Chapter 1
Understanding Surface Characteristics of Nanoparticles

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Abstract Nanoparticles are widely used in many fields of research due to their versatile nature. They can be defined as a particle that is microscopic in size, around 1–100 nanometers and due to their size possess a set of quantum properties unlike bulk material. Individual spherical nanoparticles would be considered zero dimensional, while nanowires, nanotubes, and nanobelts are categorized as one dimensional. Thin filaments (nanodiscs, nanosheets, nanomembranes, and nanoplates) are composed of nanomaterial and larger compounds, so it is categorized as two dimensional. These particles can be classified through structure analysis (electron microscopes and X-ray diffraction) and property management (X-ray spectroscopy and photoluminescence/fluorescence). Two methods of preparation of nanoparticles include "top-down" and "bottom-up" approaches, which can be further divided into gas, liquid, and solid phase synthesis. Nanoparticles are mainly used in biological applications which include nanosensors, drug delivery, and tissue engineering, but also can be found in cosmetics, electronics, and automotive industry.

Keywords Nanocarrier · Targeted drug delivery · Drug delivery · Surface modification

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1 Introduction

The use of nanoparticles in the field of pharmaceutical research has vastly grown due to their versatile nature. Nanoparticles can be defined as a particle that is microscopic in size, around one nanometer, and can be found naturally or manufactured to be used in research. Because they are larger than an atom, but small enough to not be affected by the physical laws they can be manipulated to specifically target unique structures [1]. Examples of particles having size in nano range and found in nature can be metals, proteins, polysaccharides, and viruses that can be formed by natural disasters and environmental events including wildfires and erosion [2]. The use of nanoparticles can be tracked back thousands of years with the use of clay in ceramics or metal nanoparticles for color pigments [2]. Gold and silver nanoparticles were used to make different forms of glass, including the Lycurgus Cup, in Rome as early as the fourth century. Depending on the direction and the angle of the light, the glass produces different optical properties due to the size of the nanoparticles. The gold nanoparticles gave it more of a red tint and silver resulted in a yellow color.

Nanoparticles were first discovered by Richard Feynman where he presented his findings on December 29, 1959, in a lecture titled "There's plenty of room at the bottom." He discussed the possibility of manipulating molecules and atoms at a molecular level. At this scale, gravity would no longer be a factor, but Van der Waals attraction would be of importance. Feynman wanted to create "molecular machines" that could build new molecules at an atomic level. Although this discovery influenced many fields of science, the term nanotechnology was not used or strongly studied until the 1977 when Eric Drexler brought the concept to MIT. The Foresight Institute was established in 1986 to focus on studying transformative technology, specifically nanotechnology. They gave away the "Feynman Prize in Nanotechnology" 1993 to Charles Musgrave of Caltech for his study with hydrogen abstraction tools. This award is now given away every year to individuals who show advancements in nanotechnology towards the creation of these "molecular machines" [3].

Nanoparticles can be very easy to manipulate due to their very high surface area to volume ratio and within this range of size, particles tend to have more atoms on their surface than in their interior. This ratio changes the way they interact with other materials and gives them quantum properties. Diffusion of these particles is very high, especially at higher temperatures, and they tend to have lower melting points. The size of these particles are one nanometer to one thousand nanometers so they are anywhere from the size of an antibody to the size of a virus [3]. Nanoparticles can be classified as hard or soft depending on the material that is used. Hard nanoparticles are composed of materials including titania or silica and soft nanoparticles are composed of lipids. More research has been focused on the use of these particles in medicine due to their ability to improve the efficiency of a drug delivery. Even though less material may be used, the particles tend to be more reactive [4].

Advances in medicine have promoted the use of nanoparticles because of this manipulative ability. Nanocarriers are nanoparticles, usually of polymeric materials, used to carry a drug or a target agent. When these nanocarriers are able to carry multiple agents or drugs they are referred to as a nanovector [3]. Adding different layers can create a multifunctional nanoparticle to target different functions of the body [5]. With the discovery of any new molecular substance that could be used in medicine, there is a long new drug development that must take place to get it approved. First it is evaluated on all of the physical and chemical properties it exhibits to determine its direct absorption in the body. This process can take anywhere from 1 to 2 years where everything from solubility to protein binding are tested and recorded. The toxicity and safety of the drug are both tested in the preclinical evaluation with comparable animals which could take 2 to 3 years to complete. After this process is completed, the investigational new drug application is submitted for approval. With the approval, it is legal to start preforming clinical trials on humans which could take up to 8 years to complete. A new drug application can be submitted so it will officially be on the pharmaceutical market [3].

