Overview of nano-drugs characteristics for clinical application: The journey from the entry to the exit point

ARTICLE *in* JOURNAL OF NANOPARTICLE RESEARCH · JUNE 2014

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REVIEW

Overview of nano-drugs characteristics for clinical application: the journey from the entry to the exit point

Tanima Bose · Diane Latawiec · Partha Pratim Mondal · Subhra Mandal

Received: 28 March 2014 / Accepted: 17 June 2014

Abstract The ever-increasing number of diseases worldwide requires comprehensive, efficient, and cost-effective modes of treatments. Among various strategies, nanomaterials fulfill most of these criteria. The unique physicochemical properties of nanoparticles have made them a premier choice as a drug or a drug delivery system for the purpose of treatment, and as bio-detectors for disease prognosis. However, the main challenge is the proper consideration of the physical properties of these nanomaterials, while developing them as potential tools for therapeutics and/or diagnostics. In this review, we focus mainly on the characteristics of nanoparticles to develop an effective and sensitive system for clinical purposes. This review will present an overview of the important properties of nanoparticles, through their journey from its route of administration until disposal from the human body after accomplishing targeted functionality. We have chosen cancer as our model disease to explain the potentiality of nano-systems for therapeutics and diagnostics in relation to several organs (intestine, lung, brain, etc.). Furthermore, we have discussed their biodegradability and accumulation probability which can cause unfavorable side effects in healthy human subjects.

Keywords Route of administration · Nano-drug · Drug delivery · Imaging · Health effects

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Introduction

Drug development is currently rapidly moving toward using nanomaterial-based systems. The diversity of nanomaterials is increasing every day and their unique properties are increasingly empowering them to become possible cures for these diseases. Today, the versatility of nanocarrier technology allows tailoring of the nanoparticle-based drug delivery systems with consideration of the target, desired pharmacokinetic profile, and the route of administration. For diagnostic applications, nanoparticles allow the detection at the molecular scale and earlier in the progression of the disease, e.g., the detection of pre-cancerous cells in

Published online: 04 July 2014

contrast to the conventional diagnostics methods (which mostly detects cancerous cells at post-cancerous stage). Furthermore, nanoparticle-based imaging contrast agents improve the sensitivity of magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT).

Nanoparticles are unique in their properties due to their small size (1–100 nm), high aspect ratio, reactivity, and freedom to change their surface properties along with their electrical and biochemical properties. [In the pharmaceutical field, however, nanoparticles are considered as being particles ranging between 10 and 1,000 nm (De Jong and Borm 2008)]. This unparalleled freedom gives the opportunity to modify the pharmacokinetic paradigms of a drug such as solubility, diffusivity, blood circulation half-time, immunogenicity, and drug release. Currently, morphological variability of the nanoparticle is also heralding a prime importance for its use in specific applications (Muro et al. 2008). By exploiting these unique properties, scientists are developing nano-drugs that have an enhanced efficiency over the conventional system in terms of drug delivery, diagnostic, and as imaging agents.

In the last few decades, more than 150 companies have been involved in developing nanoscale therapeutics with the success of 24 nanotechnology-based therapeutic products already in clinical use (Wagner et al. 2006). Among several types of nanoparticles, liposomal nano-drugs and polymer-drug conjugates are the two most dominant types, accounting for $\sim$80 % of the total share (Zhang et al. 2008). In this review, we have explored the different pathways and barriers which the nanoparticles have to cross, while transporting the drugs to their target organs. Finally, we propose the perspective design of nano-system models with optimal physicochemical properties according to their target organ characteristics and proper disposal.

Entry point

Route of administration

The primary aim when designing a nano-drug or a nano-drug delivery system is to enhance drug accumulation at the targeted disease site. In order to obtain maximum therapeutic efficiency, efficient crossing of all barriers must be achieved. For decades, drug administration into the human body has been accomplished by administrating drugs into the human body via various routes: oral, parenteral, topical, inhalation, etc. Of all the routes, oral route is the most conventional route for drug delivery. Although it is the safest method, it suffers from various drawbacks, such as poor bioavailability, fast metabolism, and variable absorption of the drugs, mainly due to the variability of pH conditions and digestion of peptide drugs by proteolytic enzymes present in the intestine. Hence, other important major routes of administration (parenteral, pulmonary, topical, and ocular as illustrated in Fig. 1b) are gaining administrative importance depending upon the targeted tissue locations. Therefore, the primary challenge while designing a nano-system is the need to understand which route of nano-drug administration will result in their maximal accumulation at the target site. In this part of the review, we will discuss different routes of nano-drug administration depending on the location of a tumor in different target tissues.

Topical and oral routes/surface barrier

Drug-encapsulated nanomaterials are used proficiently to deliver the drugs via traditional oral and topical routes (Fig. 1). For example, oral administration of drug, such as 5-fluorouracil (5-FU) loaded within poly-DL-lactide-*co*-glycolide (PLGA) nanoparticles for colon cancer (Nair et al. 2011) or the skin cancer drug doxorubicin with PG (propylene glycol) formulations for topical delivery (Herai et al. 2007) has been successfully developed for therapeutic purpose.

Subcutaneous route

The major barriers or obstacles (surface barriers) the nanoparticles encounter upon subcutaneous route (Fig. 1a) are the keratinous subcutaneous layer of skin and extremes of the chemically harsh environment in the intestinal inner lining layers (digestive enzymes and different acidity levels in stomach, duodenum, and small intestine). In general, there are three layers of topical/skin penetration: the epidermis (consisting of stratum corneum (SC), lucidum, granulosum, spinosum, and basale from outermost to

