Int.J.HIT.TRANSC:ECCN.Vol.8: Issue 1A (2022) Page 26-30 ISSN: 0973-6875

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ORIGINAL CONTRIBUTION

Fundamentals of Nano-scale Materials and Multifunctional Properties: Review towards Biomedical Applications

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ABSTRACT

Rare Earth Doped ZnO based nano-structured proper-shaped, defect-free bio-compatible Semiconducting Quantum Dots with high photoluminescence and quantum efficiency have great impact in modern Bio-medical applications. Doped ZnO nano-structure with proper wt% of Li, Na, N, P, Ne, or Bi shows red luminescence with high intensity. **Y_2O_3: Eu, $SrTiO_3$: Pr, or $ZnGa_2O_4$: Eu** are the promising oxide based red luminescent phosphors. Polymer-coated Fe_2O_3 with CdSe-ZnS surrounding layer QD cores shell structure acts as hybrid magnetic–luminescent QD complexes and can be coupled with antibodies via surface functionalization. Surface charged water-soluble colloidal are prepared by proper surface modification by surfactants and wet chemical etching. Fluorescent property of magnetically coupled QD can be very much effective to capture breast cancer cells through bio-conjugation.

KEYWORDS: Quantum Dot synthesis, Surface functionalization, Core-Shell Structure, Bioconjugation

1. INTRODUCTION

Surface modification by surfactants and sol-gel coatings, such as, SiO_2, TiO_2, or SiO_2-TiO_2 are carried out to obtain surface charged water-soluble colloidal for bio-conjugation. Influences of these coatings on particle growth, particle surface morphology, luminescence properties and magnetic properties play major role in bio-imaging, bio-lebelling for early cancer detection and treatment via Infrared spectroscopic methods on bioconjugated QDs for tumor diagnosis, early cancer detection on cell/animal models. The detail study on the interaction mechanism of the nanocrystals with some bio-molecules are very much essential.

In global perspective, the cancer treatment is one of the challenging issues for scientist and doctors. For early cancer detection using inorganic quantum dots will be scientifically and technically effective.

Nano-structured quantum dot phosphors are generally highly photo-luminescent and successfully developed highly efficient green, blue, red, orange phosphor by suitable doping. QDs with high photo-luminescence properties are very much effective for photo-dynamic therapy, bio-imaging for tumor cell and early cancer detection by photo-dynamic therapy.

Many cancer cell's outer surface is covered with a protein layer, and this is known as Epidermal Growth Factor Receptor (EGFR), while normal healthy cells typically do not contain such type of protein as strongly. QD nano-phosphors can stick with the cancer cell (EGFR) via bio-conjugate or proper binding through specific bio-linker and make them

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shine under irradiation. Bio-conjugation of semiconductor QD phosphor with suitably anti-EGFR, can make cancer cells detection and treatment easier to the researchers.Inorganic quantum dots (Qdots) which act as fluorescent probes can replace traditional organic fluorescent probes due to high brightness and more photo-stability. Fluorescent nanoparticle probes are very much effective for sensitive cancer cell imaging with greater success in the cellular level. Very recently cancer cell imaging in an in vivo setup has been recently realized. Fluorescent nanoparticle probes development faces several challenges for in vivo cancer imaging applications. Semiconductor Qdots have been extensively used for targeting cancer cells. Qdots in the size range between 2 and 20 nm have broad absorption band with narrow and symmetric emission band (full-width at half-maximum ∼25·40 nm). Qdots generally emit photon in the visible to NIR spectral range. Qdot emission occurs through radiative recombination of an exciton (an excited electron-hole pair with long lifetime (>10 ns)) in a narrow and symmetric energy band.

