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Chapter 6

Antimicrobial Nanostructures for Neurodegenerative Infections: Present and Future Perspectives

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1. INTRODUCTION

Nanotechnology is a recent development in the art of the manipulation of materials especially at the atomic or molecular scale level; it builds the nanoscale structures of chemicals and devices (Mukherjee, 2013; Del Grosso et al., 2015). The National Nanotechnology Initiative and ASTM International have defined nanotechnology as a term that refers to technologies that manufacture and manipulate materials with a dimension between 1 and 100 nm to exploit their novel properties. They are expanding the design, characterization, synthesis, limitations, toxicity, and applications of nanomaterials (Khajeh et al., 2013; Kaur et al., 2014). Further, nanostructure is defined as a specified structural object with

at least one dimension equal to or smaller than 100 nm. A wide variety of nanostructures have been identified, e.g., nanopores, nanorods, nanowires, nanoribbons, nanotubes, and nanoscaffolds (Wu et al., 2016; Yohan and Chithrani, 2014). The most promising features of these structures are their size-dependent properties. They are also known as nanoparticles (Samarasekera et al., 2015; Premnath et al., 2015).

Early diagnosis of disease is essential for some diseases, like cancer and tumors, to provide better treatment. It increases the probability of curing the disease and achieving a significant reduction in mortality. Traditionally, it has been difficult to detect cancer; nowadays, the use of nanostructured devices in the early diagnosis of cancer is being realized (Cheng et al., 2014a; Liao et al., 2014).

In recent decades, many more studies have explored the formulation and use of nanostructured nanoparticles in the fields of chemistry, mathematics, and bioengineering. In addition, they have a wide range of applications in the fields of biology and medicine (Sun et al., 2015). The term “nanotechnology” was first introduced by Professor Norio Taniguchi of the Tokyo Science University, in 1974. He described nanotechnology as the processing, separation, consolidation, and deformation of materials by one atom or by one molecule (Mulvaney, 2015). The European Science Foundation defines nanomedicine as “The science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body” (Satalkar et al., 2015). The first therapeutic nanoparticle, i.e., albumin-entrapped paclitaxel (Abraxane), was successfully used as an anticancer nanomedicine (Gupta et al., 2014; Matsumura, 2014). The applications of nanoparticles in the medical field are described as diagnostics, drug carriers, drug delivery vehicles, and therapeutic agents (Rakesh et al., 2015; Khan et al., 2015). This review focuses on the prospects of nanostructured nanoparticles and nanomedicine as antimicrobial agents in the possible management of neuroinfectious diseases associated with neurodegenerative disorders.

2. RELATIONSHIP OF MICROBES IN NEUROINFECTION-ASSISTED NEURODEGENERATION

Infectious diseases are the most common and potent disorders in the clinical setting. They occur when a pathogen (i.e., virus, bacterium, fungus, or parasite) and its proteins enter into the body and affect a specific organ, tissue, or system or the whole body (Huh and Kwon, 2011). They are also called communicable diseases because of their capacity to transfer from one person to another, e.g., malaria or tuberculosis, or one species to another, e.g., influenza (Rothman et al., 2006). Infectious diseases are broadly classified as: (1) old, generally well-known diseases, e.g., dengue, malaria, and tuberculosis; (2) new, previously unknown diseases, e.g., severe acute respiratory syndrome; and (3) diseases known to threaten in the near future, e.g., avian influenza (Pigott et al., 2015). Infection is the process of pathogenicity when a microbe enters with the capacity to induce damage or disease, at either a local or a systemic level, in the host organism. It may be an acute (with a short duration and severe course) or chronic (low grade and long lasting) infection. Neuroinfection is a major harmful condition of the nervous system and it induces neurodegenerative processes that lead to neurological disorders (Thakur and Zunt, 2015).

3. POSSIBLE APPROACH USING NANOPARTICLES FOR THE TREATMENT OF INFECTIOUS DISEASE

Some antimicrobial agents are hydrophilic in nature and are unable to enter into the microbial cells. In addition, the internalized antimicrobial molecules are rapidly degraded by lysosomal activity, which leads to reduced antimicrobial activity of the drug (Park et al., 2015; Parida et al., 2015). Therefore, the new technology is expected to release the antimicrobial drug within the microbial cells. It may be through the drug delivery system using passive action on infected cells via the mononuclear phagocytic system, which may enhance the therapeutic index of the antimicrobial along with a reduction in side effects (Park et al., 2015). In addition, the systemic administration of antimicrobials affects the host system. Therefore, nanoparticles and nanomedicine are the future of antimicrobial therapy because they produce cell- and target-specific actions in the nanoscale range without alteration of host cell functions (Yang et al., 2010; Basnet and Skalko-Basnet, 2013). Regarding bacterial infections, the development of resistance against antibiotics is the major problem in antimicrobial therapy (Basnet and Skalko-Basnet, 2013). Resistance to antibiotics occurs for the following three reasons: (1) modification of the active sites of drug-binding proteins, (2) destruction or modification of the antibiotic by the enzymatic mechanisms of the organism, and (3) activation of the efflux mechanism for the antibiotic by the organism (Borges-Walmsley et al., 2003; Arenz and Wilson, 2016).

The hope is that nanoparticles can carry the antimicrobial agents at the nanoscale level and release them at the target site in the infectious organism. Therefore, nanoparticles have greater potential to eliminate the microbes and avoid the

development of resistance (Pelgrift and Friedman, 2013; Leid et al., 2012). However, the mutation of some *Mycobacterium* to resist silver nanoparticles that are loaded with isoniazid has been documented. However, this resistance occurs only with silver nanoparticles, whereas CuSO₄ and ZnSO₄ particles do not produce the microbial resistance (Larimer et al., 2014). In addition, antimicrobial-loaded nanoparticles enter into host cells, including in the brain region, via the endocytosis process followed by the release of preloaded drugs in the microbes (Martins et al., 2013). A nanoparticulate system shows enormous potential in targeted drug delivery, especially in neuroinfective conditions of the brain (Leite et al., 2015b). However, the implementation of nanomedicine in neuroinfectious diseases for antimicrobial therapy has significant challenges. Generally, a drug delivery system should have multifunctional actions, i.e., “switch on” and “switch off” functions when required. And, these multifunctional drug delivery systems must be harmonized in an optimal fashion (Gendelman et al., 2015; Singh et al., 2010). Nanoparticle-assisted antimicrobial drug delivery is challenged to produce improved efficacy and avoidance of resistance and it is extremely desired in the treatment of neuroinfective disease (Garg et al., 2015b).

However, nanomedicine has some special properties; it has the advantage of antimicrobial drug delivery and drug action against microbial infections in the nervous system (Jong and Huang, 2005; Dando et al., 2014). Antimicrobial nanoparticles possess six major properties supporting their use in the clinical setting. They are as follows: (1) the surface properties of nanoparticles can be changed for targeted drug delivery. In this case, small molecules, proteins, peptides, and nucleic acids, loaded into nanoparticles are not rejected by the immune system and effectively reach the target site of the specialized tissue (Boraschi et al., 2012); (2) nanocarriers support the solubility or stability of the drug in the targeted cells and minimize the side effects in the host cells (Singh, 2010); (3) nanotechnology allows the codelivery of two or more drugs in the form of combination therapy against multiple pathogens (Singh et al., 2014; Hu et al., 2010); (4) antimicrobial nanoparticles potentially can overcome microbial resistance, which is common in bacterial organisms (Garg et al., 2015b); (5) the administration of antimicrobial drug-loaded nanoparticles enhances the therapeutic index, with extended half-life in the systemic circulation leading to the controlled release of the microbial drug and improving the overall pharmacokinetics (Bisht and Maitra, 2009; Chen et al., 2015); and (6) the administration of antimicrobial drug-loaded nanoparticles is possible via different routes such as oral, nasal, parenteral, and intraocular (Fonseca-Santos et al., 2015; Almeida et al., 2015). Therefore, there is great interest in developing antimicrobial nanoparticles as newer methods of drug therapy for neuroinfectious disease.

4. PROPERTIES OF NANOSTRUCTURED NANOPARTICLES

Various nanostructures are designed to develop nanoparticles and nanomedicines. In the medical system, they are widely used in diagnosis and as drug delivery systems for cancer treatment. Various nanomaterials, like Au, Ag, ZnO, Cu/CuO, TiO₂, Al₂O₃, and CeO₂, are used in nanomedicine for exploring their antimicrobial activity (Ge et al., 2011; Fu et al., 2012). These nanoparticles have unique physicochemical properties, e.g., ultrasmall size (less than 100 nm), controllable size, large surface area-to-mass ratio, high reactivity, no solubility, and target-specific actions. These properties of nanoparticles allow them to act as nanomedicines because the size of natural functional units in living organisms, like DNA (2 nm), small RNAs, ribosomes (20 nm), microtubules (25 nm), nuclear pores (50 nm), and various proteins and lipids is equal to or less than 100 nm (Wang and Wang, 2014; Shang et al., 2014; Matea et al., 2015). Further, it is significant that innovative nanoparticles can overcome the limitations of traditional diagnostic and therapeutic agents. Furthermore, the small size of nanoparticles provides extreme mobility and capacity to interact with the biological system (Saptarshi et al., 2013). However, some research studies have suggested that smaller nanoparticles are expected to produce toxicity because of their higher reactivity with various biological proteins and peptides (Mu et al., 2014; Zaman et al., 2014). This property of nanoparticles has raised safety issues with nanomedicine (Yang et al., 2010). In fact, initial findings revealed that nanoparticles can easily penetrate and propagate in living organisms. A comparative study showed potential benefits in the diagnosis and cure of diseases without risk to the immune system, lungs, digestive mucosa, and skin. The primary goal of nanoparticles in medicine is to design target- and site-specific delivery systems with an accurate therapeutic dose (Wang et al., 2013a). In 2013, a biodegradable polymers was used for the delivery of drugs to a specific location owing to its potential inherent capacity (Marin et al., 2013). This phenomenon attracted great interest in creating a revolution for the usage of nanomedicine in the field of pharmaceutical sciences.