Depending on the size of the nanoparticles, applications involving medicine or biology are but not limited to: tissue engineering, drug and gene delivery fluorescent biological labels etc.. In order for these actions to happen, a bioinorganic interface needs to be added to the nanoparticle to act as a coating [5]. The distribution of the nanoparticles throughout the body is determined by the size because only nanoparticles with a diameter smaller than 200 nm can pass through blood vessels. With intravenous injections and subcutaneous, different tumors and cancers can be passively targeted. Imparting charge to a particle will also affect the uptake and distribution [2]. Nanoparticles also have many different applications other than medicine including electronics, laser technology, solar energy conversion, and everyday objects including tires. Nanowires are used in molecular electronics to create an improved coating in order to enhance the quantum effects. They also act as inorganic fillers in tires to reinforce the rubber structure [4].

Nanoparticles can be divided into three categories: zero, one, and two dimensional. Individual spherical nanoparticles would be considered zero dimensional and nanowires, nanotubes, and nanobelts are one dimensional. Zero dimensional structures can be a variety of shapes from spheres to cubes and are under 100 nanometers in every measurement. One dimensional structure are long hollow structures with a diameter under 100 nanometers. Thin filaments (nanodiscs, nanosheets, nanomembranes, and nanoplates) are composed of nanomaterial and larger compounds, so it is categorized as two dimensional. Two dimensional structures are flat along a polygon shaped surface with thickness in the nanoscale measurement of 1 to 100 nanometers. Due to the size of every dimension, every category of material has a variation of abilities. The specific properties of the nanomaterial, which could be conductivity, are determined by many aspects of the materials including chemical composition, measurements of the particle, and crystal structure. The electrical activity of these particles can be affected by minuscule changes, which allows the production of single electron devices. Removing or

adding atoms to a nanoparticle can directly impact the amount of conductance channels which change the electrical ability of nanowires. This advancement has led to the applications of nanocrystal biotags, nanocrystal solar cells, and quantum dot lasers [6].

2 Characterization of Nanoparticles

Nanoparticles possess what is referred to as quantum properties due to their very high ratio of atoms on the surface compared to the interior of the particle. They are not governed by the same laws as larger matter, so they are not influenced by gravity, but forces like Van der Waals. Their unique chemical and physical properties cause them to exhibit much lower melting points and have a higher level of reactivity. Smaller nanoparticles tend to produce much lower wavelengths compared to those of greater size. The strength, color, and size of the particle will depend predominantly on the material used during synthesis. Nanoparticles are directly characterized by the physical and chemical properties and this characterization is especially important when dealing with nanomedicine and the classification of a newly formulated drug [3].

Structure analysis is a method of classifying nanoparticles with the use of microscopic techniques to observe surface characteristics. X-ray diffraction, transmission electron microscopes, scanning electron microscopes, and atomic force microscopy can all be used to determine the structures of a nanomaterial being studied. Property measurement is another method that concentrates on analyzing the exact composition and properties of the material through the use of X-ray spectroscopy and photoluminescence/fluorescence. X-Ray spectroscopy can help determine the binding energy, properties of core electrons, bonding information, and oxidation states in metals. Another form of analysis is electron paramagnetic resonance spectroscopy, which study compounds with unpaired electrons and by manipulating the alignment of these electrons a g-factor will give information on the properties of the compound [6].

2.1 Electron Microscope

The first microscope invented that gave scientists the ability to view these particles was the electron microscope, which was developed by physicist Ernst Ruska in 1931. Instead of light beams, the microscope manipulates electrons to create a high-resolution image on a fluorescent screen of their path. Transmission electron microscopes are widely used for many forms of research in this field. The cathode-ray device that was experimented with by Joseph John Thomson in 1897 greatly influenced this discovery. These rays were focused using multiple electron lenses in a vacuum to increase magnification [7]. An illumination system generates a wide

parallel beam of electrons using a thermionic or field emission source. The thermionic emission source heats either tungsten or lanthanum hexaboride compared to the field emission source that uses high voltage to create a beam of electrons. Field emission sources create a much higher density beam due to the voltage and may produce a higher resolution image [3]. Electron microscopes now have a spatial resolution of 50 picometer, which is one trillionth of a meter, compared to the distance between atoms which is 200 picometer [8].

