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Trimethylated Chitosan-based Nanoparticles: Their Syntheses and Role as DNA/RNA Delivery Carriers

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Abstract

Quaternized chitosan, a quaternary ammonium derivative of chitosan, has receiving much interests in the recent decade, due to the improved water solubility in a wider pH range, compared to a native chitosan itself. Thus, with some inherent advantages (biocompatibility, biodegradability, and mucoadhesive ability) and the additional properties (e.g. water solubility in a wider pH condition, enhanced transfection efficiency, and better antimicrobial activity), quaternized chitosan has emerged to solve the limited applications for native chitosan. Meanwhile, quaternized chitosan in the form of nanoparticles are also extensively used for diverse applications, especially biomedical application, because of their small size and large specific surface area. So, research woks in the field of syntheses and applications of the quternized chitosan particles are of interest and challenging. In the literature, there are some synthetic methods to prepare such particles: 1) ionic gelation of chitosan with anionic gelators (e.g tripolyphosphate or protein) and followed by quternization of the remaining $–NH_2$ or –OH on the chitosan structure 2) ionic gelation of quaternized chitosan with anionic gelator, and 3) self-assembly of amphiphilic quaternized chitosan.

Herein, we would like to introduce alternative routes to quaternized chitosan particles through an emulsifier-free emulsion polymerization. Trimethylated chitosan (TMC), a quaternized chitosan prepared via methylation of chitosan, is used as a starting materials. TMC itself has different types of amino groups on it structure, including 1^o, 2^o, 3^o, amines and quaternary ammonium group. The emulsifier-free emulsion polymerization makes use of some of those amines with different activators to generate free-radicals capable of initiate a polymerization of vinyl monomers, resulting in colloidally stable TMC particles without the addition of surfactants. Some of synthetic routes illustrated here consist of 1) thermally activated 1^o amine/t-butyl hydroeroxide system 2) photo-induced 3^o amine/camphorquinone system, and 3) photo-induced 3^o amine/riboflavin system. The effects of important polymerization parameters are emphasized, as well as key characteristics (e.g. chemical, physical, biological properties) of the resulting particles are illustrated.

Since these particles possess cationic nature, their ability as DNA/RNA delivery carriers is also presented. TMC-based nanoparticles were developed to use as a carriers of gene in delivery systems. Not only the high transfection efficiency, but also the controlled release of the DNA/RNA into cells are expected. Moreover, several studies have shown that TMC particles exert adjuvant-like effects on dendritic cells and can be used as potent adjuvants and delivery systems capable of inducing mucosal immunity. Therefore, 2 examples as potential DNA/RNA delivery application of TMC particles are also presented. The first one is the vaccine development from TMC particles prepared by TMC/tripolyphosphate ionic gelation as an adjuvant and carriers for HA2 and NP proteins of influenza virus. The *in vitro* study of these influenza particles against primary human intranasal epithelium cells (HNEpCs) and human monocyte-derived dendritic cells (MoDCs) is conducted. The second investigation is the *in vitro* transfection study of TMC/PHEMA particles prepared by an emulsifier-free emulsion polymerization in shrimp *(Litopenaeus vannamei).*

Keywords: Quaternized Chitosan; Trimethylated chitosan; Gene Delivery; Vaccine; Adjuvant.