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Review Article

Inorganic Nanomaterials: A Brief Overview of the Applications and Developments in Sensing and Drug Delivery

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Abstract

Recent investigations have been shown that inorganic nanomaterials including gold nanoparticles, nonporous and mesoporous silica nanoparticles, magnetic nanoparticles, and quantum dots have shown great potential in bioimaging, targeted drug delivery, and cancer therapies. Biocompatibility, ease of synthesis, and ease of surface functionalization are among the significant properties of nonporous and mesoporous silica nanoparticles in various nanomedicine applications. Quantum dots due to their high brightness, long-lasting, wide and continuous absorption spectra, and high fluorescent quantum yield are being used as the new optical probes for bioassays. In addition about gold nanoparticles, the ease of preparation, stability, low cytotoxicity, and high extinction coefficient of light from visible to NIR regions are some properties that introduced them as important candidates in cancer drug and nanocarrier development. As a specific type of inorganic nanomaterials, magnetic nanoparticles that exhibit super paramagnetic are capable of being used as contrast agents in magnetic resonance imaging, site-specific gene and drug delivery, and diagnostic agents in the presence of an external magnetic field. This review will present the physicochemical properties of most popular inorganic nanoparticles and their recent applications in sensing and drug delivery.

Keywords: Gold Nanoparticles, Silica Nanoparticles, Magnetic Nanoparticles, Quantum Dots

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Introduction

Nanomedicine is an emerging field involving the application of nanoscience to develop biomedical tools to achieve the advanced procedures of molecular diagnosis, gene/drug delivery/discovery systems, and bioimaging methods [1, 2]. Various nanostructures in size and shape with different physicochemical properties have created various types of morphologies in nanoscale including nanopores, nanospheres, nanoclusters, hollow spheres, yolk shells, nanorods, nanotubes, nanowires, core-shell, etc. [3-5].

These nano-structures can be made of metals, metal oxides, alloys, carbon, and other types of organic materials. Among these nanomaterials, silica nanoparticles (SNPs), gold nanoparticles (GNPs), quantum dots (QDs), carbon based and biopolymeric nanostructures are the most popular types which are applied in the nanomedical area.

When compared, each of them has specific applications with advantages and disadvantages. For example, silica nanostructures are usually applied as a support for drug loading while gold nanoparticles are particularly used with photothermal agents in cancer therapy and biosensing.

On the other hand, considering fluorescence features, QDs are famous because of their biosensing applications. The super paramagnetic properties of magnetic nanoparticles (MNPs) make them suitable as imaging tools in magnetic resonance imaging (MRI). Table 1 has presented the properties and the biomedical application of most famous inorganic nanomaterials. In this review, we will summarize the recent studies on the application of most popular inorganic nanomaterials in sensing and drug delivery.

Nonporous silica nanoparticles (NSNs)

Nonporous silica NPs as one of the most important types of silica nanoparticles has attracted significant interest in nano-biotechnology [6]. The surface silanol groups, (-Si-OH), that is always present on the silica nanoparticles surface, can be easily functionalized with amine and carboxyl groups [7-9]. As a result of this process, NSNs with positive, negative, or zwitterionic surface charges will be prepared. The surface charge and surface chemistry of NSNs play important roles in determining the interaction of nonporous silica nanoparticles with different biomolecules (e.g., DNA, proteins, and drugs) and cells. Different unique properties of NSNs, such as their hydrophobic surface, highly controllable size and shape, ease of surface functionalization, as well as their high mechanical stiffness, and ease of large-scale synthesis have been reported. Additionally, numerous biomedical applications of NSNs in hydrophobic drug delivery systems, as well as their utilization in gene and small molecular delivery procedures, and protein encapsulation process have also been confirmed. Different proteins and drugs can be encapsulated onto NSNs through in situ synthesis methods. Copper-zinc superoxide dismutase, cytochrome c, and myoglobin were encapsulated in transparent silica glass without any significant loss in their structure and function [10-12]. As mentioned above, as a delivery platform for protein and peptide biopharmaceuticals, NSNs not only have improved their stability, therapeutic potential, safety,

Table 1. The most famous inorganic nanomaterials, their superior properties and biomedical applications.

