A

Seminar report

On

Nanoparticles

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Preface

I have made this report file on the topic **Nanoparticles**; I have tried my best to elucidate all the relevant detail to the topic to be included in the report. While in the beginning I have tried to give a general view about this topic.

My efforts and wholehearted co-corporation of each and everyone has ended on a successful note. I express my sincere gratitude to ……..who assisting me throughout the preparation of this topic. I thank him for providing me the reinforcement, confidence and most importantly the track for the topic whenever I needed it.

Abstract

Nanoparticles can be engineered with distinctive compositions, sizes, shapes, and surface chemistries to enable novel techniques in a wide range of biological applications. The unique properties of nanoparticles and their behavior in biological milieu also enable exciting and integrative approaches to studying fundamental biological questions. This review will provide an overview of various types of nanoparticles and concepts of targeting nanoparticles. We will also discuss the advantages and recent applications of using nanoparticles as tools for drug delivery, imaging, sensing, and for the understanding of basic biological processes.

What is a Nanoparticle?

The simple answer to this question is any particle less than 100 nm. But like most things in particle technology a more thorough discussion is required to achieve an unambiguous and complete response. The experts from the ISO and ASTM standards shown below provide additional nuances to the definition. The current agreement among the standards groups is that the scale from 1 – 100 nm defines the size range of a nanoparticle. Below 1 nm may be excluded in order to avoid calling clusters of atoms a particle, but the literature contains references to particles < 1 nm. Since particles are three dimensional the ASTM standard defines two or three dimensions must be between 1 – 100 nm. This provides for nanotubes with a diameter of 10 nm, but a length > 100 nm.

Nanoparticle Applications in Medicine

The use of polymeric micelle nanoparticles to deliver drugs to tumors.

The use of polymer coated iron oxide nanoparticles to break up clusters of bacteria, possibly allowing more effective treatment of chronic bacterial infections.

The surface change of protein filled nanoparticles has been shown to affect the ability of the nanoparticle to stimulate immune responses. Researchers are thinking that these nanoparticles may be used in inhalable vaccines.

Researchers at Rice University have demonstrated that cerium oxide nanoparticles act as an antioxidant to remove oxygen free radicals that are present in a patient's bloodstream following a traumatic injury. The nanoparticles absorb the oxygen free radicals and then release the oxygen in a less dangerous state, freeing up the nanoparticle to absorb more free radicals.

Researhers are developing ways to use carbon nanoparticles called nanodiamonds in medical applications. For example nanodiamonds with protein molecules attached can be used to increase bone growth around dental or joint implants.

TYPES OF NANOPARTICLES

There are many types of NP platforms with differing size, shape, compositions, and functionalities. Furthermore, each type of NPs can potentially be fabricated using different techniques, such as both nanoprecipitation and lithography for polymeric NPs. While it is not within this manuscript's scope to discuss the differences in NP platforms and their fabrication in detail, we will discuss the major characteristics and functionalities of each NP that are relevant for biomedical research.

Liposomes

The first NP platform was the liposomes. Liposomes were first described in 1965 as a model of cellular membranes. Since then, liposomes have moved from a model in biophysical research to one of the first NP platforms to be applied for gene and drug delivery. Liposomes are spherical vesicles that contain a single or multiple bilayered structure of lipids that self-assemble in aqueous systems. Unique advantages imparted by liposomes are their diverse range of compositions, abilities to carry and protect many types of biomolecules, as well as their biocompatibility and biodegradability. These advantages have led to the well-characterized and wide use of liposomes as transfection agents of genetic material into cells (lipofection) in biology research. Lipofection generally uses a cationic lipid to form an aggregate with the anionic genetic material. Another major application of liposomes is their use as therapeutic carriers since their design can allow for entrapment of hydrophilic compounds within the core and hydrophobic drugs in the lipid bilayer itself. To enhance their circulation half-life and stability *in vivo*, liposomes have been conjugated with biocompatible polymers such as polyethylene glycol (PEG). Liposomes can also be functionalized with targeting ligands to increase the accumulation of diagnostic and therapeutic agents within desired cells. Today, there are twelve clinically approved liposome-based therapeutic drugs.

