Chapter 1
Environmental and Toxicological Implications of Nanopharmaceuticals: An Overview

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Abstract Over the last couple of years, several studies have been communicated to endorse the tremendous potential of nanopharmaceuticals for the welfare of human beings and other living organisms. However, very limited concepts have been realized in the form of final products. There are various factors which are responsible for the inadequate development of nanopharmaceuticals such as inherent faults of nanocarrier; implausible absorption, distribution, metabolism, excretion/elimina-

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tion, and toxicity (ADMET); and other associated toxicity and confined biocompatibility. Here we review various nanocarriers used in nanopharmaceuticals with respect to their environmental and toxicological implications, including their detection and contamination routes. In addition, we have put forward various concerns and guidelines for the future development of nanopharmaceuticals.

Keywords Nanopharmaceuticals · Nanocarriers · Bioaccumulation · ADMET studies · Ecotoxicity

1.1 Introduction

Over the past few years, pharmaceutical industries have grown with a tremendous potential as a huge investment has been done on the research and development of novel, safe, effective, and efficient pharmaceutical formulations. The development of novel pharmaceutical formulations is overstimulated and propelled due to the perpetual emergence of various disease outbreaks and human-/poultry-based apocalypses such as malaria, dengue, cholera, chikungunya, Zika, and Ebola virus infections, hepatitis, plague, yellow fever and many more. Besides this, cancer, diabetes, and cardiac disease based medications are the leading pharmaceutical revenue generator due to the widely affected population. The high demand of cancer, diabetes, and cardiac disease based medications results in huge and sustainable development in the advancement of respective medicaments to make them more efficacious with minimal side effects. During the advancement of respective medicaments, the existing nanotechnologies and their features have been materialized and consolidated in the last few years (Bawa et al. 2016; Cornier et al. 2017; Müller 2017).

The nanopharmaceuticals have various advantages over common medicaments such as an exceptional targeting ability with significant accuracy, followed by better stability and sustainability at the targeted sites (De Villiers et al. 2008; Jain 2008; Nagarajan 2012; Liang 2013; Ge et al. 2014). Hence, in the recent years, the field of nanopharmaceuticals or nanomedicaments or nanomedicines or nanodrugs has grown rapidly, mainly in the direction of nano-support-based drug delivery systems for the treatment as well as diagnostic applications (Kumar 2007; Peer et al. 2007; Claire du Toit et al. 2007; Bawarski et al. 2008; Weissig et al. 2014; Bassyouni et al. 2015; Bawa et al. 2016; Berkner et al. 2016). Integration of nanotechnology and pharmaceuticals provides some extraordinary features such as vast surface area and improved penetrability in comparison to their larger counterparts (Varadan et al. 2008).

Nanopharmaceuticals have quite peculiar physical, chemical, and biological properties due to their unique structures and functionalities (Kumar 2007; Mozafari 2007). These properties are closely related to the pharmacokinetics/pharmacodynamics that influence the biocompatibility and the ADMET (absorption, distribution, metabolism, excretion/elimination, and toxicity) behavior of nanodrug formulations inside the living body (Houdy et al. 2011). Basically, conventional

drug formulations show a huge variation and instability inside the living body due to their differential size and shape, chemical composition, solubility, surface charge, and other surface modifications. The combination of nanotechnology and pharmaceuticals provides improved biological adhesion, rapid or controlled dissolution, lower settling, and higher saturation solubility inside the living body. These features of nanopharmaceuticals established them as relatively more effective and proactive medicaments.

As per the current scenario, the nanopharmaceuticals cover a broad range of medicines and medical treatment related products for humans as well as animals. The major classes of those medicines and products are as follows:

- Medicines for diseases, in both solid and aqueous forms
- Vaccines
- Chemotherapeutic agents
- Anticancer or antitumor or antineoplastic drugs
- Lipid lowering agents
- Cardiac, pulmonary, and neuro medicines
- Ocular health products and instruments
- Dental care products
- Osteoporosis medicaments and bone implants
- Wound and burn healing drugs
- Medical diagnostics such as molecular diagnostics and diagnostic test cards
- Medical or surgical tools and devices
- Multivitamins, amino acids, proteins, and other nutritional products
- Medicinal personal care products such as soaps, shampoos, and hygiene products
- Over-the-counter and generic medicines

In the last few years, numerous studies have been dedicated for the exploration of nanocarrier-based medicaments that involves carbon nanotubes, nanofiber, nanoparticles, nanoshells, liposomes, dendrimers, quantum dots, nanoclay, and many other nanosized entities with exclusive shape, size, composition, surface chemistry, and targeting ligands (Claire du Toit et al. 2007; Narducci 2007; Gaur and Bhatia 2008; Menaa 2013; Hassanzadeh 2014; Chavda 2016; Loretz et al. 2016), as shown in Fig. 1.1. Nanocarrier-based medicaments are potentially being used for efficient drug delivery, amino acids or peptides delivery, chemotherapy, neurotherapy, diabetes and many other treatments (De Villiers et al. 2008; Jain 2008; Nagarajan 2012; Liang 2013). The nanocarrier-based hybrid medicaments are usually given by injection into the blood vessels or through the oral administration. Here, typically 50–200 nm-sized nanocarriers are incapable to cross the endothelial barrier except spleen and liver due to the availability of gaps (Juliano 2013).

In addition, the nanocarriers have regular tendencies to interact with each other and form agglomerates that also increase nanocarriers' effective size. Hence, the restricted biodistribution and increased bioaccumulation of nanopharmaceuticals imply various therapeutic limitations too. Therefore, the drawbacks of nanopharmaceutical technologies are also needed to be reviewed and scrutinized for the safer

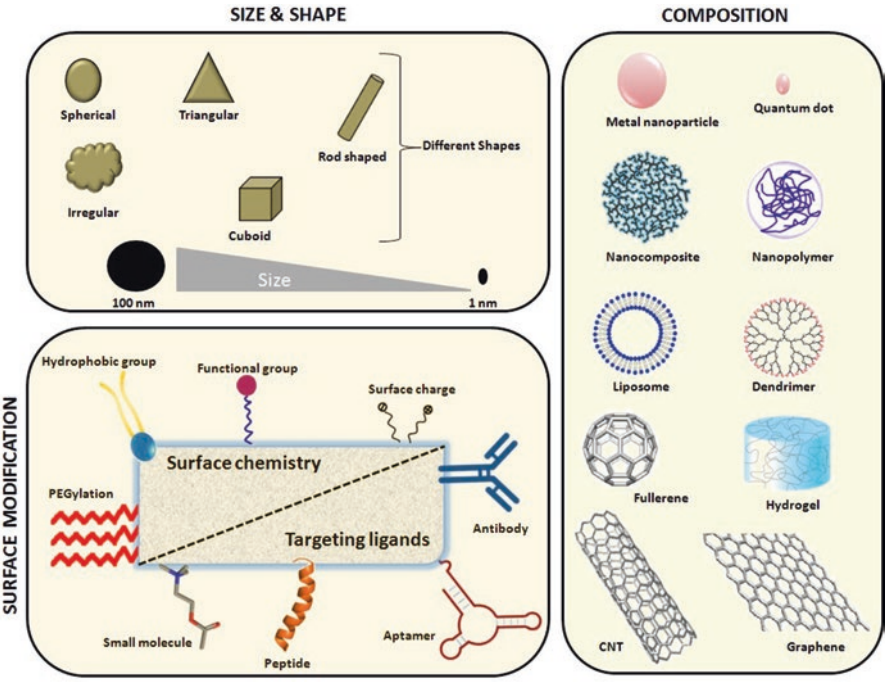

Fig. 1.1 Designing of nanocarrier-based drug delivery system: multifunctional nanocarrier medicament could be produced from the combination of various suitable materials with their specific composition and functional properties that can be further utilized for the therapeutic and/or diagnostic applications (Seleci et al. 2016; Hua et al. 2018)

and eco-friendly benefits of nanopharmaceuticals. However, the major limitations of the potential nanopharmaceuticals are the unavailability of sufficient number of ideal studies and data confirming the environmental and toxicological implications of nanomedicaments. In addition, the localized detection of nanocarriers inside the living body is quite difficult due to the nanosized characteristics. Hence, with the longer treatment duration, nanopharmaceuticals may start accumulating in the specific body regions (Buzea et al. 2007; Ray et al. 2009; Maurer-Jones et al. 2013). Long-term accumulation of nanopharmaceuticals inside the human body may lead to more disastrous health situations or hazards such as a cyst or tumor formation, activation of autoimmune system, and suppression of nearby blood vessels and nerve cell growth (Buzea et al. 2007; Ray et al. 2009; Maurer-Jones et al. 2013).

Furthermore, there are various ethical, scientific, and regulatory guidelines followed by social concerns and implications that are also posing a great restriction on the smooth evolution of nanopharmaceuticals (Koopaei and Abdollahi 2016). The major issues and health risks associated with nanomedicaments are environmental complications, cytotoxicity, translocation to undesired or nontargeted tissues or cells, unknown or unpredictable and undetermined safety norms, and bioaccumulation and non-biocompatibility inside the living body. However, in ethical

perspective, nanomedicaments may alter the genetic sequence of coding or noncoding genes that may result in an abnormal behavior of cellular system which may or may not be persistent in nature depending on the duration of exposure or treatment (Manickam et al. 2017; Sardoiwala et al. 2017). Consequently, a very few nanocarrier-based medicaments used to be approved by the Food and Drug Administration and reached in the open pharmaceutical market. The examples of such nanocarriers are liposome, nanopolymer-protein conjugate, nanopolymer-drug conjugate, and nanoparticle-monoclonal antibody complex-based medical formulations (Bawarski et al. 2008; Weissig et al. 2014; Berkner et al. 2016; Panda et al. 2017). Nevertheless, to extract the more potential benefits of nanomedicaments, it is very essential to work on the genuine guidelines and developments in the all aspects of nanopharmaceuticals under a proper coordination between various industrial, governmental, and academic research and development bodies.

Overall, there are various emerging issues related to ethical, social, and regulatory aspects of nanopharmaceuticals that affect the environment as well as public and/or animal health. In this regard, Maurer-Jones et al. (2013) summarized the toxicity of engineered nanoparticles with respect to various trophic levels such as bacteria, plants, and multicellular organisms including aquatic organisms. Maurer-Jones et al. (2013) also highlighted the important challenges within the field of eco-nanotoxicity and the kind of challenges that are being faced during engineered nanoparticles' analytical assessments.