An electromagnetic condenser lens focuses the beam with a very small focal length to bend the path and then it travels into a chamber that is sealed by O-rings. The beam strikes the object by passing through it and then arrives at an objective lens that diffracts the beam to be captured by a projector lens. The projector lens creates an image on a fluorescent screen that is black and white [7]. Multiple projector lenses can be used to magnify an image up to 1.5 million times with a TEM [3]. The lighter areas indicate higher exposure to electrons in a less dense area of the specimen and the darker areas indicate a denser area of the specimen that electrons had a more difficult time passing through [7]. A high degree of resolution in these images is due to the fact that electron waves are 100,000 times smaller than light waves used in compound light microscopes. When preparing a sample to be observed it is important that the electrons have the ability to pass through the object. The material needs to be exceptionally thin for the voltage that is used, which is around 120 and 300 kV with a TEM. To obtain the basic information from the sample, staining agents need to be used to observe many optical properties [3]. Heavy metal salts, including phosphor-tungstic acid and uranyl acetate, are the most efficient agents to use on a carbon support film [9].

Scanning electron microscopes are very similar to transmission electron microscopes but have a much finer beam maintained in a vacuum. The object being magnified gives off secondary electron currents from the surface layer due to the excitation of electrons [7]. Emitted secondary electrons or backscattered electrons are then used to construct an image of the object [8]. Scanning coils allow the microscope to scan the entire image horizontally along an x- or y-axis or vertically along the z-axis, whereas in TEM that is not possibly due to the stationary set up. The beam also has the ability to rotate 360° or be tilted at an angle. The material used, energy of the beam, and incident angle all will determine the depth of the beam in the material [3]. This microscope was not invented until 1965 due to the complexity of transforming these electron currents into a three-dimensional image [7].

2.2 X-Ray Diffraction

X-ray diffraction is mainly used to observe the crystalline structure and atomic arrangements of nanomaterials. They have no contact with the specimen and their wavelength is about 1 Å, which is about 10^{-10} m, so they are nondestructive. A collection of materials is compared to the diffraction pattern produced to determine the specific compounds present in the specimen. Information recorded about time,

pressure, and temperature can be used to calculate properties including phase transitions and solid-state reactions [6]. When observing the material, the back focal plane of the objective lens will show spots or rings referred to as electron diffraction patterns. These patterns are a result of parallel and coherent beams having interference by refracted electron waves from surrounding sources. This pattern can be viewed on a magnified screen or CCD camera with the addition of a selected area electron diffraction aperture to differentiate different regions. Atomic scale order can be determined from the pattern, such as if it is polycrystalline or single-crystalline and the grain morphology. Convergent beam electron diffraction creates wider spots that include a variation bright and dark spots to analyze the thickness of the specimen and chemical bonding [8]. Electrons emitted from the specimen after the initial beam can retain all of their energy and return to the vacuum in a process called back scattering or elastic scattering. Inelastic scattering occurs when these electrons lose their energy and it is transferred to a group of secondary electrons which transport to the vacuum or are absorbed into the specimen [3].

2.3 Infrared/Visible Spectroscopy and Photoluminescence

Spectroscopy is a property measurement method that specifically measures the absorption levels of different nanomaterials. Infrared spectroscopy used infrared light to identify chemical bonds and functional groups, which can indicate structural behavior and properties. This method can be used to measure the amount of CO_2, water, and hydrocarbon contamination due to the formation of carbonate by metal oxides. Visible spectroscopy is also referred to ultraviolet visible spectroscopy due to the fact that it uses a range of visible light on the electromagnetic spectrum. Absorption measures the change in electronic transitions when pi or nonbonding electrons absorb energy, mostly from ground state to excited state. This method can help determine the presence of semiconductor nanostructured materials, the concentration of organic molecules, and protein stability/activity in the solution. Spectroscopy only requires a small amount of sample mixed into a liquid solution, which can be recovered after testing [6]. Quantitative analysis of the concentration of the solution is directly related to the Beer–Lambert law that states that change in light absorption is directly proportional to the change in concentration. If the initial concentration and wavelength of a solution are known before a reaction, the wavelength after the reaction can be used to calculate the final concentration [10].