2. BACKGROUND INFORMATION

Semiconductor quantum dots (QDs) especially in colloidal QD family such as ZnO, ZnS, CdS, CdSe, CdTe have numerous applications in optoelectronics [1], sensing [2] and biological labeling [3] etc. Due to the unique characteristics like low cost, and low toxicity, different synthesis routes makes such colloidal QDs very much attractive in versatile application field [4–6]. Based on such studies opto-electronic properties of ZnO QDs are reported elsewhere [7], and its physibility has been investigated through different optoelectronic devices [8]. Rare-earth doped ZnO QDs may be used as efficient phosphors reported elsewhere [9, 10]. Sol–gel synthesized ZnO QDs embedded into SiO_2:Eu^{3+} powder was studied by Band et al [9, 10] and a significantly enhanced luminescence of Eu^{3+} was observed. The enhanced luminescence is due to energy transfer from the QDs encapsulated in SiO_2 to homogeneously located Eu^{3+} within SiO_2 glass matrix [4]. Significant work on the synthesis of Sr based Eu doped green phosphor for white LED fabrication is done on Rensselaer Polytechnique Institute by solid phase reaction technique.

In the past decade, ZnO, CdS, CdSe, CdTe quantum QDs were synthesized with various wet chemical methods [11, 12, 13, 14, 15]. Comparative studies on third-order nonlinear susceptibility of ZnO nanoparticles with that of bulk ZnO has been reported by Guo et al. [16] and it is almost 500 times larger than that of Bulk ZnO. The fact “optical transitions in artificial atoms that consist of one to ten electrons occupying the conduction levels in ZnO nanocrystals” is reported by Vanmaekelbergh and his co-workers [17]. More and more fundamental understanding regarding opto-electronic transition mechanism in inorganic QDs and nanoparticles need to be explored for both a fundamental science and a proposed bio-photonic application point of view.

Quantum dot core shell structure like CdSe/ZnS, CdSe/Cds, CdTe/CdS etc. growth are very much essential to achieve hydrophilic, non-toxic, water-soluble and bio-compatibility and can be used for bio-labeling via surface modification with amino or carboxyl surface groups. Wet chemical synthesis of ZnO, CdS, CdSe, CdTe QDs is very much effective to control the particle-size and shape, to prepare defect-free crystals with excellent quantum efficiency and luminescent properties. Due to size-dependent quantum confinement effects, colloidal QDs have unique photo-luminescence (PL) properties [18] and very much effective to to detect bio-molecules in human body after bio-conjugation of QDs.

3. CORE-SHELL STRUCTURE/ SURFACE MODIFICATION:

For bio-conjugation of semiconductor quantum dots suitable techniques are essential for making core-shell structure say for example

ZnO-ZnS, SrGaSe:(Eu, Ce, Y) - SrS. To neutralize the toxic nature of QDs, suitable surface modification techniques by SiO_2 or TiO_2 thin films are generally developed.

4. EVALUATION OF CELLULAR RESPONSES AGAINST NEWLY SYNTHESIZED QDS:

A cadmium selenide (CdSe) overcoated with zinc sulphide (ZnS) core-shell structure is very good example of inorganic semiconductor quantum dot (QDs) and satisfy the strong quantum confinement of their excitons in all 3- dimensions giving rise to characteristic fluorescent properties. QDs show extreme stability against photo-degradation, high-brightness and high extinction coefficients alongwith their broad absorption as well as narrow and spectrally tunable emission profiles. HeLa cells and HeLa-S cells are generally used *in vitro* studies for targeting the biological responses through toxicity testing in the environment of high-throughput systems for rapid and cost-effective screening of hazards (under highly controlled conditions). The central themes in such testing is to study the evaluation of five categories of cellular response, that includes (i) reactive oxygen species (ROS) production and accumulation,

(ii) cell viability,

(iii) cell stress,

(iv) cell morphology, and

(v) cell particle uptake.

Two cell lines HeLa cells and HeLa-S cells, are originally same and they can be grown either way depending upon application whenever needed.

