Chapter 7
Nanopharmaceuticals: Healthcare Applications and Safety Evaluations

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Abstract The prospects of nanotechnology in enhancing the quality of healthcare delivery cannot be overemphasized. Indeed, the advancement in nanotechnology is now a motivation for the increasing and wider acceptance of nanotechnology for applications in healthcare improvement particularly for diagnostic and therapeutic purposes. The use of nanotechnology to enhance the quality of pharmaceutical

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delivery forms the bulk of the emerging field referred to as the nanopharmaceuticals. This has created an interdisciplinary approach which has the potential of improving pharmaceutical delivery which is among the most promising and exciting innovations in healthcare strategy. As revealed in this chapter, nanopharmaceuticals offers remarkable prospects for improved healthcare delivery by reason of their additional potentials including increased surface area, enhanced solubility, increased oral bioavailability, dosage reduction and ease of attachment to functional groups amongst others. These unique features of nanopharmaceuticals are part of the merits which are conspicuously nonexistent with the conventional/traditional pharmaceuticals. Thus, this chapter discusses the nanopharmaceuticals vis-a-vis the applications and safety evaluations.

Keywords Drug delivery and targeting · Nanomedicine · Nanomaterials · Nanotoxicology · Safety assessment

7.1 Introduction

The pharmaceutical industry (PI) discovers, develops, produces, and markets drugs or pharmaceutical drugs for use as medications. Pharmaceutical companies may deal in generic or brand medications and medical devices. Pharmaceuticals are a vital part of human and/or animal survival, and its value has been associated with the balance between its effectiveness and side effects (Chan et al. 2013). Pharmaceuticals contribute significantly to the health and well-being of both humans and animals. Consequently, the PI has a responsibility in ensuring balance in their efficacy, side effects, and cost value (Ding et al. 2013a). As a result, the PI is encumbered with research and development (R&D), productivity, and investments (Ding et al. 2013b). It is noteworthy that the PI is more highly regulated than any other industry so as to afford the maximal service and support to healthcare while also providing investor value.

Over the years, the PI has had a continuous growth of 4–7% per year, and it currently approaches a market scope of 1 trillion USD (Ding et al. 2013a). The PI sustains itself by spending heavily on producing new prescription drugs through patents that make firms sponsor its expenses and also prevent competitions (Kappe 2013). As at 2000, 802 million USD was the average requirement to develop a drug, and the financial requirement for R&D in 2008 was 50 billion USD, rising to 160 billion USD in 2016 (DiMasi et al. 2003; Statista 2017). The increase in the cost of pharmaceutical R&D has been attributed to the need to cover the loss due to patent expiry, because this gives opportunities to generic drugs to compete (Paul et al. 2010; Kappe 2013). In the meantime, statistical studies suggest that the number of generic drugs in the market have increased from 18.6% of unit sales in 1984 to 78% in 2010 (Kappe 2013). Another reason for the increased cost in R&D is the continuous increase in the amount needed to acquire a regulatory approval for new drugs

(DiMasi and Grabowski 2007). Further, the demand by healthcare practitioners and sponsors for new, improved, and cheaper drugs with extensive clinical reports on its properties has placed pressure and strain on the PI (Betz et al. 2013). In summary, comparative analysis of reports on the current status of the PI reveals that the industry is plagued by concerns on its reliability and transparency in reference to drugs' efficacy and safety, issues pertaining to patent expirations, increased regulatory demands, lower inflow of funds for R&D, lack of innovation, and technological and societal/environmental problems (Khanna 2012; Ding et al. 2013a, b; Paul et al. 2010; Kappe 2013). Taken together, the PI needs to be more innovative in order to outgrow most of the limitations that threaten its survival. Perhaps the limitations bedeviling the PI have forced it to identify and pursue new ways of sustenance while being able to also add value to healthcare delivery at reasonable costs. Among the new strategies is the deployment of nanotechnological advancements for pharmaceutical purposes and this has birthed the emerging field of research currently termed nanopharmaceuticals (Pepic et al. 2014). A large number of innovations in health sector have been exploiting nanotechnology (Berkner et al. 2016). Applications of nanotechnology for pharmaceutical purposes include the development of efficient and intelligent drug delivery systems which possess the enhanced ability to bypass biological barriers and interact directly with target tissues. The use of nanotechnology for pharmaceutical development also enhances drug bioavailability, stability, and action, thereby reducing the dosing frequency (Thakur and Agrawal 2015). Other areas of benefits include applications in vitro rapid and portable diagnostics (Pautler and Brenner 2010), in vivo imaging, and as active implants.

7.2 Nanopharmaceuticals

The development of various pharmaceutical dosage forms in the range of 10–1000 nm using nanotechnological tools is referred to as naonopharmaceuticals or nanopharmaceutical dosage forms. Nanopharmaceuticals also comprise colloidal drug delivery carriers not exceeding 1000 nm in size (Bawa 2008; Gaur and Bhatia 2008). A recent definition describes nanopharmaceuticals as pharmaceuticals in which the nanomaterial plays the pivotal therapeutic role or adds additional functionality to the previous compound (Rivera et al. 2010). In a recent review, Weissig et al. (2014) proposed that prospective nanopharmaceuticals must satisfy the dual conditions of being manufactured via a nanoengineering process and an inherent therapeutic activity of the nanomaterial.

There are two types of nanopharmaceuticals: [i] those where the therapeutic molecules are themselves the drug (i.e., the therapeutic compound itself also functions as its own carrier) and [ii] those where the therapeutic molecules are directly coupled (functionalized, entrapped, or coated) to a nanoparticle carrier. As there is no universal nomenclature system for the classification of nanopharmaceuticals, different nanoscale structures of different shapes are often classified as

nanopharmaceuticals. In fact, some of the common shapes of nanopharmaceuticals include spheres (hollow or solid), tubules, particles (solid or porous), and tree-like branched macromolecules (Bawa 2008, 2009).

