Nanoparticle-Based Drug Delivery System for Beginners

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Abstract

Nanoparticles are the simplest form of structures with sizes in the nanometer range. They possess unique physicochemical properties such as high surface area, nanoscale size, and optical characteristics. The nanoparticle synthesis and the study of their size and properties are important in medicine as well as in biotechnology applications. Nanoparticle-based delivery provides a new drug delivery method for the treatment of chronic human diseases by site-specific and target-oriented delivery of a variety of drugs. The synthesis, characteristics, and applications of different types of nanoparticles having potential in nano-drug delivery systems (NDDSs) are described. The article illustrates various properties of nanoparticles and then, based on composition, classifies these nanoparticles in multiple categories. The advantages of different types of nanoparticles are mentioned along with many applications with emphasis on drug delivery, and then we briefly describe herein the future of nanoparticles in targeted drug delivery.

Keywords

Targeted drug delivery · Liposomes · Drug carrier · Synthesis · Applications

18.1 Introduction

Nanotechnology is an emerging branch of science that created a bridge between biological and physical sciences through diverse synthetic strategies, particle structure, and size modification in different fields of science. This engineering technology deals with the preparation of nanoparticles which range from 1 to 100 nm in size and

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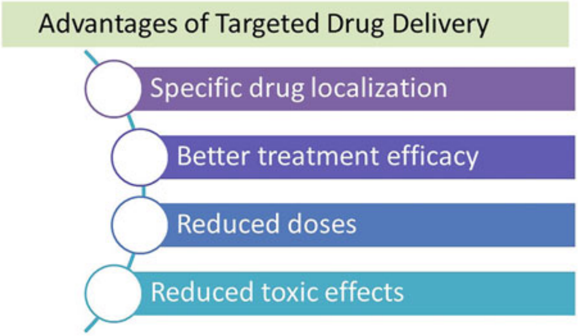

Fig. 18.1 Advantages of targeted drug delivery

primarily influences nanomedicine and nano-based drug delivery systems (Patra et al. 2018). The term nanoparticle is a combination of the words “nanos” (Greek: dwarf) and “particulum” (Latin: particle). Nanoparticles (NPs) are the particulate substances with a diameter of 100 nm (Laurent et al. 2010) with up to three-dimensional configurations depending on overall shape (Tiwari et al. 2012). By this definition, NPs have at least one nanometric dimension. For instance, 3D nanostructures and quantum dots are typically placed at the upper and lower ends of this scale, respectively. NPs have improved biological, physical, and chemical capabilities in comparison with their original equivalent materials (Dolez 2015).

Nano-drug delivery system (NDDS) is one of the promising applications of nanotechnology in medical sciences and human healthcare, which includes various classes of nanomaterials which can increase the water solubility or stability of the drug, prolong cycle time, the high uptake rate of target cells or tissues, reduction in enzyme degradation which also improves the effectiveness of many therapeutic drugs (Deng et al. 2020). In NDDS, different drug administration routes can be used, such as inhalation, oral administration, or intravenous injection. The early developed NPs were not able to cross the biological barriers to delivery, but in the present time substantial research is being directed toward the development of biodegradable polymeric nanoparticles, which incorporate complex architecture, bio-responsive moieties, and targeting agents to enhance the drug delivery system and tissue engineering. Hence, with this advancement, controlled release of drugs, stabilizing labile molecules (e.g., proteins, peptides, or DNA) from degradation, and site-specific drug targeting can be accomplished (Singh and Lillard 2009; Mitchell et al. 2021) (Fig. 18.1).

18.2 Properties of Nanoparticles

Nanoparticles are ultrafine units that are measured in nanometers (nm; 1 nm $= 10^{-9}$ m) with submicroscopic size and unique material characteristics and thus can be classified into various types. According to the Commission of the European Union, 2011, nanoparticles can be defined as “a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in size range 1–100 nm." NPs are of different shapes, sizes, and structures (www.britannica.com). The nanoparticles have three general physical properties which are highly mobile in the free states, have enormous specific surface areas, and may exhibit quantum effects.

A particle of 200 nm size or larger activates the vascular and lymphatic systems, which filter and clear out the foreign matter or chemicals and remove them from circulation quickly. Thus, the size of the ideal nanoparticles is approximately 100 nm. The particles of this size can cross the blood-brain barrier using endothelium-tight junction openings with the help of hyperosmotic mannitol, which provides target-specific controlled delivery of macro- and micromolecules of therapeutic agents which are used in the treatment of diseases like brain tumors and cancers (Prokop and Davidson 2008; Singh and Lillard 2009; Rizvi and Saleh 2018).

In drug distribution, due to hydrophobicity, surface, non-modified nanoparticles have opsonization properties, and then they also cleared by the mononuclear phagocyte system (MPS). Therefore, in the human body, deliverable drugs with their suitable nanoparticles are coated with polymers/surfactants or biodegradable copolymers which have hydrophilic characteristics, e.g., polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine, and polysorbate 80. This minimizes the opsonization and increases the circulation of nanoparticles (Singh and Lillard 2009; Chandrakala et al. 2022). Thus, the above description illustrates that in NDDS, drug release or delivery of any therapeutic agents into the human body depends on the size and surface area of particles. The controlled particle size and surface area properties contribute to faster polymer degradation as well as drug release.