Type	Superior properties	Biomedical applications
NSNs	- Hydrophobic surface - Controllable size and shape - High mechanical stiffness - Ease of surface functionality	- Encapsulation of various proteins and drugs - Reinforcement of polymer matrix for tissue engineering - Gene and drug delivery
MSNs	- High surface area - High pore capacity - Controllable morphology in size and shape	- Various drug loading by selective drug release manner
QDs	- Unique luminescence and electronic properties such as high brightness, long-lasting, wide and continuous absorption spectra, narrow emission spectra and high fluorescent quantum yield	- New generation of optical probes for biomedical assays
GNPs	- Stability - Relative biocompatibility - Coefficient of light - High extinction Surface - Localized surface plasmon resonances (LSPR)	- Photothermal agents in cancer therapy - A proper matrix for biosensing applications - Immunoassay
MNPs	- Magnetic properties and nontoxicity	- Contrast agent in magnetic resonance imaging (MRI) - Site specific gene/drug delivery - hyperthermia treatments

bioavailability, and physicochemical properties, but also reduced their side effects [13, 14]. In most of the previous studies, there are two general strategies for incorporating drugs into/onto silica matrix in nonporous silica nanoparticles: (*a*) encapsulation and (*b*) covalence bond [15, 16]. In covalence attachment, drugs are covalently bonded with siloxane groups through degradable ester bonds. However, the encapsulation strategy involves the covalence attachment of drugs with the silica matrix through co-condensation with tetraethyl orthosilicate (TEOS) via the Stöber method [17]. Decreasing in pH leads to slow decomposition of the silica nano platform and consequently leads to the gradual release of encapsulated drugs [18]. The pioneering work on the development of dye-encapsulating particles was synthesized by encapsulation of Cy5 dyes onto modified Stöber-type silica nanoparticles coated with polyethylene glycol (PEG) molecules, in the Benezra group [19]. The PEG molecules was attached to αvβ3 integrin–targeting cRGDY peptide ligands (cyclic arginine–glycine–aspartic acid) and then the peptide ligands were labeled with the positron-emitting radionuclide ^{124}I through the use of a tyrosine linker to provide a signal that can be quantitatively imaged by Positron Emission Tomography (PET) (Fig. 1). The ^{124}I-cRGDY-PEG-ylated silica nanoparticle dots were approved as effective cancer-targeted probes for a first-in-human clinical trial [20].

Mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles are promising candidates as novel drug delivery system. Large internal surface area, extremely high pore capacity controllable morphologies (size and shape), biocompatibility, ease of synthesis, and ease of surface functionalization are among their significant properties in various nanomedicine applications, particularly as nanocarriers for drug delivery systems [22, 23]. The stimulated release of loaded drugs through the grafting of lids is one of the remarkable properties that used as a strategy for preparation of the drug delivery vehicles using mesoporous silica nanoparticles. One common stimulation method is based on GSH-triggered drug release (is a redox-responsive system). Under this strategy, the disulfide linkages between the capping agents andthe surface silanol groups of MSNs are reduced by intracellular GSH, leading to the removal of capping

agents and releasing the loaded drugs. In a study by Tan *et al*., the effect of surface functional groups on the drug encapsulation and release by MSNs was investigated.