7.2.1 Applications of Nanopharmaceuticals

Materials in sizes ranging from about one nanometer up to several hundred nanometers exhibit interesting physical properties that are different from bulkier scales and, hence, present prospects for novel applications in medicine. Indeed, nanotechnology has played key role in the new lift and approach used in Science globally. It has brought scientific innovations at the intersection of engineering, medicine, and biotechnology (Bawa 2011). In recent times, the nanopharmaceuticals have been receiving attention due to their potential to reform drug delivery systems (Park 2007; 2017). Researchers have implicated nanopharmaceuticals for drug delivery and therapeutics (Adeyemi and Sulaiman 2015; Bawarski et al. 2008; Peer et al. 2007; Wagner et al. 2006), as well as for the enhancement of drug solubility and increase in drug half-life, among others (Pepic et al. 2014). Further, nanostructures like solid nanoparticles, polymeric micelles, quantum dots, and dendrimers have been explored for therapeutic and/or diagnostic purposes in conditions like infectious diseases, cancer, and pain (Bawarski et al. 2008; Pepic et al. 2014).

A recurring dilemma of pharmaceutical delivery is the accurate targeting of the pharmaceutical to the cells or tissues of choice. Since this is generally unachievable, active agents have to be administered in excessively high doses, thereby increasing the likelihood of toxicity. Nanopharmaceuticals have enormous potential in addressing this failure of traditional therapeutics. This precision targeting reduces toxic systemic side effects, resulting in better patient compliance. Also, a great number of drugs are unable to transverse the tight epithelial junctions of skin and taut endothelial interface of blood-brain barrier. However, with the advent of nanopharmaceutical delivery systems, drugs can be targeted to every part of the body (Ali et al. 2013). Compared to traditional pharmaceuticals, nanopharmaceuticals possess the following advantages (Bawa 2008):

(a) Increased surface area
(b) Enhanced solubility
(c) Increased oral bioavailability
(d) Dosage reduction
(e) Ease of attachment to functional groups

Moreover, nanotechnology has been implicated for prospects in the integration of diagnostics with therapeutics and the facilitation of the development of specific therapeutics best suited for an individual (Jain 2008).

7.2.2 *Drug Delivery*

Recently, use of nanopharmaceuticals has been reported as potentially circumventing the inability of conventional drugs to deliver effective drug dose at target sites during diseases treatment or control (Namdari et al. 2017). Rapoport (2007) reported the use of polymeric micelles for anticancer drug delivery. The author described polymeric micelles as spherically shaped core-shell structure with a hydrophobic core and hydrophilic shell as shown in Fig. 7.1. They are unique for their core-shell structure and can be conjugated with other functional groups. In drug delivery concept, the most commonly used hydrophilic group in polymeric micelle is the poly(ethylene oxide) which has the ability of reducing residence time by way of preventing micelle opsonization. This has great advantage in targeting tumor cells as it promotes permeability and retention effect (Rapoport 2007). Since most known anticancer agents have low aqueous solubility, polymeric micelles deployed as nanopharmaceuticals are used as solubilizing agents to increase the solubility of these anticancer agents. This is one of the most important applications of nanopharmaceuticals. Presently, this has given room to the encapsulation of hydrophobic drugs in micelle cores for proper targeting of disease sites.

Foldvari and Bagonluri (2008) also reported the use of carbon nanotubes (CNTs) in drug delivery. CNTs have the ability to perform controlled and targeted drug delivery which can be achieved via interaction with pharmaceutical agents in three ways. Firstly, the interaction can be viewed as a porous absorbent to entrap active pharmaceutical agents within CNTs mesh or CNTs bundle (Fig. 7.2a); secondly, it could be via functional attachment of active pharmaceutical agents to the exterior

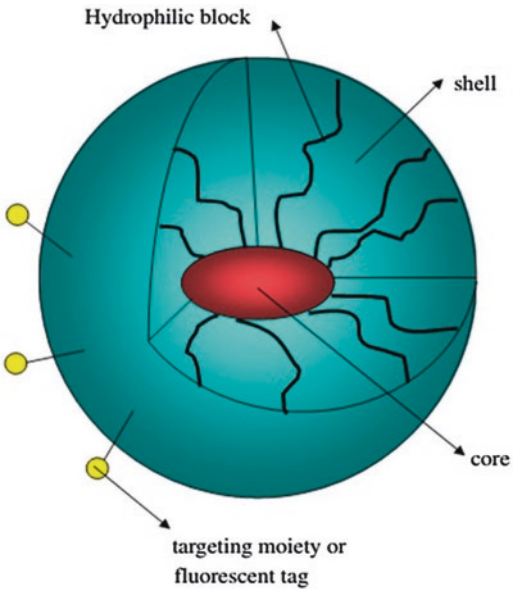

Fig. 7.1 Schematic representation of block copolymer micelle; lipophilic drug (red color) is encapsulated in the micelle core. The core-shell structure can be conjugated with other functional groups (Rapoport 2007)