The ideal NDDS should have a high drug-loading capacity and an efficient drug-release system. Drug loading can be accomplished by the incorporation method (incorporation of the drug at the time of nanoparticle formulation) and adsorption/absorption method (absorption of the drug after nanoparticle formation). Some studies have shown that the ionic interactions and isoelectric point (p*I*) can be very effective in increasing drug loading (Singh and Lillard 2009). The release of the drug depends on the type of nanoparticle used in the system; if nanocapsules were used, then the release is controlled by drug diffusion through the polymeric layer, and if nanospheres are used, then the drug is physically and uniformly dispersed by erosion of the matrix. The drug release from nanoparticle-based formulation is affected by many factors like pH, temperature, drug solubility, adsorbed drug, matrix swelling, and the combination of erosion and diffusion processes (Rizvi and Saleh 2018).

18.3 Classification of Nanoparticles

According to the composition of the materials, morphology, size, and physical and chemical properties, various nanomaterials can be categorized as carbon-based NPs, lipid-based NPs, metal, ceramics, and semiconductor. The following is a description of important nanomaterials and their features, which are compatible for use in NDDSs:

18.3.1 Carbon-Based NPs

Carbon nanotubes (CNTs) and fullerenes are two primary groups found in carbon-based NPs. Nanomaterials comprised of globular hollow cages, such as allotropic forms of carbon, are found in fullerenes. They have sparked significant commercial interest in nanocomposites for a variety of applications, including fillers (Saeed and Khan 2014, 2016), efficient gas adsorbents for environmental remediation (Ngoy et al. 2014), and support medium for various inorganic and organic catalysts (Mabena et al. 2011; Ngoy et al. 2014). The fullerene-based delivery system has the potential to carry multiple drug payloads with other chemotherapeutic drugs, e.g., Taxol® (Ashcroft et al. 2006) can load 40 fullerenes onto a single skin cancer antibody called ZME-108, which can be used to deliver drugs directly into melanomas. Thus, multiple drugs can be loaded into a single antibody in a spontaneous manner (Singh and Lillard 2009). Carbon-based NPs also have promising futures in different fields of nanotechnology due to their abundance in nature as various allotropes, minimal cellular toxicity, flexible engineering, and exceptional physical qualities at the atomic scale. The exceptional electrical conductivity, great anisotropic thermal conductivity, and mechanical durability of carbon-based NPs are frequently combined with polymer materials and nanocomposites (Parvej et al. 2022).

18.3.2 Liposomes and Micelles

Liposomes are made up of at least one phospholipid bilayer and an aqueous core, which can load hydrophobic drugs and carry the drug to target cell membranes. Liposome-based drug delivery system is FDA-approved and also called as “contact-facilitated drug delivery” (Nagalingam 2017; Li et al. 2019). Their morphological similarity to cellular membranes is one of the key characteristics that made them excellent as a nanocarrier for bioactive compounds or pharmaceutical agents (e.g., medicines, genes). Liposomes show many advantages as a type of drug carrier, such as they are nontoxic, non-immunogenic, sustained-release drugs, prolonging drug action time, etc. (Yingchoncharoen et al. 2016). Liposomes cannot develop for the entrapment for hydrophilic and ionic molecules (Chandrasekaran and King 2014), but by expanding their use, LNPs can form unilamellar or multilamellar vesicular structures, which allow liposomes to entrap, carry, and deliver hydrophilic,

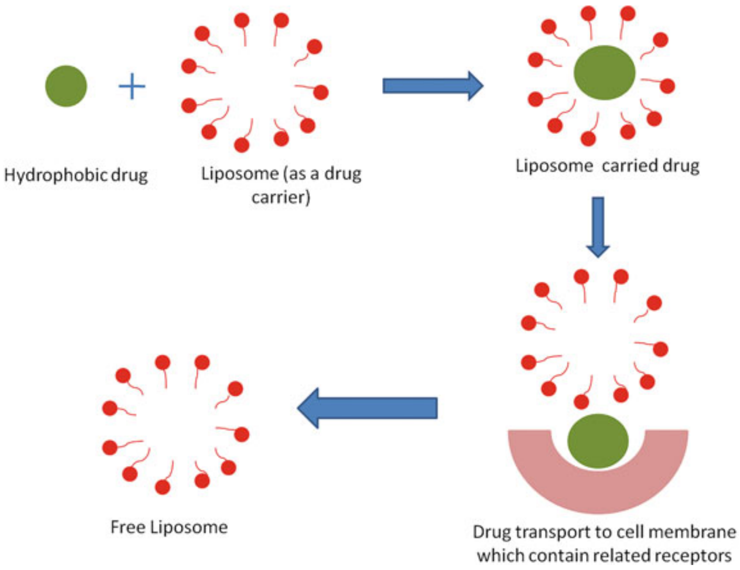

Fig. 18.2 Targeted drug delivery using liposomes as a drug carrier

hydrophobic, and lipophilic drugs (Sarfraz et al. 2018). Liposomes which deliver nucleic acids form micellar structures within the particle core. Micelles are spherical and amphiphilic copolymer assemblies that can accommodate hydrophobic drugs. Their outer shell is hydrophilic that makes the micelle water soluble. Some examples of micelle formulations are sterically stabilized micelles (SSM) which have been used as nanocarriers for CPT (CPT-SSM) for cancer treatment, SP1049C (doxorubicin-encapsulated pluronic micelles), NK911, and Genexol-PM (paclitaxel-encapsulated PEG-PLA micelle). Micelles have several advantages over other drug delivery systems but also have drawbacks (Fig. 18.2).

