Prayogik Rasayan

Biomedical applications of zinc sulfide nanoparticles

Swapnali Londhe, Sudipta Saha, Chitta Ranjan Patra*
Department of Applied Biology, CSIR-Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad - 500007, Telangana State, India.
Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, U.P., India
E mail: crpatra@iict.res.in; patra.chitta@gmail.com

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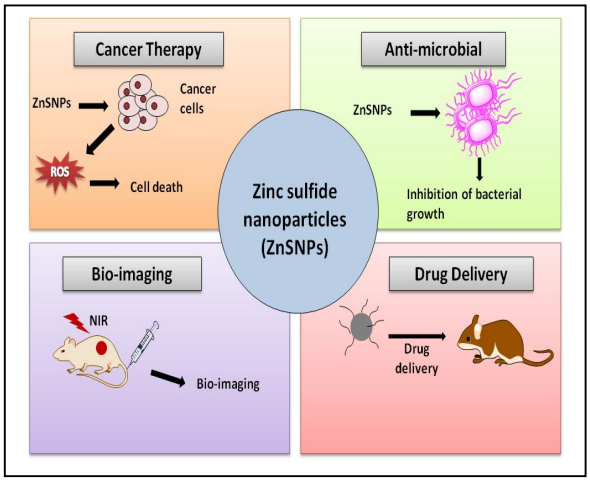
Abstract

Now-a-days, transition metal nanoparticles especially zinc nanoparticles are extensively studied by researchers all over the globe. Among various zinc based nanoparticles, the zinc sulfide nanoparticles (ZnSNPs) have received immense attention and offer significant advances in the biomedical field due to their fundamental properties and indispensable benefits. Although, there are few reports which spotlight recent advances and progress regarding ZnSNPs, unfortunately, there is no systematic comprehensive review article that describes various biomedical applications of ZnSNPs. To this context, the present review article elucidates the recent advancement of ZnSNPs and their future theranostics applications (cancer therapy, antimicrobial activity, angiogenic therapy, biosensing and bioimaging) in the biomedical field. The present review article also gives an overview about possible challenges and future perspectives of ZnSNPs in the area of biomedical science.

Keywords: Zinc sulfide nanoparticles, transition metal nanoparticles, cancer, antimicrobial, bioimaging, biomedical application



1. Introduction

The transition metal nanoparticles have received immense attention owing to photothermal conversion efficiency, long-term stability, high biocompatibility, elemental composition and less cytotoxicity.[1,2] Among transition metal nanoparticles, zinc nanoparticles (ZnNPs) have promising role in diverse biomedical applications as well as in other healthcare products.[3,4] Zinc is an important trace element found in almost all organisms including human. It occurs in all body tissues such as muscle, bone, brain, skin. It is a main component of several enzymes and involved in cell metabolism, protein and nucleic acid synthesis.[5] It has been observed that the zinc deficiency may results in several physiological issues such as immunodeficiency, impaired wound healing, delayed sexual maturity, growth retardation, neurological disorders and skin diseases.[3,5] Apart from these, the strong UV absorption property of zinc oxide nanoparticles (ZnONPs), explored them in sunscreen and cosmetics.[4,6] Among various metal based nanoparticles, metal sulfide based nanomaterials exhibit better advantages over metal oxide due to shorter band-gap from which sulfides can easily interact and utilize visible light. This response is due to presence of higher conduction band than metal oxide.[7] In last few decades, the scientists have engineered the metal sulfide nanomaterials by different approaches due to their biocompatibility and potent physiochemical properties such as radiation enhancement, immune activation and light conversion.[8]

Among various metal sulfide nanomaterials, zinc sulfide nanoparticles (ZnSNPs) have versatile applications due to various reasons such as luminescence properties, photostability, less toxicity and broad band gap.[9,10] Along with this, it is chemically stable and better alternative than other chalcogenides including CdSe, CdTe and CdS.[11] The ZnS is a polymorphous material and semiconductor which mainly found in two crystalline forms, wurtzite and zinc blend.[12] Due to large band gap than other zinc containing nanomaterials, it can be exploited for UV and visible light based devices.[12]

Apart from this, the superior optical and luminescent properties of ZnSNPs along with its biocompatible nature, explore them for various biological applications such as cancer, antibacterial activity, angiogenesis etc.[13-15] Considering versatile biomedical applications of ZnSNPs, we have discussed theranostic approaches, possible challenges and future perspectives of ZnSNPs.

2. Metal sulfide nanomaterials

Metal sulfide nanoparticles are promising semiconductor materials with potential uses in the field of biomedicine due to distinctive characteristics such as narrow band gap, high fluorescence, structural, magnetic and thermal stability, non-toxicity as well as photocatalytic activity.[16] It has potential role

in photochemical applications due to wide band gap, energy and photothermal conversion capacity. It can also be used for photocatalyst reaction.[17] Hence, to this end, these semiconductor nanomaterials are being explored for the therapeutic applications because of their significant chemical and physical attributes.[18] They can act as chemotherapeutic agents due to more absorbance ability in the NIR region, better photochemical degradation and low toxicity.[19] In several cases, the metal sulfide nanoparticles display various anti-tumor effects. It can be used as drug vehicle to accomplish chemotherapy as well as phototherapy. Apart from this, it can activate chemodynamic therapy or immunotherapy after release of metal and sulfide ions in tumor microenvironment.[8] Various metal sulfides, for examples, zinc sulfide, iron sulfide and manganese sulfide can act as gaseous therapeutic agents owing to their ability to dissociate hydrogen sulfide (H_2S) gas in acidic tumor environment.[8]

3. Synthesis and characterization of ZnSNPs

The main focus of this review article is to discuss about the biomedical applications of ZnSNPs. However, due to wide applications of ZnSNPs in various fields, scientists are focusing on various feasible synthesis approaches.[12] The following section briefly describes several synthetic approaches for preparation of ZnSNPs which mainly includes:

- Physical synthesis[11, 20-22]
- Chemical synthesis[23-25]
- Biological synthesis[26-28]

We have also briefly discussed about the characterization techniques for ZnSNPs.