Buzea et al. (2007) acknowledged that humans had been exposed to nanoparticles from very ancient eras via natural or anthropogenic sources. Buzea et al. (2007) heightened some concerns related to the development of nanotechnology due to the negative impacts of nanosubstances on the public health. For example, engineered nanosubstances could be a potential source of nanoparticle pollution if they are not safely manufactured, handled, and disposed of or recycled. Since, some nanoparticles are able to enter into the living bodies and rapidly migrate to the organs and tissues via the body's circulatory and lymphatic systems. The toxic effects of nanoparticles used to be more intensive in the cases of various pre-existing diseases such as asthma, diabetes, and allergies. Riehemann et al. (2009) discussed the biocompatibility and toxicity-related safety issues of nanomedicines that contain nanoparticles as carrier or active substance. Moreover, there are some associated risks with the nanocarrier coupled pharmaceutical compounds too that may also affect the human body and ecological health (Boxall et al. 2012). In this regard, Koopaei and Abdollahi (2016) recommended to perform well-established toxicology profiling through in vivo tests, since the in vitro tests mostly evaluate samples' toxicity in cell lines with different physiological properties rather than the realistic conditions of a host body.

Sardoiwala et al. (2017) reviewed cytotoxicity, genotoxicity, and immunogenicity-based aspects of various metal and metal oxide nanoparticles. These nanoparticles are widely being used as the nanocarrier for pharmaceutical drugs. Berkner et al. (2016) enlisted a variety of nanocarriers that fall under the European Medicines Agency's nanopharmaceutical definition. These nanocarriers basically include liposomes, polymer/copolymer particles or micelles, dendrimers, coated metal or metal

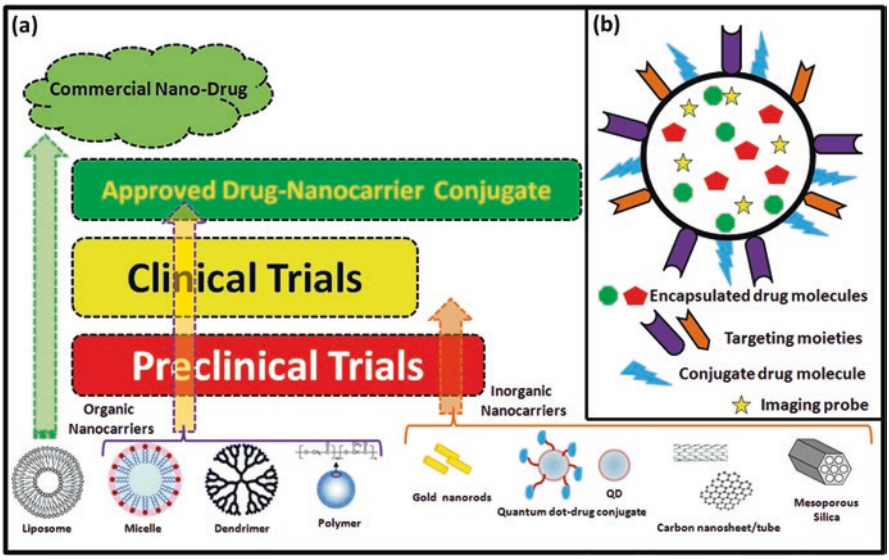

Fig. 1.2 (**a**) The schematic showing versatile conventional nanocarriers such as quantum dots (QD), carbon nanotubes, liposomes, micelles, dendrimers, metallic and polymeric nanocarriers primarily studied for the drug delivery applications with respect to the drug development stages (Mai and Meng 2013); (**b**) Schematic of a multifunctional nanocarrier (Cho et al. 2008)

oxide particles, nonmetal particles, and biological macromolecules such as proteins, peptides, and oligonucleotides (Fan et al. 2014).

As a whole, the aforementioned concerns may limit or restrict nanopharmaceuticals' future evolution, if they are not properly studied, reported, treated, or acknowledged in the literature. The associated hazards of nanopharmaceuticals may cause a negative impression and loss of faith on nanopharmaceuticals in the nonscientific communities, which represent a large section of end users for this oversold and overwhelming technology, although there are various well-characterized and developed nanomaterials, which are precisely studied and already being used as an effective and efficient carrier for medicaments (Cho et al. 2008; Mai and Meng 2013; Sachan and Gupta 2015; Seleci et al. 2016; Subramanian et al. 2016), as shown in Figs. 1.1, 1.2, and 1.3. However, in this review, a few selected ones with respect to their recognized and potential environmental cum toxicological implications have been addressed. For example, phytochemicals have been proven to be more soluble when delivered through the nanocarriers as they exhibit a notable absorption in cancerous cells in comparison to that with the direct phytochemical administered dose. Nevertheless, the half-maximal dose of phytochemicals is greatly reduced due to the nanocarrier-mediated delivery of phytochemicals (Subramanian et al. 2016). Therefore, Subramanian et al. (2016) termed nanocarriers as a crusader in advanced cancer chemotherapy attributed to their minimal side effects and site-specific delivery of drug molecules.

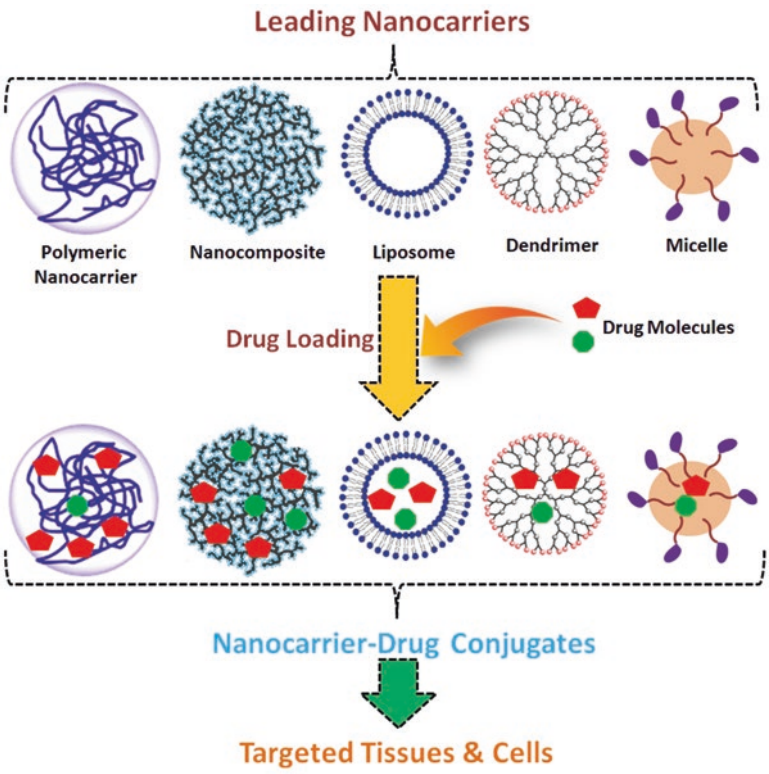

Fig. 1.3 Various leading nanocarriers as an efficient transporter of drug molecules for their better effectiveness on the targeted tissues and cells (He et al. 2016; Subramanian et al. 2016; Zhang et al. 2017a)

1.2 Conventional Nanocarriers Used in Nanopharmaceuticals

1.2.1 Pure Metal-Based Nanocarriers such as Silver, Gold, Iron, and Copper

Metallic nanoparticles are submicrometer (1–100 nm) particles of specific metals such as iron (Fe), gold (Au), copper (Cu), and silver (Ag). They are highly reactive due to their nanosized characteristics such as the large surface area to volume ratio, high surface energies, quantum confinement, and plasmon excitation and contain a large number of "dangling bonds" that provide exceptional chemical properties and additional electron storage capabilities. In addition, few metallic nanoparticles such as Cu and Ag have antimicrobial properties too. Hence, metallic nanoparticles have been widely used and studied for various pharmaceutical applications such as metallic nanoparticle-based biosensors and nanocarriers for disease diagnosis and

therapeutic implementation. However, in recent years, the metallic nanoparticle-based environmental and toxicological studies have been reported that suggest their negative aspects. Inevitably, the expeditious development and production of metallic nanoparticle-based pharmaceuticals have equal contribution in the implications that arise due to the metallic nanoparticle contamination. However, in open literature, it has also been reported that most of the environmental or toxicological implications are primarily because of hazardous chemicals (such as reagents, precursors, and capping agents) and the complex fabrication steps used in the production of metallic nanoparticles for various pharmaceutical-based applications. Furthermore, a few of metallic nanoparticles have shown toxic effects after chemical transition. For example, Ag nanoparticles show dissolution behavior by releasing silver ions which reportedly induce a potential toxic effect in cells (Pandiarajan and Krishnan 2017). However, this concluding remark is still open for intensive research and debate between the concerned researchers and observer field experts. Since, a large number of studies are in favor of the both silver nanoparticles and silver ion-induced cytotoxicity. The combined mechanism of Ag nanoparticle-based cytotoxicity follows a Trojan-horse type mechanism of action (Park et al. 2010). In this mechanism, Ag nanoparticle is supposed to facilitate the release of nontoxic Ag species followed by the entrance of these species into the cell matrices where they get ionized and become toxic in nature and ultimately kill the host cell.

Moreover, exposure to metallic nanoparticles has also been associated with other negative effects such as inflammation, oxidative stress, and genotoxic behavior. In addition, these metallic nanoparticles may accumulate in the living body parts, especially in the liver and/or spleen due to their noncompetitive endothelial barrier. However, metallic nanoparticles may also bioaccumulate in the specific sensitive organ tissues such as brain, spinal cord, and heart. In vitro and in vivo for both conditions, metallic nanoparticles may lead to the formation of reactive oxygen species (ROS) such as superoxide anions ($O_2^{\bullet -}$) and hydroxyl ($OH^{\bullet}$) free radicals, which are potential health hazard substance due to their rapid protein and cell destruction activity (Brohi et al. 2017; Jahan et al. 2017). In general, the oxidative stress in the affected tissues or cells may lead to the DNA, protein, and membrane damages followed by inflammation that ultimately results in the cell death, i.e., apoptosis or necrosis. To minimize the reactive oxygen species-mediated side effects, various antioxidants such as ascorbic acid, citric acid, quercetin, α-tocopherol, and lycopene are used in combination with the surface modification of nanocarriers (Khanna et al. 2015; Wang et al. 2016; Brohi et al. 2017).