18.3.3 Metal NPs

Metal NPs are completely made up of metal precursors. These NPs have unique optoelectrical features due to their well-known localized surface plasmon resonance (LSPR) characteristics. In the visible zone of the electromagnetic spectrum, NPs of alkali and noble metals, such as Cu, Ag, and Au, have large absorption band. Metal NPs with regulated facet, size, and shape are important in today's cutting-edge materials (Dreaden et al. 2012). Metal NPs are used in a variety of scientific fields due to their excellent optical characteristics. Gold NP coating is commonly used for SEM sampling to improve the electronic stream, which aids in the acquisition of high-quality SEM images.

(a) **Copper NPs**: Copper NPs have received a lot of attention due to low cost, chemical stability, and simple preparation (Basher et al. 2019). They have a high melting point, excellent thermal and electrical conductivity, and high ductile strength and are strongly localized. They have been used as a coloring agent since antiquity. Even now, as pigment ingredients in inkjet printing, they are a feasible alternative to noble metal NPs (gold and silver). They are frequently employed in biological and pharmaceutical applications due to their catalytic and antibacterial properties. However, there have been reports of potential negative biological effects of copper NPs on embryogenesis (Khan et al. 2022). Copper oxide (CuO) NPs are present in spherical shape with a diameter of 1–30 nm with large specific surface area. The copper atom is linked to oxygen in a rectangular shape in the monoclinic crystal structure. Saha et al. (2018) demonstrated that the other characteristics of CuO NPs are heavily influenced by its morphology. Grigore et al. (2016) highlighted the major features of CuO NPs in the light of their synthesis process and biomedical uses. The CuO NPs with a few nanometers in diameter have been reported to have weak ferromagnetic activity (Zhang et al. 2014), but Joy et al. (1998) and Bisht et al. (2010) found that standard zero field cooled (ZFC) magnetization was not present. The antibacterial characteristics of CuO NPs are used to prevent bacterial infection in the textile industry and hospitals. Verma and Kumar (2019) demonstrated biomedical applications of CuO NPs due to its sensing and therapeutic properties.

(b) **Aluminum NPs**: Aluminum NPS are used as powder in rocket fuel to boost combustion speed and stability due to their catalytic activity and high energy release. Because they have a wide optical absorption band, the LSP resonances can be modulated from UV to NIR by manipulating their shape. They are also suited for application in photovoltaic solar cells due to their high radiative efficiency (Temple and Bagnall 2011). Aluminum NPs are known to cause cellular toxicity and DNA damage (Zhang et al. 2018).

(c) **Gold NPs**: Gold NPs are the oldest and most widely used metal NPs. Due to their better physical properties, nanoscaled gold particles have been widely used. More crucially, by manipulating their morphology (both size and shape), solvent, surface ligand, temperature, etc., these properties can be fine-tuned. Localized SPR is more pronounced in spherical gold NPs than in other plasmonic particles, resulting in significant radiative, absorption, and scattering characteristics. Gold NPs have a fluorescence quenching ability and an absorption peak at 400–550 nm, depending on particle size, making them attractive in bioimaging, probing, colorimetric sensing, and sensor construction (Yeh et al. 2012). They are used to sputter coat the material in a scanning electron microscope (SEM) in order to obtain a high-quality image by increasing the electronic stream. Furthermore, gold particles are a common vehicle for carrying therapeutic compounds, targeted medications, genes, and targeting agents on their surface due to their huge specific surface area and high electron density nanoscale.

(d) **Silver NPs**: Silver NPs have a wide range of use in biomedical devices, medication, highly conductive composites, and the textile industry due to their unique physical properties. Silver NPs have excellent SPR, strong absorption, and NP characteristic packing near 400 nm and tunable scattering capabilities at longer wavelength, making them ideal for bioimaging, molecular labeling, and improved optical spectroscopy. As reported by Zhang et al. (2016), nanoscaled silver has long been regarded as a popular biomaterial with antibacterial action. Their antimicrobial properties are commonly employed to reduce biofouling. They have also shown promise against the HIV virus and cancer cell death. Furthermore, their anti-inflammatory properties make them ideal for wound healing. The toxicity of silver NPs is mostly determined by their size. When compared to particles made from other heavy metals like gold, platinum, and zinc, silver NPs have demonstrated a high level of antibacterial activity and a low level of cytotoxicity (Crisan et al. 2021). They have the ability to adhere to cells, inhibit enzyme activity, weaken the cell membrane, and ultimately cause cell death (Tang and Zheng 2018).

(e) **Iron NPs**: Iron NPs have excellent thermal and electrical conductivities with strongest magnetic properties of any magnetic NP (Rubel and Hossain 2022). Iron NPs exhibit surface plasmon resonance (SPR) which is important in memory tape, magnetic data storage, and magnetic resonance imaging (MRI). Iron NPs with a diameter of about 2 nm have magnetic characteristics, and the magnetic anisotropy energy constant increases as the particle size increased (Bedker et al. 1994). Magnetic NPs of iron oxide of less than 10 nm in size exhibit super paramagnetic properties that play crucial role for a variety of biomedical applications. The suitability of iron oxide NPs as a contrast agent for magnetic resonance imaging (MRI) and as a nanocarrier for bio-elements such as drugs, proteins, and therapeutic genes has been investigated. However, poisoning is frequently one of the drawbacks that make large magnetic components unsuitable for medicinal applications of these important NPs.

