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Oxygen Sensing in Biological Systems using Core-Shell Nanoparticles

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Abstract

Core-shell nanoparticles (CSNPs) have emerged as powerful tools for biological oxygen sensing due to their exceptional structural and functional properties. These nanoparticles, designed with a functional core and protective shell, enhance dispersibility, biocompatibility, and cytocompatibility, making them particularly suitable for intracellular and targeted oxygen sensing. Ruthenium and porphyrin complexes, commonly used as fluorescent and phosphorescent probes, are frequently encapsulated within CSNPs to enable precise fluorescence lifetime-based oxygen measurements. Inclusion of these dyes in polymers or shells offers several advantages, such as preventing dye leaching into tissues, mitigating singlet oxygen toxicity, enabling targeted sensing of cells or organelles, and extending probe lifetime. This paper demonstrates the use of fluorescence lifetime measurements in the time-domain approach, leveraging a multi-channel scaler, to evaluate oxygen levels. Additionally, it discusses CSNPs incorporating Ru and porphyrin dyes from three perspectives: (a) preparation methods, (b) spectroscopic characteristics, and (c) biomedical applications. Overall, CSNPs provide a versatile and efficient platform for real-time monitoring of oxygen levels, with significant potential in biomedical and biophysical research.This paper explores the design strategies, mechanisms, and potential of core-shell nanoparticles in advancing the field of biological oxygen sensing.

Keywords: Core-shell nanoparticles; Biomedical applications; Bioactivity; Biocompatibility; Oxygen sensing.

INTRODUCTION

The measurement of oxygen in biological systems is crucial for understanding physiological and pathological processes, including cellular respiration, tissue hypoxia, and tumor microenvironment dynamics[1]. Adenosine triphosphate (ATP), the primary energy currency of cells, is primarily derived through oxidative phosphorylation (OxPhos) in the mitochondria[2-3]. OxPhos relies on oxygen as the terminal electron acceptor in the electron transport chain.[4-5] Consequently, energy metabolism directly

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influences the dynamics of oxygen within and around cells and tissues.[6]

To maintain balanced metabolic activity, tissues and organs have evolved adaptive mechanisms, such as angiogenesis, increased haemoglobin concentration, and accelerated glycolysis, to ensure sustained oxygen delivery.[7] A thorough understanding of these mechanisms and their pathophysiological implications requires precise and localized oxygen sensing.[8]

Traditional methods for sensing oxygen include electrochemical techniques like polarography, electron paramagnetic resonance (EPR), positron emission tomography (PET), magnetic resonance imaging (MRI), and Near-Infrared (NIR) spectroscopy (commonly known as oximetry).[9-10] While these methods have contributed significantly to oxygen studies, many face limitations in resolution, invasiveness, and accuracy. For instance, Clark electrodes, widely used in laboratory settings, are unsuitable for in vivo oxygen measurements because of their large size, oxygen consumption during operation, and inability to probe microscopic or delicate biological domains.[11-12]

Optical techniques have advanced as non-invasive alternatives, employing both endogenous and exogenous probes for oxygen sensing. [13] Endogenous probes, such as NADH and Protoporphyrin IX (PpIX), exhibit limitations, including weak fluorescence signals and cytotoxicity associated with UV-A excitation. [14] Consequently, exogenous probes based on porphyrins, ruthenium (Ru), and iridium (Ir) complexes risen in prominence for their superior sensitivity and adaptability.[15] These complexes offer advantages such as tunable photophysical properties, high photostability, and compatibility with fluorescence lifetime spectroscopy, enabling precise and rapid oxygen measurements.[16]

Core-shell nanoparticles (CSNPs) represent a substantialdevelopment in the field of optical oxygen sensing. By encapsulating fluorescent or phosphorescent dyes like porphyrins, Ru, and Ir complexes, CSNPs provide enhanced stability, dispersibility, and biocompatibility, rendering them suitable for intracellular and localized oxygen measurements.[17] These nanoparticles also mitigate challenges such as dye leaching and singlet oxygen toxicity while allowing extensive chemical modifications to customize their properties for specific applications.[18-19]

This paper explores the use of CSNPs for fluorescence lifetime-based oxygen sensing, focusing on their preparation methods, spectroscopic properties, and applications in biomedical and biophysical studies. With their unique advantages, CSNPs offer a versatile framework for deepening our understanding of oxygen dynamics in biological systems.