5. NANOSTRUCTURED NANOPARTICLES IN BIOMEDICAL RESEARCH

Various structures of nanoparticles are found in their applications in biomedical research. Such nanoparticles are inorganic metal oxides, polymers, solid lipid, ferritin, liposomes, nanocrystals, nanotubes, nanofibers, nanopores, nanosheets,

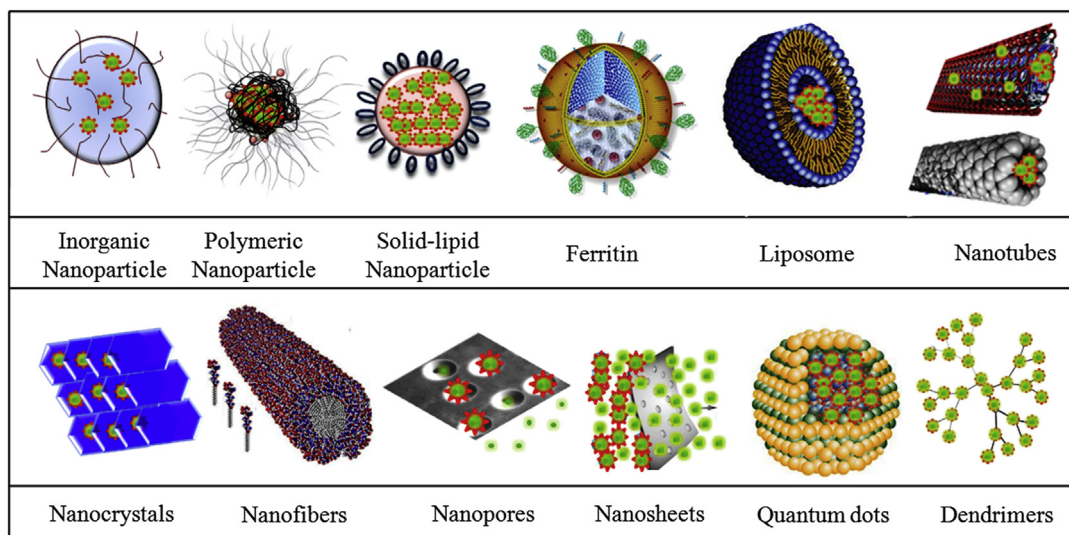


FIGURE 6.1 Structural illustrations of various nanoparticles used in biomedical research. They are potentially engaged in drug delivery, diagnosis, treatment, and the drug discovery process. Currently, they are documented to produce antimicrobial and neuroprotective activity. Therefore, in the future they may be used to treat neuroinfectious disorders.

quantum dots, and dendrimers (Mu et al., 2014; Tauran et al., 2013). These nanoparticles show promising results in drug delivery and neuroprotection systems with their own molecular mechanisms (Upadhyay, 2014; Khanbabaie and Jahanshahi, 2012). The structures of various nanoparticles are illustrated in Fig. 6.1.

5.1 Inorganic Nanoparticles

Inorganic nanoparticles, especially gold nanoparticles, have an affinity for drugs with covalent and noncovalent bonding and this property enhances the therapeutic efficacy. The combined action of gold nanoparticles and laser irradiation is useful in the controlled release of drugs (Mieszawska et al., 2013). The gold nanoshell–antibody complex is known to produce an ameliorative effect in cancer disease due to its selective transportation of drugs into cancer cell nuclei with conjugation of arginine–glycine–aspartic acid peptide and polyethylene glycol (Austin et al., 2014). In contrast, it produces hyperthermia when using noninvasive radio frequency for tumor cells (Gannon et al., 2008; Raof and Curley, 2011; Chatterjee et al., 2011). The silver-coated nanoparticle is one of the major nanoparticles in antimicrobial action. Various nanosized particles have been considered as novel antibacterial agents because of their high surface area and reactivity. The antimicrobial activity of nanostructured nanoparticles with conventional antimicrobial agents is enhanced compared to regular antimicrobial agents (Beyth et al., 2015). In addition, they are also shown to produce potent antimicrobial actions by inhibition of microbial growth and reproduction. This property is higher in silver-decorated polymer micelles and polymeric vesicles, antimicrobial polymer micelles and vesicles, and antimicrobial peptide-based vesicles (Suchomel et al., 2015; Chen et al., 2014a).

Historically, various organic compounds such as hyaluronic acid, poly(γ -glutamic acid), and polyhydroxyalkanoates have been reported to produce wide-spectrum antimicrobial activity (Lee et al., 2014). Some natural nanoparticles have been shown to produce antimicrobial activity; such compounds are metallic deposits, e.g., Au, Ag, Cd, Zn, or Fe; virus-like particles; or other nanoscale proteins (Strable et al., 2008; Arakha et al., 2015). Silver nanoparticles have been identified as broad-spectrum bactericidal and virucidal nanomaterials and are also used in cosmetics, food packaging materials, disinfectants, cleaning agents, etc. (Yah and Simate, 2015). Further, nickel nanoparticles are used in the purification of recombinant proteins for nanomagnetizable matrix preparation (Nejadmoghaddam et al., 2011). Silicon oxide nanoparticles are used in the early detection of cytotoxicity and also in the preparation of mucoadhesive nanosystems for vaginal microbicidal agents and optical molecular imaging materials for atherosclerosis (Kompella et al., 2013; Freese et al., 2014; Najafzadeh et al., 2015). The mesoporous silica material is used for the detection of the *Neisseria meningitidis* transformation process (Hollanda et al., 2011). Current research is evaluating the antimicrobial activity of polymeric nanostructures in biomedicine (Armentano et al., 2014; Chen et al., 2014a).

Iron oxide nanoparticles are inorganic nanoparticles and are classified based on the size of the iron oxide, i.e., (1) standard size of superparamagnetic iron oxide is 60–150 nm, (2) ultrasmall size of superparamagnetic iron oxide is 5–40 nm, and (3) subset size of monocrystalline iron oxide is 10–30 nm. They have various unique properties like

biocompatibility, intrinsic ability to enhance magnetic resonance imaging (MRI) contrast, and capacity for surface modification that leads to enhanced tumor imaging activity (Wang et al., 2013b). The standard-size nanoparticles are composed of ferric (Fe^{3+}) and ferrous (Fe^{2+}) iron (Wahajuddin and Arora, 2012). They have been trapped in the reticuloendothelial system through endocytosis or phagocytosis to explore their cytotoxicity profile due to the dissolving capacity of iron oxide under acidic conditions (Singh et al., 2010; Liu et al., 2013a). In addition, Fe^{3+} ions can be stored in adult humans, accumulating up to 3–5 g of iron. Therefore, the solubility of the iron oxide nanoparticle is negligible and it avoids metal toxicity (Wells et al., 2012; Yen et al., 2013). For MRI of the cellular system, iron oxide nanoparticles are coated with contrast agents such as sugars, e.g., dextran, or synthetic polymers, e.g., silicone (Ciobanu et al., 2012). In addition, it also reported to produce limited toxicity compared other nanoparticles.

Rare earth materials, e.g., lanthanides and silica materials, are also used for the preparation of nanoparticles. The lanthanides are excellent building blocks of multimodal imaging probes and have luminescent and magnetic properties (Heffern et al., 2014). Gadolinium (Gd^{3+}) has seven unpaired electrons and it shows a high paramagnetic relaxivity. Therefore, it is also used in the imaging system for MRI (Shen et al., 2013). Other doped lanthanides, e.g., NaYF_4 nanoparticles, are also used with Yb^{3+} and Er^{3+} particles (Liu et al., 2013d; Wang et al., 2014a). There is great interest in silica nanoparticles for the cancer cell imaging system because of their favorable properties; for example, they are inert, optically transparent, and easy to modify in structure and size. The hydrophilic surface of nanoparticles with silanol ($-\text{Si}-\text{OH}$) and deprotonated silanol ($-\text{Si}-\text{O}-$) groups is prepared at neutral pH and this makes the silica nanoparticles dispersible in water (Lee et al., 2010; Yang et al., 2014). It enhances the specific binding property of silica nanoparticles at targeted sites and avoids the aggregation of silica nanoparticles in vivo. In addition, silica nanoparticles are quite photostable with fluorescent dyes and reduce the photochemical oxidation by reactive oxygen species (Vatansever et al., 2013; Zhao et al., 2014b). Other silica materials, e.g., mesoporous ones, have great structural control and functionalization (magnetism and luminescence) properties due to their large surface area, high pore volume, nontoxicity, and good biocompatibility. And they are proven to be effective as a drug delivery system (Bharti et al., 2015). Moreover, mesoporous silica nanoparticles are also used for the radionuclide imaging process with labeling of radioisotopes (Xing et al., 2014).

5.2 Polymeric Nanoparticles

These nanoparticles are structurally stable inorganic systems with porous characteristics and these biodegradable polymers are widely used for controlled drug delivery systems. The drug-loading processes in polymeric nanoparticles are entrapment, encapsulation, and dissolution or dispersion. These particles are used for the loading of a wide variety of hydrophobic and hydrophilic drugs (Nitta and Numata, 2013; Zhao et al., 2013). This formulation is widely used for drug delivery, tissue engineering, and various biomedical applications. Furthermore, the surface of these polymeric nanoparticles contains various functional groups and can be modified for targeting ligands (Elsabahy and Wooley, 2012). Clinically, the conjugation of the polymer–drug has an important role in drug efficacy and reduction of dosing frequency of conventional medicines (Eliasof et al., 2013). These particles are providing greater efficacy to antiasthmatic (Lu et al., 2014), antituberculosis (Smith, 2011), pulmonary hypertension (Yin et al., 2013; Agyare and Kandimalla, 2014), and anticancer drugs (Woo et al., 2012). In contrast, there is no report on the biodegradability and toxicity of polymeric nanoparticles in pulmonary formulations (Marin et al., 2013). Research has found that typical ceramic nanoparticles such as silica and alumina also have potential drug delivery properties (Fine et al., 2013). In addition, the newer biodegradable synthetic polymers and natural modified polymers such as chitosan and albumin are also involved in drug delivery systems (Lohcharoenkal et al., 2014; Wang et al., 2011a). Furthermore, cytolytic peptide nanoparticles (“NanoBees”) and polymeric nanoparticles encapsulating curcumin are used for cancer treatment in humans (Ray et al., 2011).