(f) **Platinum NPs**: Platinum NPs with exceptional chemical and optical characteristics are gaining popularity in industrial and biological applications. Platinum NPs when suspended in aqueous solution create a brownish-red or black nanofluid. They have a high level of thermochemical stability, corrosion resistance, and catalytic activity. They can be used in catalytic converters, hydrogen peroxide (H_2O_2) breakdown, nitric acid synthesis, proton-exchange membrane fuel cells (Reddington et al. 1998), pollution reduction, etc. At ambient temperature, carbon-coated platinum NPs also demonstrate ferromagnetic properties. They are frequently utilized as dopants with other metallic particles to make ultraefficient alloys.

(g) **Lead NPs**: Lead NPs are black spherical powder, apparently prone to oxidation and susceptible to water and humid ammonia (Bochenkov et al. 2004). They have potential applications in electron microscopy for real-time imaging due to their optical and redox characteristics.

(h) **Cobalt NPs**: The appearance of pure cobalt NPs are in the form of gray or black granules. The high magnetic characteristic of this NP is most suitable for imaging, sensing, and targeted delivery of biological molecules and medicines. The detailed toxicity of cobalt NPs has been studied on osteoclast-like cells (Liu et al. 2015c).

18.3.4 Ceramics NPs

Ceramic NPs are inorganic nonmetallic solids and found in amorphous, polycrystalline, thick, porous, or hollow forms (Sigmund et al. 2006). These NPs are used in various applications like catalysis, photocatalysis, dye, photodegradation, and imaging (Thomas et al. 2015). Ceramic NPs possess superior mechanical strength, thermochemical stability, and environmental resistance. One significant drawback of ceramic NPs is the potential for toxicity in medicinal applications such as drug administration.

18.3.5 Semiconductor, Inorganic and Nanoshell NPs

Semiconductor materials are intermediate between metals and nonmetals (Ali et al. 2017; Khan et al. 2017). Semiconductor NPs contain broad bandgaps, and bandgap tuning causes considerable changes in their characteristics. Therefore, they are used in photocatalysis, photo optics, and electronic devices (Sun et al. 2000). Due to their optimal bandgap and band edge positions, large numbers of semiconductor NPs have been discovered in water splitting applications (Hisatomi et al. 2014). When compared to single semiconductor particles, nanoshells have a higher luminescence quantum yield. Changing the shell material and thickness, as well as the core form, improves the tunability of other optical parameters, including absorbance and scattering (Nayak et al. 2017).

(a) **Germanium NPs:** Germanium (Ge) is the second most extensively used indirect bandgap (0.66 eV at bulk scale) semiconductor in group IV. Ge is usually found in the crystal structure of diamonds, which can vary in a cluster of more than 40 atoms. Ge NPs are a grayish black powder with an average diameter of 70–120 nm. The mechanical stability of Ge clusters has been determined by the crystal structure (Pizzagalli et al. 2001). Ge has greater static dielectric constant and lower effective mass of the electron-hole pair. In addition, electrochemical etching of Ge has not been as successful. By utilizing differential surface tension and size purification, the emission spectra of Ge NPs may be fine-tuned to narrow lines. The Ge NPs have wide range of uses in microelectronics.

(b) **Magnesium oxide NPs**: Magnesium oxide (MgO) are normally white powder as NPs, but depending on the presence of foreign elements, they might be brown or black. The size of MgO NPs influences the optical characteristics. Stankic et al. (2005) used UV diffuse reflectance spectroscopy to study the optical characteristics of MgO nanocubes. The MgO NPs are effective while absorbing harmful ions from aqueous solutions (Hoque et al. 2018). Furthermore, by employing them as a chemical additive, their catalytic action can be exploited. They also have high-temperature dehydrating capabilities, reduce corrosion, and cleanse water by reducing bacterial development. At low concentrations, MgO has a strong antibacterial action at the nanoscale, making it a potential plant pathogenic antibacterial agent for disease management (Cai et al. 2018). Ceramics undergo grain development and a considerable increase in fracture toughness when treated with MgO NPs (Tan et al. 2013).

(c) **Gallium nitride NPs**: Gallium nitride (GaN) is a semiconductor material of the group III–V family with a 3.4 eV direct bandgap. It has hexagonal (wurtzite) single crystal structure and can be manufactured at the nanoscale in a variety of morphological assemblages (NPs, nanorods, nanotubes, nanowires, and so on) using various synthesis procedures. Due to quantum confinement, GaN NPs have a high mechanical toughness and outstanding thermal and optical characteristics that depend on nanocrystal size. GaN NPs are utilized in a variety of devices, including LEDs, LDs (laser diodes), biosensors, solar cells, field-effect transistors, photocatalysts for water splitting, and piezoelectric nanogenerators, due to tunable optical and dielectric properties (Lan et al. 2016).