5. EFFECT OF QDS SUPPLEMENT ON ROS ACCUMULATION AND OXIDATIVE STRESS:

Reactive Oxygen Species formation during QDs based cell cultures is generally evaluated using three different probes:

(i) 3,3'-diaminobenzidine (DAB),

(ii) Nitroblue tetrazolium (NBT) responsible to hydrogen peroxide (H_2O_2) and superoxide anion respectively,

(iii) 2',7'- Dichlorodihy drofluoresce in diacetate (H_2DCFDA) is used as nonspecific probe for ROS accumulation.

All assays are conventionally carried out in 6 well plates to reduce the experimental volume by standard and randomized approach. For each experiment two controls set-up need to be prepared (i) a negative control, where cells will be placed without the addition of QDs and maintain same conditions as the assay and (ii) a positive control, where cells will be heated at 45°C during 20 minutes. Details of Cell culture and cellular response in different steps are discussed below.

a) H_2O_2 detection: 3,3'-diaminobenzidine (DAB) staining technique are generally applied to examine the production of H_2O_2 at the cellular level (described by Thordal-Christensen et al., with few modifications). Brown polymerized product are formed by rapid reactions of DAB with H_2O_2 in the presence of peroxidase. After 1 and half hour samples are further examined using an inverted microscope.

b) O_{2^-} detection: The detection of O_2 ions are carried out as described by Fryer et al. with slight modifications, and similarly to the DAB assay. Nitro-substituted aromatics such as nitroblue tetrazolium can be reduced by O_{2^-} to the monoformazan (NBT+), with the accumulation of dark spots of blue formazan.

c) Cellular oxidative stress assay: 2',7'- Dichlorodihydrofluorescein diacetate (H_2DCFDA) are generally used to determine cellular oxidative stress as described by Ortega-Villasante et al. using the same procedure as for the previous assay, but adding 5 μM of H2DCFDA instead of NBT. After 1and half hour samples are to be visualized using an inverted microscope (l_{ex} = 488 and l_{em} = 525 nm). H_2DCFDA diffuses passively

through the cellular membrane and then is enzymatically hydrolysed by intracellular esterases to 2',7'-dichlorodihydrofluorescein (DCFH). This nonfluorescent product is converted by ROS into DCF (2',7'-dichlorofluorescein), which can easily be visualized by a strong fluorescence around 525 nm when excited at 488 nm. The NBT and H_2DCFDA assays can be repeated for longer periods of exposure of cell suspension cultures to the QDs.

d) Oxidative stress dose response assay: Following steps are strictly followed:

(i) Cells are placed in 6 well plates. Aliquots of QDs with different concentrations are added to each well. All plates are placed on orbital shaker at 110 rpm at 24°C in absence of light.

(ii) Each Incubation continues for 48 hours, all treatments including to the negative and positive (cells heat treated 45°C for 20 minutes) controls are followed in presence of an aliquot of H_2DCFDA to obtain a final concentration of 5 μM.

(iii) Inverted microscope is used to visualize the by-product after 1 hour, and the fluorescence will be quantified in terms of average pixel intensity, Images will be acquired 1 hour after the H_2DCFDA addition, always with the same settings and exposure time.

6. CONCLUSIONS

Quantum dots are generally synthesized by Sol gel and Solid phase reaction techniques. The synthesis condition to develop bio-functionalized size tunable, water soluble, biocompatible quantum dots (QDs) with high (blue-green-yellow-red) photoluminescence, high lifetime, high quantum efficiency, and paramagnetic property should be optimized. The specific technique to make core-shell structure/capping with suitable amine or lipid or OH- and attached with some bio-molecules (protein or DNA) i.e bio-conjugation technique has great impact for novel applications like bio-imaging, drug delivery etc. Finally, the toxicity study of these novel QDs play significant role for further biological application such as cancer detection.

ACKNOLEDGEMENT: The one of the authors would like to acknowledge **CSIR-Govt. of India to provide financial support for pursuing diverse study** to establish the R&D infrastructure in versatile field in Haldia Institute of Technology.

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