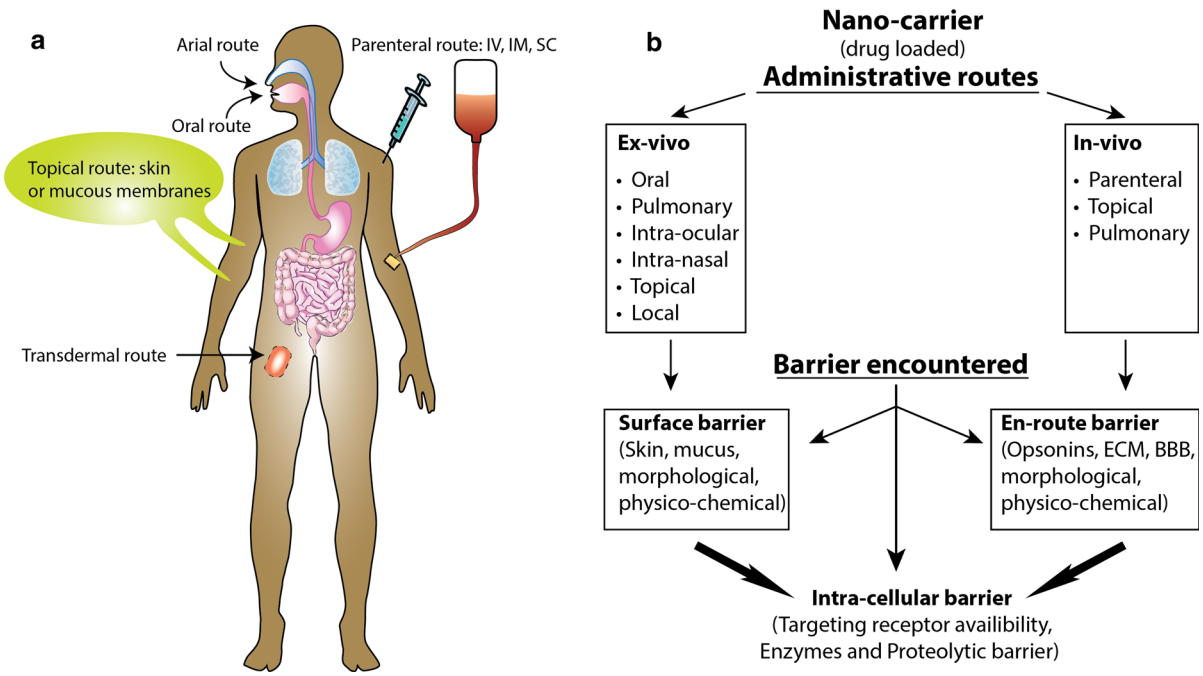

Fig. 1 Routes of nano-drug administration (**a**) and various barriers encountered (**b**) by nanoparticles before they reach their respective targeted tumor site

innermost), the dermis (a system of capillaries, nerves and epidermal appendages of hair follicles, sebaceous and sweat glands), and the hypodermis (comprising a layer of fat) (Prausnitz and Langer 2008). Drugs mainly penetrate through transcytosis and adsorption mechanisms upon surface administration (Shaikh et al. 2011). The SC layer of the epidermis is considered to be the major challenge for nanoparticles as it consists of a hydrophobic structure of several layers (10–20 μm) with non-living corneocytes (or bundles of keratin) surrounded by lipid bilayers. The macrofibrillar bundles of keratin give the SC solid rigidity, which is difficult for drugs or particles to cross. Additionally, chemical penetration enhancers (e.g., Monoolein) are in use to promote drug diffusion and solubility within this skin layer (Simonetti et al. 2009). For this reason, disruption of the lipid bilayers in the SC region is mainly employed to enhance permeation of the conventional drug through the skin (Elsabahy and Wooley 2012). However, for lipophobic or hydrophilic drugs, hydrophobic encapsulation is preferred. For example, Niosomes (a non-ionic surfactant-based liposome) are used to deliver hydrophilic drugs in its aqueous core and lipophilic drugs in the bilayer as they are made up of surfactants (Paolino et al. 2007, 2008). Polymeric nanoparticles of ~200–300 nm are favored for possible drug accumulation in the junction of corneocyte clusters for several hours (Lv et al. 2009). Below the SC layer, the viable epidermis (50–100 μm) and the dermis (1–2 mm) act as an immunological barrier for foreign materials, as these layers are immunologically active regions due to the presence of Langerhans and dendritic cells, respectively. However, polyethylene glycol (PEG) coating of nanocarrier gives them the escape power to avoid macrophage elimination as well as enhances their hydrophobicity, thus promoting the SC layer penetration (Uner and Yener 2007). Once drugs get into the dermis layer of skin, they can be directed to the systemic circulation by the blood vessels of the dermis (Elsabahy and Wooley 2012) where they encounter the next level of obstacle i.e., the blood components.

Oral route

For orally administered drugs (Fig. 1a), the major obstacle is the mucus layer present in the intestine. Mucus is a viscoelastic hydrogel secreted by mucus glands in the areas of gastrointestinal (GI) tract, eyes, lung airways, and nasal cavities. Mucus gel comprises

a network of cross-linked mucin fibers. These fibers are negatively charged (due to the presence of sialic acids and sulfated monosaccharides in the sugar chains) with alternating glycosylated hydrophilic and hydrophobic regions (Lai et al. 2009). Furthermore, components (cells, bacteria, lipid, salt, protein, macromolecules, and cellular debris) present in the mucus gel work in sync to hinder nanoparticle transportation. Additionally, enzymatic components of mucus gel can result in charge neutralization or displacement of cargo. Therefore, in designing orally administered nanoparticles, the morphological and physicochemical barriers of the GI tract have to be considered. The main obstacles in this barrier are namely the proteolytic enzymes present in the gut (pepsin, trypsin, and chymotrypsin) or the brush border membrane (endopeptidase), bacterial gut flora, and the epithelia layer itself (Elsabahy and Wooley 2012). To overcome these barriers (Fig. 1b), orally administered drugs have to be loaded in a colloidal carrier system which can promote and prolong the interaction between the drug delivery system and epithelial layer present in the GI tract (Uner and Yener 2007). For instance, the chitosan colloidal nanoparticles have been exploited to deliver drugs to the GI tract because of their unique solubility and muco-adhesiveness properties at acidic pH (Puvanakrishnan et al. 2009). Chitosan has unique solubility properties i.e., it is insoluble at neutral pH whereas it becomes positively charged and soluble at acidic pH, which promotes the muco-adhesiveness and dissolution of chitosan colloidal nanoparticles only at acidic portion of the GI track. One such example of a chitosan-based nanoparticle formulation (under Phase-II clinical trial) is CPX-1 (Harasym et al. 2007). It has shown simultaneous delivery of two drugs i.e., irinotecan and floxuridine, at colorectal cancer explants (Hu et al. 2010). In the context of pH-resistance, a new advancement in nanoparticle formulation is the design of nanoparticles that can resist the differing acidic pH condition of the compartments in stomach (pH 1.2), duodenum (pH 4.5) and small intestine (pH 6.8) (Ding and Ma 2013). For example, PLGA nanoparticles carrying the chemotherapeutic drug 5-FU, when coated with Eudragit S100 polymer (i.e., insoluble in aqueous solution of $\leq$pH 7.0), help them to resist the extremely acidic environment of stomach (Wang et al. 2013). In vivo experiments of these nanoparticles show no release of 5-FU at pH 1.2–4.5, limited release at pH 6.8, whereas an initial burst release followed by extended slow release for up to 120 h in the neutral pH range (7.4).

Parenteral route

Due to the complications of drug delivery via the oral administration route and the need to access other targets, the parenteral route has been explored (Fig. 1). This mode helps to deliver the drugs directly to the systemic circulation thus escaping the intestinal or SC route. The parenteral route can broadly be divided into three categories: intravenous (vein lumen), intramuscular (large muscle like deltoid, triceps), and subcutaneous (subcutaneous tissue under the skin). This mode is more efficient than topical delivery due to increased availability and absorption efficiency, thus bypassing the intestinal metabolism and milder toxic effects of the drug. There have been many advances to deliver the drug along with the nanoparticles [e.g., Nanospheres, Liposomes, Niosomes, solid lipid nanoparticles (SLNs), etc.] via parenteral routes. The first type of nano-system used was nanospheres (i.e., nanoparticles consisting of lipophilic fat core surrounded by a layer of phospholipids) (Zhuang et al. 2014). However, due to the non-amphiphilic nature, non-potent removal from the body, and toxicity threats, these particles now lag behind other nanoparticles in their effectiveness as an efficient nano-system. Conversely, liposomes (i.e., an aqueous volume enclosed by lipid membranes) possess characteristics which aid in making drug delivery to the target site, in a safe and faster way. The only known problem in this method of drug delivery is the stability, as they are prone to physical and chemical degradation. To solve the problem of stability, nanoscientists have designed niosomes which have vesicles made up of non-ionic surfactant (e.g., Tweens) (Bayindir and Yuksel 2010). The surfactant property enables them to efficiently cross the layers of the organs (e.g., liver and brain) and to bypass local macrophages, thus enhancing their tumor targeting efficiency (Kwatra et al. 2012). Another advanced nanoparticle type developed for the intravenous route is the SLNs. This drug delivery system has proven to easily deliver drugs which are not totally water-soluble. Their advantages include mild aggregation, less drug leakage problem, and a low cost of preparation (Li et al. 2011a).