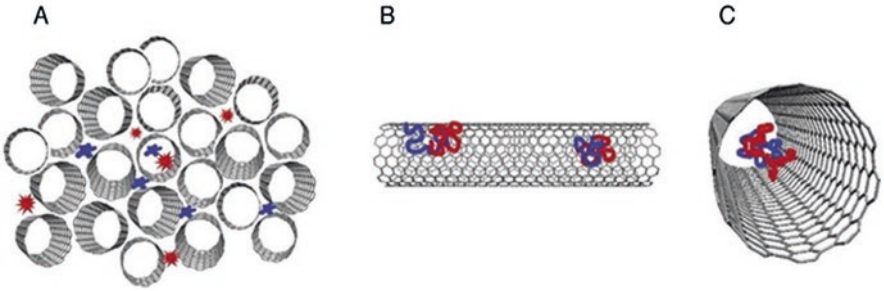

Fig. 7.2 Schematic representation of (**a**) a bundle of CNTs as a porous matrix encapsulating drug molecules between the grooves of individual CNTs, (**b**) moieties attached to the exterior of a CNT either by covalent bonding to the CNT wall or by hydrophobic interaction of moieties with the CNT walls, and (**c**) the encapsulation of moieties within the internal nanochannel of a CNT (Foldvari and Bagonluri 2008)

walls of CNTs (Fig. 7.2b); and, thirdly, this can be achieved using CNTs channels as nanocatheters (Fig. 7.2c). As nanopharmaceuticals, CNTs can be applied more specifically by controlling the conjugation of active pharmaceutical agents on it rather than making use of the bulk property of CNTs. Such conjugation can be carried out either exohedrally or endohedrally. In exohedral conjugation, the active pharmaceutical agents are bonded to the exterior of the CNTs for delivery into the cells but when endohedral, the active agents are encapsulated and transported through the inner cavities of the CNTs to the target site of delivery.

7.2.3 Cell Imaging Agents

Cellular imaging, defined as the use of a system/technology capable of visualizing a cell population, single cell or subcellular structures, applied in combination with image-analysis tools, is emerging as a crucial tool enabling the integration of biological complexity into drug discovery. Detection systems include microscopes, fluorescence macro-confocal detectors and fluorometric imaging plate readers (FLIPR) used with charge-coupled device (CCD) cameras. These systems generate a two-dimensional pixel array of information (a digital image) extracted from a particular biological event or tissue type. Various image-analysis tools have been developed to process the information in the digital image into meaningful parameters (Lang et al. 2006). Presence of nanopharmaceuticals in living organisms has revealed the involvement of nanopharmaceuticals in the differentiation of cells, cell–cell and host–pathogen interactions, immune response, etc. (Corfield and Berry 2015; Jones 2015; Pinho and Reis 2015). Studies have also revealed that the occurrence of specific structure of nanopharmaceutical agent correlates with disease invasion and the capacity to metastasize target organs at specific site which is an indication that nanopharmaceuticals can be used as disease biomarkers to screen, predict, monitor, and/or diagnose diseases most especially at early stage (Christiansen

et al. 2014; Dosekova et al. 2017). The principle of operation during cell imaging is based on selective delivery which makes use of binding receptors. Theranostic concept has been used overtime. For practical and clinical applications, Webster et al. (2015) suggested that theranostic nanomaterials should effectively combine therapeutic agents, targeting moieties, and imaging agents. However, there are situations where the nanopharmaceutical agent is self-imaging. In this case, the nanopharmaceutical agent does not require the presence of a binding receptor due to its ability to fluorescence (An et al. 2015; Dosekova et al. 2017). This has brought a major enhancement to the use of NMRi (nuclear magnetic resonance imaging) and computed tomography imaging of tissue or single cell. Theranostic medicines can provide insights into the availability of a molecular target in the tissue, the vascular permeability and retention of the molecule, the drug release from the particle, and the response of the target tissue (Kiessling et al. 2014). A recent study provided insight on the application of magnetic targeting and pH-responsive lipophilic anticancer drug delivery. A theranostic nanocage system, formed from biogenically synthesized Fe_3O_4 nanoparticles and decorated with an anticancer drug and a saponin-based biosurfactant, was developed for the targeted delivery of two anticancer agents: camptothecin and luotonin A. These theranostic nanocomposites showed better chemotherapeutic efficacy when examined in MCF-7 and HeLa cancer cell lines with a specific targeting capacity (Kesavan et al. 2018). Additionally**,** a prostate-specific membrane antigen targeted gold nanoparticle for theranostics of prostate cancer has been synthesized. The theranostic agent, AuNP-5kPEG-PSMA-1-Pc4, loaded with a fluorescent photodynamic therapy drug, Pc4, is envisioned to provide surgical guidance for prostate tumor resection and therapeutic intervention when surgery is insufficient (Mangadlao et al. 2018).

Targeted magnetic nanoparticles (MNPs) have also found use in noninvasive molecular imaging and therapy. They can be used as target-specific agents, to selectively enhance the contrast in molecular level, if functionalized, for instance, by incorporating them with antibodies. Targeted compounds improve the lesion detectability of certain pathologies and more importantly provide the localized therapy as drug delivery systems (Amiri et al. 2013). Targeted MNPs have been used to detect Aβ plaques of Alzheimer's disease (AD). For instance, Poduslo et al. (2002) targeted amyloid-β plaques of AD using a putrescine-gadolinium-amyloid-beta peptide probe detectable by magnetic resonance imaging. According to their study, the plaque-to-background tissue contrast-to-noise ratio, which was precisely correlated with histologically stained plaques, was enhanced more than ninefold in regions of cortex and hippocampus following intravenous administration of this probe in AD transgenic mice.