3.1. Physical synthesis of ZnSNPs

Physical synthesis approaches are free from use of biological or chemical precursor. The physical synthesis of ZnSNPs includes laser ablation[21], ball milling[22], microwave irradiation[20] and mechanochemical approach[11]. For example, Chernikov et al. reported synthesis of spherical ZnSNPs deposited on the silicon substrate by laser ablation in the presence of an electrostatic field.[21] In another work, Pathak et al. synthesized ZnSNPs using mechanochemical route in a high energy planetary ball mill with zinc acetate and sodium sulfide as source materials.[22]

3.2. Chemical synthesis of ZnSNPs

Chemical agents are utilized in the reduction of their respective salts to create metallic nanoparticles. Additionally, a stabilizing agent is used to prevent nanoparticle agglomeration. The chemical synthesis includes hydrothermal process[29], solvothermal method[30], sol-gel method[31], chemical precipitation[32], microwave-assisted solvothermal reactions[33], and microemulsion method.[12]Numerous literatures are available for the synthesis of zinc sulfide by chemical route. Few of them are mentioned here. For example, Kripal et al. synthesized Mn^{2+} doped ZnSNPs by co-precipitation method and explored for photoluminescence and photoconductivity properties.[23] In another study, Ghosh et al. fabricated the (PVP) polyvinyl pyrrolidone capped ZnSNPs by simple chemical method and examined for optical properties by varying concentration of S^{2-} ions and PVP concentration.[24] Vacassy et al. reported controlled spherical ZnSNPs synthesis by precipitation method from homogenous solutions using several zinc salt containing compounds, S^{2-} as a precipitating anion, produced from thioacetamide decomposition. The nucleation is accelerated by utilization of acetic acid but particle growth is restricted due to complex formation with zinc cation.[34] Alfahed et al. demonstrated morphological, structural, and Z-scan technique for a temperature controllable chemical synthesis of ZnSNPs. The annealing temperature is controlled in between 200-500℃.[25] In another study, Kumari et al. reported synthesis of self-assembled nanoparticles with the interparticle voids and mesoporosity. The self-assembled ZnSNPs were synthesized by sol-gel synthesis using lauric acid as a structure directing agent. Further, self-assembled mesoporous ZnSNPs was employed as a nano-carrier for delivery of anticancer drug doxorubicin for better efficacy.[35] Dengo et al. synthesized ZnSNPs by reproducible hydrothermal method and comprehensive characterization was performed using several physiochemical techniques. Further, ZnSNPs surface were probed by diffuse reflectance infrared Fourier transform spectroscopy using CO, CO_2, methanol and pyridine to check interaction capabilities.[36]

3.3. Biosynthesized ZnSNPs

Recently, to decline the rate of harmful chemicals used in conventional techniques, the biosynthesized methods including plant, bacteria, algae and fungus are well adapted. The presence of naturally occurring phytochemicals act as both reducing and capping agents.[37] The emergence of eco-friendly and reliable process for semiconductor nanoparticle synthesis is a significant approach of biomedical nanotechnology.[26] The synthesis of ZnSNPs by biological approach includes plant extract[27,38] and microorganisms.[26,28] The plant contains several biomolecules such as monosaccharides, amino acids, polysaccharides, minerals, enzymes, vitamins, sterols. These phytochemicals act as reducing agent for creation of nanostructured materials.[39] To this context, Kannan et al. reported synthesis of ZnSNPs using *Tridax procumbens* plant extract for better photocatalytic activity.[38] In another study, Sathishkumar et al. reported biosynthesis of ZnSNPs by chemical co-precipitation method using methanolic extract of *Syzygium aromaticum* for antimicrobial as well as photocatalytic degradation activity.[27] Alijani et al. synthesized ZnSNPs from aqueous extract of *Stevia rebaudiana*. The spherical shape was confirmed by (TEM) transmission electron microscopy and (FTIR) Fourier transform infrared spectra confirms the glucose as a capping agent.[40]

Commonly, the bacteria and other microorganism convert sulfate ions in reduced sulfides under certain conditions with the help of several enzymes. The insoluble precipitates of metal sulfides are formed when sulfide anions interact with soluble metal cations. One of the reports on microbial

biosynthesis of ZnSNPs using *Serratia nematodiphila* has been published by Malarkodi et al.[26] In other work, Gong et al. reported microbial synthesis of ZnSNPs using *Desulfovibriode sulfuricans* bacterial strain. The cellular distribution of Zn and ZnSNPs biosynthesis kinetics were evaluated by Zn^{2+} and ZnS concentrations by atomic absorption spectroscopy.[28]

Characterization of ZnSNPs

After synthesis of nanomaterials, it is necessary to characterize the materials using several analytical tools that help to determine various physiochemical parameters such as crystalline phase, morphology, size, charge etc. of nanoparticles. Several reports focused on characterization of ZnSNPs using various physiochemical techniques such as XRD (X-ray diffraction), UV-visible spectroscopy, SEM (scanning electron microscopy), TEM (transmission electron microscopy) and TGA (thermogravimetric analysis).[11,36,41] According to previous literature, the UV-visible spectra of ZnSNPs is observed to be in between 200-300nm, which reveals that, it can be used as ultraviolet blocking materials.[41,42] The XRD spectra of ZnSNPs demonstrates that the sharp diffraction pattern is indexed at (111),(220) and (311).[11,36] The **Figure 1** demonstrates the crystalline nature, size, shape and morphology of ZnSNPs. The XRD spectra reveal that the synthesized material is purely crystalline with diffraction index observed at hkl=111,002,202 and 113 (Figure 1a). The TEM micrograph shows that, the average diameter of nanoparticle is approximately 22nm (Figure 1b).