Nanoparticles for oxygen sensing

Nanoparticles have revolutionized oxygen sensing by providing advanced platforms that overcome the limitations of conventional methods. Their nanoscale dimensions, large surface area-to-volume ratio, and ability to incorporate functional materials enable precise and localized measurement of oxygen levels in biological and environmental systems.[20] (Kalyani *et al.*, 2021). Nanoparticles can be designed to carry oxygen-sensitive probes, such as fluorescent or phosphorescent dyes, that respond to changes in oxygen concentration through variations in optical properties like intensity, lifetime, or wavelength shifts.[21-22]

Among the various types of nanoparticles used for oxygen sensing, core-shell nanoparticles (CSNPs) are particularly notable. These structures consist of a functional core surrounded by a protective shell, offering enhanced stability, biocompatibility, and tailored performance (Zhao *et al.*, 2020). Commonly used oxygen-responsive dyes include ruthenium (Ru) and porphyrin complexes, which exhibit excellent photophysical properties, including oxygen-dependent fluorescence quenching or lifetime changes.[15,23] Embedding these dyes in nanoparticles prevents issues such as dye leaching, photobleaching, or toxicity, making the sensing system robust and reliable.[24]

Additionally, mesoporous silica nanoparticles, polymeric nanoparticles, and hybrid nanostructures have also been employed for oxygen sensing. These materials provide customizable pore sizes, chemical functionalities, and surface properties, enabling targeted delivery and real-time monitoring of oxygen dynamics in specific cellular or tissue environments. [25-26] (Tang *et al.*, 2010; Wu *et al.*, 2021). The versatility of nanoparticles allows their application in various oxygen-sensing techniques, such as fluorescence lifetime imaging microscopy (FLIM), time-resolved spectroscopy, and multi-channel scaler-based measurements. These methods facilitate non-invasive, high-resolution, and real-time detection of oxygen levels, making nanoparticles indispensable in studying hypoxia, cellular metabolism, and therapeutic responses.[17,27]

Core-shell nanoparticles

CSNPs are a class of nanomaterials composed of a central core material enveloped by an outer shell, both of which can be tailored to enhance the nanoparticle's functionality. The core typically provides the primary material for sensing, drug delivery, or other applications, while the shell serves to protect the core, improve stability, and impart specific functional properties. CSNPs combine the advantages of both core and shell components, making them highly versatile in various fields, particularly in biomedical applications, sensing technologies, and material sciences.

The structure of core-shell nanoparticles (CSNPs) is typically categorized into two main types: Solid Core-Shell Nanoparticles and Core-Shell Nanocomposites. In Solid Core-Shell Nanoparticles, the core is composed of solid materials, such as metals, semiconductors, or organic compounds, and the shell is typically made of polymers, silica, or other biocompatible materials.[28] This configuration is advantageous for creating controlled release systems, where the shell acts as a protective barrier, controlling the release of the core material in response to specific stimuli.[29] The core-shell nanoparticle involves the integration of different materials in the core and shell to take advantage of their distinct properties. For example, a magnetic core might be combined with a polymer shell for drug delivery and magnetic resonance imaging (MRI) applications.[30] The composite nature of these nanoparticles allows for the synergy of multiple functional properties, enhancing their utility in a wide range of applications.[31]

The main advantage of Core-Shell Nanoparticlesis that they have enhanced stability. The shell protects the core material from degradation, oxidation, and other environmental factors, significantly increasing the stability of the nanoparticle under biological conditions. This is especially important for sensitive materials like fluorescent or phosphorescent probes used in oxygen sensing.The outer shell can be engineered to recognize specific biological markers, enabling targeted delivery of drugs, diagnostic agents, or sensors to cells or tissues. This makes CSNPs particularly valuable in medical diagnostics and therapies. The shell can regulate the release of the core material, providing controlled, sustained release over time. This is beneficial for drug delivery applications, where precise timing and dosage are critical. The shell can be functionalized with various ligands, antibodies, or other biomolecules to enhance interaction with specific biological targets. This functionalization also allows for the integration of different imaging, therapeutic, or sensing functionalities into a single nanoparticle

Recent research has focused on advancing the design and functionality of CSNPs to further improve their applications. Some areas of development include:

- **Surface Modification**: Functional groups and targeting moieties are being introduced to the surface of the shell to enhance the nanoparticles' targeting ability and bioavailability.[32]
- **Nanostructuring**: More complex designs, such as multi-layered shells or multi-core structures, are being explored to enhance the nanoparticles' multifunctionality.[33]
- **Biodegradable Materials**: There is increasing interest in the use of biodegradable polymers for the shell material to ensure that nanoparticles degrade safely within the body after use, minimizing long-term toxicity.[34]