(d) **Indium NPs**: The hexagonal (wurtzite) and cubic (zinc blende) crystal forms of indium phosphide (InP) have bulk bandgaps of 1.42 and 1.35 eV, respectively. It has better electron mobility than GaAs, making it a good contender for high-speed optoelectronic devices and digital circuits (Zafar and Iqbal 2016). Furthermore, InP quantum dots are potential to be future competitor of cadmium-based quantum dots in terms of luminescence efficiency due to their decreased toxicity (Brichkin 2015). With a direct bandgap of around 0.354 eV, indium arsenide (InAs) is one of the least extensively utilized group III–V semiconductor compounds. Gray crystals having cubic (zinc blende) structure can be found. As InAs have properties similar to GaAs, they are frequently combined with InP to get the most out of their small bandgap and strong electron mobility. InAs photodiodes are frequently used in infrared detectors and diode lasers. Microorganisms have been reported to be acutely hazardous to both InAs and GaAs (Nguyen et al. 2020).

(e) **Silicon NPs**: Silicon NPs (SiNPs) are biologically compatible, metal-free quantum dots that exhibit size and surface tailorable photoluminescence. Silica NPs are mesopores (2–50 nm pores) of silica that display unique physicochemical properties. These nanocarriers can be prepared in a variety of sizes and shapes including nanohelices, nanotubes, nanozigzags, and nanoribbons (Meier et al. 2007). The nanostructure of these materials influences their optical, chemical, and material properties and hence plays an important role in their future-generation applications in sensors, battery electrodes, optical materials, contrast agents, etc. Nanosilica or silica NPs are commercial terms for nanoscaled silicon dioxide (SiO_2) particles. There are two varieties of silica NPs based on structure: P-type and S-type NPs, both of which are white powder. The P-type particles have a higher specific surface area and porosity than S-type particles. As nanopowders, they have minimal toxicity, pozzolanic reactivity, and filling ability (Challa and Das 2019). Because P-type silica NPs have a high UV reflectivity, they can be used as a protective covering.

(f) **Titanium nitride NPs**: Mechanically, titanium nitride (TiN) NPs are extremely strong. Their hardness and wear resistance are exceptional, allowing them to be used with other ceramics in cutting equipment and bearing materials to extend their life. The transmission electron microscopic observation of TiN NPs indicates that they are virtually spherical, with sizes of 5–20 nm. Because of their high thermal conductivity and melting point (2950 °C), they can endure high temperatures. TiN has a low sintering temperature, making it ideal for embedding in nanocomposites. They have outstanding UV protection and infrared absorption. The scattering efficiency is not as great as gold NPs, and the plasmonic performance of single cubic crystal-structured TiN is nearly as good (Kaskel et al. 2003; George et al. 2009).

(g) **Alumina NPs**: Alumina NPs are white powder with a spherical shape. At a certain particle size, structures of alumina NPs are temperature dependent, and this dependence is altered by particle shrinking. At the nanoscale, the most stable-phased alumina, for instance, stabilizes at a lower temperature. This considerably improves the nanoceramic's flexural strength (Zemtsova et al. 2015). Superior qualities of alumina NPs are used in cutting tools, integrated circuits, and transparent ceramics.

(h) **Titania NPs**: Titanium dioxide (TiO_2) NPs are n-type semiconductors that occur naturally in a variety of polymorphic crystal forms. They can be made in a variety of ways, i.e., crystal, powder, nanotube or nanorods, and thin films. Titania NPs are highly effective in blocking UV rays while remaining harmless. Furthermore, their transparency makes them useful for making skin-protective cosmetics such as sunscreens, vanishing creams, and beauty creams. They can also be used to process ink and as a surface coating. They also have strong photocatalytic properties (Hossain et al. 2017, 2018a, b), making them useful for the production of disinfectants and antibacterial chemicals.

(i) **Calcium NPs**: Calcium phosphate (CaP) NPs are present in a variety of shapes and sizes. Tricalcium phosphate ($Ca_3(PO_4)_2$) and hydroxylapatite ($Ca_5(PO_4)_3$) are the most prevalent types. The ratio of Ca to P has a big impact on the properties of these NPs. CaP is a common bone substitute due to its biocompatibility and likeness to the inorganic mineral compositional constituent in the skeleton of human. As a widely utilized nonviral vector in gene therapy, nanoscale CaP can thus play an important role. Because calcium carbonate ($CaCO_3$) is abundant in nature, it is one of the cheapest inorganic materials available. Slow biodegradability is an additional benefit. Calcium carbonate exists in three polymorphic crystal forms—calcite (trigonal), aragonite (orthorhombic), and vaterite—depending on the synthesis conditions (hexagonal). Calcite is the most chemically stable of these minerals, whereas vaterite is the least stable (Biradar et al. 2011). Chemically, nanosized $CaCO_3$ particles are harmless, making them environmentally beneficial. They can also be employed for regulated and harmless drug distribution because of their biocompatibility.

According to recent pharmaceutics research, building an enteric drug delivery method using calcium carbonate in a tablet-encapsulated form is possible (Render et al. 2016). Furthermore, they have a good radiopacity characteristic.

18.4 Synthesis of NPs

The following two methods are employed for the synthesis of NPs: (1) the bottom-up or building-up method and (2) the top-down method (Daniel and Astruc 2004; Wang and Xia 2004), which are further divided into several subcategories based on the operation, reaction state, and procedures used.

