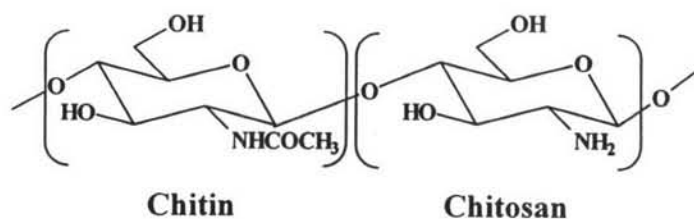


CHAPTER I

INTRODUCTION

Chitin-chitosan is the second-most abundant naturally-occurring polysaccharide, next to cellulose, presenting as a high molecular weight copolymer of β (1-4)-2-acetamido-2-deoxy- β -D-glucose and β (1-4)-2-amino-deoxy- β -D-glucose (Scheme 1), obtained from crustaceans, insects and fungi. The unique amino polysaccharide properties of chitin-chitosan, such as biodegradability (Deshpande, 1986 and Tomihata and Ikada, 1997), biocompatibility (Chung *et al.*, 1994 and Richardson *et al.*, 1999), non-toxicity (Chandy and Sharma, 1992 and Rao and Sharma, 1997), antibacterial and antimicrobial activities (Kendra and Hadwiger, 1984 and Sudarshan *et al.*, 1992), and metal adsorption ability (Peniche-covas *et al.*, 1987 and Varma *et al.*, 2004), have initiated numerous studies aiming to develop it for value-added products. It is known that chitosan is a derivative of chitin obtained from deacetylation. Compared to chitin, chitosan has received much more attention for chemists as it has not only hydroxyl but also amino groups for functionalization. In the past, most practical applications of chitosan dealt with the direct materializations from flakes to fibers (Tokura *et al.*, 1980), films (Kanke *et al.*, 1989), and beads (Bodmeier *et al.*, 1989). In recent years, the novel development for advanced applications, such as scaffolds for tissue engineering (Matsuda and Magoshi, 2002), nanoparticles for drug carrier (van der Merwe *et al.*, 2004), drug targeting (Kopeček *et al.* 2001), vaccines (Borges *et al.*, 2005), genes (Leong *et al.*, 1998) delivery system, etc., has been attempted.

Scheme 1



It is important to note that in modifying chitosan for those advanced applications, effective chemical reactions have to be considered. Although the derivatization of chitosan by conjugating with other functional molecules, either with small organic molecules or macromolecules, the fact that chitosan is inert and stabilized by inter- and intra-molecular hydrogen bonding brings the difficulty in developing chitosan to practical products. Most reactions of chitosan have to be done in a heterogeneous system or in some specific acid solutions, and this limits the substitution degree and/or the variety of the reactions. At present, various derivatives to achieve chitosan which is soluble either in organic or water solvents (so-called "organo-soluble chitosan" or "water-soluble chitosan") have been accepted as an effective pathway to functionalize and create the material, especially when one considers the chemistry at the molecular level.

Theoretically, the organo-soluble chitosan derivatives are obtained as soon as the hydrogen-bonded network is obstructed by conjugating bulky groups onto the chain, especially at the amino group. For example, Nishimura *et al.* (1991) proposed the phthaloylation of chitosan to derive an organo-soluble species which dissolves in organic solvents, such as DMF, DMSO, DMAc, and pyridine. As a consequence, the chemical reactions in the next step can be done in a homogeneous system whereas the deprotection of phthalimido group can be carried out at the final step.

As chitosan is a polysaccharide chain of which each sugar unit is polar, it can be expected that by simply lowering its molecular weight, the low molecular weight or the oligomers obtained show water solubility. Approaches to the depolymerization of chitosan by acid or base hydrolysis (Allan and Peyron, 1995), enzymatic degradation (Aiba, 1994), and photoirradiation (Andrady *et al.*, 1996) are reported. For acid or base hydrolysis case, it is an easy process low cost performance, but chemical waste and reproducibility are the main problems. Enzymatic hydrolysis is an effective way to achieve specific cleavage to obtain oligochitosan. However, it requires multi-steps, especially enzyme preparation and purification. Photoirradiation is an easy process with a large-scale production in a single step without waste generation and no purification required, but it consumes in the operating cost. It should be noted that at present the enzymatic degradation is the only approach to obtain the water-soluble one.

Chemical modification with hydrophilic groups is an alternative pathway to obtain water-soluble chitosans. Up to now, various studies and the derivatives, such as PEG-grafting (Sugimoto *et al.*, 1998), sulfonation (Holme and Perlin, 1997), quaternarization (Jia *et al.*, 2001), *N*- and *O*-hydroxylation (Machida *et al.*, 1986), and *N*- and *O*-carboxymethylation chitosan (CM-chitosan) (Krause *et al.*, 1998) were proposed.

The present dissertation focuses on the development of the 'organo-soluble chitosan' and 'water-soluble chitosan', including the uses of their homogeneous systems for effective functionalization and materialization. For organo-soluble chitosan, the present work proposes a novel gel from epoxy-chitosan obtained from *N*-phthaloylchitosan, an organo-soluble derivative. The work demonstrates the molecular design to functionalize the derivative with an epoxy group and crosslink via the epoxy ring opening reaction. The work also covers the mineralization of hydroxyapatite to show the possibility of the gel for uses in bone repairing such as bone glue, paste, or bone tissue. For water-soluble chitosan, the present work for the first time shows simple chitosan organic complexes between chitosan and conjugating additives such as 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *N*-hydroxysuccinimide (HOSu). The complexes are not only providing the water solubility to chitosan but are also promoting the conjugation in the water-based system. The present work demonstrates an example of conjugating using 1-ethyl-3-(3-dimethylaminopropyl-carbodiimide) (EDC), a water-soluble conjugating agent, to functionalize chitosan with amino acid and ethylene glycol. The compounds obtained will be a good model to develop materials for drug, vaccine, or gene delivery, including drug targeting. The work also extends to the preparation of a water-based gel from the functionalization of water-soluble chitosan with poly(ethylene glycol).