As the parenteral route is faster in delivering the drug to its target site, this is the preferred route of

administration compared to the oral delivery. One such example is the delivery of the anti-cancer drug Curcumin which shows promising results in terms of chemoprevention and bio-toxicity; however, their bioavailability is restricted (Bisht et al. 2010). Nonetheless, successful incorporation of the anti-cancer Curcumin drug with polymeric nanoparticles, a nano-drug formulation named NanoCurc (Bisht et al. 2010), illustrates a success story of nano-drug formulation, showing that the subcutaneous route of administering into patients increased systemic bioavailability of drugs and enhanced their chances to get access to their site of action.

En route/circulation barrier

The injection of nanoparticles directly into the systemic circulation bypasses the problem of the skin and mucus barrier. Furthermore, the administration into the systemic circulation aids in gaining access to certain types of cancers; e.g., leukemia and breast cancer. For example, Dexamethasone-loaded polymeric nanoparticles for treating childhood leukemia (Krishnan et al. 2013) or tamoxifen-loaded SLNs (Mudshinge et al. 2011) have been effectively introduced to the disease tissue sites via parenteral administration.

The challenge of systemic injection of nanoparticles is their affinity to interact with the plasma proteins and other blood components. This regulates the chance of nanoparticles to reach their target tissues. Opsonisation, the prime detective unit of the innate immune system is considered to be their main limiting factor. The opsonins (e.g., complement proteins, albumin, fibrinogen, etc.) mainly act by adsorbing onto on the surface of nanoparticles, rendering them visible to the phagocytic unit, and the mononuclear phagocyte system (MPS) (consisting of blood monocytes and macrophages) of the immune system. The system mainly acts as a scavenger to kill any foreign invader into the human body. The immunological reactions created by the MPS system along with other plasma proteins (e.g., albumin; β-globulin, etc.) present in the blood can destabilize and lead to the premature release of the encapsulated drug from the nanoparticles (Savic et al. 2006). For instance, a series of plasma proteins tested for polymeric micelles have been recognized as contributing to the micelle disorganization, inducing toxicity, and influencing the pharmacokinetic parameters of a nanocarrier (Chen et al. 2008). Moreover, components present in the extracellular matrix (ECM) (e.g., hyaluronidase enzyme) can also cause the degradation of the nano-cargo resulting in drug release at an unspecific target area (Elsabahy and Wooley 2012).

It is also important to mention, drug-encapsulated nanoparticle formulation strategy requires a special consideration to bypass major en route barrier of opsonin binding and escape from immune surveillance. PEG, a coiled polymer of repeating ethylene ether units with dynamic conformations can reduce the opsonin uptake and thus increase the circulation time. PEG polymer on a nanoparticle surface increases $t_{1/2}$ by reducing the opsonisation process, thus preventing recognition by monocytes and macrophages and allowing the particles to remain in the blood pool (Owens and Peppas 2006). Due to these important properties of PEG, about 40 types of nanoparticles have been FDA-approved (Jokerst et al. 2011). In brief, hydrophobic particles are far more vulnerable to immune detection, but hydrophilic PEG reduces these complications. Nevertheless, PEG formulation is dependent on the type and size of nanoparticles. For instance, larger nanoparticles in the 50–100 nm range are frequently coated with smaller lengths of PEG (Mw: 3,400–10,000 Da) (Jokerst et al. 2011), whereas smaller therapeutic particles use larger PEG (Mw: 20,000–50,000 Da) (Wortmann et al. 2008) to prevent excretion by the kidney and to maintain a high blood pool circulation for longer periods of time. PEG formulation, i.e., PEG layer thickness depends on the PEG molecular weight and surface density. Depending upon their surface density, PEG blocks could be composed of either brush-like or mushroom conformations. The first type of conformation reduces phagocytosis and complement activation, while the latter type acts as a potent innate immune system activator (Olivier 2005). Importantly, nanoparticle shape and size also determines macrophage uptake and clearance. Larger particles (>100 nm–1 μm in size) are easily detected by the MPS system. Moreover, the shape of the nanoparticles shows significant influence on the MPS uptake process. For example, the frequency of spherical particles accumulation is much less, whereas discoidal particles are shown to be compiled in most of these organs. On the contrary, cylindrical particles escape the detection and accumulate in the liver (Decuzzi et al. 2010; Champion and Mitragotri 2006).

Arial route/cellular barrier

Arial route Administration of a drug via the pulmonary route (i.e., aerosol inhalation and intra-tracheal instillation) is actively being investigated in respiratory illnesses (such as lung cancer, asthma, chronic obstructive pulmonary disorder etc.). Moreover, the pulmonary route (i.e., aerosol inhalation and intra-tracheal instillation) (Fig. 1a) is considered to be the most convenient mode of drug application for the respiratory illnesses. This is mainly due to the fact that this route leads to drug delivery directly into the lung alveoli, which have a comparatively less harsh environment that could interfere with nanoparticle stability and have a milder toxic effect. Lungs also offer the advantages of large surface area, relatively thin absorption barrier, low enzymatic activity, and slow mucociliary clearance compared to other organs (Kwatra et al. 2012). For example, the pulmonary route of methotrexate drug administration is widely in use for non-small lung cancers (Wilson et al. 2014). However, the limiting factor in pulmonary disorder is to maintain high and prolonged concentrations of drugs in the lungs via the pulmonary route of drug delivery. Over the recent decade, the use of the nanocarrier as a drug delivery system for lung cancer has gained major importance; e.g., application of doxorubicin (Dox) nanoparticles along with dry powder aerosol (act as carrier particles) (Azarmi et al. 2006) or the use of biotinylated-EGF-modified gelatin nanoparticle carrier to enhance cisplatin accumulation in cancerous drugs via inhalation (Tseng et al. 2009). However, the size of the nanoparticle does influence their absorption efficiency in lung alveoli. A particle size of ~50–200 nm is desired for maximized drug localization upon administration by inhalation (Shegokar et al. 2011; Kurmi et al. 2010). For example, SLNs (solves drug solubility issue) entrapment of anti-tubercular drugs (rifampicin, isoniazid, and pyrazinamide) has been shown successfully to reduce the number of bacilli inside the pulmonary cavity in contrast to a free drug delivery system (Pandey and Khuller 2005). This kind of formulation of liposomes or SLNs can be proposed as a mode of drug carrier in lung cancer.