5.3 Solid-Lipid Nanoparticles

The preparation of solid-lipid nanoparticles is a lipid-based submicrometer colloidal carrier formulation. The widely used solid-lipid nanoparticles are glyce behenate, glycerol palmitostearate, lecithin, triglycerides, and tristearin glyceride (Santo et al., 2013). In this case, a large amount of surfactants is needed for the stability of the formulation. These particles are used for the preparation of proteins and antigens for therapeutic purposes (Sahdev et al., 2014; Taki and Smooker, 2015). This formulation produces good anticancer and antiviral potency (Torrecilla et al., 2014; Yu et al., 2012). In addition, entrapment of a drug in solid-lipid nanoparticles has a potential penetration property (4–11 times that of traditional delivery) through the blood–brain barrier and it can treat the various central nervous system disorders (Üner and Yener, 2007; Liu et al., 2014c). Formulations of indomethacin, ketoprofen, isoniazid, pyrazinamide, and primaquine with

solid-lipid nanoparticles have been reported to produce beneficial effects in the pulmonary, hematological, and gastrointestinal systems (Mansour et al., 2009; Omwoyo et al., 2014). The major limitation of this preparation is loading efficiency, owing to the formation of a lipid crystal matrix and changes in the physical state of the lipids (Valetti et al., 2013).

5.4 Ferritin Nanoparticles

Ferritin is a functional protein of living organisms. It is made up of 24 subunits and spontaneously assembled nanoparticles show a cage-like nanostructure. It has a 8-nm internal diameter and 12-nm external diameter (Zhen et al., 2013b). These particles allow the loading of lead compounds on both sides, i.e., the inside and outside interfaces of the ferritin nanoparticles. The outer surface of ferritin particles can be modified by chemical or genetic materials and the cavity of the ferritin particles is able to carry a wide range of metals with high affinities (Theil, 2013). Ferritin nanoparticles have been applied to carry a biovector on their surface and reach the target of C₃₂ melanoma cancer cells (Xing et al., 2014; Zhen et al., 2013a). In addition, gadolinium-loaded ferritin nanoparticles have entered a specific tumor of the endothelial cells (Kitagawa et al., 2012). They are stable at pH 7.4. Therefore, they possess rigidity under physiological conditions and are easily broken down in an acidic environment (Lin et al., 2011). Hence, they can be useful for target-specific action in the diagnosis and treatment of tumors and cancer cells.

5.5 Liposomal Nanoparticles

Liposomes are spherical lipid vesicles with a bilayered membrane structure and were introduced for drug delivery in the year 1965. These liposomal nanoparticles are frequently used for the delivery of antimicrobial drugs (Kraft et al., 2014; Monteiro et al., 2014). Drug-loaded liposomes can be prepared according to the size range of the macrophage. These liposomes can be digested within the macrophage's phagosome by the phagocytosis process and release their drug contents (Schwendener, 2014; Whittenton et al., 2013). In addition, their liposomal membranes can also be incorporated with opsonins, which can activate endocytosis in other cell types. The major distinguishing feature of liposomes is their lipid bilayer structure that mimics the cell membranes of infectious microbes and can readily fuse with them (Gao et al., 2014; Wang et al., 2015; Oh and Park, 2014). Owing to this property, they play a great role in the delivery of antimicrobial drugs directly inside of microbes.

5.6 Nanotubes

Nanotubes are self-assembling sheets of atoms organized as tubes. Based on their structure, they are classified into two major categories: (1) single-walled cylindrical carbon nanotubes and (2) multiwalled carbon nanotubes, with multiple cylinders nested within other cylinders (Eatemadi et al., 2014). These particles have unique properties such as electronic, thermal, and structural characteristics. They produce a good drug delivery action in cancer cells and significantly reduce the cancer cell progression (He et al., 2013). In addition, they also play a great role in the diagnosis of disease due to their potential biosensing property. And, they are used in the treatment of cancer disease with a low dose of conventional drugs because they possess target-specific action in cancer cells (Tilmaciu and Morris, 2015; Tian et al., 2015). However, the tolerance of this nanoparticle remains unidentified in humans.

5.7 Nanocrystals

Nanocrystals are clustered arrangements of molecules, and they wrap the drug molecule with a thin coating of surfactant. These materials are widely used in chemical engineering and in biological imaging systems compared to drug delivery systems (Bian et al., 2014). They are prepared by using a hydrophobic compound coated with a thin layer of hydrophilic compound. The biological effects of nanocrystals depend on the chemical nature of the hydrophilic coating molecules. This hydrophilic layer also acts as an aid in the biological distribution and bioavailability of the crystalline drug material. These factors are responsible for drugs and drug delivery (Lv et al., 2013; Fay et al., 2013). A nanosuspension of this formulation can be used via the oral route to overcome difficulties in swallowing tablets by pediatric or geriatric patients.

5.8 Nanofibers

Nanofibers are prepared by the electrospinning method and are widely used for the drug delivery process. The nanofibers are arranged as a fibrous scaffold and it is able to entrap drugs, with a large loading capacity and high encapsulation efficiency due to its low weight and inherent large surface-to-volume ratio (Xu et al., 2010; Zhang et al., 2011). Nanofibers

are promising carrier molecules for the delivery of anticancer drugs. They are useful nanoparticles for postoperative local chemotherapy using surgical implantation of the scaffold (Tseng et al., 2013, 2015). These nanoparticles are able to protect the encapsulated drugs from enzymatic and hydrolytic degradation (Griffin et al., 2011; Wade et al., 2015). It is evidenced that insulin-loaded nanoparticles can preserve insulin activity and produce a lowering of the blood glucose level for up to 14 days in diabetic rats (Nishimura et al., 2012).

5.9 Nanopores

The nanopore is a member of the nanoparticles and is a nanoscale-level channel or hole in a free-standing membrane. Solid-state nanopores such as silicon, SiO₂, and Si₃N₄ act as biological sensors of biological transmembrane proteins (Haque et al., 2013; Majd et al., 2010). The α -hemolysin (α -HL) channel is one of the common nanoparticles used to detect single-stranded nucleic acids. A modified α -HL nanopore was used to distinguish the individual DNA mononucleotides (Wanunu, 2012). It revealed that nanopores serve as potent regulators of DNA because of their direct sequencing action on single molecules of DNA (Haque et al., 2013). And it is a reliable and low-cost nanoparticle for the DNA sequencing process in genomic research. A similar property is also expected to regulate the genetic information of cancer cells (Wang et al., 2011b). In addition, polydimethylsiloxane (PDMS) polymer has been used to produce microfluidic channels and microscale devices (Valencia et al., 2012). Briefly, this nanoscale device was prepared by sealing with PDMS polymer. It consists of two reservoirs connected by a pore of glass material and it is filled with an ionic solution. The potential difference across the pore was measured at constant applied current by a four-point technique (Jain et al., 2013; Liu et al., 2013b). The working principle of the nanopore device is that the flow of DNA molecules passing through the pore creates a downward spike wave in the current recording profile. Each downward peak mimics the movement of a single DNA molecule in the nanopore device. This nanopore device helps to detect viruses and their viral proteins (Crick et al., 2015; Dorfman et al., 2013). Furthermore, it has been attached to the biological membrane with a covalent bond and acts as a probe molecule for detection of specific target sites. The nanopore supports the detection of antigen–antibody binding reactions (Schibel and Ervin, 2014). Antibody was specifically bound to the colloidal surface of the nanopore and raised the diameter of the nanoparticle. A limitation arises in this material owing to significant current blockade and higher resistance in the current flow due to the larger diameter of the colloidal particles (Belkin et al., 2015). This device is used to detect the presence of *Streptococcus* group A, and the sensitivity of detection is four times faster than standard latex agglutination assay (Zhu et al., 2015). The major advantages of nanopores are the cost-effectiveness, simplicity, speed, and versatility of nanopore assays (Squires et al., 2015). Therefore, this particle can be useful for the preparation of nanomedical devices for the diagnosis and treatment of neurological disorders.

5.10 Nanosheets

The nanosheet is another nanoparticle and it is arranged as a single- or multiple-layer two-dimensional array of atoms or molecules. Graphene is one of the nanosheet materials and it is arranged as a two-dimensional honeycomb crystal structure of a flat monolayer of carbon atoms (Song et al., 2014). It has high thermal conductivity (~ 5000 W/m K), high specific surface area, high electron mobility (250,000 cm²/V s), biocompatibility, and thermal stability. Therefore, it is used for electrochemical immunosensors for the diagnosis of disease (Wang et al., 2012c; Zhu et al., 2015). The graphene oxide nanosheet (GO-nS) is used to detect in vivo cellular interactions and DNA cargo functions (Shen et al., 2012). The interaction of fluorescence-labeled GO-nS and DNA molecules produces an aptamer/GO-nS complex and it is used as a real-time biosensing platform of living cells. This fluorescence-labeled ATP-binding aptamer (FAM-aptamer) can potentially be used in a biosensing system with GO-nS owing to its three basic actions, i.e., (1) high fluorescence quenching efficiency in vivo, (2) potent DNA transport action, and (3) efficient protection of oligonucleotides from enzymatic cleavage (Hong et al., 2012; Sanchez et al., 2012). In addition, the FAM-aptamer/GO-nS complex has high ATP specificity and sensitivity with a wide detection range, i.e., from 10 μ M to 2.5 mM in vitro (Wu et al., 2015a). Therefore, this nanoparticle also expected to serve as a molecular tool for the diagnosis of genetic disease.