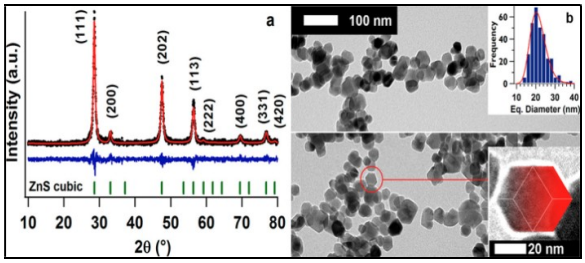


Figure 1. (a) XRD diffraction pattern, experimental (dots), fitted (red line), and residuals (blue line). (b) TEM micrograph with (inset, top panel) the size distribution obtained from the segmentation analysis fitted with a log-normal distribution and (inset, bottom panel) superimposition of a 2D projection of a rhombic dodecahedron with a particle of the sample. Reproduced from "Dengo, N., Vittadini, A., Natile, M. M., & Gross, S. (2020). In-depth study of ZnS nanoparticle surface properties with a combined experimental and theoretical approach. *The Journal of Physical Chemistry C*, *124*(14), 7777-7789" licensed under CC-BY 4.0.

4. Biomedical applications of ZnSNPs

The ZnSNPs have been used for several biomedical applications such as cancer therapy,[13,43] drug delivery,[44,45] angiogenesis,[15] anti-bacterial activity,[14,46] bioimaging[47] and biosensor,[48,49] which are elaborately discussed in following subsequent sections.

4.1. Drug delivery

The ZnSNPs with core-shell structure having uniform size, low cytotoxicity, better biocompatibility and water solubility is an unique candidate for controlled drug delivery approach.[50] For this, Pathania et al. reported the ZnS-cellulose nanocomposite fabrication for drug delivery, photocatalytic and antimicrobial activity.[44] The nanoparticles were characterized by several analytical techniques in order to determine its shape, size and surface morphology. Further, the ZnS-cellulose nanocomposite explored for controlled and sustainable delivery of ofloxacin. Moreover, it showed significant antibacterial activity against *E. coli* and photocatalytic activity was tested under visible light irradiation for degradation of phenol.[44]

Abniki et al. demonstrated desorption of famotidine on 3-aminophenol deposited allyl glycidyl ether-ZnSNPs. The co-precipitation method was employed to synthesize ZnSNPs.[45] The surface polymerization of nanoparticles was done by allyl glycidyl ether. Further, 3-aminophenol was deposited as a ligand. The famotidine adsorption study using 3-aminophenol deposited allyl glycidyl ether-ZnSNPs was evaluated by adsorption isotherms. The famotidine release was observed in biological fluids at certain time periods. The altogether result demonstrates significant role of modified ZnSNPs for controlled drug delivery.[45] In another work, Xing et al. fabricated fluorescent porous ZnS nanosphere by hydrothermal procedure and evaluated for drug delivery as well as live imaging of cell. The safranine-T was used as fluorescent dye and loaded on to ZnS nanosphere. Further, it delivered *in vitro* to HeLa cells for live cell imaging.[51] Li et al. reported chitosan sodium alginate microcapsules preparation containing ZnSNPs and their effect on controlled release of drug.[52] The microcapsules of chitosan sodium alginate were prepared with ZnSNPs via solvent-evaporation method. Aspirin was selected to evaluate the effect of drug release from microcapsules. The results demonstrate that, the release kinetics of microcapsules having ZnSNPs is significantly decreased as compared to microcapsules without nanoparticles. Hence, it is significantly effective in controlled release of drugs.[52]

4.2. Cancer therapy

The well recognized luminescent and optical properties of ZnSNPs emerged them as a significant candidate for various biomedical applications including cancer. Owing to ability of photoactivation as well as superficial tumor accessibility, it becomes most promising target for cancer theranostic platform.[13] To this context, Essawy et al. synthesized ZnSNPs by phase thermal decomposition method.[13] Moreover, they evaluated the cytotoxic potential of excited ZnSNPs on different cell lines. The result demonstrated that, it possesses profound anticancer activity over non-excited nanoparticles.[13] In another study, Dash et al. synthesized ZnSNPs by pyrolytic method and investigated their cytotoxic activity against human acute myeloid leukemia (KG-1A) cell line.[53] The ROS (reactive oxygen species) production, tumor

necrosis factor alpha (TNF-α) secretion facilitate the DNA damage followed by nanoparticle treatment. However, it did not show any toxic effect on normal lymphocytes. These findings demonstrate the potent anticancer mechanism of ZnSNPs.[53]

Liu et al. demonstrated ZnS based nanoplatform for treatment of glioblastoma in orthotopic model. The ZnSNPs were loaded with autophagic inhibitor hydroxycholoroquine and enclosed with hybrid shell of exosome and RGD peptide.[43] The resultant peptide has significant ability to cross blood brain barrier and target glioblastoma cells. It also acts as photosensitizer for ROS generation and has the ability damage the glioblastoma cell organelles. Therefore, owing to potent anti-tumor ability of hybrid exosomes, it leads to the selective damage of glioblastoma cells.[43] In other work, Tran et al. reported the inhibitory effect of ZnSNPs in breast cancer stem cells (MCF-7-SC) by restricting the invasion as well as migration properties of the cells. The metastasis of the stem cells was inhibited by nanostructures along with the suppression of epithelial-mesenchymal transition.[54]