Cellular barrier In addition to the mucociliary (surface) and the macrophagic (en route) barrier, there are cellular barriers in the lungs (Fig. 1b) which also challenge the internalization of particles (especially the hydrophilic ones) inside the cellular membrane via endocytosis. Currently, lung alveolar uptake of nanoparticles is mostly mediated by five mechanisms: phagocytosis, macropinocytosis, clathrin-mediated, caveolin-mediated, and clathrin/caveolin-mediated endocytosis (Sahay et al. 2010). However, entrapment of drug into the vesicles (e.g., endosomes) often results in their degradation due to acidic pH and enzymes found in the late endosomes (lysosomes). Essentially, liberation of the drug from these vesicles to the cytoplasm is inevitable, in order to reach the subcellular organelles. This is often hindered by the viscosity and intracellular enzymes present inside the cytoplasm. Recycling (exocytosis) of the vesicle contents is also a possible pathway for the excretion of nanoparticles from cells. An example of this are the particles formulated from PLGA (Sakhtianchi et al. 2013). This nanoparticle can cross the endosomal barrier rapidly with efficient sustained delivery of therapeutic agents into the cytoplasm and finally degrade into lactic and glycolic acids that easily metabolize in the body via Krebs cycle for elimination.

Local delivery/blood brain barrier

In order to access the central nervous system (CNS) to deliver the drug into the brain (e.g., a brain tumor), the major limitations faced are the sensitivity of the brain and blood brain barrier (BBB). This barrier strictly limits the drugs or nanocarriers, both by physical (endothelial tight junctions) and metabolic (enzymes) obstacles. To cross the stringent border of the BBB, nanoparticles should have the characteristics of high lipophilicity and a molecular weight <500 Da (Masserini 2013). Various types of nanoparticles have been developed to access different modes of transport to cross the BBB as described in Fig. 2, with necessary characteristics. Recent developments in nanoparticles for brain drug delivery show that surface-charged and targeting molecule-loaded polymeric nanoparticles reveal fast transcytosis through the brain capillary walls due to its increased absorption efficiency (Fig. 2) in the endothelial cells (Tosi et al. 2013). Administration of nanoparticles to the target specific area in the brain is still at the nascent stage. However, in our previous study we have observed that gold colloidal nanoparticles when coated with albumin show a high accumulation at some specific locations in the brain such as the hippocampus, thalamus, hypothalamus,

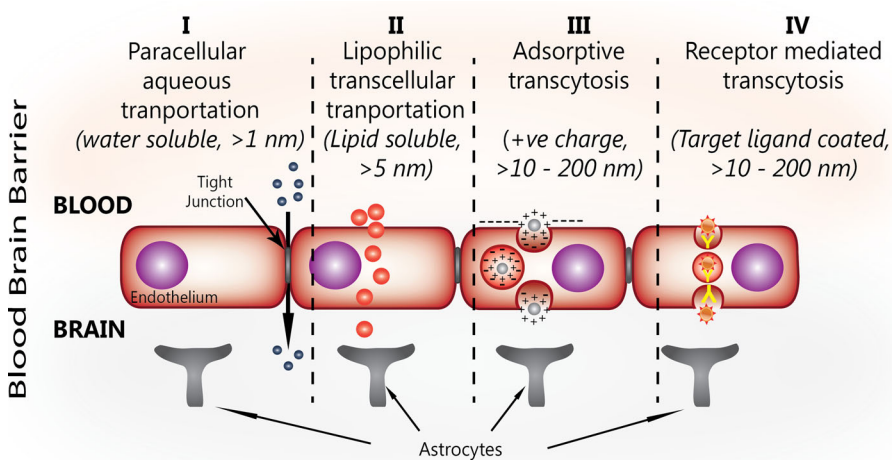

Fig. 2 Pathways by which molecules cross the BBB. Nano-drugs can be developed to exploit these mechanisms to cross the stringent border of the BBB. Smaller (<10 nm) nanoparticles can pass through the transcellular passage (*left side* I and II), while larger (>10 nm) particles are able to cross through via the transcytosis process (*right side* 111 and IV). Prevalently, molecules passing through the BBB are mediated by four major ways (as shown in **I–IV**). However, as depicted, paracellular aqueous transport mainly facilitates the water-soluble particles between the cells, whereas lipophilic transportation helps in the passage of lipid particles. The entry of nanomaterials through the BBB is completely restricted except for the charge-mediated and transcytosis process. In the case of adsorptive transcytosis, positive-charged particles move forward, while receptor-mediated passage promotes target ligand coated particles

and the cerebral cortex (Sousa et al. 2010). Hence, a bright future can be speculated with the modification of the surface properties of these nanoparticles, using compounds such as lectin or agglutinin (Murata et al. 2013). For example, the OX26 monoclonal antibody functionalized chitosan-PEG nanoparticles have been shown to be promising carriers for delivering anti-caspase peptide through receptor-mediated transport across the BBB (Aktas et al. 2005).

Other delivery methods

Other less common routes of nano-drug administration are via the intranasal and the ocular route (Fig. 1a). The intranasal route is used for the rapid onset of drug action circumventing the problem of degradation of labile drug in GI tract or insufficient transport across the epithelial cell layers. Hydrophilic coatings of nanoparticles aid in delivering the drugs via interaction with the nasal mucosa. This mode of delivery possesses a great benefit for the delivery of vaccines (Vila et al. 2004). Intraocular delivery of a drug is generally restricted by the inability of the long-term extraocular transport of drugs without affecting the intraocular organs. The cornea has a negative charge and basic pH (~7.8) mucoadhesive polymers can interact with the extraocular structure. This targeting route to the eye can be advantageous with the aid of nanoparticles, as it enhances their interaction with the ocular mucosa and thus prolongs corneal residence of the drug. For example, Tobramycin (an antibiotic used for bacterial infections) incorporated in SLNs has been shown to prolong the drug retention and therefore, promotes their bioavailability in the aqueous humor for a relatively longer time (Li et al. 2011a). Furthermore, these two modes (intranasal and ocular) have also been used for the drug delivery to the brain. This is exemplified by the delivery of the neuroprotective vasoactive intestinal peptide (VIP) encapsulated inside surface modified (with wheat germ agglutinin which has higher affinity to olfactory mucosa) PEG-PLA (poly lactic acid) nanoparticles via the intranasal route (Gao et al. 2006).

Functional point

In the cancer theranostic field, nanotechnology has gained rapid popularity due to its potential to design, construct, and utilize various functional structures at

the nanometer scale (≤100 nm). The prevalent advantage is that the fundamental characteristics of a given material can be precisely controlled by nanotechnology without changing its chemical composition (i.e., melting point or magnetic properties). Their promising applications in the field of medicine for treatment, diagnosis, monitoring, and control of biological systems have recently been coined as 'nanomedicine' by the National Institute of Health (Bethesda, MD, USA) (Park et al. 2008). In the context of nanomedicine-based therapeutics and diagnostics, effective functionality poses the major challenge which requires efficient tissue specificity, long-term systemic retention, and prolonged site-specific release of the drug.

