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Surface Engineering of Multifunctional Nanocomposites for Biomedical Applications: A Brief Update

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Context: In recent years, nanotechnology has opened up several new doors of extraordinary biomedical potential by modulating metals into their nanosize leading to significant improvement in their chemical, physical and optical properties.

Introduction: The advanced fabrication techniques have been exploited to modify nanostructured materials. The functionalized nanoscaled fibers display various exclusive features like high surface area to volume ratio, tunable porosity, and maneuverable surface with desired functions. Additionally, surface modification stabilizes nanoparticles against agglomeration, provides compatibility with the other phase and presents them in a highly self-organized structure with desired properties. This study gives an overview of nanoparticles significantly improved by fabrication technology, and made suitable for extensive biomedical applications. The strategies included the introduction of some functionalities like grafting of an already functionalized ligand on the surface of nanoparticle, exchanging a part or whole of the existing ligands on its surface, or grafting of a ligand on a nanoparticle followed by modification via organic chemical reactions have also been reviewed. The applications of various surface modified carbon nanotubes and silica based nanoparticles in biomedical/biotechnological sectors are also outlined.

Conclusions: Since purity, dispersity, and stability of multifunctional nanoparticles are highly important in a physiological environment for *in vivo* biomedical applications, the newly developed surface modified nanoconjugates can be used for cancer cell imaging, tumor ablation and drug delivery.

*Keywords:*Biomedical Application; Colloidal Stability; Ligands; Nanochemistry; Surface Stabilization

1. Context

Nanoparticles constitute intentionally engineered materials below 100 nm in diameter possessing controlled sizes, shapes and surface chemistries. The chemical, optical and electronic properties of nanoparticles lead to exceptional biological effects that are unique compared to their equivalent larger scale materials. Variations in particle size and surface chemistry can affect the degree of toxicity to expand their application in several electronic, optical and microgravimetric transduction serving different biomolecular recognition events (1, 2).

Surface modification of nanoparticles is an important challenge that needs to be properly executed to achieve the desired results. It is one of the most common methods applied to improve the dispersion stability of nanoparticles and requires designing of the surface structure based on the type of nanoparticles and the liquid media. Several types of physical and chemical methods have been recently used to modify the nanoparticles. Surface modification also enhanced the electrochemical reactivity of biomolecules by promoting electron transfer reaction of proteins. The ligands applied to modify PLGA nanoparticle surface control their growth during synthesis and prevent their aggregation due to electrostatic repulsion and steric exclusion. With the current progress, nanotechnology has revolutionized the biomedical field including diagnostic techniques and therapeutic improvements (3, 4).

2. Introduction

2.1. Surface Modification of Nanoparticles for Drug Delivery Systems

Nanotechnology has significantly contributed to the advancement of drug delivery and its application. Excellent properties exhibited by nanoparticles have enabled their extensive application as a drug delivery approach for various difficult-to-formulate pharmaceutically active ingredients. Therefore, several nanoparticle-based strategies have been adopted to make drug delivery more precise and targeted including the application of nanocomposites which has gained unprecedented momentum both in academics and pharmaceutical industry. Over the past decade, considerable efforts have been directed to formulate both hydrophilic and hydrophobic therapeutic moieties in biocompatible nanocomposites such as nanoparticles, nanocapsules, micellar systems and conjugates (5).

Several other PLGA-based nanocomposites (core-shell-type) have also been fabricated using nanoprecipitation and emulsion-solvent-evaporation methods, to impart specific functions such as longer half-life, stimuli-sensitivity, target specificity, and bioadhesion (6, 7). Bioadhesive cationic PLGA nanocomposites with a chitosan shell have also been found suitable for the oral and localized delivery of drugs as well as nucleic acids to target tissues (8-10). The drug-loaded PLGA nanocomposites containing a ligand shell of antibody, folate, peptide or protein were highly efficient in augmenting the drug uptake into the cells of interest (11-13). Nanocomposites containing chitosan, alginate, and hyaluronic acid have also undergone considerable investigation for the delivery of drugs owing to their exceptional cationic and mucoadhesive characteristics.