Mathew et al. designed (FA) folic acid conjugated (CMC) carboxymethyl-chitosan and manganese doped ZnSNPs (FA-CMC-ZnS-Mn) for controlled and targeted drug delivery along with imaging of cancer cells.[55] Then, the 5-Fluorouracil was encapsulated in above drug delivery system. The FA-CMC-ZnS-Mn exhibits non-toxicity towards mouse fibroblast cells while drug loaded nanoparticles exerts specific cytotoxicity and imaging towards MCF-7 Breast cancer cells. Hence, these quantum dots (QDs) can be utilized as a drug delivery vehicles for cancer cells.[55]

Li et al. designed the manganese zinc sulfide nanoparticles (MnZnSNPs) for immunogenic cell death of metastatic melanoma.[56] The MnZnSNPs and IR780 dye were incorporated into amphiphilic copolymer of polyethylene glycol poly (2-hexoxy-2-oxo-1,3,2-dioxaphospholane) to form polymeric micelle. It demonstrates controlled release of drug in response to the near-infrared (NIR) light. The Mn^{+2} responsive chemodynamic therapy leads to the formation of ROS and maximizes immunognenic cell death.[56] These overall findings suggested the significant anticancer activity of ZnSNPs. **Figure 2** represents schematic design of self-assembled IR780 dye with MnZnSNPs micelle. The micelles releases IR780 dye and MnZnSNPs under (near-infrared) NIR irradiation in tumor microenvironment via increased chemodynamic therapy assisted immunogenic cell death. Briefly, the polymeric micelle is formed by encapsulation of IR780 dye and MnZnSNPs into the copolymer. The intravenous administration of smartly engineered system under NIR irradiation leads to the photo-thermal conversion of IR780 in tumors. It allows controlled and targeted release of MnZnSNPs from polymeric micelle to achieve cancer metalloimmunotherapy. The MnZnSNPs act as a smart bomblet which exhibit chemodynamic therapy from Mn^{2+} responsive hydroxyl radicals which further activates immunogenic cell death related (DAMPs) damage-associated molecular patterns. The released dye IR780 can aggregate in tumor mitochondria for photothermal ablation and enhance the effect of chemodynamic therapy. The DAMPs containing tumor antigen induces central memory T cell differentiation. Hence, the application of IR780 dye and MnZnSNPs micelles controls metastasis as well as improves survival rate of B16F10 tumor containing mice.

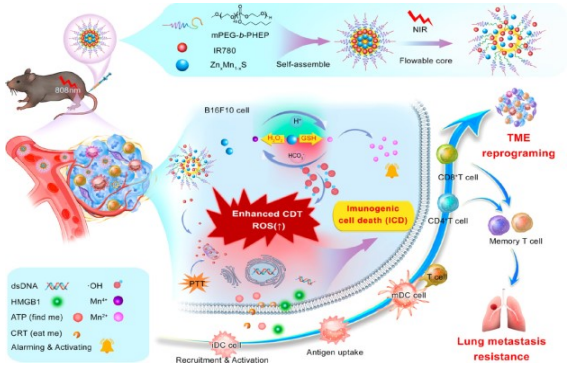


Figure 2. Schematic Illustration of Self-Assembly $PP_{IR780ZMS}$ Releasing IR780 and ZMS under NIR Irradiation for Tumor Microenvironment Education through Enhanced CDT-Associated Immunogenic Cell Death. Reprinted with permission from, "Li, Z., Chu, Z., Yang, J., Qian, H., Xu, J., Chen, B et al. (2022). Immunogenic cell death augmented by manganese zinc sulfide nanoparticles for metastatic melanoma immunotherapy. *ACS Nano*, *16*(9), 15471-15483." Copyright © 2022 American Chemical Society.

Ang et al. developed water-soluble fluorescent silica coated Mangnese (Mn) doped ZnS nanocrystal for cancer theranostic application.[57] The nanocrystal are synthesized using ZnS:Mn nanostructure and coated it with (GSH) glutathione (ZnS:Mn-GSH) by ligand exchange method. Further, they used mesoporous silica to incorporate ZnS:Mn-GSH and make the endmost nanocrystal ZnS:Mn-GSH-silica which showed approximately 35-40% quantum yield. Finally, they reported the biological applications of the nanocrystals in HeLa cell line for both the *in vitro* labeling and anticancer drug delivery.[57]

Fang et al. developed ZIF-8 (zeolitic imidazolate framework-8) coated ZnSNPs and integrated with ICG (indocyanine green) as well as TPZ (tirapazamine) (abbreviated as ZSZIT) to facilitate the H_2S augmented synergistic therapy.[58] Under NIR irradiation, the following nanosystem induces ROS by modifying onsite oxygen. Under acidic tumor microenvironment, ZIF-8 shell is degraded and ZnS core is decomposed, results in formation of H_2S gas. The considerable *in vitro* as well as *in vivo* anticancer effect is achieved due to intracellular ROS and H_2S generation, along with activation of TPZ by ZIF-8 coated ZnSNPs. Hence, the following study offers significant platform that exhibits highly effective gas amplified treatment for cancer.[58] **Figure 3** represents schematic presentation of ZSZIT as a H_2S gas sensitized photodynamic therapy and chemotherapeutic synergistic nano-platform. The ZnS core is coated with ZIF-8 and ICG molecules are incorporated. Further, the TPZ surface functionalization was carried out on nanoparticles which form ZSZIT. The ZIF-8 shell works as a pH responsive

vehicle for the ICG as well as TPZ. Due to imidazole protonation at acidic tumor environment, both ICG as well as TPZ release from the nanosystem. The NIR irradiation triggers the ROS generation from ICG. In acidic environment, both the ZIF-8 and ZnS core degrade and form H_2S gas. The gas decreases catalase expression and inhibits the formation of O_2 from H_2O_2, induces hypoxic condition. Hence, hypoxia of tumor microenvironment and cytotoxic effect of TPZ molecules exhibit better inhibitory effect on tumor, which demonstrates considerable potential for treatment of cancer.