After the excited electrons from the absorption techniques undergo relaxation, they return to a stable ground state and instead of absorbing energy, they release light energy. These relaxation times vary depending on material used and may last anywhere from fractions of a second to hours. In most cases, the energy that is emitted during this relation is less than the energy that was absorbed during the excitation process. Where this light falls on the spectrum and its intensity indicate the properties exhibited and the quality of the material/impurities can be determined by the emission transitions. This technique is mainly used for determining the exact composition of the material, but also gives some information on energy level coupling [6].

3 Synthesis of Nanoparticles

In order to synthesize nanoparticles with specific functions, they are required to be composed of multiple layers including a surface and internal structure. Unlike most bulk materials, the surface layer of the nanoparticles is most active and can be modified by different compounds to exhibit specific properties. The internal structure is made up of a monolithic matrix and core, which can be made of a multitude of compounds and layers held together by covalent and hydrogen bonding. In certain conditions, these layers can be hollow or just a medium. When the core of the nanoparticle is unfilled it is referred as a hollow particle, but if one of the layers in the matrix is unfilled it is referred to porous. Liposomes are usually filled with an aqueous phase in order to help dissolve drugs in certain pharmaceutical applications [11]. Other hollow materials may be used for catalytic support, thermal insulators, and micro vessels. Core–shell nanoparticles are made up of separate materials, which can be organic or inorganic. These materials may have different properties and can produce multifunctional nanoparticle. Coating specific cores with a shell made of a different material aids in creating a more functional and stable particle [12]. Depending on the application, the nanoparticles have to be permanently connected or may have the ability to be deconstructed to reassemble for a different use [11].

Organic nanoparticles need to be synthesized in a moderate temperature, pressure, and pH compared to inorganic nanoparticles which can be synthesized in harsher conditions if needed [3]. Inorganic particles with inorganic shells mostly contain either metal oxides or silica and are the most widely used form used due to the multiple applications. This category can be used for bio-imaging, biological labeling, information storage, and catalysis. Adding silica to these particles reduces conductivity, increases stability, and does not affect the surface reactions so inorganic material is not difficult to study. This silica coating is usually paired with a silver or gold core through the Stöber method synthesis. A precursor and water are added to an alcohol solution to create a precipitate, which then bonds together to create these particles. Particles with gold metal oxides instead of silica exhibit magnetic properties, have increased stability, increased biocompatibility, and optical properties. Inorganic particles with organic shells mainly use a polymer shell that increase biocompatibility and oxidation stability. With this organic shell, the forces between particles can be controlled to prevent too much clustering. Organic particles are very similar to the former, but the organic center creates a more flexible and strong particle for applications involving paints or microelectronics. This combination can also be used to make hollow particles [12].

Organic particles with organic shells are mainly used for drug delivery, biomaterials, catalysis, bio sensing, and many other biological applications. These particles have a special property referred to as glass transition temperature, which is the temperature at which these particles are stable. When particles fall under this they reach a state where they are too brittle and lack a tough coating, but they acquire a film-forming ability. Specific polymers can be used in drug delivery due to their biodegradable nature and also can determine how fast the drug is released. Inorganic

materials can be placed on these outer coatings for more efficient bonding with adjacent particles [12].

Two methods of preparation of nanoparticles have been presented to the public over the years which include “top-down” and “bottom-up” approaches. The top down approach follows the theory of molecular machines that manipulate smaller amounts of matter to build these nanoparticles, which is just reducing larger particles. These methods are mainly used to make inorganic nanoparticles due to the fact that the product may not be 100% pure [3]. Lithography and ion beams are two of the mainly used application in this category [13]. Bottom up synthesis involves the atoms and molecules coming together to form the particles in a medium. Most of the methods used today to produce such materials follow the bottom up approach and can include chemical synthesis, chemical vapor deposition, microemulsion, hydrolysis, and thermal decomposition [3]. This approach has proven not only to be more cost effective, but also produces smaller, more precise nanoparticles. Depending on the desired product, the top down approach can be used to produce the core and the bottom up approach can be used to coat the particle in a separate material [12]. Synthesis can take place in a liquid, gas, or vapor phase but the gas and vapor phases will produce smaller nanoparticles. The liquid phase will contain milder conditions for the nanoparticles, but the size will depend on the chemical reaction or phase separation of the solution used [3].

3.1 Gas-Phase Synthesis

Gas phase synthesis usually occurs when a gas or solid that has been evaporated reforms on substrate through condensation and then the formation of a solid or semisolid. This vapor is required to be super saturation for the synthesis of these particles, which can be accomplished through many applications. Methods in this category usually happen in very high temperatures and a controlled pressure environment [6].