Furthermore, metallic nanoparticles are also associated with the hypersensitivity of living organism that may result in the allergic and/or autoimmune response. There are reported studies in the existing literature that ascertained the role of metallic nanoparticles in allergic reactions (Dobrovolskaia and McNeil 2007; Syed et al. 2013; Yoshioka et al. 2017). In addition, a pictorial representation has also been shown for better comprehension on the mode/pathway of allergic reaction stimulated through the exposure of metallic nanoparticles or nanocarriers (Fig. 1.4). In an allergic response, cells of the immune system are activated. Here, the immune cells such as mast cell recognize the foreign substance and trigger the inflammatory response. This response also involves the secretion of cytokines or signaling

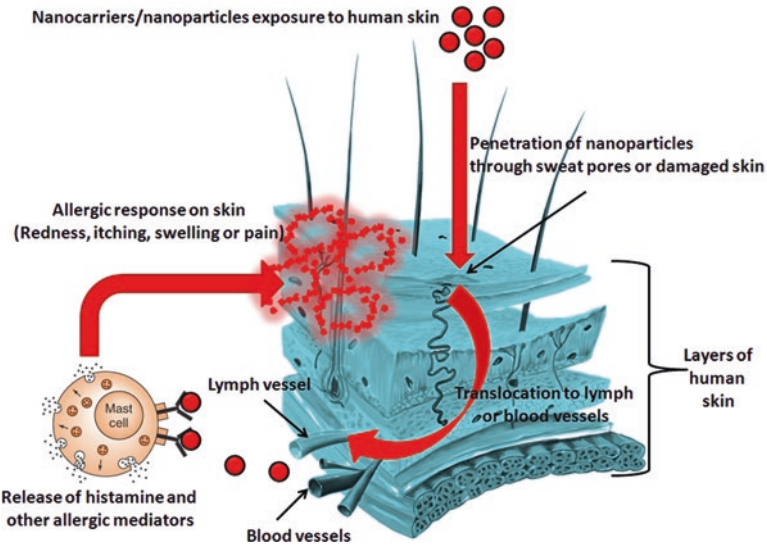

Fig. 1.4 Induction mechanism of metallic nanocarrier-associated allergic reactions in human body. It involves the penetration of human skin, followed by metallic nanocarriers' distribution to the nearby organs and tissues through the blood and lymph vessels. In vivo, these metallic nanocarriers activate the immune response by interacting with the antigen presenting cells that ultimately results in the release of signaling cytokines and histamines

molecules that attract more cells to destroy the foreign substance. In general, the immune cell recognizes nanoparticles by their surface properties and core composition and accordingly produces an inflammatory response. Therefore, Dobrovolskaia and McNeil (2007) recommended a systematic examination of different classes of engineered nanomaterials with their wide range of sizes and surface charges. It may deduce how the change in nanoparticle size and surface charge influence the immune response. In addition to this, the trace impurities present within the nanomaterial-based formulations may also potentially induce the immune response. For example, purified gold and iron oxide nanoparticles do not induce cytokine secretion (Dobrovolskaia and McNeil 2007). It confirms that the purity of metallic nanoparticles may also affect their toxicity. In general, metallic nanoparticles such as Zn, Au, Al, Ag, carbon-coated silver, and carbon black may lead to inflammation through the activation of tumor necrosis factor alpha (TNF-α). These metallic nanoparticles may also increase the levels of interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). The different metallic nanoparticles stimulate inflammation through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) regulation followed by the release of pro-inflammatory cytokines (Syed et al. 2013). However, the penetration of metallic nanocarriers to the human skin varies from individual to individual. Here, after getting physical contact with the healthy skin, nanocarriers use to penetrate to the stratum corneum or epidermis. In case of damaged skin, nanocarriers may penetrate into the epidermis and dermis

layer too (Yoshioka et al. 2017). Therefore, in case of healthy skin, it is quite difficult to predict whether the topical use of nanomedicament may result in negative allergic immune response or not. Since, most of the nanocarriers are incompetent to penetrate the healthy skin.

1.2.2 Carbon-Based Nanocarriers

Fullerenes or C_{60}

Fullerenes are closed hollow shells of carbon atoms or giant carbon molecules consisting of perfect hexagons and pentagon defects. Fullerenes have been reported for their therapeutic actions, among them the major ones are antioxidant activity, antiviral and antimicrobial behavior, neuroprotective activity, enzyme inhibition, gene delivery, and so on (Jensen et al. 1996; Piotrovski 2006; Sheka 2011). In addition, fullerenes also act as an oxidative agent under the influence of photoexcitation in the presence of molecular oxygen. Hence, it is also used in the photodynamic therapy, where triplet oxygen ($^3O_2$) to highly active singlet oxygen ($^1O_2$) transformation occurs (Mroz et al. 2008; Sheka 2011). The overall scheme of fullerene-based photodynamic therapy is given below:

$$^1C_{60} + h\nu \rightarrow {}^1C_{60}^* \rightarrow {}^3C_{60}^* \xrightarrow{^3O_2 \rightarrow {}^1O_2} {}^1C_{60}$$

However, the in vivo delivery of fullerene-based drugs may present some serious implications. Therefore, various specific routes and modifications are being followed for effective administration of fullerene-based drugs, such as suspension of micron-sized fullerenes, use of stable colloidal fullerenes, solubilization of fullerenes, immobilization of fullerenes, and so on. Additionally, the incorporation of nano-sized silica to the fullerene-based drugs has greatly enhanced the therapeutic values and offers a synergistic behavior. This advancement is mainly due to the improved hydrophobicity of the nano-drug conjugates and increased sorption of receptor proteins followed by the enhancement of drug action (Sheka 2011). Apart from this, a few studies have also raised the safety concerns of fullerenes and its derivatives with respect to their possible cytotoxic effects (Gelderman et al. 2008; Kepley 2012), although the concluding remarks of similar studies are also believed to be conflicting, ambiguous, and critically debatable. Therefore, only those studies that represent a well-characterized single species as a lead candidate of fullerene-based pharmaceutical formulation should be recommended as a suitable reference for further argumentation. The characterization studies should include the information about the surface area, size distribution, purity, crystallinity, surface reactivity or affinity, surface coating, solubility, morphology or shape, and aggregation behavior of the nanostructures. This will provide more meaningful information regarding the potential environmental and toxicological characteristics of respective

formulations. Furthermore, fullerenes show stability in aqueous medium due to their net negative charge produced by the networks of charge polarization interaction in large aggregates (Choi et al. 2015). Therefore, aggregation of water-dispersed fullerenes is quite obvious and causes the larger particle formation that consequently reduces the effective surface area of fullerenes too.

Graphene and Graphene Oxide-Based Nanostructures

Graphene is one of the most studied allotropes of carbon. Graphene is a 2D material and consists of a single layer of hexagonically arranged carbon atoms. Graphene has various unique properties such as excellent heat and electric conductivity and good transparency and great strength that makes graphene a wonder material of the twenty-first century. The versatile intrinsic qualities make graphene ideal for utilization in various combinations with improved thermostable, mechanical, and biocompatible properties (Ioniţă et al. 2017). Pure graphene structure used to be hydrophobic in nature that's why it requires to be oxidized to improve its dispersibility in aqueous medium. The oxidized graphene-based formulations have been broadly explored for various biomedical applications such as bioimaging and sensing applications, drug and gene delivery, photothermal therapy, tissue engineering, stem cell technology, and so on, whereas the use of graphene is limited to sensing or diagnostic applications only (Lalwani et al. 2016; Ioniţă et al. 2017).

However, similar to other engineered nanocarriers, the graphene and graphene oxide-based nanocarriers also have the toxicological and environmental implications. For example the inhalation of graphene and graphene oxide may induce lower pulmonary toxicity. However, the bolus airway exposure to graphene and graphene oxide-based nanomaterials may cause acute and subacute pulmonary toxicity. More often, it has been observed that in comparison to small-sized graphene oxide materials, the large-sized ones are more toxic in nature. Moreover, the accumulation of administered graphene oxide in the liver, lungs, and spleen has also been reported in the open literature (Ema et al. 2017). However, the studies showing the negative sides of graphene or graphene oxide-based engineered nanocarriers are very limited in number. Besides this, a few studies show oxidative stress and inflammation as a prominent factor behind the toxicity of pure and oxidized graphene-based nanopharmaceutical formulations (Fahmi et al. 2017). In addition, it is also believed that the surface reactivity, size, and dispersion level of graphene or graphene oxide-based formulations are very crucial factors in the induction of toxicity and undesired biodistribution inside the living body.

Zhao et al. (2014) have reviewed the behavior of graphene-based nanomaterials in the aquatic environment with respect to the adsorption, dispersion, transformation, and toxicity. Notably, graphene or reduced graphene oxides adsorb hydrophobic and aromatic molecules, whereas the graphene oxides adsorb metal ions and positively charged organic molecules, preferably. Since, the studies based on the environmental behavior of graphene are still in the lag phase and confine the understanding of environmental exposure, fate, and risk of graphene-based nanopharmaceuticals.

Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical nanostructure usually formed by rolling a single layer or multiple layers of graphene sheet and termed as single-walled carbon nanotubes or multi-walled carbon nanotubes, respectively. The cylindrical carbon nanostructures used to have dimensions in the ratio of up to 1:132000000 (diameter/length). Carbon nanotubes have various extraordinary features such as high conductivity, exceptional stiffness, excellent tensile strength, high surface area, good adsorption properties, and so on. These notable properties are mainly responsible for the emergence and development of carbon nanotube-based drug nanocarriers. Here, the hollow monolithic structure of carbon nanotubes is very advantageous for the incorporation of drug molecules that offers a controlled and targeted delivery of medicaments. In addition, the outer surface of both single-walled and multi-walled carbon nanotubes could also be functionalized through the addition of various specific functional groups that may enhance the biocompatibility and biodegradability of nanoformulations.

However, a few toxicological studies also indicated the carbon nanotubes' negative outcomes after the oral administration (Araújo et al. 2015). Interestingly, the reported toxicological studies are quite contradictory to each other as few of them report genotoxicity or toxicity with carbon nanotubes (Muller et al. 2005; Bottini et al. 2006; Smith et al. 2007; Folkmann et al. 2008; Jos et al. 2009; Cicchetti et al. 2011), whereas a few of them affirm no toxic effect with the application of carbon nanotubes (Kolosnjaj-Tabi et al. 2010; Naya et al. 2011; Simonin and Richaume 2015). Furthermore, carbon nanotubes are also believed to be capable of induction of immune responses. It further clarified that the immune responses are stimulated from the metallic impurities and contaminants inherently present in the carbon nanotubes (Pulskamp et al. 2007). In addition, the insoluble characteristics of carbon nanotubes induce their bioaccumulation that may cause health and environment-related complications.

Jackson et al. (2013) have identified carbon nanotubes as very hazardous substance for aquatic life, where single-walled carbon nanotube used to be more toxic than multi-walled carbon nanotube. In the same study, the invertebrates were reportedly found to be more sensitive than vertebrates. Since most of the observations are based on the higher exposure concentrations of carbon nanotubes than their routine possible availability in the ecosystem, therefore the negative inferences of carbon nanotubes are quite uncertain and have low impact. Therefore, more rigorous studies considering the production volume and actual contamination level of carbon nanotubes are needed for their better estimation and understanding over the therapeutic and environmental implications.