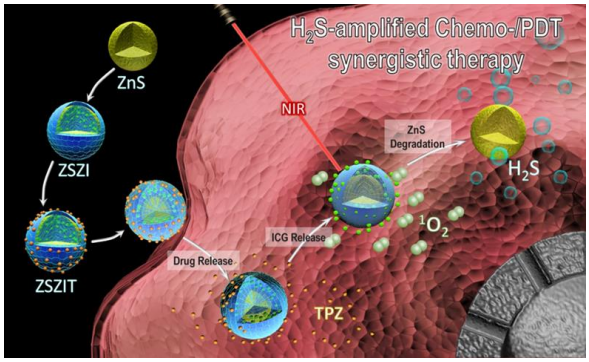


Figure 3. Schematic illustration of ZSZIT as a H_2S-sensitized PDT/chemotherapeutic synergistic nanoplatform. Reproduced from, "Fang, C., Cen, D., Wang, Y., Wu, Y., Cai, X., Li, X., & Han, G. (2020). ZnS@ ZIF-8 core-shell nanoparticles incorporated with ICG and TPZ to enable H2S-amplified synergistic therapy. *Theranostics*, *10*(17), 7671." Copyright © 2020 *Theranostics*.

Li et al. developed the theranostic agent based on (Au@MnS) gold-mangnese sulfide and zinc sulfide (ZnS) core-shell nanoparticles with functionalization of (PEG) polyethylene glycol (Au@MnS@ZnS-PEG) for (MRI) magnetic resonance imaging as well as improved cancer therapy.[59] The outcome reveals that, an Au@MnS@ZnS-PEG nanoparticle increases toxicity towards cancer cell. As the paramagnetic Mn^{2+} is present in the core-shell nanoparticle, it can act as a contrast agent for MRI that demonstrates the more accumulation as well as retention of Au@MnS@ZnS-PEG in the mice tumor after intravenous administration.[59] **Figure 4** shows Au@MnS@ZnS-PEG nanoparticle synthesis and its characterization. In these core-shell nanoparticles, the gold core can absorb (IR) ionizing radiation to induce radiotherapy. The inner shell of MnS helps in magnetic resonance imaging and outer shell of ZnS stabilizes MnS by preventing oxidation in aqueous condition, finally, the nanostructure is non-covalently modified with PEG. Further, the designed Au@MnS@ZnS-PEG nanoparticles induce significant *in vitro* cytotoxicity towards cancer cells as well as *in vivo* tumor inhibition after intravenous administration of following nanosystem (figure 4a). The figure 4b demonstrates TEM images of Au@MnS@ZnS-PEG nanoparticles in which Au core, ZnS and MnS shell are distinguishable. Figure 4c shows elemental mapping of Au@MnS@ZnS-PEG nanostructure in order to confirm the presence of all elements present in nanocomplex.

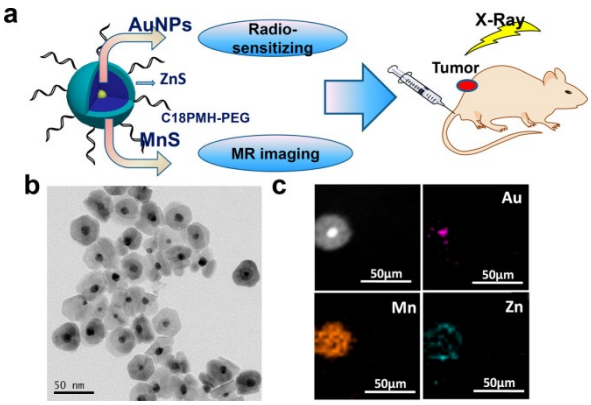


Figure 4. Preparation and characterization of Au@MnS@ZnS core@shell@shell nanoparticles. (a) Schematic illustration of the design of Au@MnS@ZnS nanoparticles. (b) TEM image of Au@MnS@ZnS nanoparticles. (c) Elemental mapping (Au, Mn, and Zn) of a Au@MnS@ZnS nanoparticle. Reprinted with permission from, "Li, M., Zhao, Q., Yi, X., Zhong, X., Song, G., Chai, Z et al. (2016). Au@ MnS@ ZnS core/shell/shell nanoparticles for magnetic resonance imaging and enhanced cancer radiation therapy. *ACS Applied Materials & Interfaces*, *8*(15), 9557-9564." Copyright © 2016 American Chemical Society.

4.3. Angiogenesis

Angiogenesis involves formation of blood vessels from pre-existing one. Several literatures reported the therapeutic angiogenic potential of zinc oxide nanoparticles.[60-62] However, ZnSNPs is not much reported for angiogenic application. The physiological angiogenesis takes place in the granulation tissue to provide supply of oxygen and nutrients.[63]

Wound healing has been extensively investigated to shorten healing duration and minimize scarring. The zinc nanoparticles have shown considerable attention in wound care. In this context, Han et al. demonstrated the ZnSNPs in wound healing in both *in vitro* 2D and 3D model as well as *in vivo* rat wound model.[15] The nanoparticle treatment results in fibroblast cell proliferation, reduction in collagen synthesis, alteration in cytoskeleton organization. The following wound healing results confirmed in rat wound model. Thus, above study evaluated the promising approach of ZnSNPs towards wound repair.[15]

4.4. Anti-bacterial activity

The ZnONPs exhibits potential antibacterial activity over large spectrum of bacterial species. The nanosized ZnO has potential to interact with surface of bacteria as well as core of bacteria where it comes in the cell and exhibits significant bactericidal mechanisms.[64] Due to quantum confinement, the ZnSNPs are potential antimicrobial agents. To this, Morshedtalab et al. reported the antibacterial activity of ZnSNPs against *Acinetobacter baumannii* and *Streptococcus pyogenes*. The ZnSNPs were synthesized by co-precipitation method and antibacterial assessment was carried out using

disc diffusion method. The result demonstrates the more antibacterial activity against *Acinetobacter baumannii*.[14]