Synthesis of Core-shell Nanoparticles

Core-shell nanoparticles (CSNPs) can be synthesized using two primary approaches: the top-down and bottom-up methods. The choice of synthesis technique significantly influences the properties of the nanoparticles, including their size, shape, and functionality, which are crucial for their application in pO_2 sensing. The top-down approach involves microfabrication techniques that deconstruct bulk materials into smaller, desired-sized nanoparticles, typically using physical methods. Conversely, the bottom-up approach builds nanoparticles from molecular building blocks, relying on chemical interactions and properties to form well-defined structures with meticulous control over size and composition.

This section focuses on two widely used protocols for the synthesis of CSNPs, particularly for oxygen sensing: (1) the Stöber method (sol-gel method) and (2) the template-assisted method.

Stöber Method (Sol-Gel Process)

The **Stöber method** is a sol-gel-based wet chemical technique frequently employed for synthesizing silica-based CSNPs. This method involves the hydrolysis and condensation of silicon alkoxide or silicon halide precursors, such as tetraethyl orthosilicate (TEOS), in alcohol or water in the presence of a base catalyst like ammonia.[35] The process leads to the formation of uniform colloidal microspheres, with a controlled core-

shell structure. In this method, the silica precursor (TEOS) undergoes hydrolysis under alkaline conditions, forming silica nuclei, which act as the core material. These silica nuclei are then seeded on the core surface, promoting heterogeneous nucleation.[36]

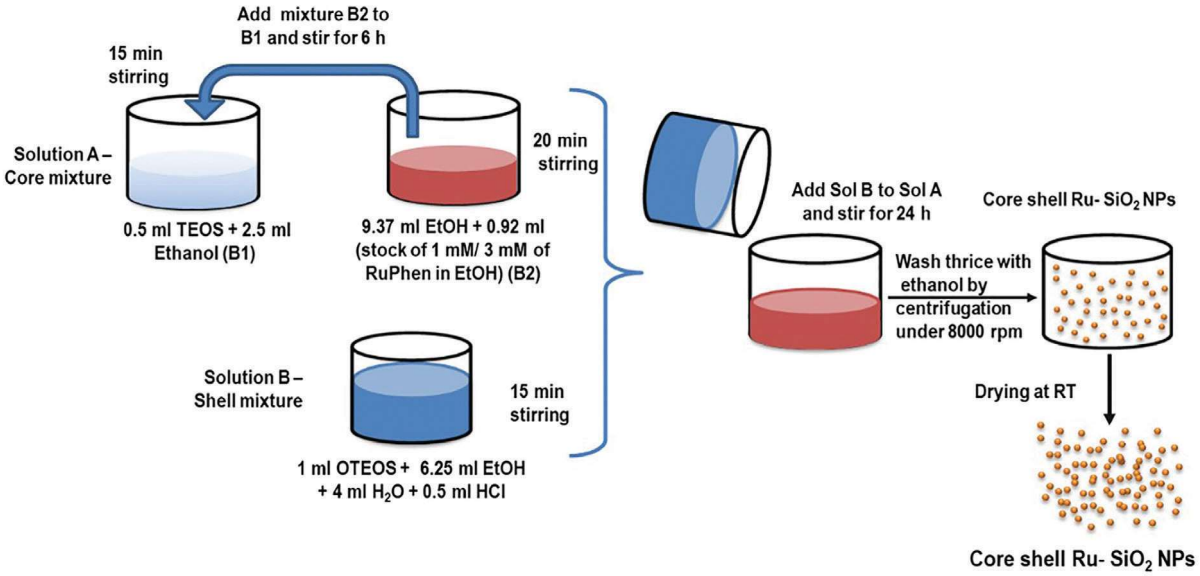

Fig. 1: An illustration of the preparation of Ru-SiO2 core-shell nanoparticles

The growth of the silica shell is regulated through the nucleation and growth phases, which can be precisely adjusted by varying the concentrations of TEOS and alkali catalysts, such as NaOH or NH_2OH. By altering the TEOS concentration or extending the reaction time, the shell thickness can be controlled (Fig. 1). For instance, mesoporous silica shells with pore sizes up to 7 nm can be synthesized using n-octadecyltrimethoxysilane (CTMS) as a surfactant. Additionally, employing block copolymer surfactants like Pluronic P123 facilitates the formation of mesoporous silica shells, enabling controlled porosity suitable for encapsulating fluorescent or phosphorescent dyes used in oxygen sensing.[35] (Stöber *et al.*, 1968).