7.2.4 Cancer Treatment

Cancer is a leading cause of death worldwide in countries of all income levels. To add to the existing burden, the number of cancer cases and deaths is expected to grow rapidly as populations grow, age, and adopt lifestyle behaviors that increase

cancer risk (Torre et al. 2016). Cancer, which is characterized by uncontrolled proliferation of cells and dysregulation of the apoptotic mechanism, requires very complex process of treatment. Because of complexity in genetic and phenotypic levels, it shows clinical diversity and therapeutic resistance. A variety of approaches, including surgical removal, chemotherapy, radiation, and hormone therapy, are currently deployed in cancer treatment. Unfortunately, each of them has some significant limitations and side effects. Chemotherapy, for example, which involves the delivering of anticancer drugs systemically to patients, suffers from nonspecific targeting and poor delivery of these agents (Jabir et al. 2012; Zhao and Rodriguez 2013). Nanopharmaceuticals, through passive and active targeting, have been designed to overcome lack of selectivity and aqueous solubility deficiencies of conventional cancer chemotherapy. Selected delivery systems used to achieve passive targeting are liposomes, polymeric nanoparticles, nanocrystals, inorganic nanoparticles, micelles, dendrimers, etc. Active targeting involves conjugation of targeting molecules (like antibodies, ligands, peptides, nucleic acids, etc.) on the surface of nanoparticles with receptors overexpressed on a tumor cell surface (Van Vlerken et al. 2007; Lammers et al. 2008; Gullotti and Yeo 2009). When conventional nanoparticles are used as carriers in chemotherapy, the cytostatic drug is usually delivered to the mononuclear phagocytes system by endocytosis/phagocytosis of their tissue localized macrophages (Moghimi et al. 2005). Moreover, enhanced chemotherapy with nanopharmaceutical formulations has been shown when treating cancers, such as breast (Goldman et al. 2017; Park 2017), ovarian, (McQuarrie et al. 2004) and lung (Das et al. 2016). The underlying mechanism is that nanopharmaceuticals trapped by organs of the mononuclear phagocyte system are able to work as a pool and release anticancer agents to cancerous cells. Apart from nontargeted drug delivery, tumor drug resistance is another key concern in conventional chemotherapy. In many cancer types, nearly 40–50% of the patients diagnosed with cancer has P-glycoprotein overexpression in the malignant tissues. A defining strategy used to overcome P-glycoprotein-mediated multidrug resistance is to encapsulate antitumor drugs with various drug delivery systems, including *N*-(2-hydroxypropyl) methacrylamide drug conjugates, micelles, hybrid lipid nanoparticles, lipid-based nanocapsules and nanoparticles, liposomes, and cyanoacrylate-type nanoparticles. Reported mechanisms included enhancement of cellular uptake of drug via endocytosis and ion-pair formation, ATP depletion, influence of function and expression of P-glycoprotein, and change of P-glycoprotein downstream signaling pathways (Dong and Mumper 2010).

Among a wide variety of proposed nanopharmaceuticals, only a handful has been approved for use in the treatment of cancer. Doxil, with the brand name Caelyx®, was obtained by encapsulating doxorubicin within liposomes. This nanoformulation boosted pharmacokinetic indices such as longer circulation half-life and maximal drug accumulation in target tissues. Clinical validation of the use of doxil in the treatment of metastatic breast cancer, ovarian cancer, and multiple myeloma has been reported. The non-PEGylated liposomal doxorubicin formulations, Myocet and DaunoXome, have also been used for the treatment of metastatic breast cancer and Kaposi sarcoma, respectively. Abraxane, a co-condensate of

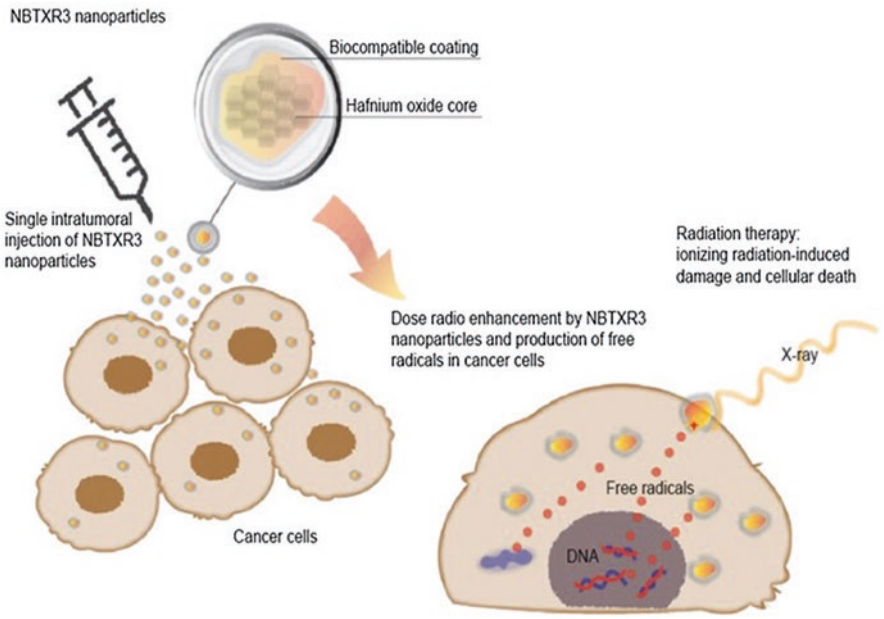

Fig. 7.3 Schematic representation of the radio enhancement mechanism of NBTXR3 nanoparticles in cancer cells after an intratumoral injection. When activated by a radiation source, these potential therapeutic agents generate high amounts of reactive oxygen species when they find their way into tumor resulting in cellular damage. (Weissig and Guzman-Villanueva 2015)

albumin and paclitaxel, is another nanopharmaceutical which has demonstrated significantly higher tumor response rates and longer times to tumor progression in patients with metastatic breast cancer (Huynh et al. 2009; Gradishar et al. 2005; Montana et al. 2011). Several strategies have also been adopted to enhance the effects of anticancer agents. Previous works reported potential therapeutic agents with high electron density which allowed the deposit of large amounts of energy within living cells due to ionization (Weissig and Guzman-Villanueva 2015; Marill et al. 2014). When activated by a radiation source, these potential therapeutic agents generate high amounts of reactive oxygen species when they find their way into tumor resulting in cellular damage (Weissig and Guzman-Villanueva 2015; Marill et al. 2014), this is illustrated in Fig. 7.3. Surface modified promising therapeutic agents are currently being screened as radio-enhancer for treatment of tumors, this ongoing research has shown high prospect with the hope of a better healthy living. Presently, there are ongoing trial studies on metal-based therapeutic agents for biopsy. Antigen-specific ligands have been employed in surface modification of nanomaterials as nanopharmaceutical agents in active targeting approach. Several studies have revealed the prospect of nanopharmaceuticals as agents for biopsy, most of the studies have shown promising results (Adolphi et al. 2010; Jaetao et al. 2009).