Physical vapor deposition (PVD) can be categorized into either thermal evaporation, Rf sputtering, and pulsed laser deposition. During thermal evaporation, a source material is heated in an ultra-high vacuum until it starts to evaporate and settles onto a substrate. Rf magnetron sputtering uses capacitive plates and magnetic coils to remove atoms at a lower pressure [6]. This is done by manipulating high energy ions to target the source material and remove the neutral particles and redeposit them on the substrate [14]. There are four categories of this which include: ion-beam sputtering, direct current, radio-frequency, and magnetron [6]. Pulsed laser deposition uses a laser beam to disrupt a target material until it evaporates to form a vapor plume and reforms onto the desired substrate [15]. When this plume interacts with the substrate, it creates a crystalline film [6]. This method has the ability to synthesize films with multiple compounds and create metastable materials, which are materials that are able to transform over time [16].

Chemical vapor deposition (CVD) is very similar to the PVD method with the addition of a gaseous reactant. Compared to other methods it is extremely versatile and precise, so it can be used to make semiconductors and microelectronics [15]. This method can be classified into many types which include thermal CVD, low pressure CVD, plasma enhanced CVD, metal-organic CVD, molecular beam epitaxy, and atomistic deposition [6]. Atomistic deposition provides a high level of control with the material which can lead to create pure materials for coating and nanodevices [15]. It has the ability to create thin films due to the splitting of the reaction into halves [6]. Molecular beam epitaxy uses thermal molecular beams with an ultra-high vacuum to evaporate a source material and deposit it on a substrate to create epitaxial growth [17]. The pure elements being used in this are kept in quasi-Knudsen cells due to their temperature control. The most common materials used in this method are gallium and arsenide. Thermal, low pressure, plasma-enhanced, and metal organic methods are all very similar as they all happen at low pressure and include evaporation. Thermal and low pressure both occur at high temperatures about 900 °C compared to plasma-enhanced which occurs at lower temperatures around 300 °C with the addition of plasma for thick films. Metal-organic precursors can be added to create thin films and one-dimensional nanomaterials [6].

Specialized furnaces can be used to vaporize a source material in the presence of an inert gas. The temperature for this method can reach 1700 °C but may be limited by the containment unit used to hold the material. After reaching such high temperatures, the vapor is condensed with a cooling process to form the desired nanoparticles. Adding the source material to a flame can be used to produce these particles, but this method is not as precise and does not produce pure particles. It is performed at high temperatures up to 2000 °C and leads to oxygenation of most materials used. Coating these particles in different elemental compounds can help prevent this oxygenation and produce pure particles [18].

3.2 Liquid-Phase Synthesis

Liquid-phase routes are a useful method to develop inorganic nanoparticles, which include products like gold. A citrate route was discovered by Turkevich which uses gold chloride, sodium citrate, and water. It produces spherical gold nanoparticles as the sodium citrate acts as a reducing and stabilizing agent in a water solvent [2]. The hot injection method produces instantaneous nucleation by injecting an organometallic cold precursor into a hot solvent, which in turn produces CdSe, CdS, and CdTe quantum dots. This method was developed in 1993 by Murray, Norris, and Bawendi in order to produce smaller particles of higher quality that are kept under isothermal conditions. The specific temperature used for this method does not greatly affect the nanocrystal's size due to the short reaction time [19].

A colloidal solution occurs when a substance is dispersed in a solution but is unable to dissolve in that solution [20]. This method is generally used to make inorganic particles with an organic coating or outer shell on them. Versatility is a

main factor on the considerable use of this method as it can be used to synthesize particles for many applications including biomedicine and optoelectronics [6]. A precursor that is primarily organometallic or inorganic salts is added to stabilizing molecules, which are then heated to higher temperatures to dissociate the precursor. This leads to nucleation of the products which are then injected into a separate solution to control the reaction. Surfactants bind to these newly formed nanocrystals and determine the surface characteristic, size and shape. Compared to other methods, colloidal synthesis is not expensive and easy to carry out to produce optically active particles that have the ability to form thin films and other two-dimensional nanomaterial [20].