In the context of CSNPs, the Stöber method is widely employed to create silica shells around cores made of metals, polymers, or other nanoparticles. [3,37] The silica shell protects the core, enhances biocompatibility, and facilitates functionalization with target-specific ligands or fluorescent dyes. For instance:

Ruthenium Complexes: Ruthenium(II) tris(1,10-phenanthroline) ($Ru(dpp)_3^{2+}$) can be encapsulated within the silica shell, ensuring stability and high oxygen permeability.[38]

Porphyrin-Based Dyes: Porphyrin derivatives, such as platinum(II) meso-tetrakis (pentafluorophenyl) porphyrin (PtTFPP), have been incorporated into silica shells for oxygen sensing due to their fluorescence quenching by O_2.[39].

The primary advantage of the Stöber method is that the particle size can be adjusted by varying the concentration of the precursor, solvent, or catalyst[40]. This method produces highly uniform nanoparticles, making it suitable for applications requiring consistency[41]. The silica shells can be modified or functionalized to incorporate fluorescent dyes, magnetic materials, or other biomolecules[42]. The process is easily scalable for large-scale production without significant loss of quality[43].

Template-Assisted Method

Template-assisted synthesis involves three distinct steps: (1) template preparation, (2) template-directed deposition of the shell material, and (3) template removal. The core material, or template, is typically made from rigid materials such as metals, polymers, or metal oxides. The shell material is then deposited uniformly over the core, creating the core-shell structure. The properties of the core material, including its porosity, dictate the final characteristics of the resulting nanoparticles.

There are two main types of template-based methods: **hard template** and **soft template** techniques.

- **Hard Template Method:** In this approach, rigid materials such as polymers, metals, and metal oxides are used as templates for the shell deposition. These templates provide the desired shape and structure, and the porosity of the resulting CSNPs is determined by the characteristics of the hard template. The hard template method is often used for the synthesis of nanoparticles with highly controlled, uniform properties.
- **Soft Template Method:**This approach utilizes surfactants or block copolymers as structure-directing agents (SDAs) to guide the formation of core-shell structures. Unlike the hard template method, the soft template technique does not rely on rigid core materials. Instead, nanoparticles are formed through intermolecular interactions between the SDAs and the molecules, resulting in mesoporous or nanoporous structures. The core of the CSNPs is typically synthesized via sol-gel processes, with the mesoporous structure emerging after the removal of the pore-templating surfactants through low-temperature calcination or washing techniques. This method enables the fabrication of nanoparticles with uniform pores and highly customizable surface properties.[44-45]

The structural precision of the Template-Assisted method enables the synthesis of nanoparticles with precise control over size, shape, and shell thickness. This method applies to a wide range of materials, including silica, metals, polymers, and composites. It facilitates the creation of unique structures, such as hollow, porous, or multilayered nanoparticles.[37,46]

Applications of Core-Shell Nanoparticles for Oxygen and Physiological Parameter Sensing

Monitoring intracellular oxygen is essential for understanding physiological and pathological processes, as oxygen levels are intricately linked to cellular metabolism, signaling, and disease progression. Oxygen sensing can be achieved by evaluating the fluorescence intensity or lifetime of oxygen-sensitive dyes. This section focuses on the applications of core-shell nanoparticles (CSNPs) in detecting oxygen and other physiological parameters, with an emphasis on fluorescence intensity- and lifetime-based measurement techniques of different CSNPs employed for O_2 sensing through various approaches.

A dual-sensor system developed that utilizes doped core-shell nanoparticles (CSNPs) embedded in a sol-gel matrix for simultaneous temperature and oxygen sensing. The sensor incorporates a CdSe quantum dot core, which functions as a temperature sensor, while the silica shell is doped with platinum (II) meso-tetrakis (pentafluorophenyl) porphyrin (PtTFPP) for oxygen sensing. The CSNPs are embedded in a composite xerogel made of n-propyltrimethoxysilane (n-propyl-TriMOS) and 3,3,3-trifluoropropyltrimethoxysilane (TFP-TriMOS), then coated onto an optical fiber. The porous silica shell facilitates the efficient penetration of O_2 molecules, enhancing the quenching effect of PtTFPP and improving the sensor's sensitivity.[46]