7.2.5 HIV/AIDS Treatment

Despite concerted efforts at mitigating the acquired immune deficiency syndrome (AIDS) menace, millions of individuals worldwide are still HIV-1-infected and rate of new infections remain unabated. Antiretroviral therapy (ART) effectively controls viremia in virtually all HIV patients and partially restores the primary host cell (CD4+ T cells) but fails to eliminate HIV-1 from latently infected T cells (Gandhi et al. 2010). In latently infected $CD4^+$ T cells, integrated proviral DNA copies persist in a dormant state but can be reactivated to produce replication-competent virus when T cells are activated, resulting in rapid viral rebound upon interruption of antiretroviral treatment. Therefore, most HIV-infected individuals, even those who respond very well to ART, must maintain lifelong ART due to the ability of virus to establish anatomical or cellular reservoirs which escape the action of antiviral drugs (Kaminski et al. 2016).

These reservoirs include the following (Clarke et al. 2000):

(a) Extracellular virions trapped on the surface of follicular dendritic cells within the lymphoid tissue
(b) Latently infected and resting $CD4^+$ T cells
(c) Microglial cells of the brain, pulmonary alveolar macrophages of the lung, and macrophages within the spleen and lymph nodes
(d) Brain tissues, such as the brain

Many antiviral drugs present problems that reduce their efficacy, such as limited solubility, a short half-life or slow, incomplete or highly variable absorption. Consequently, high doses and frequent administration are required that, in turn, can negatively affect patient compliance, causing severe side effects. Besides solubility and permeability, other factors that affect the oral bioavailability of an antiviral include the action of intestinal metabolizing enzymes, efflux transporters, and food. The oral administration of an antiviral with a low or variable bioavailability thus requires the use of higher doses and prolonged treatment durations in order to eradicate the virus. Another problem of antiviral agents is that the chronic treatment with such drugs can produce moderate levels of drug toxicity, which might lead to serious complications in the patient. Moreover, prolonged antiviral therapy increases the likelihood of drug-resistant virus strains emerging (Emery 2001; Sharma and Garg 2010; Williams and Sinko 1999).

To improve the therapeutic activity of currently available antivirals, it is possible to change the conventional dosage forms, either by modification of their formulations or by the design of novel nanopharmaceuticals. As with conventional drugs, a major concern of deploying nanopharmaceuticals in treatment and prevention of disease is the ability to reach target site(s) in their active form. This challenge may be overcome by optimizing the physicochemical properties of the nanopharmaceutical or by modifying its surface by attachment of ligands or agents that prevent opsonization, in order to facilitate transport across membranes or enable targeting (Alexis et al. 2008).

Dou and coworkers (2007) showed that effective delivery to various tissues could be achieved with a nanosuspension of the drug indinavir, stabilized by a Lipoid 80 surfactant system. The indinavir nanosuspensions were loaded into macrophages, and their uptake was investigated in mice. Results showed high distribution of the drug in the lungs, liver, and spleen. More significantly, the intravenous administration of a single dose of the nanoparticle-loaded macrophages in a rodent mouse model of HIV brain infection resulted in significant antiviral activity in the brain and produced measureable drug levels in the blood up to 14 days posttreatment (Dou et al. 2009). Furthermore, macrophages, which are the major HIV reservoir cells, have various receptors on their surface such as formyl peptide, mannose, galactose, and Fc receptors, which could be utilized for receptor-mediated internalization. The drug stavudine was encapsulated using various liposomes (120–200 nm) conjugated with mannose and galactose, resulting in increased cellular uptake compared with free drug or plain liposomes and generating significant level of the drug in the liver, spleen, and lungs. The drug zidovudine, with half-life of 1 h and low solubility, was also encapsulated in a mannose-targeted liposome made from stearylamine, showing increased localization in lymph node and spleen. In another study, the drug efavirenz was delivered to monocytes and macrophages in vitro using a mannose-targeted poly(propyleneimine) dendrimer nanocarrier. The targeted nanocarrier resulted in 12-fold increase in cellular uptake compared with free drug. A similar system was used to deliver the drug lamivudine in vitro, resulting in significantly higher anti-HIV activity for the targeted and nontargeted dendrimer systems compared with free drugs (Dutta and Jain 2007; Dutta et al. 2007; Kaur et al. 2008). Hopefully, these nanopharmaceuticals would present the needed platforms for improving targeted delivery of antiretroviral drugs to the cellular and anatomical reservoirs of HIV.