In this part of the review, we will discuss the unique properties of nanoparticles that have been exploited widely to design effective nano-drug delivery and nano-imaging systems for the chemotherapeutic and diagnostic purposes, respectively. However, before going into a detailed description of the efficacy of nanoparticles for the drug delivery and diagnostics, it is important to discuss the two general modes of tumor targeting techniques i.e., active and passive targeting. These two targeting techniques help nanoparticles to get access to the tumor sites.

Passive targeting

Tumor blood vessels are generally characterized by abnormalities such as highly proliferating endothelial cells, pericyte deficiency, and aberrant basement membrane formation leading to a fenestrated endothelial layer at the tumor site (Fig. 3a). This defective vasculature aids in providing an ample amount of oxygen and nutrients to the fast growing cancerous tissues. The vasculatures near the tumor area are dilated mainly due to the fenestrated endothelial layer, leading to a decrease in lymphatic drainage and rendering of the vessels permeable to macromolecules (Park et al. 2008). Studies using liposomes and other nanoparticles have indicated that the cut-off size of the pores in tumor vessels ranges from 200 nm–1.2 μm (Bae and Park 2011) (Fig. 3b). These fenestrations in the blood vessels aid in a greater accumulation of nano-drugs at the site of infection. Therefore, nanoparticles of size ≤200 nm are popularly used for targeting, and this passive targeting phenomenon (Fig. 3b) is called the "enhanced permeation and retention (EPR)" effect (Bertrand et al. 2014).

Active targeting

In most cases, cells of the diseased tissue display a unique set of surface proteins (e.g., tumor-associated and tumor-specific antigens) that may not be present or are found at low levels on normal cells. Active targeting is usually achieved by attaching targeting molecules that strongly interact with antigens (or receptors) displayed on the target tissue, leading to a preferential accumulation of the drug in the targeted organ, tissue, or cells (Fig. 3c). For example, folate (Kularatne and Low 2010), transferrin (Camp et al. 2013), and luteinizing hormone-releasing hormone (LHRH) receptors can be targeted (Taheri et al. 2011) as these are highly expressed in cancerous tissues. For a better understanding of the above mechanism, we have described and referenced the example of active targeting mechanism of LHRH-PEG-Camptothecin targeted anti-cancer drug delivery system in Fig. 3c. In this nano-formulation, the PEG coating aids in nano-drug solubility as well as to escape macrophage uptake; camptothecin is the anti-cancer drug and LHRH to detect the receptors on the cancer cells (Taheri et al. 2011).

Use of nano-modules as nano-drug or delivery system for cancer therapy

In spite of the fact that cancer is one of the most studied diseases that has given rise to the development of various therapeutic approaches, such as surgery, radiation therapy, and chemotherapy, the search is still ongoing for an effective and non-recurring solutions for cancer therapy. All of these conventional therapies have major limitations with regards to inefficient target delivery, toxicity to the normal cells, and acquisition of drug resistance by the cancer cells (Park et al. 2008). However, nanomaterials have shown promising results by overcoming many of the drawbacks of conventional therapy, leading to the introduction of many productive drugs for cancer therapy (Table 1).

The main goal of chemotherapy is to deliver a large portion of the administered drug to the target site and for a sufficiently long duration. This can be achieved by adjusting the composition and process parameters of nanoparticle formulations. Improved drug targeting can be achieved by considering both the formulations (e.g., surface charge and hydrophobicity) of nanoparticles and

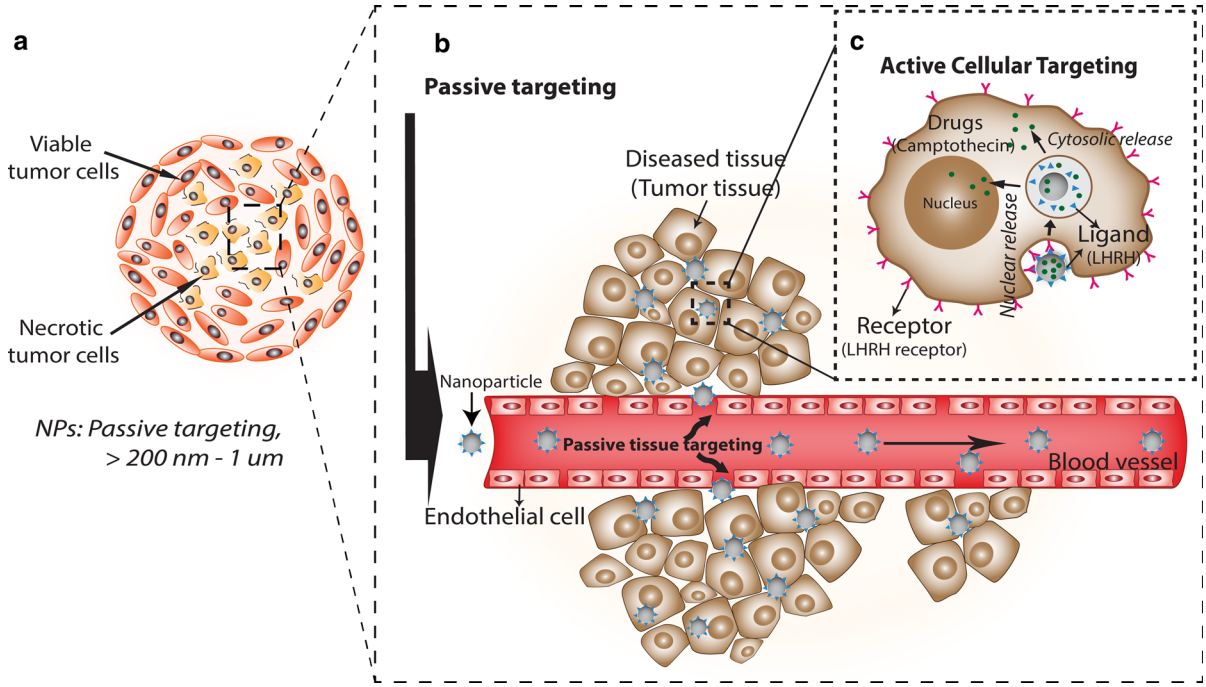

Fig. 3 Nanoparticles mediated drug delivery according to the characteristics of cancer disease sites. Tumor inner core contains both dead and necrotic cells (**a**). The blood vessels in the tumor are highly fenestrated leading to an EPR effect. In the case of passive targeting, (**b**) nanoparticles easily accumulates in the tumor due to the EPR effect, while active targeting (**c**) depends on the presence of receptors on tumor cells. Examples of active targeting are the folic acids which are targeted by the caveolin-assisted machinery or the LHRH-PED-Campothecin formulation which is mainly endocytosed by receptor-mediated mechanism. The part **c** of the figure explains the LHRH-PEG-Camptothecin formulation mediated active targeting mechanism. The breast cancer drug (e.g., Camptothecin drug) is delivered in the specific tumor cell due to the interaction of LHRH of LHRH-PEG-Camptothecin formulation with the LHRH receptors present on tumor cells (Taheri et al. 2011) which leads to endocytosis via a receptor-mediated mechanism. Endocytosis is the procedure by which cells internalize foreign particles, packing them into membrane-bound vesicles, and releases their content at target sites identified by specific receptors. The various cellular uptake and release mechanisms of the vesicles are receptor- and clathrin-mediated, caveolin- and lipid raft-assisted, and cell-adhesion molecule directed

exploiting the characteristic features of cancer sites (Fig. 3) such as high hydrostatic pressure, high requirements of nutrition, and the presence of over-expressed receptors etc. (Park et al. 2008).