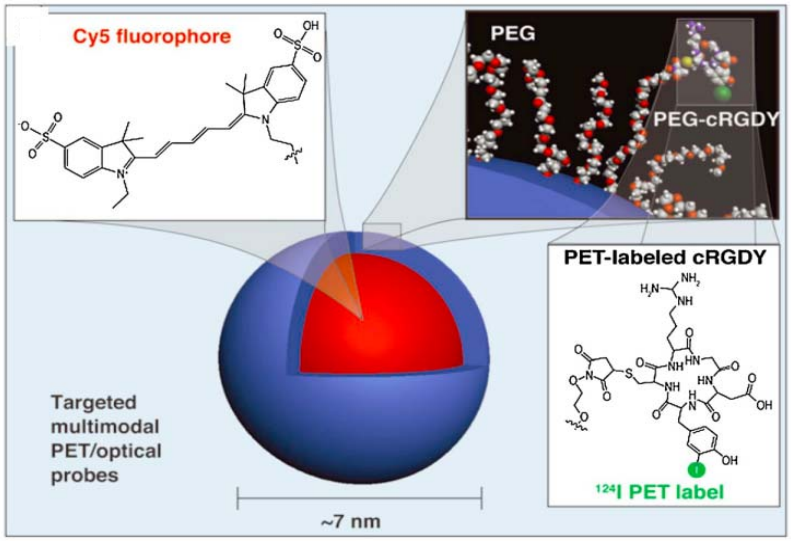

Figure 1. Schematic representation of the ^{124}I-cRGDY-PEG-ylated core-shell silica nanoparticle with surface-bearing radiolabels and peptides and core-containing reactive dye molecules [20]. cRGDY, cyclic arginine–glycine–aspartic acid peptides; PEG, polyethylene glycol; PET, Positron emission tomography

Their study concluded that the length and terminal groups of ligand could affect the drug-capping and release efficiency. In addition, the amount of the ligand on the surface of MSNs and the binding of the ligand with β-CD (as the end cap) are two main parameters that can be affected bythe surface coverage, drug loading capacity, and release kinetics. The release mechanism from β-CD-capped and DOX-loaded MSNPs was triggered by GSH [24].

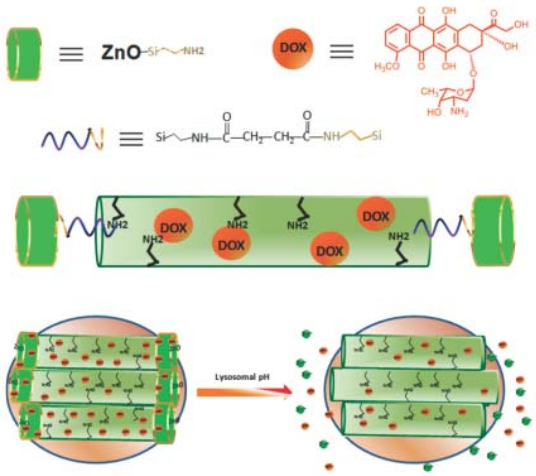

Figure 2. Representation of ZnO@MSNs-DOX. Mesoporous silica nanoparticles are loaded with the cationic anticancer drug doxorubicin molecules and end-capped with amine-functionalized ZnO nanoparticles. At the acidic environment of cancer cells, the ZnO lids are decomposed and the doxorubicin drugs released from the pores into the cancer cell [28].

The pH-triggered uncapping is another common strategy for selective drug release in cancerous cells. Muhammad *et al*., have developed a pH-triggered system from MSNs via intracellular dissolution of ZnO nanolids to the controllable release of cationic anticancer drug doxorubicin (ZnO@MSNs-DOX) [25]. In summary, they have demonstrated that ZnO quantum dots lids on MSNs can efficiently inhibit the release of the loaded DOX in undesirable sites. On the other hand, ZnO quantum dots lids dissolved in the acidic environment (lysosomal pH) of cancer cells, led to the release of the drug cargo from the pores of the MSNs into the cytosol (Fig. 2). Super paramagnetic iron oxide nanoparticles (SPION), CdS nanocrystals, and (G2) PAMAM dendrimer are examples of other lids that were used to achieve controlled release of different drugs [26-28].

In overall, targeted delivery system based on the polymeric nanoparticles as a drug carrier indicates the odd route for cancer therapy. The vital characteristics of this system comprise non-toxicity, biodegradability, prolonged circulation, biocompatibility, and a broad payload spectrum of a therapeutic agent. Other prominent aspects are their shape properties and their specific size for tissue penetration through an active and passive targeting, specific cellular/subcellular trafficking pathways and facile control of cargo release by sophisticated material engineering [29].