Sol–gel methods involve the process of my steps to form a cell that can be dehydrated to form metal oxide nanoparticles. Metal precursors are hydrolyzed to form a colloidal solution similar to the method above, but then form wet porous gel. This product is left out until the solvent has completely separated from solid product which is converted to Xerogel or Aerogel. Aqueous sol–gel methods involve the addition of water and are primarily used to create bulk materials. Due to the high reactivity of the metal oxides and water, this method has shown some difficulties with controlling the procedure. Nonaqueous sol–gel methods involve organic solvents instead of water and are more precise in their nature, so this method is favored in the synthesis of smaller nanomaterials and powders [21]. This gel product can undergo high temperatures to be transformed into glass products, ceramic fibers, thin film coatings, and other gel like materials [6].

Water-in-oil microemulsions are synthesized using a hydrocarbon fluid colloidal solution and water, which with the use of surfactant, creates small aggregates of molecules. These micelles are in a reverse form than the ones usually formed in water with their polar groups pointed inwards because they are formed in oil. When these particles are formed, the surfactant polar molecules are pulled towards the core while the hydrocarbon nonpolar chains are on the outside [22]. According to the Brownian motion theory, these particles are constantly moving and colliding in a random fashion. These particles mix and exchange material to form new particles and then dissociate again [23]. The energy triggering method involves creating a reaction though the involvement of reactant precursors which triggers the reaction. A second method is referred to as one microemulsion plus reactant, which instead of a precursor, a reactant itself is just added to the solution with a second reactant. After this, a precipitating agent is added to create the final product [22].

Supercritical hydrothermal synthesis is a method that uses water at the super critical temperature to create nanoparticles [24]. This could also be categorized as a solvothermal synthesis but is more precise in the material it produces [6]. Nanocatalysts are added to solution with a precursor and a reagent to synthesis crystals that undergo a nucleation process. Along with the catalysts already added, water can also act as a catalyst. At this temperature, because water is close to evaporating, the components are more likely to evenly dissolve in the solution [24]. This process is performed in an enclosed unit, like an autoclave, with a stable pressure which determines the density of the product. Most of the products synthesized with this method are one-dimensional structures or further used for ceramics [6].

3.3 Solid-Phase Synthesis

The solid-phase method focuses the grinding and milling of larger matter into smaller particles, which is referred to as ball milling. This matter is placed in a cylindrical vessel that rotates with the help of steel ball grinding mediums. Impact from the balls, vessel, and other particles break the material up into smaller nanoparticles [25]. Materials like metals with a face centered cubic crystal structure are not stable enough to undergo this method under normal conditions, so they must be synthesized with the use of hydrogen to prevent softness [6]. This method produces metallic particles in bulk but does not have the same high quality as other methods do [25]. In mechanical attrition, energy is added to coarse grained powder to reduce the grain size by a factor of 10^3 [26]. The main devices used are attrition mills which spin on a vertical axis, a horizontal mill which spin on a horizontal axis, 1D vibratory mill that shakes up and down with a large steel ball, a planetary mill that includes a spinning plate with small containers that are also spinning in the opposite direction, and a 3D vibratory mill that shakes in all directions [27]. These particles exhibit higher atomic internal strains, enthalpy, and specific heat due to high-angle grain boundaries [26].

4 Applications of Nanoparticles

Due to the versatility of inorganic and organic nanoparticles, there are many applications that these materials are involved in. In medicine, nanoparticles can be involved in protein detection, gene delivery, and biological labels. Nanoparticles are similar size to most protein and have a biological layer that makes them suitable for biological tags. The many biological tags can have functions including fluorescent signaling, shape recognition, biocompatibility, linkers, protective layers, or antigen detection [5]. Ligands including peptides and antibodies are covalently bonded to nanoparticles, so they can actively target cells. This can lead to higher concentrations of the drug being delivered and easier detection of the targeted cells [28]. Tumors can be passively targeted with polymeric micelle nanoparticles that are specifically synthesized for the increased vascular density of the tissue [29].

Nanoparticles can also be used as sensors in the body to detect change in cellular functions. Magnetic biosensors, which are magnetic nanoparticles that contain antibodies, can be used to detect specific pathogens in the body and trigger the body's immune system to react. Using a microfluidic device, these detected molecules can be removed from the body and could be utilized for drug-resistant bacteria [30]. The Weissleder group at MGH Center for Systems Biology has developed a system that uses nucleic acid probes to specifically detect 16S rRNA in bacteria. This is only found in bacteria, so this system is very precise in detecting even trace amounts in a small portion of blood [31]. These sensors can not only detect nucleic acid but differentiate in peptidoglycan walls as well. With the addition of quantum dots, these

metallic sensor nanoparticles can exhibit optical bio-sensing, which is just an amplification of the sensing activity. Quantum dots are small semiconductor particles with high efficiency and optical properties. These nanoparticles can differentiate between two bacteria with thick peptidoglycan walls and double-stranded DNA, which they could not do without the use of quantum dots [30].