18.4.1 Bottom-Up or Building-Up Synthesis

In bottom-up or building-up synthesis procedure, NPs are produced from relatively simple elements. Two methods, viz., sedimentation and reduction procedures, are included in this category. Other minor methods like spinning, green synthesis, sol-gel, and biological synthesis are also included (Iravani 2011). Using this method, TiO_2 anatase NPs containing graphene domains have been created (Mogilevsky et al. 2014). Needham et al. (2016) have used a solvent-exchange approach to create low-density lipoprotein (LDL) NPs of limit size for medical cancer medication. Nucleation is the bottom route in this procedure, followed by growth, which is the top approach. The LDL nanoparticles were made without using phospholipids having high hydrophobicity which is important for the administration of drugs (Needham et al. 2016).

18.4.2 Top-Down Synthesis

For syntheses of NPs, the destructive technique is used in top-down procedure. For the synthesis, first, the large-sized molecules are broken into smaller units, and then appropriate sized NPs are synthesized. In this direction, grinding and milling, chemical vapor deposition (CVD), physical vapor deposition (PVD), and other decomposition process technologies are generally employed (Iravani 2011). Coconut shell (CS) NPs were produced using this method. Initially the raw CS powders were finely milled for various intervals of time using ceramic balls and planetary mill as per the requirement of the size of the NPs. The reddish tint vanished with each hour increment as the NPs shrank in size (Bello et al. 2015). From the top-down methods, different approaches like mechanical milling, laser ablation, etching, sputtering, and electro-explosion are used for the production of NPs for nanostructured materials. By using a top-down laser irradiation approach, monocrystalline, well-uniform, and spherical-shaped Au nanospheres have been created (Liu et al. 2015a, b).

Both top-down and bottom-up techniques were used to prepare monodispersed spherical bismuth (Bi) NPs (Wang and Xia 2004). The colloidal characteristics of these NPs are found to be excellent. In bottom-up approach, bismuth acetate was boiled in ethylene glycol, but in the top-down approach, bismuth was converted to molten form and then emulsified within boiled diethylene glycol to synthesize NPs. The size of the NPs produced by both procedures ranged from 100 to 500 nm (Wang and Xia 2004). Because of the feasibility and less hazardous nature of processes, green and biogenic bottom-up syntheses are widely used. These techniques are both cost-effective and environmentally beneficial as they normally use plant extracts from biological systems to synthesize NPs. To prepare NPs, bacteria, yeast, fungi, *Aloe vera*, tamarind, and even human cells have been employed. The microorganisms and plant extracts were used as reducing agents to synthesize Au NPs from wheat and oat biomass (Ahmed and Ikram 2016; Parveen et al. 2016).

18.5 Applications of NPs

NPs possess a variety of potential applications, namely, in preparation of food, environmental cleanup, preclinical medicine, clinical medicine, physics, optics, and electronics. According to reports, 90% of drugs are insoluble in water and thus are not able to reach their targets (Carissimi et al. 2021). Various studies have been performed to improve drug delivery and higher efficacy of targeted drug delivery. In recent times, the development of nanoparticle-based delivery systems has instigated site-specific and target-oriented delivery of a variety of drugs or therapeutic agents or natural-based active compounds for the treatment of various chronic human diseases. In NDDSs, targeted drug delivery using nanomaterials or nanoformulations can be done actively or passively. In active targeting, therapeutic agents such as antibodies or peptides conjugated to a tissue- or cell-specific ligand, which anchors them to reach at the receptor site of the targeted cell. In passive targeting, conjugated therapeutic drug and nanocarrier reach the target organ through bloodstream, and this type of target method is influenced by pH, temperature, molecular site, and shape (Singh and Lillard 2009; Patra et al. 2018). For NDD, the main target sites in the body are lipid components or receptors of cell membrane and cell surface proteins or antigens. NDDSs show their most applications are in the delivery of chemotherapeutic agents, immunotherapeutics, anti-inflammatories, antibiotics, anesthesia, hormones, etc. The most commonly used targeting agents for drug delivery are liposomes, peptides, antibodies, designed proteins, nucleic acid aptamers, and other small organic molecules (Rizvi and Saleh 2018; Carissimi et al. 2021). For the development of immunotherapeutics, T cells are the direct targets in the pathology and in giving immunotherapies in diseases like T cell lymphocytic leukemia, T cell lymphoma, and human immunodeficiency virus (HIV) infection (Cevaal et al. 2021) (Fig. 18.3).