Quantum dots

Quantum dots, also called colloidal semi-conductor nanocrystals, are defined as the crystals of a fluorescent semiconductor material composed of atoms of elements from groups II–VI or groups III–V, with a diameter of as few as 10 to 100 atoms (2-10 nm) [30]. Structurally, QDs

are composed of an enclosed core-shell configuration with a core (typically composed of CdS, CdSe, and CdTe) and a shell (typically composed of ZnS, ZnCd, and CdS) [31, 32]. In general, the overall size of these core-shell nano-assemblies is small, ranging from 4 to 12 nm in diameter (Fig. 3). Due to their unique intrinsic features, including high brightness, long-lasting, wide and continuous absorption spectra, narrow emission spectra and high fluorescent quantum yield, they are widely used as the generation of optical probes for bioassays.

Figure 3. The schematic core-shell configuration of the quantum dot, with a core that typically composed of CdS and CdSe and a shell that typically composed of ZnS, ZnSe, and CdS [38].

It must be noted that the synthesis of quantum dots results in an organic core-shell nanocrystals that are always nonpolar. Therefore, to make them "water soluble," an amphiphilic polymer is used to encapsulate the QDs. More recently, Gordon *et al*., coated the CdSe/CdS quantum dots with a radioactive ZnS. Subsequently, the prepared radioactive core-shell nanostructure was encapsulated by an amphiphilic polymer for in vivo experiments (Fig. 4) [33].

Functionalization of quantum dots with PEG, polyethyleneimine (PEI), dihydrolipoic acid (DHLA), dendrimers and multidentate phosphine polymers provides a super physicochemical stability and biocompatibility for the QDs within aqueous environments. For liver cancer diagnosis, water-stable quantum dots (QDs) were prepared using QDs with oleylamine ligand coated with poly (aspartate)–graft–poly (ethylene glycol)–dodecylamine (PASP–Na–g–PEG–DDA). The prepared nanocompositewas conjugated with vascular endothelial growth factor (VEGF) antibody for detecting liver cancer cells. The surface of quantum dots can be covalently or non-covalently conjugated to antibodies, proteins, peptides, aptamers, and nucleic acids as cellular imaging contrast agents [32]. For example, the CdTe QDs-F3O_4 nanoparticles were conjugated with hCC49 antibodies Fab region to assess their potential as fluorescent probes for LS174T cancer cells [34, 35]. For in vitro imaging of cancer biomarkers, Mee *et al*., developed RGD peptide-conjugated QDs (QD-RGD) and AS1411 aptamer-conjugated QDs (QD-AS1411) called integrin αvβ3 and nucleolin, respectively. Infact, QDs-based imaging has opened up a new field in proteins, nucleic acids, and differentbiomarkers detection, as well as in cellular and in vivo targeting and imaging. It should be highlighted that silicon QDs (Si QDs), carbon dots (C-dots), graphene quantum dots (GQDs) and near-infrared QDs such as Ag_2Se and Ag_2S have attracted much interest from researchers as the new generation of QDs over the past few years [36-39]. The unique optical and electrical properties and low toxicity have provided them considerable advantages over commercial quantum dots.

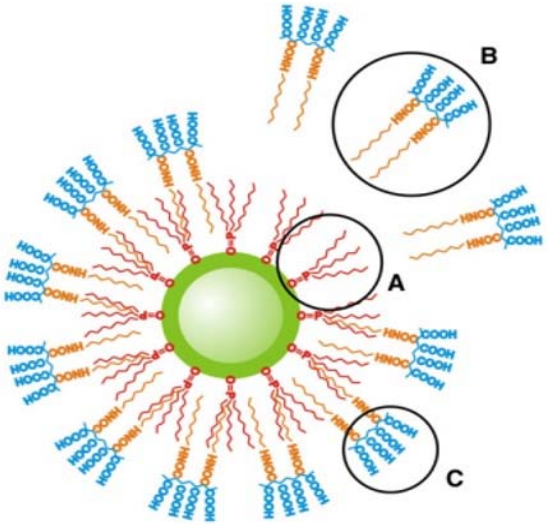

Figure 4. Amphiphilic polymer encapsulation strategy, (A) attachment of the original nonpolar polymer on the surface of bare QDs. (B) an amphiphilic ligand is used as the second layer on the bare QDs to make them in water-soluble form. (C) chemically functionalization of water-soluble QDs for conjugation of different ligands [39].