4.1 Drug Delivery

Most of the drug delivery research is currently focused on the detection and treatment of cancer cells [30]. Cancer cells can be identified using an immune-magnetic technique which targets a positive epithelial cell adhesion molecule. This cell search system uses iron nanoparticles that are coated with biotin and anti-epithelial cell adhesion molecule to locate the cells. These molecules are coated with a polymer layer to help initiate detection and capture the cells targeted [32, 33]. Nanoparticles used for this treatment are synthesized from many materials including polymers and lipids that carry a drug. Tumors can either be passively or actively targeted through a combination of multiple drugs. During passive transport, the nanoparticles are not carried along and do contain ligands, so they reach the tumor through leaky vessels and intraorgan pressures. Active transport nanoparticles do contain ligands that specifically search and bond to the targeted mass [34].

Through receptor-mediated endocytosis, ligands can increase the concentration of the drug in the tumor and enhance the desired activity. This method can be utilized to attempt to treat multidrug resistance strains. If further treatment is needed in cases, the option of creating a combination therapy drug is a possibility. The only issue faced with this method is the adverse effects the drugs might unknowingly have on each other [30]. Enhanced permeability and retention effect cause nanoparticles of greater size to passively target tumor cells over average tissue cells in the body. Tumors cells proliferate at a much higher rate than normal cells which leads them to release more vascular endothelial growth factors. Blood vessels in tumors are larger, which provides a preferred pathway for larger molecules, similar to nanoparticles, causing them to accumulate in this area. Nanoparticles can also be manipulated to target and release drugs at a higher pH levels or higher temperature, which are usually conditions around tumor cells and tissues [34].

Methods to combat this disease through the use of nanoparticles include magnetic therapy, photodynamic therapy, photothermal therapy, radiotherapy, and ultrasound. Magnetic therapy involves the use of metal nanoparticles that penetrate deep into the targeted tissue and are heated by an electric field to release a desired drug. Perfluorohexane nanoparticles are used in photodynamic therapy to carry photosensitizers to the tumor cells to convert oxygen to cytotoxic reactive singlet oxygen. Photothermal therapy uses gold nanoparticles that convert light energy in order to increase temperature to kill tumor cells and tissues. Nanoparticles with antineoplastic drugs can be combined with radiation therapy or ultrasound techniques to damage the DNA in these cancer cells [34].

Issues that are faced during these applications involve the instability of the carriers and poor oral availability. A study done in 2016 resulted in only 0.7% of the administered dose actually reached the targeted solid tumor [35]. An attempt to overcome the drug resistance is to envelop nanoparticles in endosomes to avoid the *P*-glycoprotein recognition. Research pertaining to these issues is still an ongoing battle for scientists due to the safety and regulatory requirements they have to follow [34].

4.2 Tissue Engineering

Recent advancements in medicine have incorporated nanoparticles in the process of tissue engineering. These nanoparticles create a surface layer across the bone implant to prevent the body from rejecting the unfamiliar surface. It also reduces inflammation while healing and stimulate the production of osteoblasts. Ceramic and other materials have been used for these procedures and more than 90% of implants heal without complications. The only material that shows complications with proper film development is metal due to its nonreactivity with biological features [5]. When targeting tissue development, the one factor that needs to be considered is the relationship with the extracellular matrix. Nanotopographic surfaces have been created to control the release and activation of biological drugs and factors in the body [36]. Nanogratings and nanopits have been synthesized to mimic the layer of tissues specifically for cell interactions through the process of anodization and micelle lithography [34]. This structure directly affects the morphology and differentiation of the cell and has allowed researchers to manipulate these properties [36].

Nanofabricated scaffolds have been designed for the reconstruction of these tissues, including bone, nerve, muscle, and cardiac, due to their similarities to protein nanofibers. Porous PLGA scaffolds are patterns created to increase the roughness of the surface to improve adhesion and growth. Polymeric nanoparticles with growth factors are loaded into these scaffolds to control the release of biological drugs from the extracellular matrix [36]. These nanoparticles are made from biocompatible polymers which form a core–shell micelle to carry a vast array of macromolecules. The use of these particles can also improve the efficacy and safety of the materials leading to improved outcomes for the target. Dendrimers are branched polymeric nanoparticles that can be sensors or carriers. The increased size of these molecules allows them to carry many molecules that are attached to the cores through chemical linkages [30].

