitosan to entrap metal ions; as a result, chitosan can be used for waste water treatment. Unique properties of chitosan attract attention to use in biomedical field. However, chitosan has limitation to dissolve in any solvents except acid solution. Accordingly, most of the application of chitosan is based on acid solution and fabricate to fibers (Hirano *et al.*, 1999), gels (Hirano *et al.*, 1975), films (Chatelet *et al.*, 2001), beads/spheres (Aydin *et al.*, 1996), etc. by neutralizing the protonated amino groups. Basic chemical modification such as; crosslinking with epichlorohydrin (Wei *et al.*, 1992), diisocyanate (Welsh *et al.*, 2003) or 1,4-butanedioi diglycidyl ether.(Roy *et al.*, 1998) to form gel is also the way to develop chitosan novel material. However, the safety reasons limit the uses of chitosan in acid solvent and some toxic crosslinking agent when we consider the biomaterials.

To overcome the limitation of chitosan, structural modifications at molecular level as follows are considered; (i) reducing chitosan molecular weight to oligomer such as enzymatic hydrolysis (Aiba *et al.*, 1994), and photoirradiation (Andrady *et al.,* 1996) to enhance the solubility, and (ii) functionalizing chitosan with hydrophobic or hydrophilic group to interrupt inter- and intra-molecular hydrogen bond to enhance the solubility in aqueous and/or organic solvent (Nishimura *et al.*, (1991)).

In the past Yoksan *et al.* succeeded in preparing amphiphilic chitosan nanospheres. At that time, it is well-understood that chitosan flakes in micrometer or

millimeter scale can be changed to nanometer particle scale by simply introducing hydrophobic N-phthaloyl group and hydrophilic mPEG group. This simply process initiates the suspect mechanism that chitosan forms self-assembly based on the differences in hydrophobicity/hydrophilicity. The core-corona structure (Akashi *et al.*, 1999) found in the case of polystyrene system is also a good related example to explain how and why the nanoparticle chitosan is formed.

Although those successful researches bring us to develop chitosan nanoparticle and to further study on the applications for drug delivery system, the understanding of the factors related to the control of nanospheres including the drug incorporation models and the toxicity of nanospheres has to be understood in details before we can reach the ultimate goal of applications. The present dissertation, thus, focuses on the clarification of the efficiency of the hydrophobic group and/or hydrophilic group conjugation, including the quantitative analysis to study how we can control the nanosphere formation. The work extends to study how the nanosphere formation is accomplished in the details of the surface charges, the sizes and shapes related to the colloidal phenomena. The work also covers the studies on nanospheres toxicity, model drug incorporation, and release performances.

The well-understanding of this amphiphilic chitosan nanosphere performance will not only ensure us to qualitatively and quantitatively prepare the nanospheres but also a guideline for further studies on the applications of chitosan nanospheres for drug delivery system.