7.2.6 Intravaginal Microbicides

Intravaginal application of drugs has long been of interest to researchers, who had explored it for the local delivery of therapeutic agents such antimicrobials (Vanić and Škalko-Basnet 2013). Intravaginal route of drug administration bypasses the gastrointestinal tract and delivers directly into the vagina. This avoids loss of active compound through incomplete absorption or degradation in the acidic environment of the stomach and duodenum or bacterial flora in the gut. More importantly, the first-pass effect in the liver, which could have resulted in structural modifications of the nanopharmaceutical, is circumvented. The vagina could also provide a platform for systemic treatment if drug is resorbed through the vaginal venous plexus into the body. The vaginal venous plexus empties into the iliac or hemorrhoidal veins that do not pass the liver circulation, thus avoiding the first-pass effect. But vaginal route of administration is not a straightforward approach. Drug formulations for vaginal application must be retained at the site for the sufficient period, in spite of the normal vaginal clearance and discharge. To achieve an optimal retention,

mucoadhesive and muco-penetrative delivery systems have been explored. However, the presence of cross-linked mucin fibers limits drug penetration across the vaginal tract. In order to penetrate the mucus, delivery vehicles must be small enough to overcome significant physical hindrance by the dense mucin fiber mesh (Ensign et al. 2014; Katz et al. 2011). Nanopharmaceuticals offer an opportunity to achieve uniform epithelial delivery to the vagina. The choice of optimal nanocarrier will be dependent on the characteristics of the particular drug and expected dosage regimen of the therapy. Since majority of the drugs of interest for vaginal administration have limited solubility, nanocarriers that can solubilize these drugs enhance their bioavailability. In addition, nanopharmaceutical formulations could increase the retention time of the drugs at the vaginal site if composed of substances capable of promoting mucoadhesion (Caramella et al. 2015; Wong et al. 2014). Additionally, the small size of nano-agents facilitates their cellular internalization and release of the drug directly to the cytosol.

Furthermore, the small size of nanoparticles means that some of these particles can interact with viral agents and thus may offer protection against STDs such as HIV (Notario et al. 2017). For example, studies have demonstrated in vitro viral adhesion with silver nanoparticles, while silver-coated PVP nanoparticles have demonstrated antiviral activity ex vivo at nontoxic concentrations (Lara et al. 2010). Their large surface area improves the dissolution and absorption of slightly soluble drugs and also allows optimization of these nanoparticles according to their functionalization; they can bind to specific targets by multivalent conjugations and attach at the drug release site. These nanosystems can either exhibit HIV inhibitory activity by themselves or serve as a vehicle for drug delivery. Recent research has focused on the possibility of developing microbicides based on nanoparticles for HIV prevention (Notario et al. 2017). These nanoparticles consist of cross-linked polymer chains formed thanks to crosslinking agents, creating a structure within which to load the drug. Nanoparticles have been loaded with antiretroviral microbicides such as dapivirine (DPV) and tenofovir (TFV) in order to improve cellular internalization of the microbicides (Yang et al. 2013). PLGA nanoparticles loaded with the antiretroviral drug saquinavir have been conjugated to the anti-CD4 antibody. The nanoparticles thus bind to the $CD4^+$ immune cells, and the drug is specifically released inside them. Nanoparticles of PLGA and methacrylic acid copolymer (Eudragit® S-100) have been loaded with TFV and are capable of releasing the drug in a pH-dependent manner in the presence of seminal fluid (Zhang et al. 2011). Another example of release in response to stimuli is the nanoparticles of hyaluronic acid loaded with TFV, which release the drug in the presence of semen due to the degradation of hyaluronic acid in the presence of the enzyme hyaluronidase (Agrahari et al. 2014). An alternative option is to include the nanoparticles in a stimuli-sensitive dosage form, such as temperature-sensitive gels that are liquid at room temperature, convenient to apply and gain consistency at body temperature, thus avoiding vaginal seepage after application and maintaining the nanoparticles in contact with the mucosa for longer. Formulations with PLGA nanoparticles loaded with TFV or with rilpivirine (Destache et al. 2016) have been developed using these gels. For all these reasons, despite the current scarcity of microbicides based on

nanosystems for the prevention of HIV, coming years will see a boom in research in this field, since nanoparticles provide a delivery strategy for targeted and controlled delivery of drugs to the vagina (Notario et al. 2017).

7.2.7 Enhancement of Anticancer Agents

Previous works reported potential therapeutic agents with high electron density which allowed the deposit of large amounts of energy within living cells due to ionization (Weissig and Guzman-Villanueva 2015; Marill et al. 2014). When activated by a radiation source, these potential therapeutic agents generate high amounts of reactive oxygen species when they find their way into tumor resulting in cellular damage (Weissig and Guzman-Villanueva 2015; Marill et al. 2014), this is illustrated in Fig. 7.3. Surface modified promising therapeutic agents are currently being screened as radio-enhancer for treatment of tumors, this ongoing research has shown high prospect with the hope of a better healthy living. Presently, there are ongoing trial studies on metal-based therapeutic agents for biopsy. Antigen-specific ligands have been employed in surface modification of nanomaterials as nanopharmaceutical agents in active targeting approach. Several studies have revealed the prospect of nanopharmaceuticals as agents for biopsy; most of the studies have shown promising results (Adolphi et al. 2010; Jaetao et al. 2009).

7.3 Safety Evaluations

It is undeniable that nanotechnology has the potential to appreciably lower drug production costs, while providing prospects for success in areas where the traditional pharmaceuticals have failed (Moghimi et al. 2011). Thus the emerging field of nanopharmaceuticals is increasingly being accepted globally. However, there are still safety concerns as well as potential of the unknown complications that may arise as a result of long-term exposure to nanoformulations (Cao and Sim 2007; Bawarski et al. 2008; Pepic et al. 2014). Though the safety concerns associated with the use of nanopharmaceuticals may be overshadowed by the benefits and prospects that the nanopharmaceuticals offer, nevertheless, these concerns are real and, therefore, necessitate consideration.