Carbon Dots

Carbon dots are one of the carbon element-based nanoparticles with the size of less than 10 nm. Carbon dots are water soluble or perfectly dispersible, biocompatible, and cheaper to produce. In addition, carbon dots might also have specific

fluorescence nature and photostability (Lim et al. 2015; Singh et al. 2017). In general, carbon dots used to be a prime choice as a suitable nanocarrier due to their nontoxic nature. Carbon dots have shown a tremendous biocompatibility with blood at lower concentrations (Li et al. 2015a). Carbon dots are widely being used and studied for their potential application in drug and gene delivery, primarily as a photosensitizer and for other sensing applications (Hu et al. 2014; Lim et al. 2015). Here, the functional groups attached on the surface of carbon dots are primarily responsible for their water solubility and suitable conjugation with the chemical entities such as polymers and inorganic compounds including DNA for carbon dots wider theranostic applications (Hu et al. 2014; Hassan et al. 2017; Singh et al. 2017). Moreover, carbon dots also provide a significant flexibility over the surface functionality that could be wisely utilized or selected to hold a desired medicament through various surface interactions. This modification results in an improved control over the release of the conjugated drug molecules. Therefore, carbon dots are widely being used as a potential carrier for pharmaceutical compounds.

Besides this, intrinsically, carbon is not considered as a toxic element; however the specific material morphologies or structures of carbon dots have shown few potential hazards related to human health and to the environment (Wang et al. 2013). Havrdova et al. (2016) suggested that neutral carbon dots have most promising biological applicability as neutral carbon does not induce any impairment in the cell morphology, intracellular transportation, and cell cycle, up to a certain level, whereas negatively charged carbon dots may seize the G2/M phase of the cell cycle and may also increase the oxidative stress. Moreover, negatively charged carbon dots are incapable of cell nucleus penetration. Interestingly, positively charged carbon dots are found to be more cytotoxic in nature, due to their nucleus penetration capability that induce a significant change in G0/G1 phase of cell cycle, even at very low concentration. However, Li et al. (2015b) shown that pristine carbon dots have very low cytotoxicity and recommended their application in the pharmaceuticals, especially for the processing and formulation of insulin due to carbon dots inhibitory effect on human insulin fibrillation.

Furthermore, Xiao et al. (2016) have investigated the toxic effects of carbon dots on different developmental stages of rare minnow's embryo. That study reported a significant developmental toxicity on rare minnow embryos or larvae that may result due to the induced oxidative stress followed by abnormal development-related gene expression led by the carbon dots exposure. Therefore, it is also very essential to re-investigate and ascertain the suitability of carbon dots as a potential nanocarrier for various medical applications.

1.2.3 Quantum Dots

Quantum dots are ultrafine nanoparticles, usually of less than 10 nm, composed of pure elements such as Au, Ag, and C and semiconductor materials such as ZnS, ZnSe, CdS, CdSe, CdTe, and InP. In comparison to nanoparticles, quantum dots' short size causes a shift in the electronic excitation, i.e., towards higher energy, and

concentrates oscillations to a few transitions that results in a unique electronic and photonic behavior of respective quantum dots. Due to the size tunable properties, quantum dots are widely being used to obtain a broad adsorption profile, narrow size, and symmetric photoluminescence spectra depending on the material composition of quantum dots. Quantum dots have also shown a tremendous stability or resistance towards photo and/or chemical degradation followed by their higher quantum yield (Conde et al. 2014). However, in nanopharmaceuticals, quantum dots are widely being used for protein or drug-based sensing applications including the role as drug carrier to cross versatile cell barriers due to quantum dots characteristic smaller size. Very recently, Ranjbar-Navazi et al. (2017) have reported the possible application of doxorubicin-conjugated D-glucosamine- and folate- bi-functionalized InP/ZnS quantum dots for cancer cell imaging and therapy, where this nanocarrier complex is acting as theranostics for simultaneous imaging and cancer treatment. Lai et al. (2017) have synthesized Ag and Mn co-doped In_2S_3/ZnS quantum dots conjugated to hyaluronic acid for selective and efficient internalization in CD44-expressing tumor cells. The study confirms that the resultant quantum dots could be used as dual-mode imaging probes for more accurate and rapid diagnosis.

Since quantum dots exhibit unique luminescence and electronic properties like broad and continuous absorption spectra, narrow emission spectra, and high light stability (Valizadeh et al. 2012), they are highly used for tracking studies of nanopharmaceuticals and quantum dots biodistribution. Hardman (2006) revealed that the assessment of quantum dots exposure routes and related toxicity of the same are not very straightforward, because all the quantum dots are not similar and their toxicity depends on multiple physicochemical and environmental factors. Tsoi et al. (2013) stated that the in vitro and in vivo quantum dot studies have improved our knowledge regarding quantum dots cellular transport kinetics, mechanisms of toxicity, and biodistribution. The cell culture-based experiments have shown that quantum dots encounter design-dependent intracellular localization and cause cytotoxicity, probably by releasing free metals into the matrix and also by generating reactive oxygen species (ROS), whereas in case of tissues and organs the quantum dots primarily enter the liver and spleen. However, there are some apparent discrepancies in the in vitro and in vivo toxicity of quantum dots, since the available dose of quantum dots may vary significantly and quite uncertain in case of in vivo model studies due to their absorption, distribution, metabolism, and excretion-/elimination-based mechanisms. Consequently, the organ-/tissue-specific dose of quantum dots could not be sufficient to induce a perceptible toxic effect, although quantum dots may retain within the tissues or organs and are also susceptible to induce a long-term toxic effect due to their progressive bioaccumulation. Hence, the quantum dot-induced toxicity studies need to be more standardized and systematized to overcome the existing difficulties. Tsoi et al. (2013) also recommended some steps to obtain a consistent and comparable toxicology data, which are as follows: (1) standardize dose metrics; (2) characterize quantum dot uptake concentration; (3) identify in vitro models that replicate cells and quantum dots interactions similar to in vivo; and (4) use multiple assays to determine sublethal dose and biocompatibility of quantum dots.

1.2.4 Metal Oxide-Based Nanocarriers

Metal oxides such as titanium dioxide (TiO_2), zinc oxide (ZnO), aluminum oxide, cerium oxide, and silicon dioxide (SiO_2) are comparatively more stable than pure metal-based nanocarriers and are less prone to dissolution and/or ionization. The metal oxide-based nanocarriers have gained significant interest as an effective and targeted transporter of pharmaceutical compounds. It is mainly due to their unique characteristics like unusual shape, size, and other morphological and structural properties (Jahan et al. 2017; Huang et al. 2017). Vinardell and Mitjans (2015) reviewed the role of various metal oxide-based nanocarriers for antitumor activity. The reported studies have shown that metal oxide nanocarrier-drug conjugates can selectively kill the cancerous cell without any negative impact on the normal cells.

However, metal oxide-based nanocarriers have also shown substantial toxicity towards the human body and the environment as well (Chen et al. 2008; Vega-Villa et al. 2008). It is primarily due to the bio-persistence and nondegradable nature of metal oxide-based nanocarriers that make them a potential source of sustainable chronic hazards, although a few of them are often reported as less toxic than many others, which is quite insignificant to judge the comparative toxicity of metal oxide-based nanocarriers. Since, the protocol, condition, and host used for the toxicity assessment of respective materials are very different from each other (Jahan et al. 2017). Therefore, in spite of the large number of studies related to the assessment of metal oxide-based nanocarriers' toxicity, a limited information is available about the toxicity expressiveness, evaluation routes, influencing factors, accurate reasons, and mode of actions (Ding et al. 2015; Simonin and Richaume 2015). Therefore, it is an incessant necessity to acquire a better understanding of metal oxide-based nanocarriers for their safe and effective utilization in therapeutic and diagnostic applications.

1.2.5 Nanoclays

Clay is a natural material composed of different minerals such as phyllosilicate mineral that show polymeric behavior and have specific water activity. It has tetrahedral and octahedral structural symmetries. There are various classes of clay; however the major ones are kaolinite, montmorillonite, illite, and chlorite. The difference between the nanoclay and normal clay is that nanoclays have high aspect ratios with at least one dimension of nanometer range (Nazir et al. 2016). Nanoclays have better surface integrity with comprehensible thermal and mechanical characteristics. Nanoclay has a great potential as compared to carbon nanotubes and polymers for controlled release of drug compounds (Ward et al. 2012). Conventional immediate release of the drug compounds causes a sudden raise or imbalance in the plasmatic level of the human body that may induce a negative impact or side effect too. Therefore, the use of nanocarriers like nanoclay is quite significant that can

supervise the release of drug compounds, help in the reduction of the undesirable plasmatic level, and reduce the therapeutic side effects with improved performance and treatment outcomes (Jafarbeglou et al. 2016; Jayrajsinh et al. 2017). In clay-based nanomedicaments, the drug molecules are encapsulated in clay minerals to modify the drug release rate or time and also to target the selected site of drug release. Here, clay minerals not only are used as inert fillers but also offer the functionalities of targeted release, prevention or reduction of side effects, and increase in the formulations' shelf life (Lazzara et al. 2017; Zhang et al. 2016, 2017b). The affinity of drug molecules on nanoclay is governed by the functional groups present in the drug molecules, which can generate different interactions such as hydrogen bonding, hydrophilic/hydrophobic interaction, and ion exchange (Lazzara et al. 2017). There are reported studies that concern with the application of various clay minerals such as montmorillonite, sepiolite, and halloysite nanotubes as the suitable nanocarrier for medical applications (Lee et al. 2005; Saha et al. 2014; Lvov et al. 2016; Jafarbeglou et al. 2016; Jayrajsinh et al. 2017; Zhang et al. 2016, 2017b).

Similar to the other nanocarriers, the clay-based nanocarriers also have therapeutic and environmental implications that have been reported in the existing literature (Lee et al. 2005; Ellenbecker and Tsai 2011; Lordan et al. 2011; Verma et al. 2012; Isoda et al. 2017 and many more). The referred studies have indicated about the probable cytotoxic, hepatotoxic, and nephrotoxic nature of nanoclay-based nanocarriers. Therefore, it is necessarily required to fully elucidate the toxicological profiles of nanoclay-based pharmaceutical compounds for their safer applications.