Current drugs use for treatment of cancer has several disadvantages like high toxicity, which have been overcome by apply the direct targeting property of QDs. QDs could selectively deliver drug to the target location, and by the imaging property, we could analysis whether the drug reached the target location or not. Nanoparticles of QDs has long blood circulation time, controlled drug release profile, protection, large drug-loading capacity, and integration of multiple targeting ligands on surface. Also , the improvement can be gained through carbon nanotubes (CNTs) for intracellular delivery of antisense oligonucleotides tagged with QDs [40]. QDs are used as biomarkers for cancer detection in cancer cells. This is for diagnosis, forecasting of disease stage, and clinical management. QDs are 20 times brighter and 100 times more stable than traditional fluorescent reporters. QDs are dramatically better than existing methods for delivering a gene-silencing tool, known as siRNA, into cells [41].

Gold nanoparticles

Colloidal gold nanomaterials with different size and shape (e.g., nanorods, nanocages, nanocubes) are good candidates as nanocarriers for biomedicine and drug delivery. The ease of their preparation, their stability, low cytotoxicity, and high extinction coefficient of light from visible to NIR regions have introduced them as importantcandidates in cancer drug and nanocarrier development. Au nanorods (NRs) due to their NIR absorption characteristics were used for laser-induced hyperthermia treatment of cancer cells [42]. Due to the unique properties of a gold nanoparticle, they can be functionalized by different biomolecules, including proteins, antibodies, and different biomarkers. Over the past two decades, their high molar absorption coefficient in the range of visible to near IR region and surface plasmon resonance (SPR), made them as superior photothermal agents in cancer therapy and biosensing of different biomolecules in therapeutic applications [43, 44]. In addition, gold nanoparticles are ideal nanocarrier for reversibly binding of hydrophilic as well as the hydrophobic drug. Doxorubicin (Dox) and pyrene (Pyr) as model hydrophilic and hydrophobic molecules, respectively, were encapsulated into Au NP–Lysozyme agglomerated particles by Khandelia group [45]. The findings suggest that the fabricated novel Au NP–Lysozyme agglomerate-based nanocarriers have excellent potential in drug-loading and releasing processes and can act as multimodal drug delivery vehicles. On the other hand, it has been demonstrated that Au NPsare, effective photodynamic therapy agents. A 4-component photodynamic agent (antibody-zinc phthalocyanine-PEGylated GNPs) was fabricated by covalent attachment of the anti-HER2 monoclonal antibody to the PEGylated gold nanoparticles and used as a potential drug for targeted photodynamic cancer therapy in breast cancer [46-48]. Moreover, gold nanoparticles are introduced as an effective platform for the detection of foodborne pathogens.

For example, new antibody/GNPs/magnetic nanoparticle nanocomposite was used for the detection of a food borne pathogen, *S. aureus* in milk. The prepared nanocomposite (antibody/AuNPs/MNPs) was synthesized by the magnetic nanoparticles coated with BSA (bovine serum albumin) then gold nanoparticles and anti-*S. aureus* antibody adsorbed on the surface of BSA coated MNPs [49].

Gold nanoparticles (AuNPs) are a good application for engineering and studying bio interactions. The surfaces of these particles can be tuned using thiol-based ligands that bind forcefully to the gold surface. Well-formed monolayers can be generated for small particles, providing chemical control of the surface through the generation of homogeneous and mixed monolayer particles. Larger particles can be similarly functionalized; although, their surface structure is by nature minus regular, featuring ligands and ionic species at the surface. Next, elemental gold is nontoxic, meaning that the lessons we learn with AuNPs can be directly translated to real-world applications [50].