Paclitaxel (National Cancer Institute, 1967) which was the first and most commonly used chemotherapeutic drug has various limitations, such as hydrophobicity and short blood retention period, etc. (Chipman et al. 2006). Intravenous injection of this poorly soluble drug can cause a embolization of blood vessels due to the accumulation of the insoluble drugs, and often leads to local toxicity due to higher drug concentrations at the site of deposition. Overcoming the above constraint, nanoparticles loaded with Paclitaxel called AI850 (Zhang et al. 2008) have proven successful in cancer treatment, mainly due to its enhanced accumulation at cancerous tissues.

Another serious problem of cancer treatment is the multi-drug resistance (MDR) of the cancerous tissues. This is due to the fact that these tissues have high hydrostatic pressure (unlike normal tissues) which leads to an outward convective interstitial flow that can flush the drug away from the tumor (Park et al. 2008). MDR is mainly characterized by the expression of plasma membrane P-gp (P-glycoprotein) which is capable of repelling drugs from the cell. Several strategies have been developed to avoid the P-gp mediated MDR. One of them is the formulation of the co-administration of P-gp inhibitor on the anti-cancer drug-loaded nanoparticles (Amin 2013). Furthermore, angiogenetic molecular factors (e.g., vascular, endothelial, transforming, epidermal growth factor, and angiogenin; Banerjee et al. 2011) are targeted to design cancer-specific nanoparticles. To utilize the

Table 1 Most popular nano-drugs for Cancer

Nanomaterials	Commercial name	Usage	Reference
Liposomes (organic)	DoxilCaleyx, Myocet (Doxorubicin); DaunoXome (Daunorubicin); Onco TCS (Vincristine); Abraxane (Paclitaxel); INGN-401 (tumor suppressor gene FUS1)*; Marqibo (Vincristine sulfate); OSI-211 (Lurtotecan)#	Drug delivery	(Zhang et al. 2008; Scodeller et al. 2008; Gindy and Prud'homme 2009; Wei et al. 2012)
Dendrimers (organic) & dextrans (organic)	Endoderm Feridex, Resovist, Sinerem (super paramagnetic iron oxide), Dendrimer-Magnevist complex (PAMAM dendrimer); Cyclosert Camptothecin* (Cyclodextrin NPs), CRLX-101*,# (Camptothecin)	Contrast agent for MRI imaging; drug delivery	(Gindy and Prud'homme 2009; Wei et al. 2012; Barone et al. 2009)
Carbon nanotubes (inorganic)	SW(Smooth-walled)CNT*(Paclitaxel; Doxorubicin), MW(Multiple-walled)CNT* (Doxorubicin)	Drug delivery	(Madani et al. 2011)
Polymeric micelles (organic) & other polymers	NKTR-102#,$,Irinotecan,Genexol-PM#,$,Paclitaxel, ProLindac# (DACH platinate), SP1049C#,Transdrug*,# (Doxorubicin), Oncaspar (Asparaginase); Neulasta (colony stimulating factor)	Drug delivery; therapy associated with chemotherapy	(Zhang et al. 2008; Wei et al. 2012; Kim et al. 2007; Saif et al. 2010; Davis 2009a, b; Davis et al. 2010)
Quantum dots (inorganic)	Luminescent quantum dots (Luminescent quantum dots encapsulated with ABC triblock copolymer); Quantum dot-800 conjugate	imaging (pre-clinical); imaging	(Koo et al. 2011)
Magnetic nanoparticles (inorganic)	TNT-Anti-Ep-CAM, NanoTherm (polymer-coated iron oxide, magnetic hyperthermia); Combidex (iron oxide nanoparticles)	Drug delivery; tumor imaging	(Wei et al. 2012; Wang 2011)
Gold nanoparticles (inorganic)	CYT-6091*, CYT-21001(TNFα PEGylated colloidal gold particles), Aurolase (Gold nanoshell)	Drug delivery	(Wei et al. 2012)
Other nanoparticles	Panzem NCD# (nanocrystalline 2-methoxyestradiol), AI-850* (paclitaxel); Ceramic nanoparticles	Drug delivery; imaging	(Zhang et al. 2008)

'*', '#', '$' symbol signifies nano-drugs which are under Phase I, II, III trial, respectively

behavior of cancer cells, nanomedicines are being actively developed to co-administer anti-angiogenetic and chemotherapeutic drugs. For example, a polymer-based nuclear nanoparticle within an extra-nuclear PEGylated lipid envelope leads to simultaneous release of anti-angiogenetic as well as chemotherapeutic agent (Sengupta et al. 2005).

Among the different drug carriers used for therapeutic purpose, liposomes are one of the best choices (Fig. 4), because they are vesicles made up of phospholipid bilayers comparable to the mammalian cell membrane. This bilayer structure aids to further enhance tissue-specific absorption of drug-loaded liposomes. Thus, they are excellent in biocompatibility and tissue penetration. Furthermore, another added beneficial property is their size flexibility from small to large, and from unilamellar to multilamellar vesicles (Barreto et al. 2011). Moreover, the hydrophilic surface and biphasic lipid layer further aid in easy surface modification with target molecules (Torchilin 2005). Conversely, the main drawback of the liposomal system is its negative surface charge. It is seen that negatively charged particles can rapidly clear the injecting drugs (Immordino et al. 2006), thus surface modification (e.g., using PEG) to render the positive charge is generally done for the higher potential of inflicting effects in the case of cancerous tissues.

Other nanomaterials that have been proven as potential drug delivery system are dendrimers (Fig. 4). Dendrimers are extremely flexible among various nanomaterials. Its surface and size modification are relatively easy to achieve. Their sizes and shapes are dependent on the number of generations or the number