1.2.6 Dendrimers

Due to the inherent limitation of monofunctional nanocarriers, the need of various multifunctional nanocarriers such as dendrimers has been significantly increased (Bai et al. 2006; Menjoge et al. 2010). Dendrimers are basically multibranched macromolecules that have a specific molecular architecture which makes them more advantageous for being used as a multifunctional nanocarrier (Hsu et al. 2017). Dendrimers have precise control over their size, shape, number of branches, and attached functional groups or drug conjugates. Therefore, dendrimers offer exceptional potential in terms of enhanced solubility, stability, stimuli responsiveness, targeted biodistribution, parallel monitoring, and many other characteristics. Hence, dendrimer-based multifunctional nanocarriers present an unmatched capability for various applications in the continuously expanding nanopharmaceutical field. In this way, it may also reduce the possible therapeutic and toxicological implications in human as well as in animals (Sharma and Kakkar 2015). Very recently, Nierengarten (2017) has reported the use of hexa-substituted fullerene-based scaffolds for the faster and bigger construction of globular dendrimers. He has used this method to prepare giant glycoclusters with the medicinal values of antiviral activity and multivalent glycosidase inhibition properties. This example is basically a combination of two different categories of nanocarriers where one

nanocarrier such as fullerene is acting as a support for another nanocarrier like dendrimer. Similarly, different combinations could also be prepared and studied for dendrimers' safer and effective implementation in nanocarrier-based drug delivery and sensing applications.

Despite the substantial lab-scale applicability of dendrimers in nanopharmaceuticals, the full-scale application of dendrimers is quite limited due to the inherent toxicity of associated submolecules or building blocks (Duncan and Izzo 2005; Jain et al. 2010). The toxicity is mainly attributed to the interaction of the positively charged branch of dendrimers with the negatively charged biological membranes in vivo. These interactions may result in the membrane disruption via nano-hole formation, membrane thinning, and erosion (Jain et al. 2010). Dendrimer-based toxicity could be defined as hemolytic toxicity, cytotoxicity, and hematological toxicity, depending on the mode of action. Designing of biocompatible dendrimers and masking of their peripheral charge are the major ways to reduce their toxicity; for example, acetylation, PEGylation, carbohydrate and peptide conjugation, and introduction of negative charge or charge neutralization could be used (Jain et al. 2010).

1.2.7 Polymeric Nanocarriers

In the last few years, polymeric nanocarriers such as micelles, capsules, vesicles, polymersomes, hydro- or nanogels, nanospheres, nanofibers, and polyplexes have gained tremendous attention in the field of nanopharmaceuticals (Park et al. 2008; Ding et al. 2016). Development of advanced and smart polymeric nanocarriers could offer personalized and on-demand treatment possibilities. In general, polymer-based nanopharmaceuticals represent a very heterogeneous form of nanosized drugs where polymer core provides biodegradable and biocompatible features and polymer shell or surface used to have hydrophilic nature (Kadajji and Betageri 2011). Basically, the pharmaceutically active compounds are incorporated or attached to the polymer-based nanosized substances. These modifications offer a significant change in pharmacokinetics, in passive or active targeting via enhanced permeability and retention followed by sustained release of drug compounds (Weissig et al. 2014). The availability of a wide variety of monomers for assembly of polymeric nanocarriers offers a large versatility due to the variation in the structural and physiochemical properties of monomers. As a result, there are significant examples of application of synthetic polymers such as polyethylene glycol (PEG), polylactide–co-glycolide) and polylactide (Shroff and Vidyasagar 2013). The conventional examples of polymers used as gene carrier are polyethyleneimine (PEI), poly(L-lysine) (PLL), synthetic biodegradable polycations, polyacrylamide, chitosan, and cyclodextrins. The examples of poorly water-soluble and amphiphilic drug-based polymeric carriers are PEG–poly(amino acid), PEG–polyester, PEG–lipid, and polysaccharides.

Unlike the other nanocarriers, the polymeric or lipid-based nanocarriers are quite safe and less toxic in nature due to polymers organic composition. However, any associated toxicity of polymeric nanocarriers might be attributed to the polymers' inherent toxic nature, such that monomer of polyacrylamide has neurotoxic behavior. On the other context, Voigt et al. (2014) reported that polybutylcyanoacrylate-based polymeric nanocarrier could be used as a potential drug delivery candidate for the central nervous system. Polybutylcyanoacrylate-based polymeric nanocarriers can cross the blood–brain barrier and are nontoxic in nature with reference to the reported in vivo and in vitro studies (Voigt et al. 2014).

1.3 Quantitative Techniques for Nanopharmaceuticals

Transportation and delivery of xenobiotics, peptides, antibodies, and gene-based medicament by the means of nanocarriers have tremendous potential to reduce drug resistance and ineffectiveness during their therapeutic application. Hence, to compare the performance of transported drugs, the in vitro and in vivo quantification of nanocarriers are very essential. There are various techniques which are widely being used for the similar objective. The most conventional techniques for the quantification of nanocarriers are ICP-MS (inductively coupled plasma mass spectrometry) and ICP-AES (inductively coupled plasma atomic emission spectroscopy) that can quantify the nanocarriers' uptake with respect to their elemental composition. These techniques have the advantage of very low concentration-based detection with a great precision and accuracy.

Paya-Perez et al. (1993) compared the performances of ICP-AES and ICP-MS for the analysis of trace elements present in soil extracts such as Cr, Ni, Cu, Zn, Cd, and Pb. Overall, Paya-Perez et al. (1993) found that the reproducibility of ICP-AES measurements were relatively better than ICP-MS measurements, possibly due to the less involvement of various reagents. However, for Pb and Ni, the ICP-AES sensitivity was not reportedly up to the mark. Hence, ICP-MS was recommended for the samples with very less concentration of some elements. Altogether, the ICP-MS provides a fast estimation of the concentration of various trace metals with good precision and higher sensitivity.

Recently, Legat et al. (2017) reported a capillary electrophoresis-combined ICP-MS technique to study the behavior of different gold nanoparticles during the interaction with the serum proteins and their mixtures. This technique reportedly provided a somewhat real-time measurement of bare nanoparticles and different protein conjugates, followed by their conversion into the protein-attached forms with respect to their reaction time. The capillary electrophoresis-combined ICP-MS technique looks quite suitable for bioanalysis of metallic nanoparticles under more realistic physiological conditions.

It should also be noted that the ICP-MS (inductively coupled plasma mass spectrometry) and ICP-AES (inductively coupled plasma atomic emission spectroscopy) are limited to quantify element-based nanocarriers such as pure metal, metal

oxide, or carbon-based nanostructures only. Moreover, there are other targeted techniques too, such as "mass barcoding" in which specific nanoparticles are tagged with specific functional group and their transportation is monitored by LDI-MS (laser desorption/ionization mass spectrometry) (Shi and Deng 2016). Unfortunately, LDI-MS (laser desorption/ionization mass spectrometry) technique is not widely adopted due to its inherent complexities, uncertainties, and time-intensive behavior.

Furthermore, a new technique was also reported by Lin et al. (2010) that employs cell mass spectrometry (CMS) for the quantitative measurement of micro- and/or nanocarriers uptake in cells. It has a unique ability to rapidly detect the elements from different nanomaterials, simultaneously. This technique exclusively helps in the evaluation of drug targeting efficiency of nanocarriers and their cellular uptake and associated cytotoxicity emerging due to the differential size and surface properties. Therefore, it is believed that the cell mass spectrometry (CMS)-based technology could be efficiently utilized for the rapid and accurate tracking of therapeutic nanocarriers. More interestingly, cell mass spectrometry (CMS) could be used to determine the exact number of nanocarrier uptake in each cell, whereas ICP-MS (inductively coupled plasma mass spectrometry) can only provide an average uptake of nanocarriers for all cells. In addition, cell mass spectrometry (CMS)-based technique could also be used to measure the cellular uptake of nonmetal-based nanotherapeutic agents (Peng et al. 2010).

Moore et al. (2013) reviewed noninvasive measurement-based techniques for the assessment of the release of nanomedicine. Mostly, the pharmaceutical nanoparticles have been studied in laboratory scale for noninvasive measurement of in situ drug release. However, there are various approaches such as optical upconversion, fluorescence, luminescence, radioluminescence, and magnetic resonance imaging-based techniques that could be utilized for nanopharmaceuticals noninvasive measurements in full scale. These approaches involve the complementation of pharmaceutical nanocarriers with some probes like MRI (magnetic resonance imaging) contrast agents and optically or thermally active species. Besides this, there are some obstacles in the development of noninvasive techniques too, such as the physical limitations of optical techniques, imaging sensitivity and resolution-based limitations, and toxicity of complemented species. In addition to this, for further details about the available techniques that could be effectively utilized for the physicochemical characterization of nanopharmaceuticals, it is suggested to go through the referred literature (Lin et al. 2014; Moore et al. 2013).

Moreover, Summers et al. (2013) shown a promising route to assess the dose of nanocarriers in the form of nanoparticle–cell interactions that used to be very difficult due to the complex multiplicity of possible mechanisms and metrics controlling nanocarriers' uptake. Here, the dose basically signifies the number of nanocarriers internalized per cell. Through the use of limited cell sampling using high-resolution electron microscopy, a calibration can be made relating large population and cytometric measurements of fluorescence to the exact nanocarrier dose taken through the endocytosis. Then, through a probabilistic approach, one can easily quantify the level of nanocarriers per cell.

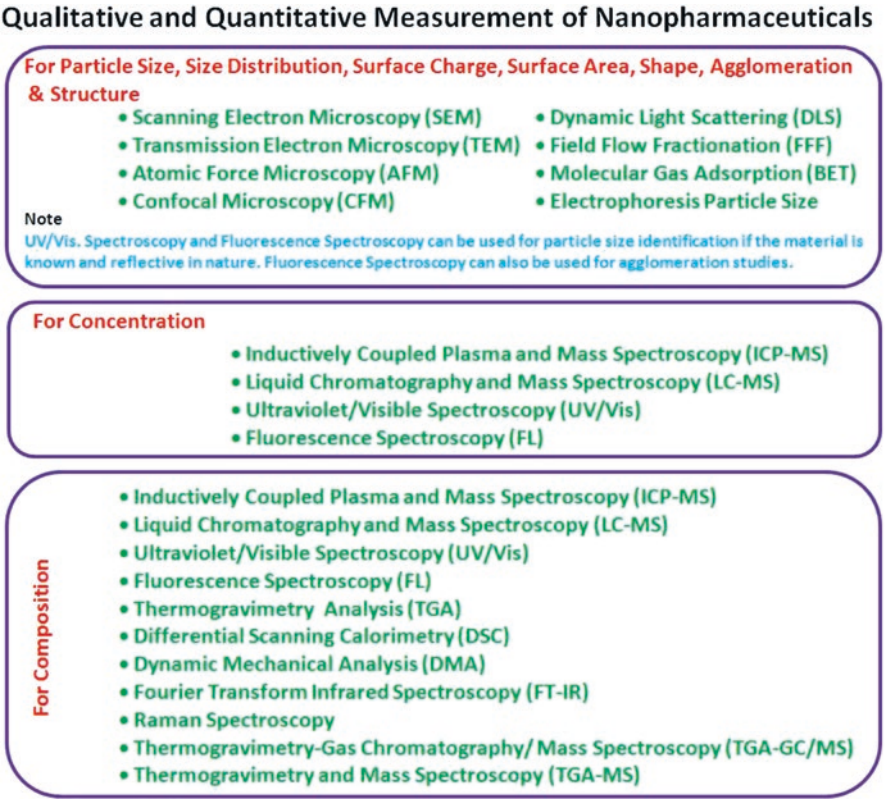

Fig. 1.5 Different techniques used for the qualitative and quantitative characterization of nanopharmaceuticals