Kusrini et al. reported synthesis of ZnS capped with chitosan to form CS-ZnSNPs complex and utilized as antibacterial agent for handwash disinfectant applications.[65] The liquid handwash formulation was prepared using 1% CS-ZnSNPs complex and evaluated for antibacterial activity against *Escherichia coli* as well as *Staphylococcus aureus*. The above formulation demonstrates potent antibacterial activity which suggests it can be used as alternative antibacterial agent for handwash detergent.[65] In other work, Alnehia et al. synthesized ZnSNPs using a garlic extract and characterized by several analytical technique.[46] The antibacterial activity was checked against *Escherichia coli* and *Staphylococcus aureus* which evaluates dose dependent capacity is closer to standard drug azithromycin. The biocompatibility test was checked by erythrocyte hemolysis, exhibits non-toxic nature at highest concentration. Hence, the desired properties of ZnSNPs are potential for biomedical applications.[46]

Figure 5 shows synthesis of chitosan capped zinc sulphide nanoparticle (CS-ZnS) composites for anti-microbial formulations. The zinc nitrate hexahydrate ($Zn(NO_3)_2$•$6H_2O$) was added in chitosan solution. Further, the precursor of nanoparticle was formed by dissolving $Zn(NO_3)_2$ in sodium sulfide (Na_2S) solution. After that, in the mixture of nanoparticles and CS solution was added resulting in the formation of CS-ZnS nanocomposites.

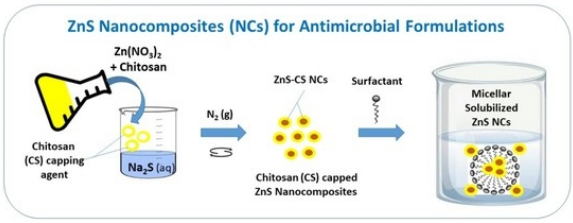


Figure 5. The representative graphical abstract for synthesis of chitosan capped zinc sulphide nanoparticle composites. Reproduced from, "Kusrini, E., Wilson, L. D., Padmosoedarso, K. M., Mawarni, D. P., Sufyan, M., & Usman, A. (2023). Synthesis of Chitosan Capped Zinc Sulphide Nanoparticle Composites as an Antibacterial Agent for Liquid Handwash Disinfectant Applications. Journal of Composites Science, 7(2), 52." Copyright © 2023 MDPI licensed under Creative Commons Attribution (CC BY).

Labiadh et al. reported synthesis of ZnSNPs by combination of thioacetamide and zinc acetate. Further, it screened for antibacterial, antifungal as well as antioxidant profiling.[66] It demonstrates efficient antibacterial activity against *Enterococcus faecalis* and *Bacillus subtilis* as well as antifungal activity against *Alternaria alternate* and *Fusarium solani*. Besides these, ZnS nanocrystals also exhibit better *in vitro* antioxidant activity than ascorbic acid[66].

4.5. Bioimaging

Optical bioimaging is a potential approach for molecular imaging which is useful in recording of cellular as well as molecular processes for therapeutic applications.[67] For this context, Bujňáková et al. synthesized chitosan coated ZnS nanocrystals for bioimaging applications.[47] The nanocrystals were synthesized in chitosan solution using wet ultra fine milling. The nanoformulation was treated in four different cancer cells (HCT116, CaCo-2, MCF-7 and HeLa) and distribution was observed by fluorescence microscopy. The particles crossed the cell membrane, assembled in the cytosol and did not cause cytotoxic effect. Hence, these findings evaluate the significant application of ZnS nanostructure in bioimaging.[47] In another study, Tajoli et al. reported surfactant free doped ZnSNPs for optical bioimaging applications. The crystallization of ZnSNPs doped luminescent ions was attained by microfluidic approach. The effect of ZnSNPs was tested on A549 cells. It did not exert any cytotoxic effect, which strengthening their application as contrast agent for bioimaging.[67]

The nanocrystal semiconductor, QDs are widely utilized as bio-molecular detection tool due to its significant optical properties. The superior brightness, long-term chemical as well as photostability of QDs explore them to enhance bioassay sensitivities.[68] In this context, Verma et al. developed a micro-disk sensor composed of manganese-doped zinc sulfide QDs with a co-immobilized arginine deiminase for arginine detection. It helps in quantitative detection of arginine concentration in several fruit samples.[68] In another work, Caires et al. formulated ZnS fluorescent QDs functionalized with a pH sensitive biopolymer, CM (carboxymethylcellulose) using green colloidal process. The synthesized nanohybrid did not exert much toxicity towards both cancer and normal cells. Hence, these nanoformulations act as the fluorescent nanoprobes for bio-imaging of glioma cells.[69]

In another study, Zhou et al. reported the low-toxic, aqueous and single-pot synthesis of antibody (immunoglobin G)-derivatized luminescent ZnS immuno-QDs.[70] Deng et al. synthesized oil soluble (CIS/ZnS) CuInS2/ZnS QDs by non-injection approach and used for the *in vitro* as well as *in vivo* bio-imaging. Further, the CIS/ZnS QDs were loaded with folate-modified (FA-SOC) N-succinyl-N'-octyl chitosan micelles and targeting efficiency was observed using optical imaging technique in both systems (*in vitro* and *in vivo*). Hence, study confirmed the versatile use of biocompatible CIS/ZnS QDs for multicolor *in vitro* as well as *in vivo* bio-imaging application.[71]