The physical and chemical properties of materials tend to become very different from those of their parent compounds when they become highly reduced in size (Ray et al. 2009). Exposure to nanomaterials may proceed through inhalation (respiratory tract), topical application (skin contact), intravitreal, transscleral, suprachoroidal, subretinal, oral administration (ingestion), and injection (blood circulation) routes (Oberdorster et al. 2005; Kompella et al. 2013). Due to their extremely small dimensions and large surface-to-volume ratio, nanomaterials may gain assess into both the circulatory and lymphatic systems and induce irreversible injuries through

promotion of oxidative stress (Fu et al. 2014). Therefore, in a bid to maximize the benefits and minimize the potential harms that could be caused by exposure to nanomaterials, it becomes expedient to consider the safety impacts of nanopharmaceuticals through the lens of public health (Pautler and Brenner 2010). For the safe development of nanotechnology and the safe use of commercial nanomaterials, investigations regarding the toxicity and safety profiling of nanomaterials are needed (Fu et al. 2014).

7.3.1 Potential Health Risk

At the cellular level, nanomaterials could interact with vital cell components such as the nucleus, mitochondria, and membrane and thus exert adverse effects such as damage to organelles or DNA, apoptosis, oxidative stress, mutagenesis, and protein up-/downregulation (Pan et al. 2009). The toxicity profiling of nanomaterials has been investigated in vitro by studying the effects of the nanomaterials on cell culture over a given period of time, e.g., 24–48 h. Effects such as cell proliferation and survival, membrane permeability, inflammatory cytokine levels, and ATP production have been reported (Mo et al. 2007). However, considering the complexity of a whole organism as compared to that of a single cell, the safety evaluation of nanopharmaceuticals in vivo is more dependable and should be sought for. The evaluation in the whole animal should include investigation of general health indicators such as weight loss, mortality percentage, average life span, and behavioral abnormality (Alkilany and Murphy 2010). As with the conventional pharmaceuticals, the absorption, biodistribution, metabolism, and excretion of nanopharmaceuticals must be explored and put into consideration prior to acceptance by regulatory bodies (Alkilany and Murphy 2010). Important pharmacokinetic parameters such as the volume of distribution (V_d), maximum plasma concentration (C_{max}), half time in the blood ($t_{½}$), and total body clearance (Cl) are also necessary, and these can also be obtained by the application of classical pharmacokinetic models (Cho et al. 2009).

Currently, the most sought-after emerging therapeutics in biomedical applications include the biocompatible and biodegradable nanomaterials. It is wisdom that carrier materials for pharmaceutics should ideally be easily metabolized to safe products in order to afford ease of clearance from the system, or if the material is intended to remain in the body, it should be inert, biocompatible, with no adverse effects even after a long-time exposure. Organic materials such as carbohydrates, lipids, and proteins are being used in the preparation of nanomedicines, as well as inorganic compounds such as gold and porous silica. However, toxicity concern arises with the use of inorganic materials as they persist without breaking down unlike the organic materials. The key physicochemical properties influencing the biocompatibility of nanomaterials include the composition, shape, size, surface charge, surface modifications, and lipophilicity (McNeil 2005). Also, the route of administration, dose, dose frequency, and patient idiosyncrasies should be put into consideration in order to minimize potential toxicity.

For example, the mechanism of the clearance of a nanomaterial, following periocular administration, was recently investigated in live and dead animals (Amrite and Kompella 2005; Amrite et al. 2008). According to their reports, at 6-h post-administration of nanomaterials in both living and dead animals, only 45% of the nanomaterial was retained at the periocular site in living animals, while 77% was retained in the dead animals. The percent retained in dead animals was however close to the observed retention immediately after dosing. Their results further revealed a possible breakdown of some of the transport barriers in the dead animals as the tissue level of the nanomaterials in the sclera-choroid were 19-fold higher in the dead animals than the live animals. Again, the particles were found in the retina and vitreous of the dead animals but absent in the live animals (Amrite et al. 2008). Perhaps, the role played by the reticuloendothelial system (RES) in the clearance of intravenous injection of particulate systems cannot be over emphasized (Gèze et al. 2007; Schipper et al. 2009). In separate studies with fluorescent latex particles (size 200 nm) where particles were instilled into the conjunctival cul-de-sac, the conjunctival follicle-associated epithelium in rabbits was able to bind to and translocate particles. The visualization of the translocated particles in the cervical lymph nodes after being translocated from the conjunctival epithelium was an indication of the role of the lymphatic circulation in the clearance of these particles (Liu et al. 2005). The presence of inflammatory cells as observed in the histological sections of periocular tissue 60 days following the administration of 200 and 2000 nm particles suggests the possibility of the inflammatory cells playing a role in the clearance of the particle after administration (Amrite and Kompella 2005). Taken together, the potential risks posed by nanomaterials seem to be dependent on the route of delivery, the nanoparticle composition, and target tissue. These risks include immune stimulation, immunosuppression, inflammation (Zolnik et al. 2010), aggregation, membrane disruption, accumulation in nontarget tissues (Panessa-Warren et al. 2009), hemolysis, generation of oxidative stress (Medina et al. 2007), and adsorption of plasma proteins onto the surface. A summary of the health risk of nanopharmaceuticals is presented in Table 7.1.