Albumin-bound

Albumin-bound NPs (nab) uses the endogenous albumin pathways to carry hydrophobic molecules in the bloodstream.[7] Albumin naturally binds to the hydrophobic molecules with non-covalent reversible binding, avoiding solvent-based toxicities for therapeutics.[8] As a result, this platform has been successfully adapted as drug delivery vehicle. Abraxane, a 130-nm nab paclitaxel was approved by the FDA in 2005 for the treatment of metastatic breast cancer.[9] Abraxane concentrates in cells through albumin receptor (gp60)-mediated transport in endothelial cells. It may also target the albumin-binding protein SPARC (secreted protein acidic and rich in cysteine), which is overexpressed in certain tumors. Further understanding of the mechanism of action may lead to better targeting and development of novel therapeutics using the nab platform.

Polymeric

Polymeric NPs formed from biocompatible and biodegradable polymers have been extensively investigated as therapeutic carriers. Polymeric NPs are formulated through block-copolymers of different hydrophobicity. These copolymers spontaneously assemble into a core-shell micelle

formation in an aqueous environment. Polymeric NPs have been formulated to encapsulate hydrophilic and/or hydrophobic small drug molecules, as well proteins and nucleic acid macromolecules. The NP design can allow for slow and controlled release of drug at target sites. Polymeric NPs are usually able to improve the safety and efficacy of the drugs they carry. Functionalizing polymeric NPs with targeting ligands for improved drug delivery has been an important area of investigation since polymeric NPs are unique in their ability to be tailored prior to particle assembly. The incorporation of targeting ligands on the NPs can lead to their increased uptake along with their cargo, leading to enhanced therapeutic outcomes.

Another type of polymeric NP is dendrimers. Dendrimers are regularly branched macromolecules made from synthetic or natural elements including amino acids, sugars, and nucleotides. They have a central core, interior layers of branches, and an exterior surface. The varied combination of these components can yield dendrimers of well-defined size, shape, and branching length/density. As a result of their unique design, dendrimers can be developed as sensors as well as drug and gene delivery carriers. Dendrimers can be loaded with small molecules in the cavities of the cores through chemical linkage, hydrogen bond, and or hydrophobic interaction. The exterior surface can also be readily modified to produce chemical functional groups for molecular targeting groups, detecting and imaging agents, and therapeutic attachment sites.

Iron oxide

Iron oxide NPs are widely studied as a passive and active targeting imaging agent as they are mainly superparamagnetic. The superparamagnetic iron oxide NP (SPION) generally have an iron oxide core with a hydrophilic coat of dextran or other biocompatible compound to increase their stability. The most widely used SPIONs consist of a magnetite (Fe_3O_4) and/or maghemite (γFe_2O_3) core. These NPs exhibit size-dependent superparamagnetism, which allows them to become magnetized with the application of an external magnetic field and exhibit zero net magnetization upon removal of the magnetic field. SPIONs have been successfully used as T2-weighted magnetic resonance (MR) contrast agents to track and monitor cells.

SPIONs have several advantages over conventional gadolinium-chelate contrast agents including decreased toxicity and increased imaging sensitivity and specificity. SPIONS can also be degraded to iron and iron oxide molecules that are metabolized, stored in cells as ferritin, and incorporated into hemoglobin. Currently, two SPIO agents, ferumoxides (120–180 nm) and ferucarbotran (60 nm) are clinically approved for MRI. SPIONs have also been used in molecular imaging applications such as the detection of apoptosis and gene expression. SPIONs can be functionalized with magnetic, optical, radionuclide and specific targeting ligands for multimodal imaging. They can also potentially be used as non-invasive diagnostic tools and as drug delivery vehicles.

Quantum dot

First discovered in 1980, quantum dots (QDs) are semiconductor particles that are less than 10 nm in diameter. QDs display unique size-dependent electronic and optical properties. Most QDs studied consist of a cadmium selenide (CdSe) core and a zinc selenide (ZnS) cap. The absorption

spectra of these particles are very broad and emission is confined to a narrow band. QDs can also emit bright colors, have long lifetimes, high efficiencies and are stable against photobleaching. They can be generated to have different biochemical specificities and can be simultaneously excited and detected. As a result, QDs have several significant advantages over many organic fluorophore dyes for optical applications. They are widely used in biological research as fluorescence imaging tools for applications such as cell labeling and biomolecule tracking. The small size of quantum dots also enables them to be suitable for biomedical applications such as medical imaging and diagnostics.

Gold

Gold NPs offer many size-and-shape dependent optical and chemical properties, biocompatibility, and facile surface modification. Gold NPs can strongly enhance optical processes such as light absorption, scattering, fluorescence, and surface-enhanced Raman scattering (SERS) due to the unique interaction of the free electrons in the NP with light. These properties have enabled the realization of gold NPs in many applications such as biochemical sensing and detection, biological imaging, diagnostics, and therapeutic applications.