5.11 Quantum Dots

Quantum dots are inorganic fluorescent semiconductor nanoparticles and they are composed of 10–50 atoms with 2- to 10-nm diameters (Breger et al., 2015). They are mainly used for biological imaging, sensing, and detection. In medicine, they are used for targeted drug delivery for the treatment of cancer (Wang et al., 2014b). Apart from the drug delivery process, quantum dots are also useful in the delivery of other biomolecules such as small interfering RNA (siRNA) (Probst

et al., 2013; Hong and Nam, 2014). They have some limitations due to long-term in vivo toxicity and degradation properties (Liu et al., 2013c; Sobrova et al., 2013).

5.12 Dendrimers

Dendrimers are well-structured globular macromolecules and they have three regions: (1) a core, (2) layers of branched repeating units, and (3) functional end groups on the outer layer of the repeating units (Bumb et al., 2010). The highly branched nature of dendrimers provides a large surface area and allows them to react with microorganisms in vivo (Shao et al., 2011). Dendrimers with drug molecules are prepared by either complexation or encapsulation. They allow loading of both hydrophobic and hydrophilic agents. Hydrophobic drugs can be loaded inside the cavity in the hydrophobic core, whereas hydrophilic drugs are attached to the multivalent surfaces of dendrimers through covalent conjugation or electrostatic interactions. This formulation can be used for oral, transdermal, ocular, and intravenous routes of drug delivery (Madaan et al., 2014; Yavuz et al., 2013). In addition, dendrimers have been shown to cross cell barriers by paracellular and transcellular pathways (Wu et al., 2013; Jones et al., 2012). The polyamidoamine dendrimers are most widely used for drug delivery because of their potential action of facilitating transport through the epithelial barrier (Xu et al., 2014; Tyssen et al., 2010). However, polyamidoamine dendrimers affect the function of platelets (Jones et al., 2012). The structure–activity relationship of dendrimers revealed that they have a dual action on human immunodeficiency virus (HIV) and herpes simplex virus (HSV), i.e., virucidal action on HSV and viral entry inhibitory action on HIV (Tyssen et al., 2010). In addition, they carry siRNA and deliver it to a specific target site for the silencing of gene sequence (Wu et al., 2013). They have great potential drug delivering capacity in the CNS (Xu et al., 2014). Therefore, dendrimer particles can be useful for the delivery of siRNA in gene therapy as well as in nanomedicine for neuroinfectious disorders. A summary of various nanoparticles and their applications has been tabulated in Table 6.1.

6. PRINCIPLE OF NANOPARTICLE ENTRY INTO CELLULAR SYSTEM

The entry of nanoparticles along with ligands into the cellular system has great challenges due to multiple factors such as size, biocompatibility, stability, and affinity (Mu et al., 2014; Kettiger et al., 2013). The entry of nanoparticles into the cellular system has the following principles: (1) uptake of nanoparticles by the tissues and (2) cellular receptor–mediated endocytosis (Yameen et al., 2014).

6.1 Uptake of Nanoparticles by the Tissues

The major achievement of the treatment process with therapeutic agents is the entry into or uptake of drug by the targeted tissue because the membrane layers create an obstacle to entry of drugs due to inefficient partitioning capacity (Kettiger et al., 2013). The partitioning capacity depends upon the polar and nonpolar properties of the drugs. Lipophilic molecules bypass this obstacle because they have a potent membrane permeability via diffusion (Mu et al., 2014). Nanoparticles are able to mask the therapeutic agent and provide efficient delivery into the cytosolic region. Nanoparticles are involved in the endocytosis process by natural phagocytosis, pinocytosis, and receptor-mediated endocytosis (Oh and Park, 2014). Phagocytosis involves the ingestion of materials up to 10 μm in diameter by a few cells of the reticuloendothelial system, e.g., macrophages, neutrophils, and dendritic cells. It is an uptake mechanism by almost all cell types and normally it involves the submicrometer range of material or substances in solution (Kruth, 2011). Larger microparticles enter into the cytosol by the action of phagocytic cells, whereas nanoparticles cross into all types of cell.

6.2 Cellular Receptor–Mediated Endocytosis

Receptor-mediated endocytosis has potential selectivity in the entry of molecules into cellular target sites. The nanoparticle surface binds to the extracellular surface and the cell allows carrying the ligands into the cytosolic region (Wang et al., 2012a). Sometimes, it transduces the signal to the intracellular space and triggers various biochemical pathways. Furthermore, it may also enhance the internalization of the ligand and its nanoparticle via the endocytosis process. This process is potentiated by biomolecules such as caveolin and clathrin (Rattanapinyopituk et al., 2014; Smith et al., 2012). The cross-linking of receptors and nanoparticles is more prone to membrane enfolding and reunification leading to the formation of an endosome. Nanoparticles between 25 and 50 nm in size are involved in this kind of entry into the cellular system (El-Sayed and Harashima, 2013; Stekete et al., 2011). Cellular endocytosis follows five steps to carry the nanoparticle with ligands into the cytosolic region. The steps are as follows: (1) association of nanoparticles with receptors

TABLE 6.1 Applications and Limitations of Nanoparticles in Biomedical Research

Sl. No.	Class of Nanoparticle	Type of Particles	Application	Limitations	References
1	Inorganic particle	Silver-coated particle	1. Antimicrobial action 2. Reduction of microbial growth and reproduction	Metal toxicity	Wang et al. (2013b), Bharti et al. (2015), Liu et al. (2013d), and Wang et al. (2014a)
		Silver-coated polymer micelles			
		Au, Ag, Cd, Zn, and Fe particles			
		Silicon oxide particles	1. Vaginal microbicides 2. Optical imaging		
		Iron oxide nanoparticles	1. MRI on tumor activity	Lack of toxicological data	
		Iron oxide coated with dextran or silicone			
		Silica materials	1. Cancer cell imaging 2. Fluorescence image probe		
		Mesoporous	1. Drug delivery system	Biotransformation	
		Lanthanides	1. MRI with radionuclide 2. Diagnosis and treatment of cancer		
		NaYF ₄ nanoparticle coated with Yb ³⁺ and Er ³⁺ particle			
Gadolinium (Gd ³⁺)					
2	Polymer	Ceramic nanoparticles (silica and alumina) coated with polymer	1. Drug delivery system 2. Cancer treatment	Biodegradability	Lohcharoenkal et al. (2014) and Marin et al. (2013)
		Polymer coated with chitosan and albumin			
		Cytolytic peptide nanoparticles (NanoBees)		Toxicity of pulmonary system	
3	Solid-lipid nanoparticle	Glyce behenate, glycerol palmitostearate, lecithin, triglycerides, and tristearin glyceride	1. Delivery of proteins and antigens 2. Anticancer and antiviral action 3. Drug delivery in CNS, pulmonary, hematological, and gastrointestinal system	Loading deficiency with lipid crystal matrix formation	Sahdev et al. (2014), Taki and Smooker (2015), and Liu et al. (2014c)
				Changes in physical state of lipids	
4	Ferritin	—	1. Drug delivery in cancer cells 2. Treatment of tumor of the endothelial cells	Rigidity under physiological conditions	Xing et al. (2014) and Zhen et al. (2013a)
5	Liposome	—	1. Delivery of antimicrobial drugs 2. Controlled release property 3. High drug loading capacity	Degradation by phagosomes	Kraft et al. (2014) and Monteiro et al. (2014)
				Variable kinetics	
				Physical instability	
				Lipid crystallization	

Continued

TABLE 6.1 Applications and Limitations of Nanoparticles in Biomedical Research—cont'd

Sl. No.	Class of Nanoparticle	Type of Particles	Application	Limitations	References
6	Nanotube	SWCNTs and MWCNTs	<ol style="list-style-type: none"> 1. Drug delivery in cancer cells 2. Reduction of cancer cell progression 3. Biosensing 	Tolerance	He et al. (2013)
7	Nanocrystal	—	<ol style="list-style-type: none"> 1. Biological imaging system; minor role in drug delivery system 2. Overcome difficulties of swallowing tablets in pediatric or geriatric patients 	Degradation by biochemicals in the body	Bian et al. (2014)
8	Nanofibers	—	<ol style="list-style-type: none"> 1. Delivery of anticancer drugs 2. Insulin delivery and monitoring the insulin activity 3. Analysis of insulin efficacy in diabetic patients 	Enzymatic and hydrolytic degradation	Tseng et al. (2013) and Wade et al. (2015)
9	Nanopores	SiO ₂ and Si ₃ N ₄ α -hemolysin channel	1. DNA sequencing process	Blockade of analysis with colloidal particles	Haque et al. (2013)
		PDMS polymer-coated nanopore	<ol style="list-style-type: none"> 1. Preparation of nanoscale device 2. Detection of viruses and their proteins 3. Monitoring of antigen–antibody binding reaction 4. Detection of <i>Streptococcus</i> group A bacteria. 		Crick et al. (2015) and Zhu et al., (2015)
10	Nanosheets	Graphene GO-nS	<ol style="list-style-type: none"> 1. DNA molecules 2. FAM-aptamer 3. Real-time biosensing 4. ATP specificity and sensitivity 	Toxicity Degradation property	Hong et al. (2012) and Wu et al. (2015a)
11	Quantum dots	Semiconductor nanoparticles	<ol style="list-style-type: none"> 1. Drug and siRNA delivery 2. Treatment of cancer disease 	Toxicity Degradation property	Wang et al. (2014b) and Liu et al. (2013c)
12	Dendrimers	Globular macromolecules.	<ol style="list-style-type: none"> 1. Facilitate epithelial barrier transport 2. Virucidal action on HSV 3. Viral entry inhibition of HIV 4. siRNA delivery in gene therapy 5. Drug delivery in CNS 	Degradation property Cellular toxicity	Wu et al. (2013) and Xu et al. (2014)
		Polyamidoamine dendrimers		Lack of carrying capacity for hydrophilic drugs	

FAM-aptamer, fluorescence-labeled ATP-binding aptamer; *GO-nS*, graphene oxide nanosheet; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *MRI*, magnetic resonance imaging; *MWCNT*, multiwalled carbon nanotube; *PDMS*, polydimethylsiloxane; *siRNA*, small interfering RNA; *SWCNT*, single-walled cylindrical carbon nanotube.

on the cell membrane, (2) internalization of nanoparticles with ligands, (3) release of ligands (also known as endosomal escape) from nanoparticles by the endolysosomal process or lysosomal degradation of nanoparticles, (4) interaction of free ligands (therapeutic agent) with cytoplasmic organelles or proteins, and (5) exocytosis of nanoparticles via the endosomal recycling process (Xu et al., 2013; Herd et al., 2013; Serda et al., 2010; Strobel et al., 2015). A summary of nanoparticle entry and elimination in the cellular system is illustrated in Fig. 6.2.

