Development of Water Soluble, White Light Generating Highly Biocompatible Lanthanide Oxide Nanoparticles for Applications in Health Care

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BY

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Chapter 6

6. Conclusion and Future Scope

6.1 Conclusions

In a nutshell, we have developed a facile approach for synthesizing Gd_2O_3 nanoclusters (NCs), which can provide a nanoclusters size regime in the range of 1–3 nm with a narrow size distribution. Gd_2O_3 NCs' size range lies within the optimal size range needed for maximal contrast enhancement in MR imaging. Furthermore, it has been demonstrated that the Gd_2O_3 NCs' size and luminescence intensity can be tuned simply by varying the amount of stabilizing agent (BSA and Chitosan) employed in the synthesis. Other advantages of our proposed synthesis procedure compared to other reported techniques are the low synthesis time and moderate temperature (55 °C). Apart from using a simplified technique, we used nontoxic and inexpensive chemicals in the water reaction medium instead of organic solvents and toxic reagents, which were commonly used in previously published reports.

In detail, we exclusively developed multifluorescent BSA-capped Gd_2O_3 NCs without mixing any impurities and dopants (elements, metals, and C-dot). The prepared Gd_2O_3 NCs (1.25 ± 0.5) size lies in the range of 1-3 nm, which is highly desirable for deep tissue imaging. It has been demonstrated that the Gd_2O_3 NCs retained their fluorescence properties in the physiological pH range and different ionic strengths (up to 250 mM). Further, BSA protein granted anomalous stability (up to 30 months in aqueous medium) to the prepared Gd_2O_3 NCs and imparted excellent water solubility, which is needed for imaging purposes. Interestingly, the tuneable emission in three primary colors (RGB) collectively fluoresced to give ultra-pure white light. This novel procedure to develop multi-fluorescence Gd_2O_3 NCs and its role in bioimaging could diversify its role in several other biomedical applications.

After successfully synthesizing highly biocompatible BSA-capped Gd_2O_3 NCs and availing its anomalous properties in deep tissue imaging, we tend to unrevealed its applicability in *in-vitro* MR imaging and real-time fluorescence imaging. Hence, we developed a new dual-modal bioimaging nanoprobe that was facilely synthesized via surface conjugation and Gd^{3+} chelation through chitosan and ascorbic acid. The resultant nano-imaging probe exhibits excellent water dispersibility, strong fluorescence efficiency, high relaxivity, and negligible cytotoxicity. A series of lucid and accurate characterizations validated the successful development of Gd_2O_3 NCs. In vitro relaxivity characterization and *in-vivo* imaging demonstrate that Gd_2O_3 NCs possess both the high sensitivity of fluorescence imaging and the high spatial resolution of MRI, providing an opportunity for its practical applications in biological and clinical fields. The calculated relaxivity r_1 value is almost double the commercialized gadolinium-based contrast agent. In addition, CTCF analysis estimated depth penetration in human glioma cancer cell lines, and IVIS imaging in mice confirmed its candidature in real-time imaging application by retaining its luminescence property in physiological conditions.

As we are aware, stability and optimized reaction condition for size prediction is foremost for any application; in order to do this, estimation of interfacial energy, nucleation rate, and thermodynamic parameters is essential. Hence, we utilized the appropriate technique to compute the value of apparent activation energy ($E\alpha$), pre-exponential kinetic factor ($A\alpha$), thermodynamic parameter, nucleation rate (Jn), and interfacial energy (Υ) at high temperatures for the Gd_2O_3 nanoclusters in the BSA matrix. Moreover, the average value of activation energy was found to be 143.98 kJ mol^{-1} using the most accurate Vyazovkin AIC method with minor systematic error. Furthermore, the differential function $f(\alpha)$ was found to vary as (1-α)3 upon monitoring the z(α) master plot against the experimental value. The pre-exponential kinetic factor was calculated, 8.9× 1015 min^{-1}, through a KAS-derived equation at high temperature, and both Eα and Aα values were utilized to compute thermodynamic parameters. The values of nucleation rates were found to increase exponentially with conversion points and temperature. In contrast, interfacial energy changed linearly with the temperature rise. The average interfacial energy value for pre-nucleating Gd_2O_3 NCs at 10 °C min^{-1} was found to be 54 $mJm^{-2.}$ This innovative approach has the potential to greatly enhance our understanding of nanomaterial nucleation rate and interfacial energy patterns as temperature and conversion points vary, thus contributing to the field of nanoscience.

6.2 Future Implications

In the future, due to their unique properties and applications, these Gd_2O_3 nanoclusters will hold great promise and potential in various sectors in the future. These nanoclusters are anticipated to play a major role in the following fields:

- Apart from CTCF analysis in glioma cell line, CTCF analysis in other cell lines should also be investigated in future work for better understanding of cellular events.
- The *In-vivo* magnetic resonance imaging on cancer induces rat model using as a contrast agent.
- The targeted drug delivery potential of nanoclusters should be investigated through encapsulation with anti-cancerous drugs like taxol and methotrexate (MTX)

- Cytocompatibility, structural complexity and pharmacokinetic studies of prepared Gd_2O_3 NCs should be investigated in animal model to insure its safe clinical application in future.
- The possible photothermal activity of prepared Gd_2O_3 nanoclusters functionalized with NIR-activated agents within its full potential.
- The investigation of peroxidase-oxidase-like nano-enzymatic properties of Gd_2O_3 NCs due to their small size and significant surface-to-volume ratio to develop effective bio-electrochemical sensors
- The antibacterial potency of Gd_2O_3 NCs should be examined for better use of its in biological application.
- The ability to maintain stability at high temperatures renders it suitable for implementation in optoelectronics applications.