AuNPs have been also uses as tags for molecular detection and characterization protocols for in vitro applications. In the in vivo technology, AuNPs have been shown to be able to carry therapeutically active compounds, to be suitable for surface functionalization with multiple targeting moieties with high affinity and specificity for cancer cells and to show a high capability to accommodate therapeutic and imaging agents simultaneously, turning them into powerful theranostic platforms [51].

Commonly radiation therapy (RT) is used for cancer therapy with ionizing radiation. The final purpose of RT is to eradicate all the abnormal cells while sparing healthy tissue. The targeted RT with gold nanoparticles (GNPs) is survey as a tool to enhance the RT therapeutic ratio further [52].

Magnetic nanoparticles

As a specific type of inorganic nanomaterials,magnetic nanoparticles (MNPs)that exhibit superparamagnetic, are capable of being used as contrast agents in magnetic resonance imaging (MRI), site-specific gene and drug delivery, and diagnostic agents at the presence of anexternal magnetic field[53, 54].Their specific physical and chemical properties make them ideal materials for biological studies. Super paramagnetic iron oxide nanoparticles (Fe_3O_4, Fe_2O_3), gadolinium oxide nanoparticles (Gd_2O_3) and manganese-based nanoparticles (e.g. MnO, Mn_3O_4) are the most frequently used MNPs that have gained tremendous interests in clinical MRI [55-56]. To make these biocompatible MNPs for biological applications, they are usually coated with different water-soluble molecules including, cationic polymers (e.g. PLL, PEI), cationic lipids, and dendrimers (e.g. polyamide amine, PAMAM)[57-58]. For target-specific delivery, MNPs can be conjugated with suitable biomolecules, such as antibodies and positively charged amino acids to increase their uptake by tumors [59]. Also, the selectivity and cellular transfer of magnetic nanoparticles can be improved. Brian *et al*., reported a biocompatible ironoxide MNPs conjugated with the prostate-specific membrane antigen (PSMA)-targeting antibody, J591, to enhance MRI of prostate cancer [60]. This study demonstrates that PSMA-targeted MNPs can significantly increase the magnetic resonance contrast of prostate tumor compared to MNP alone (non-targeting MNPs).This study provides that compared to MNP alone (non-targeting MNPs), PSMA-

targeted MNPs can significantly increase the magnetic resonance contrast of prostate tumor, In another representative study, Xing *et al*., fabricated a multifunctional nanoprobe for simultaneous molecular imaging and target-specific delivery of siRNA, comprising a magnetic-nanoparticle platform (MEIO) doped with manganese nanoparticle and coated with serum albumin on witch, a cell-specific targeting moiety (RGD), a fluorescent dye (Cy5), and therapeutic siRNA in one system (MnMEIO-siGFP-Cy5/PEG-RGD). The prepared "all-in-one" nanoprobe can be delivered to target cell by integrin receptors via endocytosis process [61].

Conclusion

This overview presented recent studies in the application of nonporous silica nanoparticles, mesoporous silica nanoparticles, quantum dots, gold nanoparticles, and magnetic nanoparticles as therapeutic agents in the sensing and drug delivery. However, there are various organic FDA-approved nanodrugs; only a few FDA-approved inorganic nanoparticle-based nanomedicine have been used in the clinic. Since most inorganic nanodrugs remain in the preclinical stage or at the cellular and intact animal level. To achieve maximum prosperities in the field of inorganic based nanodrugs, further research is required on the understanding of possible interactions between inorganic nanomaterials and biological systems from the molecular-prospective. The emerging nanotechnology helps to build drug delivery systems as a potential approach to overcome some of the barriers for efficient targeting and therapy in cancer cells. However, great efforts and innovations are needed to overcome the challenges of using inorganic nanocarriers used in sensing, clinical imaging, drug delivery, and therapeutics.

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