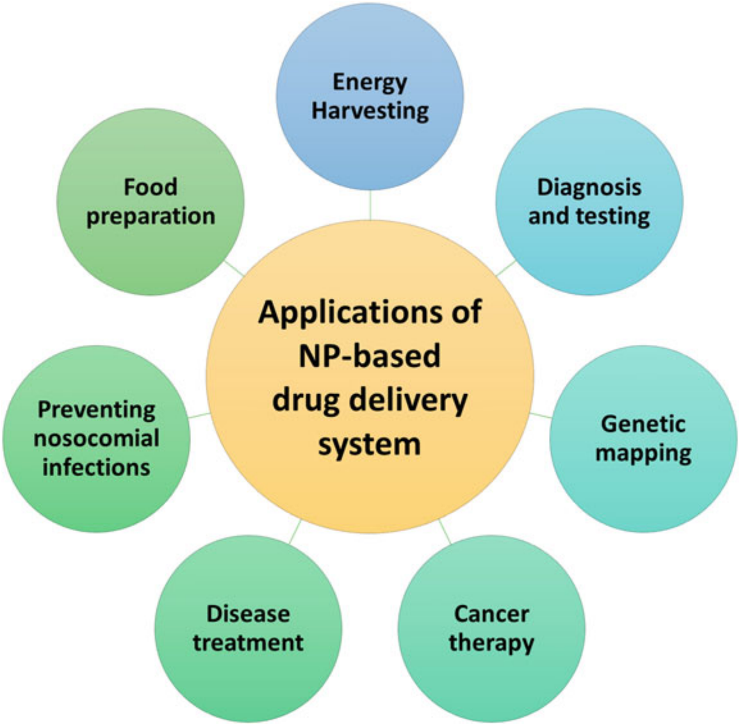

Fig. 18.3 Application of nanoparticle-based drug delivery system

18.5.1 Cancer Therapy

The use of nanotechnology in cancer detection, therapy, and management has opened a new area of research. NPs increase the intracellular concentration of medications while avoiding toxicity in healthy tissue, through either active or passive targeting. To establish and regulate drug release, targeted NPs can be developed and adjusted to be pH-sensitive or temperature-sensitive. Within the acidic TME, the pH-sensitive drug delivery system can distribute pharmaceuticals. Temperature-sensitive NPs release medications into the target site in response to temperature changes brought on by sources such as magnetic fields and ultrasonic waves. Furthermore, NPs' physicochemical properties, such as shape, size, molecular mass, and surface chemistry, play an important role in the process of immunotherapy using NPs. The immune system plays a crucial role in the establishment and growth of cancer cells. The development of immunotherapy has transformed cancer treatment. NPs have been discovered to aid in the delivery of chemotherapy to specific targets and can also be utilized in conjunction with immunotherapy. Immune checkpoint blockade therapy, cancer vaccine therapy, and chimeric antigen receptor (CAR)-T cell therapy are all examples of immunotherapy techniques aimed at stimulating the immune system against cancer cells. Moreover, the nanotechnology has given tremendous outcomes for cancer diagnosis, detection, and therapy and circumventing multidrug resistance (Levinsen et al. 2016). The inorganic NPs like dendrimers, micelles, liposomes, and nanotubes are used for the delivery of chemotherapeutic agents. Many metal NPs such as silver, gold, palladium, platinum, zinc oxide, titanium oxide, and metal sulfides have also been used in the drug delivery systems for cancer treatment.

18.5.2 HIV/AIDS Treatment

For the treatment of HIV/AIDS, highly active antiretroviral therapy (HAART) is used in which multiple drugs (three or more) were given in a combined form. Many studies have shown that the nanoparticles loaded with antiretroviral drugs were able to target monocytes and macrophages in vitro. For example, poly(lactic-co-glycolic acid) (PLGA) was used to prepare nanoparticles in which three antiretroviral drugs—ritonavir, lopinavir, and efavirenz—were entrapped, and this NDDS sustained drug release for over 4 weeks (28 days), while free drugs were eliminated within 48 h (2 days) from the body (Destache et al. 2009; Rizvi and Saleh 2018).

18.5.3 Diagnosis and Testing

The use of nanoparticles for diagnostic purposes is a highly explored area of NDDSs. Nanoparticles help in diagnosis and identification of the stage of diseases which can report the location and provide information regarding treatment responses (Patra et al. 2018; Rizvi and Saleh 2018). The development of quantum dots allows monitoring of various biological events simultaneously by tagging which can be defined by many customized specific colors. Their absorption spectrum ranges from UV to a wavelength of a visible spectrum which provides photostability, high quantum yield, and tunable emission spectrum. Size of the nanodot specifies the spectrum where individual particle falls, e.g., larger particles have longer wavelengths and narrow emission (Rizvi and Saleh 2018). According to studies, theranostic nanoparticles such as surfactant aggregates (micelles and vesicles), dendrimers, drug conjugates, core-shell particles, and carbon nanotubes are used for monitoring of pathway and localization of nanoparticles at the site of drug target and also monitor action of drug to assess therapeutic response by combining both drug and imaging agent (Bhojani et al. 2010; Janib et al. 2010).

18.6 Other Applications of NPs

18.6.1 Nosocomial Infections

Hospital acquired infections (nosocomial infections) are the greatest cause of death (Wenzel 2007). The 60–70% of nosocomial infections are linked to bacterial contamination of medical devices that have been implanted (Donlan 2001; Bryers 2008). The antimicrobial properties of a large number of synthesized NPs such as silica/iron oxide NPs, graphene, graphene oxide, bifunctional Fe_3O_4-Ag NPs, titanium, copper, zinc, silver, and gold have been investigated (Kang et al. 2008; Rodrigues and Elimelech 2010; Narayanan and Sakthivel 2011; Santos et al. 2012; Mejias Carpio et al. 2014; Musico et al. 2014;Rodrigues et al. 2015).

18.6.2 Preparation of Food

Nanotechnology-based applications are used to improve the procurement of raw materials, sorting and grading, primary processing, packing, transportation and storage, and food processing. Enhancing palatability, toxin elimination, enzyme deactivation, spoilage organisms, pathogens, and additional fortification and enrichment with micronutrients are the key deliverables of food processing in which nanotechnology based techniques are invariably used. Nanostructured food ingredients are being produced with the promise of better taste, texture, and consistency. Nanotechnology is also used to extend the shelf life of various food ingredients and reduce the amount of food waste caused by microbial infestation (Pradhan et al. 2015).