Sensing techniques include the use of gold NPs in colorimetric arrays and the use of gold NPs as substrates in SERS to significantly enhance Raman scattering, allowing for spectroscopic detection and identification of proteins and single molecules at the NP surface.Gold NP probes have also been used to detect heart disease and cancer biomarkers. They can also transform absorbed light into heat and therefore, have high potential for infrared phototherapy.

TARGETED NANOPARTICLES

The concept of targeting has become a significant focus in biological research in recent years. In proteomics, targeted proteomics has gained traction as an approach to address specific biological questions by focusing on a subset of proteins of interest. In genetics, gene targeting in mice has become a gold standard for determining gene function in mammals. In the areas of drug discovery and molecular therapeutics, the development of small molecules and monoclonal antibodies such as imatinib, trastuzumab, bevacizumab, and rituximab have considerably changed the treatment of cancer.

NPs show much promise in biological applications. In particular, NPs offer many unique properties that enhance or confer advantages over current techniques in biological and biomedical research. As a result, there has been significant interest in applying targeting concepts to NP design. NPs can be targeted by active targeting and passive targeting under *in vivo* conditions.

3.1 Passive Targeting

In the case of passive targeting, NP systems have been successfully developed for cancer therapy by taking advantage of tumor tissue biology. Normal tissue vascular biology has an organized structure while tumor vasculature is irregularly branched and disorganized. Tumors also have high vascular density, increased vascular permeability, and impaired lymphatic drainage, an attribute of solid tumors and inflamed tissue.

Together, these features are known as the enhanced permeability and retention (EPR) effect, which allows NPs to accumulate preferentially in tumor tissue. NPs have extended retention times in tumor tissue, which results in higher concentrations than in other tissues. Properties that mediate this passive targeting process include particle composition, size, shape, and surface characteristics. Thus, NPs can be engineered to better target a particular tissue or cell by optimizing their physicochemical characteristics.

3.2 Active Targeting

Active targeting involves the use of targeting ligands for enhanced delivery of NP systems to a specific site. Typical targeting ligands include small molecules, peptides, antibodies and their fragments, and nucleic acids such as aptamers. These ligands have all been conjugated to NPs.

Conjugating targeting ligands to NP surfaces can be performed *via* covalent and non-covalent methods. With covalent conjugation, the same chemical methods for functionalization can be applied to various types of NPs since conjugation of functional groups to the NP surface is dependent on the functional groups on the NP surface and the functional groups of the ligand being conjugated. Certain conjugation techniques are also suitable for specific targeting ligand classes.

The maleimide-thiol coupling is commonly used for conjugation of peptides, antibodies and their fragments to NPs. In this reaction, maleimides (maleic acid imides) spontaneously reacts with

sulfhydryl groups at pH 6.5 to 7.5. Thus, nanoparticle surfaces incorporated with maleimide modified polymers or lipids can be readily conjugated with targeting ligands engineered with thiol groups or cysteine, which has a thiol side chain. Another commonly used conjugation method is the carbodiimide-mediated amide coupling between carboxyls and amines to form amide bonds. In this reaction, carboxylate groups on a molecule can be converted to active esters by using a variety of carbodiimides such as the water-soluble 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and *N*-hydroxy-succinimide (NHS) or sulfo-NHS.

The activated ester intermediate can react with a primary amine to form an amide bond. This method is generally preferred for aptamers, which can be modified with amines, and small molecules, which can contain carboxylates or primary amines. Click chemistry reactions are another method used to conjugate functional groups with high yield and selectivity under moderate reaction conditions. One of the most popular reactions with this class is the [3+2] cycloaddition between alkynes and azides.

Conjugating targeting ligands to the NP surface can facilitate active targeting of NPs to receptors that are present on target cells, leading to enhanced cell internalization and/or specific uptake through receptor-mediated endocytosis. For NP delivery of therapeutics, these advantages result in higher drug concentrations and reduced systemic toxicities compared to non-targeted NPs and their small molecule counterparts.

Thus, there has been intense interest in identifying new disease biomarkers and their ligands for use in targeted drug delivery. Targeted NPs can also identify molecular targets with good affinity and selectivity. These NPs can bind to analytes, pathogens, and biomarkers, amplifying their signal for detection and molecular imaging.

Conclusions

The basic definition of a nanoparticle (between 1-100 nm) is common to the documents referenced here. The fact that all of the documents contain one or more nuances to the definition is an indication that the phrase "it depends on the sample" is common in the world of particle characterization. A consideration of particle size distribution is appropriate and is addressed in the SCENHIR document.

References

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