In addition, there are various characterization techniques which are widely being used to study the qualitative and quantitative properties of versatile nanocarriers used in nanopharmaceuticals, both in discrete and conjugate forms. A detailed chart of those suitable and advanced techniques has also been represented in Fig. 1.5. Moreover, the quantification of nanocarriers used in nanopharmaceuticals has also become quite essential for the environmental risk assessment. This quantification gives information about the environmental availability of nanocarriers and also helps in the estimation of minimum concentration or limit that may induce any toxic or unfavorable effect. This information could be further used for the estimation of the environmental risk quotient (ERQ). To estimate the environmental risk quotient (ERQ), we need to have the information about the following two parameters:

- Environmental concentration of nanocarriers (X)
- Nanocarriers' minimal dose for negative outcomes (Y)

Environmental risk quotient (ERQ) could be easily calculated from Eq. 1.1.

$$\text{Environmental risk quotient}(\text{ERQ}) = \frac{\text{Environmental concentration of nanocarriers}\,(X)}{\text{Nanocarriers' minimal dose for negative outcomes}\,(Y)} \quad (1.1)$$

If the value of the environmental risk quotient (ERQ) is less than one, then it is non-hazardous for the environment. However, if the obtained value is greater than or equal to one, then it is considered to be hazardous for the open environment; and the extent of hazards could be assessed by its magnitude.

1.4 Absorption, Distribution, Metabolism, Excretion/ Elimination, and Toxicity-Based Studies of Nanopharmaceuticals

Nanocarriers used to have a prominent control over the nanodrugs' pharmacokinetics and pharmacodynamics. The pharmacokinetics and pharmacodynamics of nanodrugs are significantly different from the bare or pure drug molecules (Moss and Siccardi 2014; Griffin et al. 2016; Li et al. 2017). Thus, the better understanding and estimation of the physiological pharmacokinetic parameters of nanopharmaceuticals are very crucial for their development and pharmacodynamic cum biodistribution-based studies.

Therefore, a thorough study of nanocarrier-mediated absorption, distribution, metabolism, excretion/elimination, and toxicity (ADMET) routes, as represented in Fig. 1.6, is always recommended for nanomedicaments to ascertain their

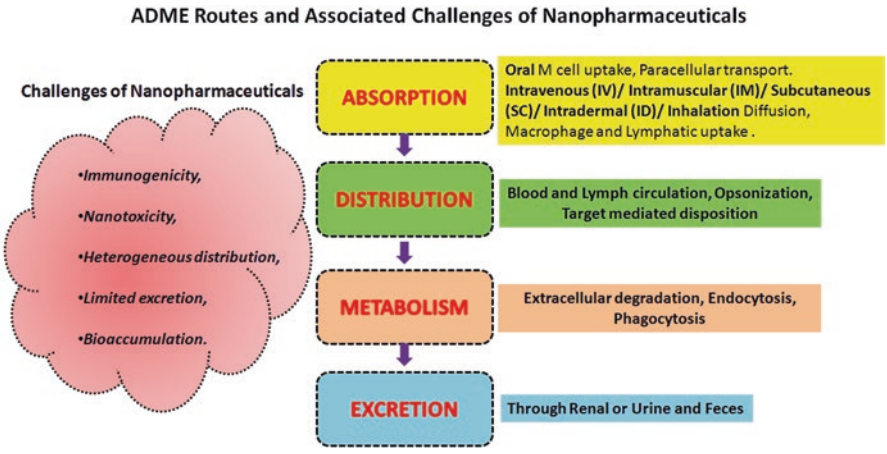

Fig. 1.6 Absorption, distribution, metabolism, excretion/elimination, and toxicity routes of nanomedicaments

effectiveness, biodistribution, and toxicity in a living organism. It will greatly improve the commercial applicability of nanopharmaceuticals, specifically in terms of their enhanced delivery, facilitated targeting, and reduced immunogenicity or nanotoxicity followed by low bioaccumulation.

In general, the environmental safety and toxicological data of nanocarriers used to be considered as a prime requirement for any associated risks or benefit assessment. In the available literature, there is a significant lack of thorough and systematically defined nanocarrier-based environmental and toxicological studies. Hence, the absorption, distribution, metabolism, excretion/elimination, and toxicity (ADMET) studies are highly desirable to ascertain the suitability or efficacy of nanopharmaceuticals. Moreover, it has been also observed that the impact of nanocarriers' toxicity from different administration routes is greatly influenced by some specific factors such as size, shape, composition, surface chemistry, and presence of the targeting ligands (Moss and Siccardi 2014; Griffin et al. 2016; Brohi et al. 2017; Li et al. 2017).

Almeida et al. (2011) summerized the in vivo biodistribution of various nanoparticles such as iron oxide nanoparticles, gold nanoparticles and quantum dots, and their associated immune response. Here, small nanoparticles with less than 50 nm size show enhanced distribution to the lymph nodes and also have long circulation time, whereas large nanoparticles are preferably captured by the liver and spleen and exhibit short circulation time. Since the metallic nanoparticles have tendency to be quickly removed from the bloodstreams by the reticuloendothelial system and they may remain in the liver and spleen for a longer duration, raised various biodistribution and toxicity related concerns. Although the renal excretion based removal of nanocarriers is also feasible and highly size dependent, the need of the additional coatings and surface modifications of the nanosubstances has reduced their renal excretion. Besides this, gold nanoparticles have shown both inflammatory and anti-inflammatory behavior in vitro studies. The in vivo studies have ascertained that the nanocarriers could induce the activation of macrophages and engagement of leukocytes that may result in immunogenic toxicity. However, there is a further scope of understanding of in vivo immunotoxicity.

Furthermore, due to the inherent variations in the biodistribution, biocompatibility, and biodegradability of nanocarriers, the toxicity of nanocarriers may also vary from micro- to macro-sized carriers made up of similar materials. Therefore, it is always recommended to improve the existing toxicological methods through the employment of novel and accurate bio-relevant tools. The follow-up of the recommendation may provide a more comprehensive information about the risk of nanopharmaceutical-based toxicity. However, the frequent changes in absorption, distribution, metabolism, and excretion/elimination profiles of nanomedicines are due to their complex nature and presence of various excipients and need new or revised regulatory frameworks to assess the quality, safety, and efficacy of complex nanodrug formulations.

Figure 1.7 illustrates various rate constants (k) influencing the absorption, distribution, metabolism, and excretion of nanomedicaments administered through oral intravenous (IV) or intramuscular (IM) or subcutaneous (SC) or intradermal (ID) or inhalation routes. Table 1.1 summarizes the salient features of versatile nanocarriers affecting the rate constants of ADMET stages and the intensity of the impact on pharmacokinetics rate constants in terms of less, moderate, and high order.

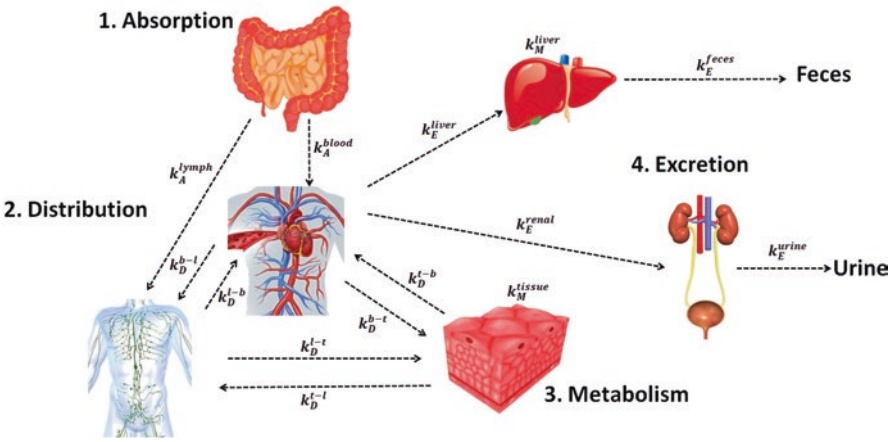

Fig. 1.7 Kinetic factors affecting or controlling the activity of nanomedicines inside the human body (Griffin et al. 2016)

Table 1.1 Impact of nanocarriers' characteristics on pharmacokinetics rate constants

	Salient features of nanocarriers used in pharmaceuticals			
Factors (rate constant)	Size and shape	Composition	Surface chemistry	Targeting ligands
Absorption (k_A)	***	***	***	*
Distribution (k_D)	***	***	***	***
Metabolism (k_M)	***	**	**	***
Excretion (k_E)	**	*	**	**
Toxicity (k_T)	*	***	***	***

*Less impact; **Moderate impact; ***High impact

The detailed summary of the specific nanopharmaceuticals with respect to their absorption, distribution, metabolism, excretion/elimination, and toxicity (ADMET)-based studies have not been discussed here to maintain the brevity of this review article. However, the interested ones are requested to go through the referred scientific literature (van de Waterbeemd and Gifford 2003; Li et al. 2010, 2013, 2017; Hamidi et al. 2013; Moss and Siccardi 2014; Griffin et al. 2016).

1.5 Environmental Contamination of Nanopharmaceuticals

Due to a rapid and sustainable development, production, and commercialization of nanopharmaceuticals or nanoparticle-based drug carriers in the current era (Buzea et al. 2007; Wagner et al. 2014), the ecosystem has become a major victim of nanocarrier-induced pollution or toxicity, especially the aquatic environment (Klaine et al. 2008; Navarro et al. 2008; Brar et al. 2010; Gottschalk et al. 2011; Miralles et al. 2012; Maurer-Jones et al. 2013; Wang et al. 2016; Brohi et al. 2017; Jahan et al. 2017). The nanopharmaceuticals are coming into the environment through

different exposure routes starting from the initial manufacturing and production of nanopharmaceuticals to their consumption and use followed by their excretion and repudiation. A flowchart of major contamination routes of nanopharmaceuticals is also presented in Fig. 1.8 that indicates soil, ground water, and surface water as the end sufferer of nanopharmaceutical-based contamination. The exposure of the nanocarriers which are substantially used in nanopharmaceuticals to the human body through contaminated soil, ground water, and surface water or through the direct administration as a medicament may induce related diseases depending on the regions of human body that get affected (see Table 1.2). Besides this, it should also be noted that the environmental contamination of nanoparticles is also proliferating due to the extended usage of various nanoparticles in the wastewater treatment-related applications such as photocatalysis, adsorption, and advanced oxidation processes (Ghasemzadeh et al. 2014; Ma et al. 2016; Verma and Samanta 2017, 2018a, b, c). Metal oxides such as TiO_2, ZnO, and carbon nanomaterials including graphene and graphene oxide-based nanostructures and quantum dots are the very established and overused candidates for the water and wastewater treatment-based applications (Ghasemzadeh et al. 2014; Lu et al. 2016; Verma and Samanta 2017, 2018b).