4.6. Biosensor

ZnSNPs have been used for real time and label free detection of biological species. The ZnS QDs have ability to overcome the limitations of organic dyes.[12] Cowles et al. reported the use of ZnSNPs for detection of cardiac biomarker. The ZnSNPs were used as fluorescence signal transducers for detection of C-reactive protein. The C-reactive protein quantification depends on release of zinc ions from ZnSNPs.[72]

Zhang et al. designed the ZnS QDs based uric acid biosensor. It has ability to detect uric acid also in the absence

of an electron mediator. The carboxyl group was functionalized on ZnS QDs. The functionalized ZnS QDs are conductive and biocompatible. It provides more binding site which leads to the better enzyme binding. Thus, this biosensor has more amperometric response than without ZnS QDs.[48] In other study, Negahdary et al. used ZnS nanospheres for design of DNA biosensor for molecular diagnosis of *Aeromonas hydrophila*. The ZnS nanospheres act as electron transfer facilitators and signal enhancers. It detects DNA of *Aeromonas hydrophila* with specificity and high sensitivity.[49]

5. Other Applications of ZnSNPs

5.1. Environmental remediation

The semiconductor based nanomaterials have attracted considerable attention as a novel photocatalyst for environmental remediation. In this context, Lonkar et al. synthesized heterostructured (ZnS-ZnO) zinc sulfide-zinc oxide graphene nanostructured photocatalyst for the environmental remediation. The ZnS-ZnO-graphene nanostructure resulted in the narrowing of band gap than pristine ZnSNPs. Further, it tested for photocatalytic degradation of toxic phenol and harmful organic dyes. This overall strategy provides production of large scale nanophotocatalyst for the environment remediation.[73] **Figure 6** shows schematic presentation of ZnS-ZnO-graphene nanosystem synthesis by solid state thermal process. The zinc hydroxyacetate acts as zinc source and surfeit as a source of sulfur. The graphite oxide acts as a graphene precursor. In ball milling synthesis, the sulfur and zinc hydroxyacetate were made uniform by intercalation on layered graphite oxide. The Zn^{2+} reacts with reactive sulfur under thermal condition and oxygenated species released by disintegration of zinc salt and graphite oxide to generate ZnS and ZnO respectively. The thermally reduced graphite oxide sheets offer support for nucleation sites of ZnS-ZnO, which leads to the uniform dispersion of nanoparticles on graphene.

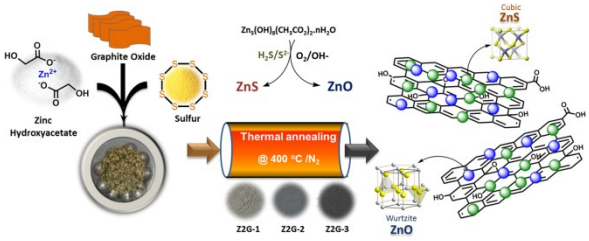


Figure 6. Schematic illustrations for the preparation of the ZnS-ZnO/graphene nanohybrids using solid-state thermal synthesis method. Reprinted with permission from, "Lonkar, S. P., Pillai, V. V., & Alhassan, S. M. (2018). Facile and scalable production of heterostructured ZnS-ZnO/Graphene nano-photocatalysts for environmental remediation. *Scientific reports*, *8*(1), 13401." Copyright © 2018 Nature.

5.2. Photocatalytic dye degradation

The metal sulfides, including ZnS are widely explored for photocatalytic degradation of organic pollutants and their activity.[74,75] For this context, Amakali et al. reported hydrothermally synthesized spiked ZnS nanostructures using $NaBH_4$ as a reducing agent. Further, it is evaluated for photocatalytic degradation of rhodamine B dye and hydrogen evolution from the water splitting reaction.[74] In another work, Thomas et al. reported photocatalytic degradation of dye malachite green by ZnS nanostructures.[75] The ZnS nanostructures were synthesized by hydrothermal method using sodium sulfide and zinc acetate as precursors. Then, the photocatalytic dye degradation potency of ZnS was evaluated for malachite green dye. The altogether result demonstrates that ZnS can be used as an efficient photocatalyst.[75]

6. Toxicological issue, Challenges and future perspective

The tremendous advancement in transition metal technology especially zinc containing nanoparticles is popularly employed in several biomedical fields due to its peculiar chemical and physical properties.[76] These attributes of zinc containing nanoparticles enable them as suitable anticancer, antimicrobial and bioimaging agents. Also, it has been recognized that, it can generate synergistic action when administered with therapeutic agents.[77] Nevertheless, despite their several biomedical applications, it associated with various toxicological issues and challenges regarding ZnSNPs, which obstruct their progress in commercial area.

The metal sulfide nanoparticles have been commonly found in the environment particularly in soil, water and sediments. It is regarded as stable species, though risk and hazard of nanoparticles have attracted huge attention because of their unique physicochemical characteristics compared to the bulk materials.[78] The ZnS was predominant under sulfate reducing condition. It is documented that, the dissolution rate of ZnSNPs in aqueous solution is lower than that of ZnONPs. However, the aquatic organism *Hyalella azteca* exposure to ZnSNPs leads to the similar accumulation of zinc ions as compared to exposure of ZnONPs. It suggests that, tropic transfer of ZnSNPs leads to danger for the environment.[79] Furthermore, the chemical transformation of ZnSNPs to zinc phosphate greatly enhances the bioavailability to organism which cause risk to soil organisms.[78] In another study, Reshma et al. studied the toxicological effect of (ZnSe:ZnS) zinc selenium:zinc sulfide QDs in the *in vitro* (HEK cell line) as well as *in vivo* (swiss albino mice) model. It demonstrated that, the more exposure of ZnSe:ZnS for 24h induces necrosis to the HEK cells. The internalized nanostructure caused lysosomal destabilization and mitochondrial hypopolarization. However, *in vivo* study did not demonstrate any toxicological effect in mouse model.[80] The numerous literatures are focused on *in vitro* studies of ZnSNPs in both cancer and normal cells. For example, the uptake of Zn^{2+} after ZnSNPs treatment was estimated by atomic absorption spectroscopy. The intercellular uptake of ZnSNPs was found to be more in cancer cells, while smaller amount of nanoparticles was internalized in normal cells. This clearly indicates that cell specific internalization of Zn^{2+}.[53, 81]