7. APPLICATION OF NANOSTRUCTURED NANOPARTICLES IN PHARMACEUTICAL SCIENCE

Nanoparticles have been successfully developed in the fields of material science, information technology, and chemical and tissue engineering science. In addition, the nanostructured particle has potent action against microbial organisms, and it has great potential action in the drug delivery process (Babu et al., 2014; Weingart et al., 2013). The investigation of nanoparticles for medical applications is in the stage of preclinical and clinical trials. A few nanoparticles have been shown to produce their potential action in drug delivery, diagnosis of disease, molecular imaging of cellular function, and drug development (Liu et al., 2014b; Gomes et al., 2014). In addition, nanomedicine also has shown their therapeutic action in regenerative medicine, stem cell and gene therapy, brain tumors, cancer, implants, bone repair, drug discovery, and cosmetic applications (Nitta and Numata, 2013; Jain, 2005; Auffinger et al., 2013; Cheng et al., 2014b; Baetke et al., 2015; Tautzenberger et al., 2012). Some of the nanoparticles with antimicrobial agents have reached the market for the treatment of various microbial infections (Zhang et al., 2010; Gao et al., 2014; Ku et al., 2011). The postmarket surveillance is still under way. Nanostructured medicine has great scope in the treatment of life-threatening diseases such as cancer, acquired immune deficiency syndrome, and neuroinfectious disease (Masserini, 2013).

Viral infections are the most important factor in neuroinfection-associated neurodegeneration, for example, HIV-1, human T-cell lymphotropic virus, Epstein–Barr virus, encephalitis viruses, HSV, and parainfluenza virus infection (Gaikwad et al., 2013; Ahmed et al., 2009; Bily et al., 2015). Viral infection causes the neurodegeneration of the central as well as the peripheral nervous system (Zhou et al., 2013; Koyuncu et al., 2013). In addition, Theiler’s murine encephalomyelitis virus is known to cause neurodegenerative disease, i.e., multiple sclerosis (MS) (Sato et al., 2011). The chronic stage of viral infection-associated neuronal damage is responsible for producing neurodegenerative disorders like HIV-associated dementia, Alzheimer’s disease (AD), Parkinson’s disease (PD), MS, and amyotrophic lateral sclerosis (ALS)

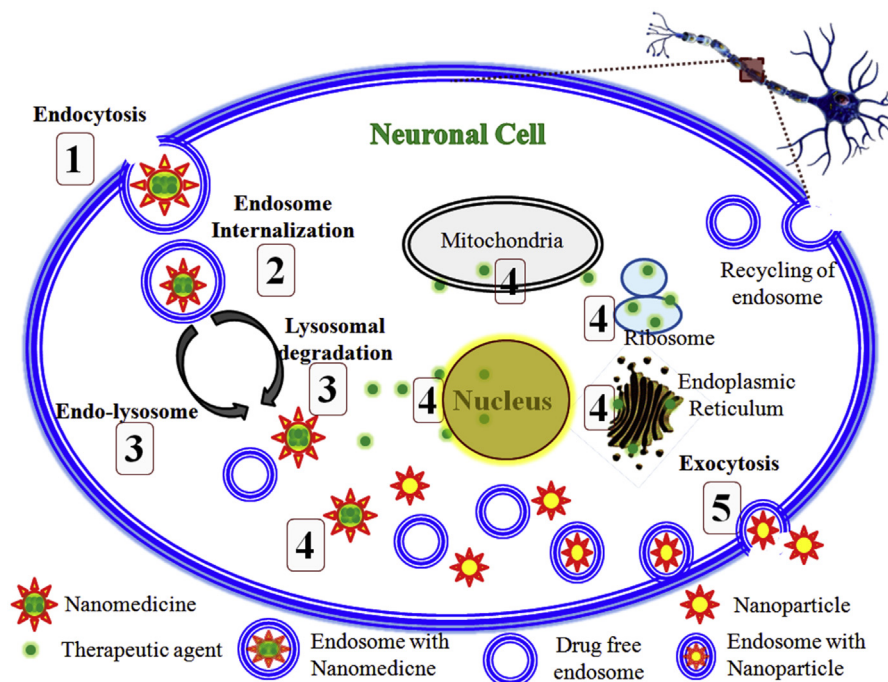


FIGURE 6.2 The process of nanomedicine entry and elimination of nanoparticles in the cellular system. It has five major steps, i.e., (1) association of nanoparticle with cellular membrane, (2) internalization of endosomal complex, (3) endolysosomal or lysosomal degradation, (4) release of drug and activation at targeted site, and (5) release of nanoparticles from cellular system by exocytosis with endosome.

(Zhou et al., 2013). Some nanoparticles are reported to prevent viral infection in the nervous system (Gomes et al., 2014; Bolhassani et al., 2014). Therefore, nanomedicine is expected to cure the neuroinfection-assisted neurodegenerative disorders. However, clinical evidence of nanomedicine therapies is limited. The novel medical applications of nanoparticles and nanomedicine are not exhaustive, but they need to be investigated in a scientific manner for the treatment of life-threatening diseases like neuroinfectious disease with suitable molecular mechanism and therapeutic efficacy as well as avoidance of any toxic principles.

7.1 Diagnostic Approach

Nanotechnology provides improvements in imaging systems for the human body through fluorescence microscopy or MRI scanning. Inorganic nanoparticles, e.g., quantum dots (QDs), possess luminescence properties and are employed as a novel tool for the diagnosis of biological functions and disease progress (Kiessling et al., 2014). In addition, they have a strong fluorescent property under ultraviolet light illumination. The major application of QDs is to image tissues and cells, e.g., lymph nodes and tumors (Helle et al., 2012). However, the other types of nanoparticles possess superparamagnetic iron oxide potential; therefore they are recognized to detect cancer cells and their progression such as in prostate cancer (Sterenczak et al., 2012). Furthermore, gold and silver nanoparticles are very commonly used for the diagnosis of various cancer cell types such as skin, ovarian, pancreatic, breast, and lung cancer (Austin et al., 2014; Patra et al., 2010; Swanner et al., 2015).

7.2 Drug Delivery Process

For the delivery of drugs by nanoparticles a variety of materials such as proteins, polysaccharides, and synthetic polymers are used. The selection of materials for nanoparticle preparation depends upon the size of the nanoparticles, inherent properties of the drug, permeability, and degree of biodegradability (Lohcharoenkal et al., 2014; Bolhassani et al., 2014; Sizovs et al., 2010). Nanoparticles have the ability to carry the drugs into various types of the cells, such as cancer, tumor, and human cells. The nanoparticle-mediated delivery of drugs has been observed in a cancer cell line (Cui et al., 2014). Albumin-loaded nanoparticles are used for the delivery of paclitaxel into cancer cells, and they reduce the adverse side effects associated with the chemotherapeutic agent Abraxane (Zhang et al., 2013a). In addition, nanoparticles help to deliver HIV antiviral agents into HIV-infected organisms and they have overcome the challenge of bioavailability of HIV antiviral agents due to their poor water-solubility (Parboosing et al., 2012). The US Food and Drug Administration (FDA) has approved more than 250 nanomedicines for various pathological disorders in humans such as cancer, tumors, and infections (Kamaly et al., 2016; Etheridge et al., 2013). The clinically important nanomedicines and their therapeutic applications are listed in Table 6.2.

7.2.1 Drug Delivery in Neurological Tumors

The delivery of drugs in the CNS is challenging because of the arrangement of the blood–brain barrier (BBB). Generally, the physiological barrier limits the brain's uptake of neurotherapeutic agents and neuroimaging contrast agents (Ashton et al., 2015). Anatomical and cellular manifestations of the CNS, such as the neurovascular capillary of endothelial cells, pinocytosis, and tight junctions, limit drug delivery. The brain microvasculature has four types of cells, i.e., endothelial cells, pericytes, astrocyte foot processes, and nerve endings, which contribute to the modulation of drug delivery in the CNS and prevent drug entry into the brain (Shilo et al., 2015; Gomes et al., 2014). In this case, lipid-mediated free diffusion and receptor-mediated endocytosis have a great role in the entry of molecules into the CNS. Therefore, lipid-derived nanoparticles like liposomes have contributed to the great success of drug delivery in the neurological system (Fonseca-Santos et al., 2015; Fiandaca et al., 2011). Current investigation is focused on the delivery of nanostructured medicines in the treatment of neurological and neuroinfectious diseases such as glioblastoma, dementia, AD, PD, and ALS (Fonseca-Santos et al., 2015; Ramos-Cabrera and Campos, 2013). The current concept of drug delivery in the CNS is focusing on low-density lipoprotein (LDL) particles. The size of natural LDL particles is 22–27 nm in diameter, with a core of lipids, e.g., cholesteryl esters, with small amounts of triglyceride (Feng and Mumper, 2013; McMahon et al., 2015). Plasma-derived LDLs are used to deliver nanomedicines for neurological tumors (glioblastoma). Synthetic LDL nanoparticles also provide the efficient delivery of paclitaxel for glioblastoma (Feng and Mumper, 2013).