Phanapavudhikul et al. (14) reported the details of an iron oxide nanoparticle composite achieved by encapsulating nanosized magnetite with an acrylate-based cationic copolymer made from methyl methacrylate, butyl acrylate, and quinolinyl methacrylate and modified with methoxy polyethylene glycol methacrylate by water-replacement method using aspirin as its model drug. Polyethylenimine-coated hollow manganese oxide nanoparticles were surface functionalized by 3,4-dihydroxy-L-phenylalanine for cancer targeted siRNA delivery and MRI. They proved to be highly efficient in delivering therapeutic siRNA into human breast cancer cells. They could be potentially utilized as multifunctional agents for cancer therapy by siRNA and MRI based diagnosis. Wang et al. (15) have demonstrated that nanoparticles of Fe_2O_3core with fluorescent SiO_2 shell, grafted with hyperbranched polyglycerol and conjugated with folic acid (FA) are preferentially up taken by human ovarian carcinoma cells (SKOV-3) compared to macrophages and fibroblasts.

Several research efforts have also been recently directed to develop pharmaceutical applications of chitosan based nanoparticulate drug delivery systems for efficient release of drug and to impart improved colloidal stability, biocompatibility and specific target ability to them (16). A study was conducted in which polyethylene glycol (PEG), FA and their conjugate, PEG-FA were used to functionalize the surfaces of magnetite nanoparticles for intracellular uptake of nanoparticles to human breast cancer cells, BT-20 (17). Biocompatible superparamagnetic nanoparticles have been exploited earlier for MRI contrast enhancement, hyperthermia, magnetic field assisted radionuclide therapy, and tissue specific release of therapeutic agents. The superparamagnetic magnetite nanoparticles have been surface modified with PEG and FA to improve their intracellular uptake for targeting specific cells (mouse macrophage and human breast cancer cells), and quantified by inductively coupled plasma emission spectroscopy. It indicated that both PEG and FA modifications facilitated nanoparticle internalization into the breast cancer cells. However, the uptake amount of PEG-modified nanoparticles into macrophage cells was much lower than that of unmodified nanoparticles. Therefore, PEG and FA modification of magnetite nanoparticles can be used to avoid protein adsorption, which can facilitate nanoparticle uptake of specific cancer cells in cancer therapy and other related diagnoses (18). This approach has been exploited to solubilize paclitaxel (PTX), a difficult to dissolve anticancer drug. FA coated paramagnetic iron nanoparticles (Fe-NP)-PTX conjugate was found to possess significantly higher solubility. The surface functionalized magnetic nanoparticles have also been studied to evaluate their suitability in implant assisted magnetic drug targeting. Hua et al. coated surface modified Fe_2O_3 nanoparticles with 1,3-bis(2-chloroethyl)-1-nitisourea and reported its elevated concentration in brain tumors using an externally applied magnet (19).

Yamamoto et al. (20) investigated surface modification of poly (N-isopropylacrylamide) onto magnetite nanoparticles. Temperature responsive behavior of modified magnetite nanoparticles was studied by XPS, TEM, and dispersion measurement. It exhibited a highly sensitive temperature responsive behavior compared to unmodified magnetite nanoparticles under similar conditions. Another versatile method involving hydrolysis and condensation of cyanoethyltrimethoxysilane (CES) was developed to introduce cyano groups on the surface of iron oxide nanoparticles. The optimal concentration of silane coupling agent was determined to obtain an appropriate surface density of activating groups on nanoparticles whereas size distribution of nanoparticles was optimized by the magnetic size sorting procedure. The synthesized nanoparticles proved to be very good candidates for biomedical applications and provided

new perspectives on vectorization in *in vitro* cellular labeling studies (21).

Manganese doped zinc oxide nanoparticles have been surface modified by n-butylamine and characterized using XRD, FTIR, zeta potential and UV-Vis spectroscopy. It was observed that these modified nanoparticles possessed a very thin layer of organic coverage around inorganic nanoparticles, thereby giving rise to hybrid nanoparticles. These modified nanoparticulates were hydrophilic in nature and were well dispersed in various solvents. Moreover, photo degradation of Brilliant Blue dye showed higher efficiency of modified nanocomposites compared to the reagent grade ZnO under similar incubation conditions (22).