The distribution of zinc oxide nanoparticle mainly relies on physiochemical properties and route of administration. The report by Mishra et al. suggests that, after intraperitoneal injection, zinc was observed to accumulate in liver, heart, lung, spleen, and kidney, with liver as a major site of deposition.[77] Another study demonstrated that, the maximum accumulation of ZnS QDs in spleen may be due to uptake by the local phagocytes in the spleen.[80] Apart from this, our group has recently reported the detailed toxicity profile of zinc oxide nanoflower (ZONF) in *in vivo* model. It suggests that, ZONF did not exert much genotoxicity as well as *in vivo* toxicity in mice model. It is biocompatible in terms of histopathology of different organs. The maximum accumulation is found in spleen may be due to intraperitoneal administration.[82] These overall finding demonstrate the biocompatible and non-toxic nature of zinc based nanoformulations.

There are a number of challenges in fully comprehending the stability and risk of ZnSNPs in the environment. Firstly, the stability and toxicity of ZnSNPs at relevant concentration have not been studied. The prior studies demonstrate about transformation, stability and risk of ZnSNPs at more doses, which may provide conclusions about environmental risk assessment. Secondly, the ZnSNPs are transported and accumulated through food chain, but their impact on acute toxicity to organisms have not been sufficiently studied, especially with regard to metabolic response. Lastly, the metal sulfide nanoparticles are semiconductor material with photocatalytic and photoresponsive properties that could influence the phototransformation of organic contaminants in the environment. Hence, it is important to address the transformation of organic pollutants in the environment in the presence of ZnSNPs.

Although, ZnSNPs based cancer therapeutic approaches have undergone immense advancement, but therapeutic efficacy is still in infancy. The therapeutic effectiveness mainly relies on its intrinsic properties, for examples, specificity and accumulation efficacy at tumor site. Hence, additional research should be attempted for functionalization of ZnSNPs with appropriate target molecules for better accumulation at tumor site. Additionally, more attention should be given towards biosafety, degradation as well as metabolism of ZnSNPs.

Several aspects are involved in future potential for the development of effective ZnSNPs for a range of biomedical applications. Therefore, prior to commercialization, several factors such as low cost, biocompatibility, characterization and reproducible formulation must be investigated. To increase the therapeutic efficacy, the active targeting through peptide, drugs should be employed. Moreover, the detailed profile of toxicity including biodistribution, clearance, pharmacokinetics, pharmacodynamics and metabolism should be properly evaluated in undergoing clinical trials. ZnSNPs will therefore have an opportunity to become FDA-approved in the future for several of biological purposes after required bio-safety testing in large animals and humans.

7. Conclusion

In past decades, due to multifunctional properties, zinc based transition metal nanoparticles have revolutionized theranostic applications in biology. The ZnS is one of the semiconductors that can be explored for versatile applications in several fields including cancer theranostics, antibacterial, angiogenesis, biosensor and bioimaging. Considering the significant biomedical applications of ZnSNPs, the effective, economically affordable, and safe ZnSNPs can be used as alternative strategy for several diseases. The additional factors including metabolic fate, immunogenicity, efficacy and pharmacodynamics studies should be strictly investigated prior to their commercialization. Considering the multiple benefits in healthcare, the current article will attract the broader view of the scientific community.

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9. Notes and References

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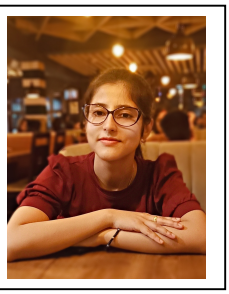
9. About the author(s)

Swapnali Londhe received her B.Sc. (2018) in Nanotechnology and M.Sc. (2020) in Biotechnology from Shivaji University, Kolhapur. She secured 153th rank in Ph.D. entrance exam (CSIR-UGC-NET) held at the national level in June 2020 and joined Dr. Patra's group at the Department of Applied Biology, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad as a CSIR-JRF in 2021. Currently, she works as CSIR-SRF at the Department of Applied Biology and her Ph.D. research involves the design and development of advanced novel nanomaterials for cancer therapy.



Sudipta Saha received her B.Sc. (2018) in Zoology from University of North Bengal and M.Sc. (2020) in Biotechnology from Bangalore University. She secured 94th rank in Ph.D. entrance exam (CSIR-UGC-NET) held at the national level in June 2022 and joined Dr. Patra's group at the Department of Applied Biology, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad as a UGC-JRF in 2023. Currently, she works as UGC-JRF at the Department of Applied Biology and her Ph.D. research involves the design and development of advanced novel nanomaterials for drug delivery for neurodegenerative diseases.

Dr. Chitta Ranjan Patra received his Ph.D. in Chemistry from the CSIR-National Chemical Laboratory (NCL), Pune. Dr. Patra is currently the Senior Principal Scientist at the Department of Applied Biology, CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad. He is also an Associate Professor of Biological Sciences in the Academy of Scientific & Innovative Research (AcSIR), Ghaziabad. Dr. Patra's research group is pursuing various nanomedicine research projects aimed at developing advanced biomaterial- and nanoparticle-based drug delivery systems (DDS) for the treatment of cancer, cardiovascular and ischemic disease, wounds and bacterial infection.

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