Quantum dots for tumor-targeted drug delivery and cell imaging

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'The drug-loaded chitosan-encapsulated ZnO:Mn²⁺ quantum dots represent a potential platform to deliver tumor-targeted drugs and document the delivery process simultaneously.'

Early detection of cancer and targeted drug delivery, specifically in and around tumors and at concentrations that would decrease the growth rate and/or viability of the tumors, continues to be the primary challenge in the treatment of cancer. In many cases, the malignancy of tumors is detected only at advanced stages when chemotherapeutic drugs become increasingly toxic to healthy cells. To reduce this problem, targeted drug delivery and early detection of cancer cells continue to be investigated extensively. A tumor-targeting drug delivery system generally consists of a tumor-recognition moiety and a drug-loaded vesicle. Detection systems often involve invasive methods, such as tissue biopsy and sophisticated diagnostics tools, such as magnetic resonance imaging. However, there is no known single system currently that is capable of targeting drug delivery and imaging the delivery process simultaneously to monitor the time course of subcellular location. Integration of biomaterials and semiconductor nanocrystal quantum dots (QDs) fields has good potential for addressing the current problems faced in cancer therapy by using biodegradable chitosan (*N*-acetylglucosamine) for tumor-targeted drug delivery and QDs for noninvasive imaging. The drug-loaded chitosan-encapsulated ZnO:Mn²⁺ QDs represent a potential platform to deliver tumor-targeted drugs and document the delivery process simultaneously [Hein S, Pers. Comm.].

Doping enables us to tune into desired fluorescence emission. The doping of ZnO with low concentration of manganese is expected to increase the band-gap energy of ZnO with a

consequent increase in luminescence. Considering that the high-molecular-weight chitosan of approximately 200 kDa can increase the size of QDs, the use of low-molecular-weight chitosan of approximately 50 kDa is preferred. Furthermore, to increase the efficiency of QD solubilization in aqueous medium, fully deacetylated chitosan prepared by thermochemical deacetylation is favored [Hein S, Pers. Comm.] [1]. Subsequently, the low-molecular-weight, fully deacetylated chitosan can be conjugated with folic acid for *in situ* encapsulation of water-dispersible ZnO:Mn²⁺ QDs. A possible flow chart for the synthesis of Mn-doped ZnO QDs is presented in Figure 1, based on some practices reported in the literature [2,3].

The role of diethanolamine (DEA) in Figure 1 includes: preventing aggregation of QDs; coordinating with unsaturated metal atoms on the QD surface to prevent the formation of bulk semiconductors by coordination of N in DEA with the unsaturated metal ions [2-4]; and providing hydroxide (OH⁻) ions for the synthesis and stability of QDs [2]. The surfactant, oleic acid (OA), is believed to have carboxyl groups that react with the hydroxyl group of DEA and forms a complex on the surface of QDs, resulting in high stability in the aqueous medium [2,3]. Retention of coordinating organic ligands is necessary for maintaining the optical properties of QDs and for shielding the QDs from the environment. The presence of chemically bonded OA groups on the surface is expected to provide stability to the QDs in the aqueous medium. Furthermore, the hydroxyl group (OH⁻) of the DEA molecules will contribute additionally to the stability of nanocrystal QDs in the aqueous environment [2].

Given that a high-molecular-weight chitosan can increase the size of QDs, use of a low-molecular-weight chitosan of approximately 50 kDa is preferred [Hein S, Pers. Comm.]. Furthermore, to increase the efficiency of QD solubilization in aqueous medium, fully deacetylated chitosan is favored. Chitosan is a linear polysaccharide copolymer of D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). The degree of deacetylation (%DD) determines

Figure 1. Flow chart for the synthesis of water-dispersible Mn-doped ZnO quantum dots.

the content of free amino groups in the polysaccharides and is the key chemical characteristic that dictates the physicochemical and biological properties, including sorption property and metal chelation, change of solubility in dilute acid, biocompatibility and biodegradability. %DD affects the crystallinity and hydrophilicity of chitosan owing to variations in hydrophilic interactions that ultimately control the ligand attachment, drug loading and release characteristics of chitosan [5–7]. In general, the process of deacetylation involves the removal of an acetyl group (NHCOCH_3) from the molecular chain and this obtains a complete and chemically reactive amino group ($-\text{NH}_2$). The functionality and properties of chitosan essentially depend on the chemical-reactive amino group.

Considering that, the preferred approach is to encapsulate ZnO:Mn^{2+} QDs with folate-conjugated chitosan. This involves synthesis of the folate-chitosan conjugation, followed by encapsulation of ZnO:Mn^{2+} QDs with folate-conjugated chitosan to get folate-chitosan- ZnO:Mn^{2+}

QD nanoparticles (Figure 2). The nature of a cationic polyelectrolyte that has one amino group and two hydroxyl groups of chitosan provides a strong electrostatic interaction with negative-charged biomolecules and QDs [8]. The folic acid binding covalently to chitosan maintains the nanoparticle size, while keeping a positive-charge ratio of more than +2. Thus, the low-molecular-weight (50 kDa) and fully deacetylated chitosan can be conjugated with folic acid. Because folic acid is difficult to conjugate to the surface of the polymer, owing to the low reactivity of the carboxylic acid group, the carboxyl group of folic acid is first activated.

It is expected that the drug-loaded, biofunctionalized chitosan-encapsulated QDs will enhance the cellular apoptosis of tumor cells [1]. Recently, it was observed that chitosan exhibits good proliferation of transfected cells [Thein-Han WW, Misra RDK, Unpublished Data]. Moreover, by using drug-loaded, biofunctionalized chitosan-encapsulated QDs, the time taken for tumor cells to go into an apoptotic state can also be monitored by

Figure 2. Representation of the encapsulation of ZnO:Mn²⁺ quantum dots with folate-conjugated chitosan (2) and the drug-loading step (3) in which biofunctionalized chitosan loaded with drug is used to coat quantum dots.

confocal laser-scanning microscope. This information will determine the dosage necessary for targeted drug delivery [Hein S, Pers. Comm.].

Acknowledgements

Some of the viewpoints expressed here are an outcome of scientific interaction and communication with San Hein and those expressed in the open literature. Thus, they are not necessarily solely of the author. Any omission of references is unintentional.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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