2.2. Surface Modification of non-Magnetic Nanoparticles

There has been a significant refinement in the techniques employed for surface engineering of non-magnetic nanocomposites to introduce a variety of organic or inorganic ligands to obtain well defined nanostructured materials like nanorods with controllable shapes and crystal structure. These surface modification techniques have also allowed different kinds of polymers, molecules and peptides to be "decorated" on NPs to achieve minimal nanoparticle aggregation and reduce nanoparticle non-specific binding.

Functionalization of TiO_2-NPs surfaces was investigated in a 2-stage process by utilizing 1-decylphosphonic acid and diethyl 1-decylphosphonate as surface modifiers, and was characterized by thermogravimetric analysis (TGA), transmission electron microscopy (TEM), differential light scattering (DLS), atomic force microscopy, and fourier transform infra-red spectroscopy (FTIR) (23). A solvothermal method was employed to prepare TiO_2-NPs while controlling their rod shaped growth by titanium (IV) isopropoxide and butyl ether as the precursor and solvent, respectively, and oleic acid and decanoic acid as the surfactant. The synthesized TiO_2 nanospherical particles (3.5 nm) and nanorods were uniform and transparent in toluene. The direction of TiO_2 nanorods growth was [001] and band gap energy of TiO_2 nanorods was 3.34eV as evaluated by optical absorption (24). Similarly, silica nanoparticles were surface modified with tetraethyl orthosilicate and other organosilane reagents for biomedical applications by Maurer et al. (25). Moreover, Campoa et al. have introduced amine groups onto the surface of magnetite and silica-coated magnetite nanoparticles by APTES condensation. Amine modified nanoparticles were grafted with oligonucleotide, and were used in capturing a complimentary sequence to correlate with amine group surface density in producing high performance materials (26).

A novel reversible addition-fragmentation chain transfer (RAFT-CTA) was synthesized by Ranjan and Brittain (27) which permitted the possibility of using a combination of RAFT polymerization and click chemistry for surface modification. Silica nanoparticles were surface modified with polystyrene and polyacrylamide via this approach. A click reaction was used to attach polymers onto the surface which produced relatively high grafting density. Kinetics of 6-azidohexyl methacrylate (AHMA) polymerization mediated by 4-cyanopentanoic acid dithiobenzoate (CPDB) anchored nanoparticles was investigated and compared with that of AHMA polymerization mediated by free CPDB under similar conditions. The subsequent post functionalization study of PAHMA-grafted nanoparticles was demonstrated by reacting with various functional alkynes via click reactions. Kinetic studies showed that the reaction of surface-grafted PAHMA with phenyl acetylene surface-grafted PAHMA was much faster than that of free PAHMA (28). RAFT-CTA was also used to synthesize SH-functionalized poly (N-isopropylacrylamide) (pNIPAAm), and was utilized to generate pNIPAAm surface modified microspheres via thiol-ene modification. The accessible double bonds on microsphere surfaces allowed direct coupling with thiol-end-functionalized pNIPAAm. In another approach, pDVB microspheres were grafted with poly (2-hydroxyethyl methacrylate) (pHEMA). For this purpose, the residual double bonds on microsphere surfaces were used to attach azide groups via thiol-ene approach of 1-azido-undecane-11-thiol. In the second step, alkyne end-functionalized pHEMA was used to graft pHEMA to the azide-modified surface via click-chemistry (29, 30).

2.3. Surface Modification of Carbon Nanotubes

Carbon nanotubes (CNTs) have been actively explored for various biomedical applications because of their certain unique structural, optoelectronic, mechanical, thermal, and chemical properties. However, there are several difficulties (poor solubility in organic and inorganic solvents, high cytotoxicity, formation of highly complex and enmeshed structural bundles and finally their relative chemically inert nature under many chemical reaction conditions) in manipulation of CNTs in order to make them suitable for large scale biological utility. Many of these issues have been partly addressed by surface modification of CNTs by chemical means which has resulted in enhanced dispersion, increased solubility, and reduced cytotoxicity (31). The surface modification of CNTs with dendrimers or hyperbranched polymers resulted in significantly enhanced solubility in organic solvents.

Shi and He (32) have illustrated that plasma deposition of thin films on CNTs resulted in great enhancement of dispersion and interfacial bonding in polymer composites. The fracture behavior and tensile strength data indicated that well dispersed CNTs enhanced interfacial shear strength. CNTs were also functionalized by polymer wrapping and oxidation, followed by reduction of

copper ions in hydrogen atmosphere, producing copper decorated carbon nanotubes. The synthesized hybrid nanostructures were used as conductive fillers to tailor the heat transport capabilities of a copper matrix.