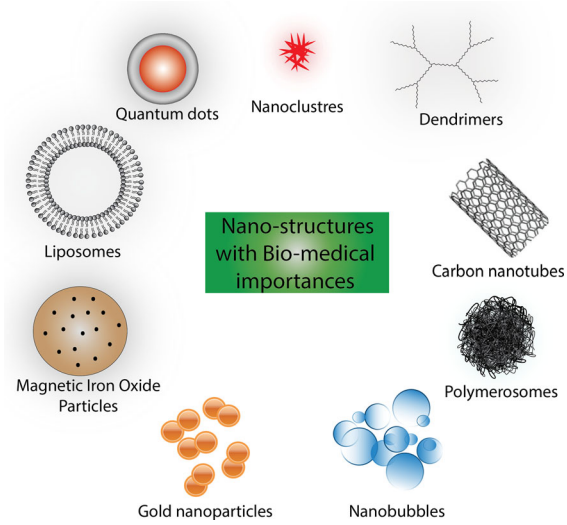

Fig. 4 Different types of nano-modules in use for drug delivery and bio-imaging of diseased tissue. Liposomes are conventionally used for drug delivery; however, they are also emerging as imaging modules(Allen and Cullis 2013). In the same notion, dendrimers, nanoclusters, and polymerosomes are also used for drug delivery system, whereas, *quantum dots*, magnetic iron oxide, and gold nanoparticles are extensively used for imaging or diagnostic purposes (Barreto et al. 2011). Among these nanoparticles, dendrimers and nanoclusters have similar features that can be applied to both procedures for the functional aspects. Furthermore, cationic and anionic nanobubbles are new classes of nanomaterials that are being currently used for both purposes (Pan et al. 2012)

of layers it contain (Sato and Anzai 2013). In contrast to liposomes, an increased positive charge on the dendrimer can render them toxic (Svenson and Tomalia 2005). Thus to overcome this, PEG-mediated surface modification is promoted (Qi et al. 2009). One of the major limitations of using positively charged dendrimers is the interaction with either the negatively charged cell membrane and form or the expansion of existing holes in lipid bilayer membrane. Furthermore, the higher the generation ($G = 5, 7, 9, 10$ etc.) of dendrimers, the greater is the severity it possess on the cells. For example, G5-PAMAM dendrimers are able to disrupt the lipid bilayers, while G7- generation can create holes via electrostatic interactions (Majoros et al. 2009).

SLNs were developed in the 1990s as an alternative carrier system to emulsions, liposomes, and polymeric nanoparticles (Fig. 4). They are more stable in the biological system due to their structure (hydrophobic lipids surrounded by a monolayer of phospholipids) and biodegradability. Furthermore, because drugs have been shown to be capable of entering the core of SLNs at lower temperatures and exiting at higher temperatures, techniques to induce hypothermia and hyperthermia can be used to load and unload SLNs with therapeutic agents. The major drawback of SLNs, however, is the vulnerability to temperature during storage or administration, which can lead to premature expulsion of the drug from the lipid matrix (Thakor and Gambhir 2013).

A polymeric nanoparticle is a collective term given to any type of polymeric nanoparticle, but specifically corresponds to nanospheres and nanocapsules. Liposomes, polysomes, and nanobubbles are considered under the common name of nanospheres or nanocapsules as they have nanoscale shells in which targeted drug can be loaded (Guterres et al. 2007) (Fig. 4). Major advantages of these types of nanoparticles are the easy manipulation of their desired properties, such as surface modifications to improve biodistribution properties, pharmacokinetic control, and entrapment of therapeutic agents. Consequently, they have been intensively investigated for drug delivery in the last decade, with the FDA approving biodegradable PLA and PLGA for human use (Faraji and Wipf 2009).

Additionally, inorganic nanoparticles synthesized from metals, metal oxides, and metal sulfides (Fig. 4) can be formed into a plethora of different designs for better drug targeting efficiency, evading opsonin uptake and attaining a better stability than liposomes, and SLNs over large ranges of pH and temperature. However, their lack of biodegradation and slow dissolution rates raise concern on their reproducibility (Thakor and Gambhir 2013).

More recently, porous silica nanoparticles have been paving their way into biomedical applications. The application of silica nanoparticles in the preparation of silica–polymer nanocomposites (SPN) has drawn a lot of attention due to the increased demand of new nanomaterials with improved mechanical and physical properties. Freshly prepared synthetic silica (e.g., colloidal silica, silica gels, pyrogenic silica, and precipitated silica) is advantageous in comparison to natural polymers due to the absence of impurities and flexibility of modulation of their physicochemical properties (Napierska et al. 2010). SNPs used for drug delivery purposes [classified as xerogels and mesoporous silica nanoparticles (MSNs) (Czarnobaj 2008)] are most often chosen for biological purposes due to its biocompatibility, highly porous framework, and are

easy in terms of functionalization (Trewyn et al. 2007). The mechanism of drug loading into MSNs is by physical or chemical adsorption, and the release is usually controlled by diffusion (Li et al. 2010; Di Pasqua et al. 2009). By these processes, several anti-cancer drugs have been embedded in MSNs (He et al. 2011). Along with the controlled release during the drug delivery (Slowing et al. 2008), this kind of nanoparticle has also been used for thermal therapy of tumors (Hong et al. 2011). Despite these advantages, however, these kinds of nanomaterials suffer from in vitro and in vivo toxicity and hazardous effects on the cells. Their cytotoxic effects range from the formation of reactive oxygen species (Liu and Sun 2010), decreased glutathione levels (Wilczewska et al. 2012), induction of MAPK signaling pathway (Eom and Choi 2009), and release of various chemokines or cytokines (e.g., IL-8, IL-6, TNF-α, etc.) (Popovici et al. 2011).

Exploitation of nanoparticle properties for cancer diagnosis

Diseases need early and accurate diagnostics, coupled with therapy. The major drawbacks of current day diagnostic probes are their poor biodistribution and reduced systemic retention time. Nanomaterials have evolved as a new hope for future diagnostics due to their unique features such as long persistence, better penetration, and near inertness.

Nanoparticle-based carriers have increased the efficiency of diagnostics, largely through passive and active accumulation (Barreto et al. 2011). Prolong blood retention along with porous and leaky blood vessels enhances passive accumulation of nanoparticles at the disease tissues employing EPR effects (Barreto et al. 2011) (Fig. 3a). The porous and leaky vessels around the tumor tissue enhance nanoparticles accumulation at the tumor site. Moreover, to induce target site accumulation via passive targeting strategies, the advantages of the variation in the pH, temperature, or redox potential of the pathological tumor sites must be taken into consideration. For example, the pH-sensitive polymeric carrier, such as polyvinyl pyrrolidone-co-dimethyl maleic anhydride (PVD) loaded with diagnostic agents (e.g., Tumor Necrosis Factor-α) (fulfills these considerations) showing gradual release in response to changes in pH at the tumor site (Foulds et al. 2011).

On the other hand, to target tumor cell accumulation, active targeting has to be considered along with passive targeting. Active targeting needs a 'homing device' comprising of specific receptors identified around the diseases tissues (Fig. 3b). Active targeting mostly aims at recognizing a target within the disease-affected organ, tissue, cell, or intracellular organelle, leading to preferential accumulation of the nanoparticles. Some of those targeting agents that have been used are albumin, folic acid, galactose, peptides, vascular endothelial growth factor (VEGF) peptide, aptamers, proteins like transferrin, LHRH, and antibodies (Spuch and Navarro 2011).