Aratiometric core-shell nanoprobedesigned with excellent biocompatibility for intracellular pO_2 sensing. The core incorporated an O_2-sensitive dye, platinum (II) octaethylporphyrin (PtOEP), and two additional fluorophores: coumarin 6 (C_6) as a reference dye and dinaphthoylmethane (DNM) as an energy donor. Upon excitation, C6 provided a stable, O_2-insensitive green fluorescence via intraparticle Förster resonance energy transfer (FRET) from DNM, while PtOEP emitted red phosphorescence, which was quenched by O_2 with a 94% response.[47]

A novel luminescent ratiometricnanosensor designed for pO_2 measurement.[48] The nanosensors featured spatially separated probe and reference dyes within the core and shell, respectively. This configuration ensured a stable reference emission unaffected by environmental factors. The nanosensors exhibited high stability, negligible cytotoxicity, and excellent monodispersity, making them suitable for biological applications.

Anovel, real-time, non-invasive method for O_2 measurement using a custom-built system was studied comprising a custom scalar fluorometer (CSMF), a photomultiplier tube (PMT), and a multi-channel scalar (MCS).[49] CSNPs doped with $Ru(dpp)_3^{2+}$ were prepared using a modified Stöber method and embedded in a TEOS composite xerogel. The system demonstrated improved oxygen diffusivity and sensitivity due to the high surface area and porosity of the silica shell.[49]

Chu *et al.* developed a sensitive optical pO_2 sensor by coating an optical fiber with PtTFPP-entrapped CSNPs embedded in a composite xerogel of n-octyltriethoxysilane (Octyl-triEOS) and tetraethylorthosilane (TEOS). These sensors demonstrated good sensitivity, making them suitable for real-time oxygen monitoring.[50]

The synthesized CSNPs with a hydrophobic core embedded with O_2-sensitive PtTFPP dye and

a biocompatible silica shellwas demonstrated.[51] These nanoparticles exhibited enhanced O_2-sensing performance due to their improved photophysical properties. The biocompatible shell reduced cytotoxicity and minimized chemical interferences, making the nanoparticles ideal for intracellular measurements.

The use of dual lifetime referencing with core-shell nanoparticles (CSNPs) for the simultaneous detection of pO_2 and pH was demonstrated by Ehgartner *et al.*[52] These nanoparticles featured the O_2-sensitive dye Pt(II) meso-tetra(4-fluorophenyl) tetrabenzoporphyrin (PtTPTBPF) in the polystyrene core, while a pH-sensitive BF_2-chelated tetraarylazadipyrromethene (aza-BODIPY) dye was incorporated into the polyvinylpyrrolidone shell. This system enabled reliable, multi-parameter sensing, making it suitable for applications in biological environments.

Xue *et al.* reported the use of poly(ether sulfone) (PES) or polysulfone (PSU) fibers with a polycaprolactone (PCL) shell designed for cell attachment.[53] Oxygen-sensitive dyes, such as PtTFPP or PdTFPP, were incorporated into the fiber core via electrospinning. The PdTFPP-based fibers demonstrated improved sensitivity, attributed to the extended lifetime of the porphyrin dye, enhancing the detection of oxygen levels.

CONCLUSION AND FUTURE WORK

Core-shell nanoparticles (CSNPs) represent a transformative advancement in the field of biological oxygen sensing, owing to their unique structural attributes and functional versatility. By incorporating oxygen-sensitive dyes such as ruthenium and porphyrin complexes into the core or shell, these nanoparticles enable highly precise and efficient fluorescence lifetime-based pO_2 measurements. The protective shell not only enhances the stability and biocompatibility of the dyes but also minimizes issues such as dye leaching, cytotoxicity, and interference from environmental factors. This makes CSNPs an excellent choice for intracellular and targeted oxygen sensing applications.

The combination of robust synthesis techniques, such as the Stöber method and template-assisted approaches, with state-of-the-art spectroscopic systems offers a reliable platform for real-time, non-invasive oxygen monitoring. The ability to fine-tune the properties of CSNPs, including their fluorescence characteristics and surface functionalities, further enhances their adaptability to diverse biomedical and biophysical research needs.

As demonstrated in this study, CSNPs have immense potential in advancing our understanding of physiological and pathological processes associated with oxygen dynamics. The integration of these nanoparticles with advanced imaging and sensing technologies paves the way for groundbreaking applications in cellular biology, disease diagnosis, and therapeutic monitoring. Moving forward, continued innovation in nanoparticle design and dye incorporation strategies will be critical to unlocking the full potential of CSNPs in oxygen sensing and beyond.

Support: Not applicable

Conflicts of interest: None to declare

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