Similarly, Najeeb et al. (33) have prepared nanocomposite ink with carboxyl-functionalized single walled carbon nanotubes (SWCNTs) to decrease electrical resistance for line patterns, making them suitable for extensive application in various fields such as flexible high speed transistors, high efficiency solar cells, and transparent electrodes. SWCNTs have also been modified with polyethylene via in situ Ziegler Natta polymerization. Scanning electron microscopy and solubility measurements showed that the surface of SWNTs was covered with polyethylene resulting in the formation of cross-links. Surface modified SWCNTs exhibited better mechanical properties compared to naked SWCNTs. Several approaches have been recently used to graft functional groups non-covalently or covalently at the surface of carbon nanotubes to add new properties like dispersion in organic and aqueous media or their dispersion in polymer matrixes aiming to enhance properties like tensile strength, thermal stability, and electrical conductivity (34, 35). A detailed study on surface modification of multi-walled carbon nanotubes (MWCNTs) by trifluorophenyl has been reported. They were also modified using plasma polymerization with ethylene glycol and plasma-polymerized ethylene glycol coating and were characterized by TEM and FTIR. The modified MWCNTs exhibited improved hydrophilic behavior in water, methanol, and ethylene glycol as solvent. TGA analysis suggested that hydroxyl groups of ethylene glycol coated MWCNTs possessed higher thermal stability (36). Such functionalized MWCNTs may prove promising reinforcement in polymers and other matrices to produce nanocomposites materials of unique physical properties in automotive and aeronautic industries. MWCNTs were recently modified with tridecafluoro-1,1,2,2-tetrahydrooctyl-trichlorosilane with improved efficiency. The Kevlar fibers have been surface modified by MWCNTs via hexamethylene diisocyanate, 1,4-diazabi-cyclo [2,2,2] octane and toluene to introduce pendant amine groups onto the surface of the modified fibers under ultrasonic condition. The obtained fibers were characterized by scanning electron microscopy, IR spectroscopy and tensile measurement, and exhibited improved tensile strength and inter laminar shear strength (37).

2.4. Surface Modification of Novel Nanoparticles

Surface chemistry of nanoparticles governing interaction with other materials present in the environment holds critical importance. Therefore, chemical alteration of the surface properties of novel nanoparticles (AuNP and AgNP) is being actively explored with oligonucleotides, carbohydrates, and peptides for various applications. Moreover, AgNPs have attracted the major attention among nanomedicine researchers due to their plasmonic properties and easy surface chemistry. Major findings proposed by nanobiotechnologists to use AgNP for various biomedical, and biotechnological application include (i) selective targeting of cells can be achieved by functionalizing them with carbohydrates (e.g. selecting cancer cells by silencing strategy) and oligonucleotides, (ii) toxicity can be manipulated, and (iii) wound healing properties.

Bhattacharya et al. (38) have reported functionalization of AuNP by FA and its fine tuning by PEG. The nanoconjugates were characterized with UV spectroscopy, TEM, TGA, FTIR, and inductively coupled plasma analysis to find the correlation between uptake of nanoconjugates and folate receptor expression. Earlier, Sarkar et al. (39) showed that reduction of Ag+ ions in formamide takes place spontaneously at room temperature without addition of any reductant. They proposed that the growth of AgNP was dependent on Ag+ ion concentration. Surface modification of silver film done in the presence of the tetra sodium salt of ethylene-diamine-tetra-acetic acid resulted in greater reactivity of the silver film while the Fermi potential of AgNP was found to be in the range of −0.30 to−0.40 in the presence of ligand.

A novel finding on the vibrational analysis of the thiol and thione forms of methimazole (antithyroid drug) and their various possible silver complexes was reported by Biswas et al. (40). Fourier transform infrared spectroscopy, Raman spectroscopy, and surface-enhanced Raman scattering (SERS) showed that thiol form of methimazole was chemisorbed to the silver surface through N atom of imidazole ring with an edge-on orientation and imidazole ring lying in the plane of silver surface. It was concluded that thione form of methimazole is adsorbed to the silver surface in acidic medium. Thus, pH-dependent SERS spectra have shown the preferential existence of thione and thiol tautomeric forms on silver surface in acidic, neutral, and alkaline media.