7.2.2 Drug Delivery in Neurovascular Disease

Vascular diseases contribute to the progress of neurological ischemia that leads to stroke, cerebral aneurysm, and intracranial hemorrhage (Liu et al., 2014a; Sehba et al., 2011; Chen et al., 2014b). The delivery of nanoparticles to the CNS

TABLE 6.2 List of Clinically Important Nanomedicines and Their Therapeutic Applications

Sl. No.	Name of the Drug	Therapeutic Application	Company
1	Liposomal amphotericin B	Fungal infections	Enzon
2	Liposomal cytarabine	Malignant meningitis	Pacira
3	Liposomal amphotericin B	Fungal and protozoal infections	Gilead Sciences
		Invasive fungal infections	Sigma Tau
4	Liposome-PEG doxorubicin	HIV-related Kaposi's sarcoma.	Ortho Biotech
		Metastatic breast cancer	
		Metastatic ovarian cancer	Schering-Plough
5	Liposomal daunorubicin	HIV-related Kaposi's sarcoma	Gilead Sciences
6	Liposomal vincristine	Acute lymphoblastic leukemia and melanoma	Spectrum Pharmaceuticals
7	Liposomal morphine	Endo postsurgical analgesia	SkyePharma
8	Liposomal IRIV vaccine	Hepatitis A	Crucell
9	Liposomal verteporfin	Wet age-related macular degeneration	QLT Ophthalmics
		Myopia and ocular histoplasmosis	
10	Liposomal cytosine arabinoside	Lymphomatous meningitis	Pacira
11	Micellular estradiol	Menopausal therapy	Novavax
12	Polymeric docetaxel	Advanced solid malignancies	Samyang Biopharmaceutical Corp.
13	Polymeric micelle for paclitaxel	NSCLC	
14	Albumin protein-bound paclitaxel	Metastatic breast cancer	Celgene
15	Pemetrexed	Nonsquamous NSCLC	Lilly
		Malignant pleural mesothelioma	
16	PEGylated adenosine	Severe combined immunodeficiency	Sigma Tau
17	PEGylated Fab' fragment of a humanized anti-TNF- α antibody	Crohn's disease	UCB Pharma
		Rheumatoid arthritis	
18	Glatiramer acetate (copolymer composed of L-glutamic acid, L-alanine, L-lysine, and L-tyrosine)	Multiple sclerosis	Teva
19	Amine-loaded polymer	Serum phosphorus control with CKD	Genzyme
20	Leuprolide acetate and PLGH polymer formulation	Advanced prostate cancer	Sanofi
21	Aprepitant nanocrystal particles	Chemotherapy-related nausea and vomiting	Merck
22	Pegfilgrastim	Chemotherapy-associated neutropenia	Amgen
23	PEG-asparaginase	Acute lymphocytic leukemia	Sigma Tau
24	Interleukin-2 diphtheria toxin fusion protein	Cutaneous T-cell lymphoma	Eisai
25	Peginterferon alfa-2a	Hepatitis B and C	Genentech
26	Peginterferon alfa-2b	Hepatitis C	Merck
27	PEGylated human growth hormone receptor antagonist	Acromegaly	Pfizer
28	Pegaptanib (PEG-anti-VEGF aptamer)	Wet age-related macular degeneration	Eyetech
29	Methoxy PEG-epoetin β	Symptomatic anemia associated with CKD	Hoffman La Roche

CKD, chronic kidney disease; IRIV, immunopotentiating reconstituted influenza virus; NSCLC, non-small-cell lung cancer; PEG, polyethylene glycol; PLGH, poly(D,L-lactide-co-glycolide); TNF, tumor necrosis factor; UCB, Union Chimique Belge; VEGF, vascular endothelial growth factor (Ventola, 2012; Wolfram et al., 2015; Paliwal et al., 2014).

helps to detect neurovascular disease, such as detection of atherosclerotic plaques. Similarly, it also acts to target and deliver therapeutic agents to these plaques. Tissue factor-targeted nanoparticles loaded with paclitaxel are shown to reduce smooth muscle cell proliferation (Chan et al., 2011). In addition, nanoparticles loaded with fumagillin (antiangiogenic agent, targeted to α Vb3-integrin epitopes of the vasa vasorum) have been documented to produce an antiangiogenic effect (Lanza et al., 2010). The utilization of taxol-loaded albumin nanoparticles limits the restenotic response in experimental animals (Chan et al., 2011).

7.2.3 Drug Delivery in Neurodegenerative Diseases

The degeneration of the neurological system is triggered by infection, inflammation, and oxidative stress, and subsequently modulates the various cellular and molecular events in the nervous system (Mishra et al., 2015; Alirezai et al., 2008). The nanoparticle has a great potential to regulate microbes with antimicrobial agents (Durán et al., 2010). Nanoparticles are able to cross the CNS and alter the neurological proteins (Upadhyay, 2014). Based on this evidence they are expected to control the various neurological diseases. Conventional medicine is limited in treating neurodegenerative diseases by the difficulty of drug delivery and the toxicity profile of neurological as well as systemic organs (Carroll et al., 2010; Chhabra et al., 2015; Perreault et al., 2012; Singh and Ramarao, 2013). Therefore, nanoparticles and nanomedicine are a promising technology for the treatment of neurodegenerative disorders. However, the experimental and clinical evidence exploring the role of nanomedicine in the treatment of neurodegenerative disease is limited. In contrast to their possible benefits, various nanoparticles are metallic in nature and metal compounds are well documented to produce neurological damage (Willhite et al., 2014). Chelators are reported to reduce the metal compounds associated with neuronal damage (Zhang et al., 2013b; Zhao et al., 2014a). On the other hand, metal chelators, e.g., desferrioxamine, exhibit serious neurotoxicity and neurological changes due to strong covalent binding properties with membrane proteins (Olivieri et al., 1986; Kapoor, 2013). LDL-receptor-targeted polymeric nanoparticles can potentially cross the BBB or be taken up by the brain endothelial cells and deliver drugs to the brain. And, they effectively mask the covalent bonds of chelators and facilitate the delivery of drugs and minimization of toxicity (Kreuter, 2013). Therefore, nanoparticles can play the significant role in the management of neurodegenerative disease.

7.2.4 Drug Delivery for Infective Disease

The science of nanotechnology is expected to treat neuroinfective, neurodegenerative, cerebrovascular, and inflammatory diseases. The major challenges for drug delivery to the brain are the low permeability of the BBB and its role as the natural brain-protective layer against the entry of foreign substances and blood microbes (Li et al., 2015; Monopoli et al., 2012). The usage of polymeric nanoparticles has demonstrated that they are potentially noninvasive drug carriers that can cross the BBB and enter into the brain (Ong et al., 2014; Patel et al., 2014). The antitubercular drug-loaded nanoparticle has the capacity to enter into the *Mycobacterium tuberculosis* organism and produce a potent efficacy against tuberculosis (TB) (Garg et al., 2015a; Pandey et al., 2003). The oral administration (five oral doses every 10 days) of coencapsulated poly (DL-lactide-co-glycolide) nanoparticles with antitubercular drugs (e.g., rifampin, isoniazid, and pyrazinamide) produces complete bacterial clearance from the organs compared to conventional TB drugs in mice and guinea pigs (Pandey et al., 2003; Sharma et al., 2004).

Moreover, the oral administration of poly(DL-lactide-co-glycolide) nanoparticles encapsulating ethionamide produces a potent tissue distribution and manages multidrug-resistant TB. And, the sustained release of ethionamide for 6 days in plasma comparable to the 6-h plasma concentration of free ethionamide in mice has been shown (Kumar et al., 2011). Therefore, nanoparticles have the potency to deliver drugs into the infective organism at the level of the nervous system.

8. NEUROINFECTION-ASSOCIATED NEURODEGENERATIVE DISEASE

The nervous system has various self-defensive cells like glial cells, astrocytes, oligodendrocytes, macrophages, and T and B cells (Alluri et al., 2015; Tsunoda, 2008). Generally, they play roles in central sensitization and protect the CNS, whereas overactivation of these cells is responsible for changes to the neurological function and at the extreme stage can cause neurodegeneration (Jungner et al., 2016). The abnormal activation of these cells is due to various internal and external factors such as stress, drugs, chemicals, trauma, surgery, heat, hormones, microbes, and peripheral nerve injury (Alizadeh et al., 2015; Goncharenko et al., 2014; Lee et al., 2015; Matilla-Dueñas et al., 2014; Villanueva et al., 2013). The mechanism of neurodegeneration takes place via the release of various proinflammatory cytokines (tumor necrosis factor and leukotrienes), excitatory neurotransmitters (glutamate and aspartate), and oxidative stress in the neurons (Camara-Lemarroy et al.,

2012; Wang et al., 2012b; Ramesh et al., 2013). The endothelium of the CNS is the primary target site for neuroinfection and neuroinflammation (Di Marco et al., 2015). Changes in the central endothelium affect neurological function via activation of neuronal glial cells, and at the chronic stage it undergoes the enhancement of neurodegeneration (Loane et al., 2014). Infectious agents cause neuroinflammation by affecting the endothelium of the cerebral blood vessels and astrocytes (Combes et al., 2012; Freeman et al., 2014).

Meningitis is a neuroinflammatory condition of the CNS, which is caused by bacterial (*Streptococcus pneumoniae*, *N. meningitidis*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Escherichia coli*, and *M. tuberculosis*), viral (varicella zoster, influenza, mumps, HIV, and HSV), fungal (*Cryptococcus neoformans*), and parasitic (cysticercosis) infections (Inoue et al., 2015; Richie and Josephson, 2015). Encephalitis is another neuroinflammatory condition of the CNS and it is caused by enteroviruses (herpes simplex), rabies virus, and arboviruses (Nile virus). The virus particle is most prone to causing neuroinflammation and neurodegeneration (Kurkowska-Jastrzebska et al., 2013; Richie and Josephson, 2015). Generally, viruses are able to infiltrate the nervous system. The entry of the virus particle into the nervous system involves two methods, i.e., transneuronal and hematogenous spreading methods (Chaves et al., 2011; Coller and Smith, 2008; Taylor and Enquist, 2015).