7.3.2 Environmental Risks

Understanding the implications of the process of syntheses, products, and byproducts of nanotechnology on the environment and human health is crucial to its acceptable utilization. With over 1000 nano-enabled consumer products in the market, knowledge gaps still exist regarding their fate and transportation within humans, the environment, and ecosystems (The Project on Emerging Nanotechnologies Consumer Products 2010). Some nanoparticles appear to persist more in the environment than others, hence, the need to explore and obtain more information as touching risk assessment and management (Kahru and Dubourguier 2010). Further, many topical creams which are intended for direct application, for example, sunscreens, contain nanoparticles (The Project on Emerging Nanotechnologies Health

Table 7.1 Summary of in vitro *and* in vivo nanoparticle toxicity

Nanoparticle	Side effect	Experimental model/organ/tissue	References
AgNP; 1, 10, and 100 μg/ml; incubated at 1, 4, and 24 h	No hemolysis observed for 1 and 10 μg/ml washed red blood cell, hemolysis observed for 100 μg/ml washed red blood cell incubated at 24 h	In vitro red blood cell	Laloy et al. (2014)
AgNP	Chromosome instability	In vitro normal human lung fibroblast	AshaRani et al. 2009
AgNP	Mitotic arrest (although normal human fibroblast eventually recovered while cancer cells did not recover)	In vitro normal human lung fibroblast	AshaRani et al. 2009
AgNP	Alterations in cell morphology	In vitro normal human lung fibroblast	AshaRani et al. 2009
AgNP	Oxidative stress and apoptosis	Rat liver cell	Hussain et al. (2005)
AuNP; 4, 12 & 18 nm; spherical; 0.001–0.25 μM; 72 h incubation period	Nontoxic	K562 human leukemia cell line	Connor et al. (2005)
AuNP	Nontoxic	Dendritic cells	Villiers et al. (2009)
AuNP; 2 nm, spherical, quaternary ammonium, carboxylic acid. 0.38–3 μM dose; incubation time 1–24 h	Cationic nanoparticles were toxic while anionic were not	COS-1 mammalian cells, red blood cells, *E. coli*	Goodman et al. (2004)
AuNP; 10, 50, 100, 250 nm; spherical; intravenously administered; 77–108 μg/rat	No side effect. Most nanoparticles were found in spleen and the liver; the 10 nm particles were also found in the brain, heart, kidney, testis, and thymus	Rat liver, spleen, brain, and heart	De Jong et al. (2008)
AuNP; spherical; 0–4 mM dose, 24–144 h incubation time	Decreased cell proliferation rate, adhesion and motility	Human dermal fibroblast	Pernodet et al. (2006)
AuNP; 15–20 nm; spherical; intravenous 0.8–1.88 mg/gold/kg	AuNP accumulated. No hematological or renal side effects	Pig liver, lung, kidney, and blood	Kattumuri et al. (2007)

and fitness 2010). Some of these materials could be absorbed through the epidermis, while, some, while being washed off, enter into the public waste water systems. Also, nanomaterial utilized for medical interventions have multiple entry points into the environment; while some nano-enabled drug products are excreted into waste

water, some novel imaging agents and medical devices are disposed at the end of their life cycle into a landfill. The Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) currently provides guidelines on how to dispose of unused medications to the public as this and other byproducts could cause harmful effect to the environment (U.S. Environmental Protection Agency 2010; U.S. Food and Drug Administration 2010). The ability of bionanomaterials to accumulate in the environment, food chain, and work force represents a direct proportional rise in the risk of environmental damage (Nel et al. 2006). More so, certain toxins have been found to enter the food chain by bioaccumulating in organisms. Hence, the ecological fate of nanomaterials needs to be considered and the environment monitored for potential threats (Patil et al. 2015).

For example, researchers studied the fate of CTAB-coated gold nanorods (65 nm length 9 15 nm width) in replicate estuarine mesocosms which was modeled to mimic a high tidal marsh creek (Ferry et al. 2009). The mesocosms consisted of seawater, sediment, fish, snails, microbial biofilms, clams, and shrimps. The authors of the study found out that the nanomaterials were differently partitioned into most of the organisms to varying extents, with a low concentration remaining in water. The largest accumulations of nanomaterials were the microbial biofilms and clam (filter feeders). Nevertheless, no death was reported at the dosage used (Ferry et al. 2009). In a separate report by Bar-Ilan et al. (2009), the toxicity of different sizes (3, 10, 50 and 100 nm) of gold and silver nanoparticles were assessed using zebrafish embryo. The study demonstrated that the gold nanoparticles unlike the silver nanoparticles of comparable sizes were not toxic to zebrafish. The silver nanoparticles were highly toxic, inducing 100% death after 120-h postfertilization. In addition, other environmental fates of nanoparticles particularly in the marine ecosystem include its ability to sink very slowly to the ocean floor, where it may pose a risk to pelagic species, deposition in sediments where it may pose a risk to benthic species and accumulation in the surface microlayers of the oceans (Wurl and Obbard 2004). Furthermore, crops may uptake nanomaterials if exposed to nanopesticides and the uptake varies, depending on the plant species, the source of growth media, nanomaterials, and mode of application. For example, exposing lettuces and cilantro to nanopesticides via soil resulted in the uptake of nCu, nCuO, and the two $nCu(OH)_2$ nanopesticides leading to the accumulation of Cu mostly in the roots, with little translocation to the stems (Hong et al. 2014; Zuverza-Mena et al. 2015). Also, when the mode of application of the nanopesticides was foliar, a much larger fraction of the Cu taken up by the plant remains in the leaves or fruits.

7.4 Conclusion

At present, use of nanopharmaceuticals is cogent in sustaining the future growth of the pharmaceutical industry (PI) in both developed and developing nations of the world. Research efforts are being made to advance the applications of nanopharmaceuticals that will better benefit the healthcare industries. However, as

nanotechnology emerges as promising tool in the field of medicine and particularly for the healthcare industry, the environmental exposure will continue to rise. Therefore, investigations aimed at profiling the safety and environmental fate of these particles become highly essential. Further, the general public needs to be educated on the safe disposal of byproducts of nanomaterials in order to ensure safe community health while the government needs to put in place policies to monitor and adequately regulate the synthesis and utilization of nanomaterials for biomedical and for pharmaceutical applications.

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