Parthasarathi (2011) and Dev et al. (2017) reviewed the effect of various nanosubstance-based toxicity in the plants and food crops which are also widely being used as the nanocarrier for the pharmaceutical compounds. They included latest studies based on phytotoxicity of different nanosubstances such as TiO_2, ZnO, CeO_2, NiO, CuO, Ag, Au, SiO_2, nano zerovalent iron, fullerenes, graphene, graphene oxide, carbon dots, and carbon nanotubes and elaborated individual nanoparticle-based toxic effects observed in plants. The studies show a clear negative impact on the plant growth, root and shoot lengths, biomass accumulation, and seed germination. In addition to this, the oxidative stress and cytotoxic and genotoxic effects of nanoparticles have also been observed in plants (Sardoiwala et al. 2017). Hence, nanopharmaceuticals-mediated phytotoxicity in plants could also be emerged as a major concern for the environment.

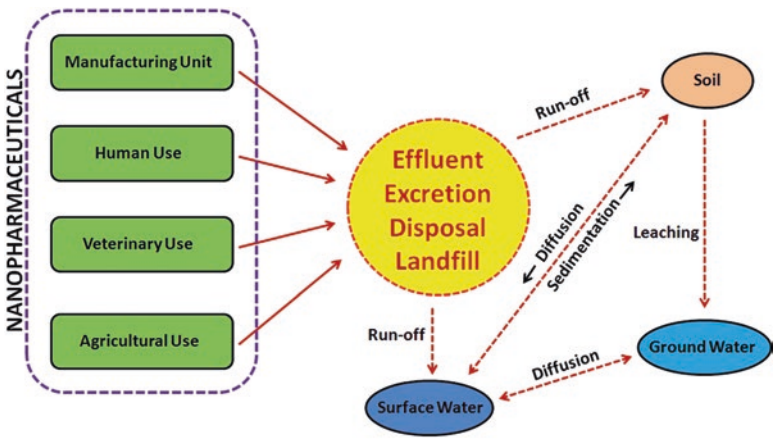

Fig. 1.8 Environmental contamination routes of nanopharmaceuticals

Table 1.2 Various human diseases related to the exposure of nanocarriers (Buzea et al. 2007; Manickam et al. 2017; Sardoiwala et al. 2017)

Route of administration	Primarily affected body part(s)	Associated diseases
Ingestion or oral administration	Gastrointestinal system	Crohn's disease
		Colon cancer
		Ulcer
Inhalation	Brain	Neurological diseases:
		Alzheimer
		Parkinson
	Lungs	Asthma
		Bronchitis
		Emphysema
		Tumor
		Cancer
Injection (IV/IM/SC)	Circulatory system	Atherosclerosis
		Vasoconstriction
		Thrombus
		High blood pressure
	Lymphatic system	Podoconiosis
		Kaposi's sarcoma
	Heart	Arrhythmia
		Heart failure
	Other organs	Unknown impairments of kidneys, liver, and spleen
Topical application	Skin	Allergy
		Autoimmune diseases
		Dermatitis
Orthopedic implant residues	Around implant region	Autoimmune diseases
		Dermatitis
		Urticaria
		Vasculitis
Cellular absorption	Cells and tissues	Bioaccumulation of nanocarriers in cell organelles such as mitochondrion, vacuoles, nucleolus, cell membrane, and cytosol
		Apoptosis
		Necrosis

Jahan et al. (2017) reviewed the silver, graphene oxide, zinc oxide, titanium dioxide nanoparticles, and single-walled or multi-walled carbon nanotube-induced toxicity in aquatic plant and microbial and vertebrate models. They have also enlightened the double-edged sword nature of versatile nanocarriers due to the nanoparticles toxic effects on aquatic ecosystem. They also summarized that both the physicochemical properties such as shape, size, and surface charge and environmental factors such as pH, temperature, type of irradiation, dissolved natural organic matter, ionic strength or presence of electrolytes, and other contaminants primarily control the transportation,

transformation, and toxicological behavior of respective nanoparticles. Since the nanoparticles also have the preeminent potential to cause oxidative response, cellular toxicity, and inflammatory responses, they have become an impetuous source of damage to the aquatic ecosystem. Therefore, it is always essential to know about the physicochemical properties of nanopharmaceuticals followed by their effective concentration prediction in the open environment to calculate the environmental risk quotient (ERQ), nanocarrier transportation, and transformational nature. Subsequently, the evaluation of benefits and risks associated with the use of nanopharmaceuticals has been always crucial and required to be discussed in a specific manner. Hence, more detailed case-by-case toxicity analyses of versatile nanopharmaceuticals are recommended to obtain a more trustworthy predictive model that could estimate and quantify the possible short-term and long-term outcomes of nanopharmaceuticals in the open environment.

Furthermore, with the similar opinion of Jahan et al. (2017), it is recommended that the toxicity, fate, and behavior of engineered nanomaterials or nanopharmaceuticals from a large-scale synthesis to industrial application and disposal should be the prime focus of concern and necessary steps should be taken in the direction of the following: (1) nanocarriers' synthesis and modification parameters; (2) determination of nanocarriers' source, point of entry, and end point; and (3) safety regulations, which are highly essential in case of nanopharmaceuticals. Hence, ecotoxicological tests for nanopharmaceuticals are always required and recommended with the suitable or desired adaptations depending on nanopharmaceutical usage and applications. The potential risks of nanocarriers used in nanopharmaceuticals have been tabulated in Table 1.3, where oxidative stress, cytotoxicity, phytotoxicity, genotoxicity, and immunogenicity are the ultimate toxic response emerging from the biological interaction of these nanosubstances.

Table 1.3 Various associated potential risks of nanocarriers used in nanopharmaceuticals (Ray et al. 2009; Sardoiwala et al. 2017)

S. no.	Nanocarriers	Potential risks
1.	Carbon nanomaterials and silica nanoparticles	May induce pulmonary inflammation, granulomas, and fibrosis
2.	Silver and gold nanoparticles	Widespread biodistribution to different organs and possible passage through the blood–brain barrier
3.	Iron oxide nanoparticles	Significant distribution in reticuloendothelial system based organs
4.	Quantum dots, carbon dots, and titanium dioxide nanoparticles	Skin penetration followed by immunogenic responses
5.	Manganese dioxide, titanium dioxide, and carbon nanoparticles	May enter in the brain through the nasal olfactory epithelium
6.	Titanium dioxide, aluminum oxide, carbon black, cobalt, and nickel nanoparticles	Usually more toxic than micron-sized particles

Note: Oxidative stress, cytotoxicity, phytotoxicity, genotoxicity, and immunogenicity are the ultimate toxic effects associated with these nanosubstances

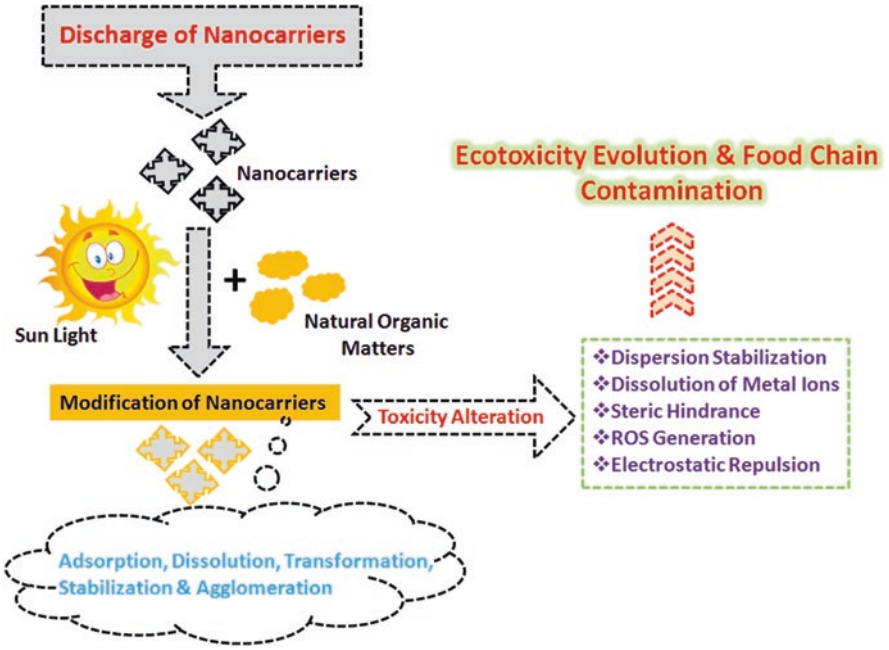

Fig. 1.9 Mechanism of alteration or evolution in the ecotoxicity of nanocarriers discarded or exposed to the natural aquatic system containing natural organic matters, under the influence of solar irradiation (*ROS* reactive oxygen species)

A summarized mechanism of alteration or evolution in the ecotoxicity of nanocarriers which are potentially being used in nanopharmaceuticals is shown in Fig. 1.9. Here, the discarded or runoff nano-contaminants are exposed to the natural aquatic system containing various types of natural organic materials such as humic acid and sulfides in the presence of solar irradiation. These conditions cause an unpredicted change or transformation in the bare nanocarriers that may result in either a positive or negative way depending on the characteristics of transforming or modified nanocarriers (Wang et al. 2016; Jahan et al. 2017). In addition, these nanocarriers may also enter into the food chain due to their bioaccumulating behavior and may cause various diseases in the consuming human as mentioned in Table 1.2. Therefore, it is very essential to study and obtain the data of aquatic life exposure test of versatile nanopharmaceuticals. It should also include the tests with and without drug molecules using nanocarrier–drug conjugates and bare nanocarriers, respectively. Here, activated sludge microbes, algae, daphnia, fishes, earthworms, and various sediment organisms should be considered as the test microorganism for the evaluation of respective nanopharmaceutical-mediated toxicity in aquatic life. In addition, aquatic plants should also be considered for the estimation of bioaccumulation of nanopharmaceuticals or associated nanocarriers using suitable qualitative and quantitative measurement techniques as presented in Fig. 1.5.