The exact mechanism of transneuronal spreading of viruses is not known yet. But it is expected to involve the virus and its proteins escaping from the immune system by traveling via the axons of the nerves (Feldman et al., 2014; Rall et al., 1995; Turner et al., 2014). In the hematogenous spreading method, the virus uses one of two main ways to enter into the brain. The first way is to infect an immune cell; thereafter, the infected immune cell carries the virus into the nervous tissue, for example, infection of B cells by John Cunningham virus (a type of human polyomavirus) and infection of CD4 T cells and macrophages by HIV (Chapagain and Nerurkar, 2010; Tebas et al., 2014). The second way is to cross the blood capillaries, similar to free virus or leukocyte entry (Roe et al., 2014). Furthermore, neurons lack essential molecules for the binding of killer cells with viral peptides on the viral surface. Therefore, the neuron is a safe house in which the virus can replicate (Deauvieu et al., 2016; Voss and Bryceson, 2015). Once a virus infects a neuron it can persist for the lifetime of the host. Further, it interferes with the function of neurons and their homeostasis of the nervous system, leading to the generation of neuronal damage and neurodegeneration (De Chiara et al., 2012). The infective agents affect the neurological system and cause neurodegenerative diseases such as AD, PD, and ALS (Alkhwajah et al., 2015; Bourgade et al., 2015; DeVaughn et al., 2015; Wu et al., 2015b). Further, progressive infective neurodegeneration occurs with a wide range of molecular and cellular mechanisms leading to deterioration or loss of neurons in the CNS.

Infectious neurodegeneration occurs not only in the CNS. It also affects the peripheral nervous system and it enhances neuronal inflammation and neurodegeneration (Ramesh et al., 2013; Wada et al., 2013). This leads to peripheral neuropathy. Peripheral neuropathy mainly develops from infection with herpes varicella zoster (called shingles), HSV, or cytomegaloviruses (Guedon et al., 2015; Muneshige et al., 2003; Sansone and Sansone, 2014). Epstein–Barr virus and West Nile virus do not play a role in the development of peripheral neuropathy. Viral infections are able to affect the nervous system and cause severe damage to the sensory and motor nerves leading to sharp and severe pain (Chikakiyo et al., 2005; Jo et al., 2013; Kokotis et al., 2013). Moreover, infection with West Nile virus, which occurs through mosquitoes, causes severe motor neuropathy along with various forms of inflammatory neuropathies. Infection of post-herpetic neuralgia is also shown to produce long-lasting and intense pain after an attack of shingles (Sansone and Sansone, 2014). HIV infection-associated neuropathy shows different forms depending on the nerves affected and the specific stage of active HIV disease (Kokotis et al., 2013). Furthermore, bacteria can attack nervous tissue, causing peripheral nerve damage and neuropathic pain. Such bacterial infections are diphtheria, leprosy, and Lyme disease (Benoliel et al., 1999; Reis et al., 2014; Zimering et al., 2014). In addition, the tick-borne infection also contributes to neuroinfection-associated neuropathic pain. It is a rapidly developing infection that progresses to painful polyneuropathy that occurs within a few weeks of infection (Logigian and Steere, 1992; Zimering et al., 2014). Therefore, the prevention of neuronal infection may be a promising approach in the treatment of neurodegenerative disorders.

9. THE MECHANISTIC APPROACH OF NANOMEDICINE FOR NEUROINFECTIOUS NEURODEGENERATIVE DISEASE

Nanoparticles and nanomedicines contribute to various pharmaceutical applications, like diagnosis of disease progression, drug delivery, and treatment of various ailments, such as cancer, thrombosis, wounds, osteoporosis, vertebral fracture, and microbial infective diseases, e.g., TB and HIV-associated opportunistic infections (Khajuria et al., 2014; Palekar et al., 2016; Sagar et al., 2015; Tang et al., 2015; Wolfram et al., 2015). Furthermore, it is expected that they will produce potential therapeutic agents for neuroinfective disorders. The possible cellular and molecular mechanisms are as follows.

9.1 Cellular Mechanism of Nanomedicine for Neuroinfectious Disease

In the nervous system, nanomedicines can cross the BBB directly and regulate the physiological response of the BBB and brain functions. They can carry circulating immunocytes, such as monocytes, macrophages, and lymphocytes, and stem cells into the brain (Nowacek and Gendelman, 2009). Further, they can release their cargo material and control the ongoing disease progress by clearing microbial infections, repairing the neuronal system, eliminating proinflammatory mediators, and inducing the antiinflammatory response (Raymond et al., 2015). The combined action of nanomedicine and neuronal function may restore the glial homeostasis function in the brain. The cellular mechanism of nanomedicine in the treatment of infectious neurodegenerative disease is illustrated in Fig. 6.3.

9.2 Molecular Mechanism of Nanomedicine for Neuroinfectious Disease

Nanostructured antimicrobial drugs are targeted mainly to the receptors of brain endothelial cells, such as the insulin, leptin, transferrin, and epidermal growth factor receptors for the transfer of lead molecules across the BBB (Gendelman et al., 2015; Hu and Kesari, 2013). In addition, they are also targeted to the receptors of monocytes/macrophages, such as the folate, CD4, mannose, and CD44 receptors, to enhance cellular uptake of the nanomedicine for macrophage-based drug delivery in the brain via the BBB (Irvine et al., 2015). The nanomedicine follows six steps to eliminate microbes from the nervous system and other biological systems (Hollmann et al., 2015). After entry of the nanomedicine into the nervous system it attracts and binds to the microbes. Thereafter, it carries out the following steps: (1) it destroys the peptidoglycan (membrane) layer of the microbe, leading to the control of microbial growth; (2) it releases toxic metal ions into the cytosolic region of the microbe and can cause microbial death; (3) it alters the cellular ionic environment by activating the proton efflux pumps, leading to a change in pH; (4) it enhances the generation of free radicals, especially reactive oxygen species (ROS), leading to raised oxidative stress; (5) it damages the genetic material of the microbial organism, thus stopping the regulation of microbial growth and replication; and (6) it reduces ATP production, thus increasing energy demand and controlling microbial growth and proliferation (Rizzello et al., 2013; Upadya et al., 2011; Watkins et al., 2015; Shah et al., 2015). The molecular mechanism of nanomedicine for the elimination of microbes from the nervous system is illustrated in Fig. 6.4.

Therefore, nanomedicine can achieve therapeutic action against neuroinfection-associated neurodegenerative disease. Based on this discussion, the approach of using nanostructured antimicrobial agents and nanomedicine can be useful in the treatment of neuroinfectious and neurodegenerative disease.

10. TOXICOLOGICAL HAZARDS OF NANOPARTICLES

The imaging and drug delivery functions of nanoparticles have been successfully explored in pharmaceutical science. They can even produce a potent therapeutic ratio or index up to the marginal level. Nanoparticles can act as drug carriers and can

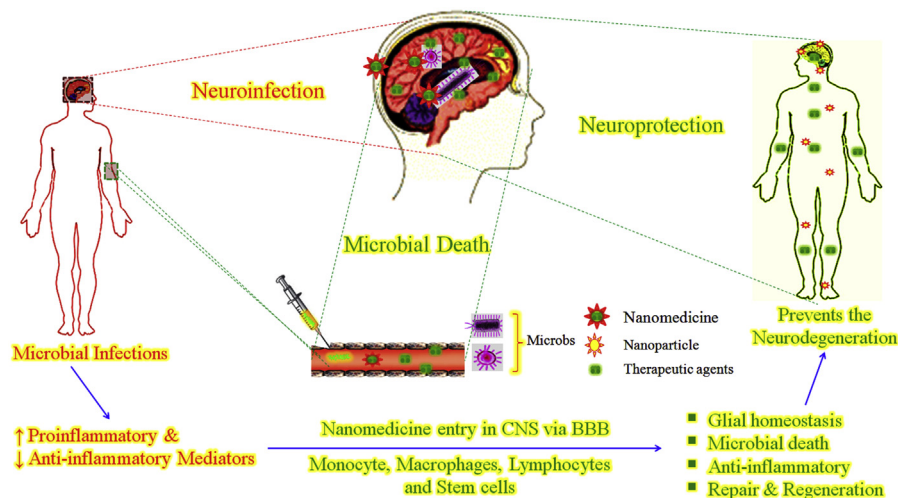


FIGURE 6.3 The cellular mechanism of nanomedicine in the treatment of infectious neurodegenerative disease. Microbial infection potentially alters the function of neuronal glial cells and enhances the inflammatory reaction via proinflammatory mediators. Nanomedicines can cross the blood–brain barrier (BBB) with the help of monocytes, macrophages, lymphocytes, and stem cells. Furthermore, they induce microbial death, regulation of glial function, and repair of neuronal damage, leading to prevention of infection-associated neurodegeneration.