4.3 Nonbiological Applications

Many of the uses of nanoparticles have a strong involvement in medicine, but these particles may also be used in cosmetics. Silver nanoparticles makes up 12% of all the nanomaterial used in cosmetics and can be found in makeup, hair care products, toothpaste, shampoo, and even sunscreen. There are many claims that the use of

nanoparticles may cause issues with toxicity in the body, but studies show that silver is naturally removed from the blood stream making it very safe to use in these products. Its main use is to protect against certain skin diseases due to its antibacterial properties as it attacks the respiratory chain in bacteria to cause cell death. These particles can help with wound recovery by targeting the dermis cells and prevent scarring [37]. Along with cosmetics, nanomaterial is widely used in the electronics industry with computers, batteries, and circuits and in the automotive industry with tires and fuel [11].

5 Conclusion

The manipulation of nanoparticles can be used in many applications including the pharmaceutical industry. Zero-dimensional nanomaterials are individual spherical nanoparticles or powders, one-dimensional nanomaterial are nanowires, nanotubes, and nanobelts, and two-dimensional materials are nanomembranes or nanosheets used for larger applications. Due to their size, which is much smaller than bulk material but larger than atoms, they exhibit quantum properties specific to their overall structure. They have a high surface area-to-volume ratio which makes them extremely reactive and easy to manipulate. Electron microscopes use high energy beams of electrons to produce a high-quality magnified image of these particles. X-Ray diffraction is used to view the crystalline structure of materials and can help determine specific properties including phase transitions and solid-state reactions. Infrared–visible spectroscopy uses a liquid solution to measure absorbance of the material, which helps determine chemical bonding, functional groups, concentration of organic molecules, and protein stability/activity in the solution.

Two methods of preparation of nanoparticles “top-down” and “bottom-up” approaches. The top down approach involves mainly solid phase synthesis that breaks larger matter down to synthesize new microscopic particles. Bottom up synthesis involves the atoms and molecules coming together to form the particles in a liquid or gas medium. Physical and chemical vapor deposition methods are categorized as gas-phase synthesis because they use high temperature and pressure to evaporate a source matter in a vacuum. These evaporated molecules are then transported to a substrate to create new microscopic materials and films. Colloidal solutions are used in liquid phase synthesis with a precursor and stabilizing molecules, which are then heated to higher temperatures to dissociate. This solution is injected into another medium to bind to surfactants and create nanocrystals. Sol–gel methods are similar to colloidal solutions with metal precursors to create a gel leading to nanoparticles used for glass products, ceramic fibers, and thin film coatings. Ball milling and mechanical attrition are solid phase synthesis that involve a cylindrical vessel with steel balls to grind up matter into smaller microscopic particles.

There are many applications that nanoparticles are involved in including nanosensors, drug delivery, tissue engineering, cancer treatment, cosmetics, and electronics. Nanosensors can detect changes in biological functions and can be

manipulated to target specific mechanisms. Biological tags and ligands can be added to nanoparticles to control fluorescent signaling, shape recognition, biocompatibility, linkers, protective layers, or antigen detection. Tumor cells can be targeted actively or passively by the use of drug delivery methods. Magnetic therapy, photodynamic therapy, photothermal therapy, radiotherapy, and ultrasound are the main methods being applied to treat this disease. Nanofabricated scaffolds can be used to help reconstruct bone and tissue by manipulating the surface layer and extracellular matrix. Nanoparticles can also be found in many other nonbiological applications including cosmetics, automotive, and electronics.

6 Future Trends

The main focus of current research is drug delivery in cancer treatments and genetic applications. Nanoparticles provide a more efficient, safer method for gene therapy and RNA interference [36–45]. Many of the drugs are difficult to practice with due to their issues involving enzymatic degradation and intracellular entry, so different combinations of polymers and lipids are being tested to create a carrier. Overuse of these nanoparticles has exhibited high toxicity levels, immune response, and instability. Cyclodextrin-containing polymers are currently being researched on its safety and efficiency [46]. Gold particles are now being researched on their possibility of destroying tumor cells. They are very optically active and do not degrade easily over time, so will the addition of light waves they can be heated to high temperatures. This would help destroy tumors using the photothermia method and is completely biocompatible with humans and thus a huge degree of risk or toxicity is avoided [47].

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