There are various categories of tests which are widely being used for the assessment of nanopharmaceuticals. The examples of such major categories have been presented in Table 1.4 with respect to their specific objectives and limitations that

Table 1.4 The categories of tests with their objectives and limitations that are commonly used for the toxicity evaluation of nanomaterials

S. no.	Test	Objectives	Limitations	References
1.	Cytotoxicity	Study of nanosubstance-induced cytotoxicity including cellular metabolic activity, oxidative stress, apoptosis or necrosis, cell membrane damage, and impedance-based analysis	These tests are very time-consuming, labor-intensive, complex in nature Most often, they are unreliable and non-reproducible owing to the nanomaterial and environmental interferences	Parthasarathi (2011), Sardoiwala et al. (2017) and Accomasso et al. (2018)
2.	Phytotoxicity	Study of change or inhibition in the seed germination, root, and shoot growth. Change in biomass of whole plant or specific parts	These tests are highly time-consuming Used to be very inconsistent in nature. Generally not recommended for comparisons with separately reported or conducted studies	Lin and Xing (2007), Parthasarathi (2011) and Dev et al. (2017)
3.	Genotoxicity	Rapid measurement of DNA and/or chromosomal damage Detection of unregulated DNA damage signaling pathways	Various other factors may substantially influence the assay results such as variation in the same material properties and environmental conditions	Parthasarathi (2011), Manickam et al. (2017), Sardoiwala et al. (2017) and Accomasso et al. (2018)
4.	Band gap analysis	Prediction of toxicity level via conduction band energy level of metal oxide or semiconductor-based nanocarriers Study of in vitro toxic effects related to energy of conduction band and metal dissolution	Suitable for metal/metal oxide or semiconductor-based nanocarriers	Accomasso et al. (2018)
5.	Quantitative structure activity relationships (QSAR)	Prediction of nanocarriers or nanopharmaceuticals exposure-dose-response that includes data assembling, structure characterization, model construction, model evaluation, interpretation, and review of mechanisms	Availability of small number of data sets	Accomasso et al. (2018)

are commonly used for the toxicity evaluation of engineered nanomaterials. In contrast, Berkner et al. (2016) enlisted various protocols concerning about the physicochemical properties, fate, and ecotoxicity behavior of nanopharmaceuticals that could be further used for the environmental risk assessment (see Table 1.5). In this regard, Maurer-Jones et al. (2013) enlisted various bacterial monoculture models which are reportedly used for the toxicity assessment of various nanoparticles. In addition, Wang et al. (2016) exclusively reviewed about the alteration of various metallic nanocarriers' toxicity in the presence of natural organic matters with the possible mechanisms. Reviewed studies include bacteria, algae, plant, vertebrates, and invertebrates as the test organism. Overall, the assessment of the fate of an active pharmaceutical ingredient in the open ecosystem as conducted for small drug molecules and bare nanoparticles is mostly found to be missing or not suitable for nanopharmaceuticals. Therefore, for nanopharmaceuticals and nano-bio drug conjugates, the biodegradability test is also recommended for more informative and

Table 1.5 Type of studies related to the physical and chemical properties, fate, and ecotoxicological effects of nanopharmaceuticals which are primarily recommended for the environmental risk assessment (European Medicines Agency 2006; Berkner et al. 2016)

S. no.	Study type	Recommended protocols
1.	Water solubility	OECD 105
2.	Dissociation constants in water	OECD 112
3.	Vapor pressure	OECD 104
4.	*n*-Octanol–water partition coefficient	OECD 107/123
5.	Adsorption–desorption using a batch equilibrium method: a study using two types of sludge and three types of soil is preferred	OECD 106
6.	Ready biodegradability	OECD 301
7.	Aerobic and anaerobic transformation in aquatic sediment systems	OECD 308
8.	Freshwater alga and cyanobacteria, growth inhibition test	OECD 201
9.	*Daphnia magna* reproduction test	OECD 211
10.	Fish, early life stage toxicity test	OECD 210
11.	Fish full life cycle test	ENV/JM/MONO(2008)22[a]
12.	Activated sludge, respiration inhibition test	OECD 209
13.	Bioaccumulation in fish: aqueous and dietary exposure	OECD 305
14.	Sediment–water Chironomid toxicity test using spiked sediment	OECD 219
15.	Sediment–water *Lumbriculus* toxicity test using spiked sediment	OECD 225
16.	Aerobic and anaerobic transformation in soil	OECD 307
17.	Soil microorganisms: nitrogen transformation test	OECD 216
18.	Terrestrial plants, growth test	OECD 208
19.	Earthworm, acute toxicity tests	OECD 207
20.	*Collembola*, reproduction test	OECD 232

OECD Organisation for Economic Co-operation and Development
[a]OECD Series on testing and assessment: Number 95

factual details. Moreover, a few ideal study protocols should also require to be developed to characterize the transformation and alteration in the nanopharmaceuticals inside the human and/or animal body or in other suitable media during the metabolism.

1.6 Future Research Directions

In the last few decades, nanotechnology has evolved in different directions, such as catalysis, electronics, sensing, biomedical applications, and many others. However, various human-, animal-, and plant-related concerns have hindered the comprehensive utilization of this promising technology due to the associated environmental and toxicological implications. Interestingly, humans are routinely exposed to airborne nanosized dust particles from a very early age; however the exposure to such particles has dramatically increased in the last few years due to various human activities in the field of nanotechnology and related applications (Doong et al. 2013; Brohi et al. 2017). Therefore, the large-scale application of nanomaterials in industries, food products, and medicines has alarmed major concerns about the humans as well as animals and plants (Navarro et al. 2008; Houdy et al. 2011; Miralles et al. 2012; Dev et al. 2017; Kaphle et al. 2017; Manickam et al. 2017; Sardoiwala et al. 2017). It is mainly due to the significant number of reported and validated studies claiming the potential toxic hazards of various nanomaterials. The reported hazards are primarily associated with nanocarriers' composition, concentration, administration routes, modification, and the exposed species. Therefore, a proper understanding of the impacts of nanocarriers on human, animal, or plant growth and reproductive system is very essential, so that the minimization of adverse effects of various nanocarriers could also be planned and implemented on the vulnerable population of humans, animals, and plants.

For the same objective, some novel study protocols are needed to be developed and standardized to study the contamination level, bioaccumulation limit, environmental risk quotient (ERQ) measurement, chemical and physical transformation in nanocarriers, and resulting alteration in the toxicity of associated nanopharmaceuticals. Inevitably, the more comprehensive absorption, distribution, metabolism, excretion/elimination, and toxicity (ADMET) studies in addition to the routine pharmacokinetics and pharmacodynamics are recommended for the newly developed nanocarriers which are being planned to be utilized in the nanopharmaceuticals for effective transportation and targeting of medicaments. Moreover, the inherent modification in the nanocarriers such as surface modification, coating, and co-doping of other nontoxic or toxicity retardants are also recommended for safer application of nanopharmaceuticals.

Furthermore, the researchers need to consider and scrutinize at least few prominent concerns before going for any conclusive solid remarks related to the usage and development of nanopharmaceuticals. The concerns were mainly proposed by Boxall et al. (2012) for pharmaceuticals and personal care products (PPCPs) presence in the open environment; and the most important concerns were selected

through the experts voting at an international expert workshop. However, the similar and most important concerns with more than 30% votes are rephrased here with respect to the nanopharmaceuticals. These prominent concerns are as follows: (1) importance of nanopharmaceuticals relative to other chemicals and non-chemical stressors in terms of biological impacts in the natural environment; (2) approaches to prioritize nanopharmaceuticals for research on the environmental and human health exposure-based effects; (3) environmental exposure to the nanopharmaceutical residues that results in the selection of antimicrobial-resistant microorganisms and affects human health outcomes; (4) observation of ecotoxicological responses such as histological and molecular-level responses for nanopharmaceuticals, and their translation into traditional cum ecologically important end points such as survival, growth, and reproduction of a species; (5) usage of pharmaceuticals preclinical and clinical information to assess the potential of adverse environmental impacts of nanopharmaceuticals; (6) evolutionary conservation of nanopharmaceutical targets across species and life stages in the context of potential adverse outcomes and effects; and (7) effects from long-term exposure to low concentrations of nanopharmaceuticals mixtures on the nontargeted organisms.

On the similar note, Ågerstrand et al. (2015) recommended ten directions for improving the European Medicines Agency's guideline on environmental risk assessment of human pharmaceutical products. The recommendations were based on the up-to-date available scientific information in combination to the experiences from other chemical endorsement entities. Those recommendations are as follows: "(**1**) *Expanding the scope of the current guideline*; (**2**) *Requirements to assess the risk for development of antibiotic resistance*; (**3**) *Jointly performed assessments*; (**4**) *Refinement of the test proposal*; (**5**) *Mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action*; (**6**) *Use of all available ecotoxicity studies*; (**7**) *Mandatory reviews*; (**8**) *Increased transparency*; (**9**) *Inclusion of emission data from production*; and (**10**) *A risk management option*". The implementation of the aforementioned recommendations with respect to nanopharmaceuticals is equally rational and crucial for the protection of the environment, human, and other living organisms.

1.7 Conclusions

Overall, nanopharmaceuticals have a tremendous potential to have a significant impact on the human beings and other living organisms. However, the proper risk evaluation either related to the environment or related to the health of the living organism is still a major challenge in the development of nanopharmaceuticals. The concerns related to the nanopharmaceuticals and their associated nanocarriers are quite indispensable for the ethical and legal acceptance of nanomedicaments. Here, the presented study is a sincere attempt to emphasize the environmental and toxicological implications of nanocarriers used in various nanopharmaceuticals. The discussion includes the key issues related to the nanopharmaceutical types, exposure,

effects, quantification, absorption, distribution, metabolism, excretion/elimination, and toxicity (ADMET) behavior and potential hazards of nanopharmaceuticals.

The inferences made in this review article suggested that the understanding of the in vivo biodistribution of nanocarriers is significant but still inadequate for the critical evaluation of the efficacy and safety related to the nanopharmaceuticals. Hence, for the development of nanopharmaceuticals with improved efficacy and safety, various nanocarriers' assessment techniques and toxicity measurement protocols have been pointed out for the long-term safety and sustainability of nanopharmaceuticals. Moreover, there are various experts' recommendations and concerns too that have been positively put forward for the further development of nanopharmaceuticals. More precisely, the factors and processes affecting nanopharmaceuticals and their associated nanocarriers' biodistribution, such as physicochemical properties of nanosubstances, interaction with membranes and proteins, extravasation or transportation to the tissues and specific cells via lymph and blood vessels, uptake by the reticuloendothelial system, and clearance through the liver and kidneys, need to be scrutinized very carefully. Hence, more advanced and systematic in vitro and in vivo approaches are needed to be developed and recommended for the better correlation of nanopharmaceuticals properties with their biological effects.

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