18.6.3 Solar Power

Nanotechnology-enhanced prototype solar panels convert sunlight to electricity more efficiently than normal designs, paving the way for less expensive solar power. Because they can be produced in flexible rolls rather than isolated panels, nanostructured solar cells are already cheaper to make and install. Through improved catalysis, nanotechnology is increasing the efficiency of fuel generation from regular and low-grade raw petroleum materials as well as fuel consumption (Hussein 2015).

18.6.4 Cleanup of the Environment

Nanotechnology is helpful in identification and cleaning up of environmental toxins. Through quick, low-cost detection and treatment of contaminants in water, nanotechnology could assist in addressing the demand for affordable, clean drinking water. For energy-efficient desalination, a thin film membrane incorporating nanopores has been developed. The molybdenum disulfide (MoS_2) membrane filtered two to five times the amount of water as contemporary filters. NPs are being created to remove industrial water contaminants from groundwater by chemical processes that render the pollutants harmless. This method would be less expensive than systems that require the water to be pumped out of the ground for treatment. Current cleanup technology is not significantly and economically adequate to solve all of today's cleanup needs. Nanotechnology is one of the most important trends in science and perceived as one of the key technologies of the present century (Zhang and Elliot 2006). Nanoscale iron particles are very effective for the transformation and detoxification of a wide variety of common environmental contaminants, such as chlorinated organic solvents, organochlorine pesticides, and PCBs (Rickerby and Morrison 2007).

18.6.5 Energy Harvesting

The NPs have large surface area and optical characteristics and they are catalytic in nature. NPs were frequently used to generate energy from photoelectrochemical (PEC) and electrochemical water splitting (Mueller and Nowack 2008; Avasare et al. 2015; Ning et al. 2016). There are many advanced choices for generating energy such as solar cells and piezoelectric generators (Fang et al. 2013; Lei et al. 2015; Gawande et al. 2016; Li et al. 2016). Nanotechnology can be used for affordable and safe drinking water through filtration and purification system (Mishra et al. 2012; Rabbani et al. 2016; Mobasser and Firoozi 2017).

18.6.6 Agriculture

Nanotechnology has been used to modify the genetic architecture of crop plants (Prasad et al. 2017). For targeted or controlled release of agrochemicals, nano-coated fertilizers, nano-sized nutrients, carbon-based nanomaterials, or engineered metal oxide and nano-pesticides are used, and they also have full biological effect without overdosing (Iavicoli et al. 2017).

18.6.7 Improving Life Standards with Nanoelectronics

The nanotechnology has a lot of promise for improving the capabilities of electronic components, particularly in terms of reducing their size, weight, and power consumption. Indeed, because electronic components are typically small and light, shrinking these dimensions to the nanoscale level allows for the creation of electronic devices with far greater capabilities, as it allows for the incorporation of far more components while also reducing the device's size and weight. The advances in nanotechnology may enable the development of new types of electronic components that can be employed in both traditional and modern electronic devices. Researchers are working on a memory chip that could have a memory density of one terabyte per square inch or higher (Bhatia et al. 2013).

18.7 Nanotechnology in Future

Nanotechnology has the potential to generate multifunctional materials in the construction and maintenance of safer, smarter, lighter, and more efficient vehicles like spacecraft, airplanes, and ships. Nanotechnology also provides a number of options for nanoengineered materials in automotive products such as structural parts made up of polymer nanocomposites, high-power rechargeable battery systems, thermoelectric materials which can be used for temperature control, lower rolling-resistance tires, high efficiency and low-cost sensors or electronics, smart solar panels having thin films, fuel additives, and improved catalytic converters for cleaner exhaust and extended range.

The nanoengineering of steel, aluminum, asphalt, or concrete and other cementitious materials with their recycled forms has a lot of potential as they can enhance the performance, resiliency, and life span of roadways and infrastructure of transport components while lowering their costs. Nanotechnology proves its great usage in either chemical or physical modification of individual atoms and molecules at a specific location. This new age technology also makes possible to develop devices which can scan and manipulate objects at near atomic scale (Kubik et al. 2005).

18.8 Conclusion

Nanotechnology established itself as an advanced field of science where intense research is carried out to implement the technology. The size of NPs ranges from a few nanometers to 500 nanometers. Based on material used in synthesis, NPs are classified as carbon-based, metal-based, ceramic, semiconductor, nanoshell, etc. NPs can also be categorized into organic and inorganic NPs. Morphology, structure, particle size, surface area, and optical properties are used in characterization of different NPs. Each category of NP has a significant application based on its properties. Despite the fact that NPs are valuable for a variety of applications, their unpredictable use and discharge pose significant health risks. Due to recent advances in nanotechnology, poorly soluble, poorly absorbed and labile biologically active compounds have been re-modified into viable, delivery able pharmaceuticals. In recent years, toxicity profiling of NPs has become a popular study topic all around the world. Natural NPs have been around for a long time in the ecosystem, and they contain some processes that make them less toxic to living things. In past few years, NPs are tested for many new and different applications which enhance the efficiency and performance of the object or process, and subsequently cost is reduced which makes NP-based nanotechnology accessible to everyone. Thus, nanotechnology has a great future because of its efficiency and environment-friendly properties.

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