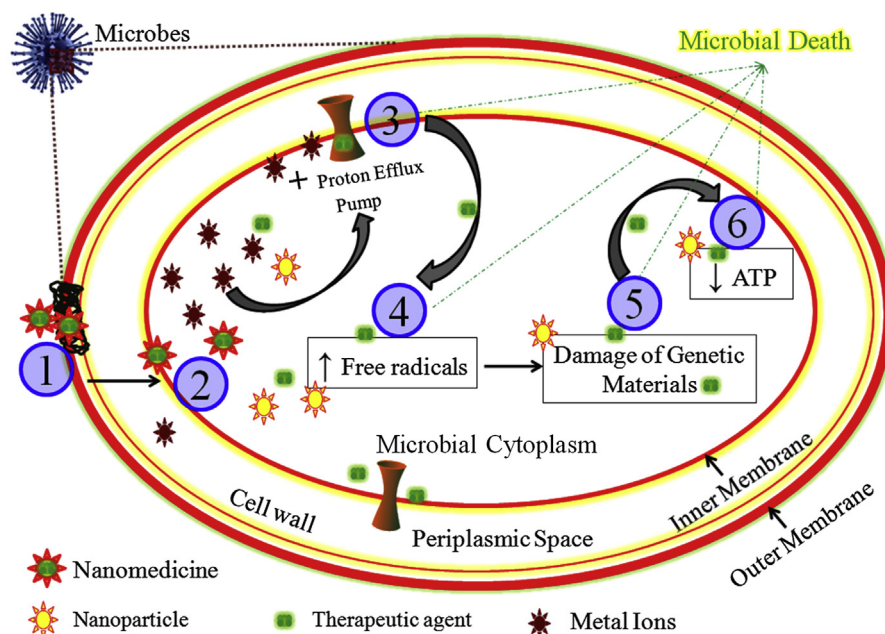


FIGURE 6.4 The molecular mechanism of nanomedicine for the elimination of microbes from the nervous system. It has six major steps: (1) destruction of the peptidoglycan layer, (2) release of toxic metal ions, (3) alteration of proton efflux pumps, (4) generation of free radicals, (5) damage to the genetic material, and (6) reduction of ATP production.

reduce the toxicity of a drug. However, the toxic effect of the whole formulation (nanoparticle and drug) or the nanoparticle itself is not described yet. Therefore, the potential usage of nanostructured nanoparticles and nanomedicines remains questionable because of their potential toxicity, clinical efficacy, and adverse side effects (Baeza-Squiban, 2014; Krishnaraj et al., 2016; Walters et al., 2014). And, scientific studies need to explore their complete safety and efficacy in humans. Further, studies on their bioavailability, biotransformation, environmental toxicity, etc., are needed (Battani et al., 2014; Walters et al., 2014). The true applications of nanoparticles for the treatment of disease require improvement in the specific formulations, more safety and efficacy, and minimized cellular toxicity. The opinion of toxicologists is that new science, methods, and protocols are needed with a higher safety profile for the utilization of nanoparticles and nanomedicines (Hofmann-Amttenbrink et al., 2015).

Based on this discussion the following points must be considered for the development of nanostructured nanomaterials and nanomedicines: (1) proper testing of nanoparticles, nanomedicines, and devices with advanced techniques; (2) study of the pharmacokinetics (especially distribution and biotransformation) and pharmacodynamics properties of nanoparticles in the biological system; and (3) study of the effects of nanoparticle exposure to the biological and environmental levels with respect to degradation and toxicity (Hofmann-Amttenbrink et al., 2015; Schutz et al., 2013; Lin et al., 2015).

Toxic exposure can be overcome in the following way. The method of risk assessment for the nanomedicine and nanodevice must be appropriate. Further, assays are performed to detect all the potential risks. The methods of assays and techniques needed depend upon the type of nanoparticles used, whether biological or nonbiological in origin. As of this writing, the study of nanoparticles is lacking a basic understanding of nanoparticle pharmacokinetic behavior in biological systems, especially the distribution and biotransformation of nanoparticles at the organ and cellular levels. Because nanoparticles are very small sized particles, they may change bodily functions, pass through the BBB, and trigger abnormal blood coagulation pathways. The nanoparticles must be degraded without the development of harmful effects in animals, plants, and environmental natural resources. Therefore, the presence of nanoparticles must be detectable in biological and environmental systems at this stage. This will have major importance in detecting slowly or nondegradable nanoparticles.

11. NANOTOXICOLOGY

Nanotoxicology is a newer branch of science and it deals with the study and application of nanomaterials with regard to toxicity in humans and the environment. Mainly nanotoxicological studies are intended to determine the extent to which the toxic properties threaten the environment and human beings (Guadagnini et al., 2015). The types of toxic exposure of nanoparticle are as follows: (1) consumer exposure—usage of nanoparticle-containing personal care products, cosmetics,

sunscreen preparations; (2) occupational exposure—for workers in nanomaterial manufacturing and research; (3) environmental exposure—the increasing concentrations of nanomaterials in groundwater and soil may produce a significant environmental risk (Malysheva et al., 2015). Moreover, the toxicity of nanomaterials is broadly classified into two areas: (1) biological toxicity and (2) environmental toxicity. In biological systems, the nanostructured nanoparticles enter the body via six principle routes, i.e., oral, intravenous, dermal, subcutaneous, inhalation, and intraperitoneal. The particles enter the systemic circulation and are distributed to the various organs of the body and may remain structurally the same or be modified or metabolized. In cellular systems, they can cause biological toxicity by DNA damage or ROS generation. This leads to tissue damage, inflammation, cytotoxicity, and organ failure from the deposition of nanoparticles. And it also causes fibrosis and allergies (Fu et al., 2014; Malysheva et al., 2015). In environmental systems, nondegradable nanoparticles are ready to deposit in the groundwater, leading to production of environmental pollutants. Further, they may also be harmful to plants and microbes. The removal of nanoparticles from the environment is another challenging task in the management of nanotoxicity (Hussain et al., 2015; PourGashtasbi, 2015).

12. CHALLENGE TO USAGE AND MANAGEMENT OF NANOPARTICLES

Nanoparticles already exist in nature, e.g., volcanic ash, ocean spray, and forest fire smoke; and they are highly toxic. The existing chemical nanoparticles, e.g., carbon nanotubes, are also able to produce toxic effects (PourGashtasbi, 2015). It is argued that natural nanoparticles are not considerable as a new phenomenon because they come from daily human activities like mining, cooking, and combustion of materials (Gao et al., 2015). Nanoparticle studies have shown that they have some special properties, i.e., (1) ultrasmall-sized particles have extreme mobility and higher propagation in living organisms if not controlled, (2) they can create more toxic effects per unit compared to larger particles of the same chemicals, (3) they can be absorbed more quickly by cells, and (4) they move more quickly, contaminating the environment through air, soil, and water, leading to damage of plants and animals (Baalousha and Lead, 2013). Some kinds of nanoparticles are responsible for causing inflammatory reactions in the lungs, such as carbon black nanoparticles (QDs or polymeric nanoparticles). And, they cannot be considered as a uniform group of nanoparticles because they interact and behave in different manners depending upon several factors (Podila and Brown, 2013).

The lack of data on the potential risks of nanoparticles and nanomedicines with respect to the human body and the environment, has raised some questions and issues. Scientific research must answer many questions to allow the utilization of nanoparticles in human beings with an environmentally friendly approach. Such questions are as follows: (1) How do nanoparticle pathways affect the human body? (2) How long can nanoparticles remain in the human body? (3) What are the nanoparticles' effects on cellular and tissue functions? (Cochran et al., 2013). The main challenges of nanoparticle usage are the identification of toxicity-free nanoparticles, legal evaluation of the final medical products, and elimination of particles from biological and environmental systems. Nanomedicine remains challengeable because it does not fall into the traditional classifications of drugs or medical devices. Furthermore, the risk analyses of nanoparticles are complicated because of the lack of data, techniques, and issues (Ilinskaya and Dobrovolskaia, 2013a,b).

The outcome of using nanomedicine for treatments must satisfy regulatory, environmental, social, and ethical issues. The US FDA has effective regulations for the use nanoparticles with strong technologies and scientific advances. Generally, the FDA classifies the regulatory processes for medical products as drugs, devices, and biological or combination products. But it lacks regulation for nanomedicine in aspects such as lack of scientific expertise and classification difficulties (Bowman and Gatof, 2015; Leite et al., 2015a). As for the environmental aspect, the excretory materials are mainly suspended in the air for long periods and cause respiratory disorders. The National Science Foundation and the Environmental Protection Agency are raising issues about the potential impact of nanomaterials on the environment and the adverse effects. A social issue is the usage of neurobiochips that stimulate the brain in humans and manipulate neuropsychological factors. Social and ethical issues are debated regarding implantable nanodevices that closely monitor illness, privacy rights, and risk of abuse. The prices of nanodevices would be very high, which is another social issue and one that affects the developing nations (Leite et al., 2015a). The ethical issues concern proving that nanoparticles are nontoxic, eco-friendly, unable to be used for terrorism purposes, and easy to remove when toxic effects are produced in the body (King, 2012; Resnik, 2012; Sechi et al., 2014).

13. FUTURE PERSPECTIVES

The major concern of nanoparticle applications is nanostructure toxicity and it depends upon the physical characteristics of the individual new particles. Ongoing research reports will give the answer and solve the biological and environmental toxicity. At this stage, nanostructured nanoparticles and nanomedicine will provide the high sensitivity, specificity, low

cost, portability, and reusability of nanoparticles. It is a great invention in the field of pharmaceutical and medical sciences. Various technologies are being established to detect the very fine particles and scientific uncertainties surround the outcome of nanomedicine (Bello et al., 2013; Ji et al., 2013). The best case scenario brings the success of nanoparticle usage in the pharmaceutical and other fields. It will provide the fundamental basis to intensify the research in science and other disciplines. On one side, data are needed for scientific evidence and the toxicological profile of the nanoparticle. On the other side, the development of the nanoparticle process is not only a scientific task, but also requires answers to all the issues and questions. Jurists and legal scholars have reported that scientific discoveries following standard guidelines and providing the minimum safety standards are acceptable for protecting human health. In this point of view, nanotechnology offers an opportunity for major integration among the different disciplines and especially between science and law. Therefore, the nanostructured antimicrobial agent can be a future nanomedicine for neuroinfection-assisted neurodegenerative disorders.

14. CONCLUSIONS

Various nanomaterials have been reported for the drug delivery process with therapeutic levels in biological systems. They have great potential to enter into microbes and release a drug. Thus, drug delivery through nanostructured systems and their antimicrobial actions have been widely explored in preclinical as well as clinical research. The most important advantage of nanomedicine is low side effects and delivery of an accurate dose in site- and target-specific regions. Nanomedicine offers the possibility of preventing, diagnosing, and treating diseases and opens up a very promising area in the field of medicine. Therefore, nanostructural medicine is a future goal in the treatment of neuroinfection-associated neurodegenerative disorders like HIV-associated dementia, AD, PD, ALS, and MS, including neuropathic pain.

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