Considering the importance of AgNP in therapeutic applications, several researchers have used glucose- and lactose-modified AgNP and exposed L929 and A549 cancer cells to unmodified and modified AgNP to reduce their toxicity for extending the use of AgNP in clinical cancer diagnosis and other therapeutic applications (41). In another study, AgNPs were modified by phospholipid derivatives to enhance their biocompatibility and cell affinity for biosensing and drug delivery applications (42). A highly efficient immobilization method was developed by attaching amine-modified DNA to AuNP to obtain highly yielded homogeneous microarrays that exhibited greater binding capacity for the complementary DNA (43). The biomedical application of surface modified AgNP and AuNP was extended in forming a rapid and firm soft tissue sealing around dental implants that resisted bacterial invasion.

Similarly, titanium surface was modified by immobi-

lizing AgNP/FGF-2 on titania nanotubular surface which displayed excellent cytocompatibility, negligible cytotoxicity, and enhanced cell attachment. Additionally, titanium nanotubes were incorporated with AgNP to provide long term antibacterial ability and good tissue integration to provide promising applications in orthopedics, dentistry, and other biomedical devices. These materials possessed satisfactory osteoconductivity in addition to increased biological performance (44).

In another study, glucose oxidase (GOX) was covalently immobilized on the surface of thiol-modified AgNPs. GOD-AgNP bioconjugate complex exhibited greater stability at higher temperature and pH range than soluble GOD. Additionally, the fabricated carbon rod/GOD-AgNPs/nafion/chitosan electrode showed rapid response and linear calibration range from 0.5 - 6.0mM for detecting glucose (45). Moreover, urease was immobilized on polyaniline and AgNP was stabilized in polyvinyl alcohol (PAni/PVA-AgNP) to investigate amperometric measurements toward urea hydrolysis. It revealed a fast increase in cathodic current with a well-defined peak upon addition of urea to the electrolytic solution. Similarly, Sadjadi et al. (46) assembled AgNPs on zeolite surface through amine groups of APTES for immobilizing fungal protease. The bound fungal proteases were easily separated from reaction medium by mild centrifugation and exhibited excellent reusability, and their biocatalytic activity was significantly enhanced in bioconjugate compared to the free enzyme.

Ren et al. (47) have prepared an amperometric glucose biosensor based on immobilization of GOX with AgNP followed by crosslinking with polyvinyl butyral and glutaraldehyde. Similarly, α-amylase was immobilized on templated polymerization of tetramethoxysilane to obtain improved starch hydrolysis. Kinetic parameters for immobilized (Km = 10.30 $mg.mL^{-1}$, Vmax = 4.36 $\mu mol.ml.min^{-1}$) and free enzyme (Km = 8.85 $mg.mL^{-1}$, Vmax = 2.81 $\mu mol.ml.min^{-1}$) suggested that immobilization improved the overall stability and catalytic property of the enzyme. Immobilized α-amylase showed excellent repeated use and negligible loss in its activity even after 30 days storage at 40°C (48). Moreover, glutathione oxidase was immobilized on AgNPs/c-MWCNT/PANI/Au electrode to construct the glutathione biosensor for measuring glutathione content in hemolyzed RBC. The biosensor showed optimum response within 4s at +0.4V and a detection limit of 0.3 μM (49). This approach afforded a large library of nanostructures with varying chemical nature, microstructure, radius, and morphology.

3. Conclusions

The current review presented detailed description of various nanoparticles modified through fine tuning the attachment of organic or inorganic ligands. Since purity, dispersity, and stability of multifunctional nanoparticles are highly important in a physiological environment for *in vivo* biomedical applications, the newly developed nanoconjugates can be used for cancer cell imaging, tumor ablation, and drug delivery. Several biofunctional magnetic nanoparticles were also employed for bacterial detection, protein purification, tumor targeting, and multimodal imaging. Thus, authors hoped to provide a succinct overview of the current state of the art and the future impact of fabrication technology on polymer chemistry, nanotechnology and macromolecular engineering.

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Shakeel Ahmed Ansari and Rukhsana Satar are the first and second author, respectively, of this review article, They have contributed mainly in writing the manuscript.

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