However, nanomaterial usage as a bio-detector for imaging needs proper consideration based on their physicochemical properties. The most popular imaging techniques used for diagnostics are fluorescence imaging, MRI, and PET. Conventionally, MRI and computerized tomography (CT) provide three-dimensional morphology information of a diseased area. These techniques are extensively used in determining the tumor size and morphology for cancer prognosis. Furthermore, the advantage of MRI is that it can depict soft tissue at higher resolution (<1 mm) without having the ionizing radiation effect. Among various nanomaterials, dendrimers are widely used as an MRI contrast agent due to their appropriate pharmacokinetic properties along with shortening of proton relaxation time and signal intensification (Svenson and Tomalia 2005). Moreover, the use of PAMAM dendrimers functionalized with Gd^{3+} complexes has gained intense interest in visualizing tumor cells and lymph nodes, in order to gain information about the angiogenesis (Barreto et al. 2011). PAMAM dendrimers with targeting ligands (e.g., folate) are in use for both MRI and fluorescent imaging (Barreto et al. 2011). Other nanomaterials which are in use for MRI imaging are liposomes loaded with radio-labeled elements. Liposome-based nanoparticles are a main focus area in the imaging and drug delivery fields due to its amphiphilic features which enable them to potentially penetrate any cellular barrier (Torchilin 2007). Its promising properties have led ^{9m}Tc, ^{111}In, and ^{67}Ga-loaded liposomes to be used in the clinical study stage (Torchilin 2005).

Among various molecular imaging technologies, SPECT and PET are the two key nuclear imaging techniques that have revolutionized the clinical practice. Although SPECT and PET exhibit low

spatial resolution compared to MRI, they show a high sensitivity in magnitude and widened imaging time window. Thus, they provide much functional information such as the pharmacokinetics and the biodistribution of the drugs. The major drawbacks of conventional imaging probes are their poor biodistribution and reduced systemic retention time. The use of nanoparticles has shown a way to bypass these problems. Target-specific radio-labeled nanoparticles (<100 nm) have maximized passive and active accumulation by inducing enhanced binding affinity via receptor-specific biomolecules on the target cells of respective tissue (Hong et al. 2009). The most noticeable nanoparticles for imaging are those with near-infrared (NIR) fluorescence [e.g., nanocrystals or Quantum Dots (QDs)] or magnetic properties [e.g., iron oxide nanoparticles (Montet et al. 2006)] (Fig. 4). The colloidal metallic nanoparticles have proven to be very promising contrasting agents for imaging purposes. Among various metallic nanoparticles, gold nanoparticles have received special attention due to their strong photo-thermal energy converters ability over typical organic dyes. This is due to their properties such as higher photon-capture cross-section around the Surface Plasmon absorption band (Jain et al. 2008).The presence of the plasmon layer on gold nanoparticle surfaces produces the phenomenon called Surface Plasmon Resonance (SPR). The SPR properties of gold nanoparticle are used in the surface enhanced Raman spectroscopy (SERS) technique, which in turn are in use for single molecule detection and identification. Moreover, we have previously demonstrated that these gold nanoparticles with some modification can be used for a multipurpose imaging system (Mandal et al. 2011). Other sophisticated techniques are being developed to visualize them, by exploiting their very strong light scattering property at their localized SPR frequency (Taylor et al. 2011). As the SPR effect is very sensitive, the changes in size, shape, and dielectric constant of the surrounding environment can also be detected reliably by these nanoparticles. The metallic nanoparticles are also in use for imaging tumor tissues via simple optical microscopy methods (Scheinberg et al. 2010).

Another class of nanoparticles used successfully as image contrast agents is iron oxide nanoparticles (Fig. 4). Due to their large magnetic moment, they generally produce enhanced proton relaxation rates than paramagnetic ions (e.g., Gd^{3+}) at a significantly lower dosage. For diagnostic purposes, it is exemplified by radio-nucleotide particles (e.g., F^{18} and Cu^{64} loaded nanoparticles) which are in use for PET imaging (Jarrett et al. 2008). Importantly, QDs are used efficiently in fluorescent and MRI imaging. These semiconductor nanocrystals vary in their sizes and they are extremely bright due to their high extinction coefficients in the visible spectrum. There are various advantages of using QDs as an imaging module. For instance, they are resistant to chemical degradation and photo-bleaching, show long-term stability compared to conventional organic fluorophores, as well as having high quantum yields. These nanomaterials are profitably used in fluorescent imaging along with MRI or PET imaging. For example, QD conjugated with Gd^{3+} is used for Fluorescence-MRI imaging, whereas Mn^{2+} or Cu^{64} conjugations are used in PET imaging. Furthermore, other contrasting agents such as nano- and macro-bubbles (Fig. 4) are also attracting scientific interest as a probe for the ultrasonography imaging (Wang et al. 2011a).

While MRI, PET, and SPECT are known to detect diseases in their early stage, their resolution is limited to a few millimeters. This is insufficient for understanding the intrinsic biological mechanism (at the molecular level) involved in the disease progression. Such a discrete and accurate understanding is possible with the emergence of fluorescent microscopy that is capable of near-molecular resolution. In this section, we will explore a few key fluorescence-based imaging techniques specifically focusing toward cancer therapy.

This form of microscopy technique utilizes fluorescent markers/nanoparticles for producing an accurate map of the specimen with high spatial and temporal resolution. This is an important feature for the early detection of malignancy in growing tumor cells which holds the key for cancer therapy. In this regard, it has been clinically validated that image-guided surgery based on specific fluorescent markers can be used for accurate localization of tumors with efficient removal (Mieog et al. 2011). Due to the prominent scattering and auto-fluorescence from tissue, this surgery requires synthesis of near-infrared fluorescent markers (emission from 700–980 nm range). This, however, causes some concern as it comes with a few pre-requisites on the nanoparticles. Nanoparticles must be highly target specific. Superior

colloidal stability to avoid aggregation and near complete clearance from the biological system must be ensured after imaging is completed. PLGA is one of the most extensively and reliably used nanoparticles for imaging and drug delivery (Rao et al. 2007) having the added advantage of excellent biocompatibility. Poly-methyl-methacrylate (PMMA) is another nanoparticle that has good stability and biocompatibility but is non-biodegradable (Wang et al. 2011b).

Another area to consider is the quantum yield which is required for bright and photo-stable markers. Specifically, QDs fit this bill since they are engineered to show stable highest quantum efficiency (Badr and Tannous 2011; Xie et al. 2012). Moreover, QDs are available for the entire spectrum ranging from ultraviolet to visible to infrared. Their inorganic composition makes them resistant to photo-bleaching and they possess a longer shelf-life. The main drawback, however, lies in their toxicity nature. In competition with QDs, entrapped fluorescent markers in polymeric nanoparticles are finding their way into clinical applications. The key benefits of using polymeric nanoparticles are the protection of dyes from the biochemical environment, increased surface area for strong attachment with functional groups, and multiple loading of fluorophores for enhanced fluorescence intensities. Of late, polymeric nanoparticles are evolving for their dual functionality allowing simultaneous diagnostic and drug delivery applications. Consequently, the concept of fluorophore encapsulation by polymeric nanoparticles is promising for image-guided surgery and other clinical applications (Pittet and Posfay-Barbe 2012; Kamaly et al. 2012).

As far as the fluorescence microscopic imaging is concerned, preferred fluorophores must have certain properties such as, high quantum yield, long lifetime, broad absorption spectra, high molar extinction coefficients, and less photo-bleachability. These fluorophores can be conjugated directly or in an entrapped form, such as inside polymer nanoparticles. Many organic fluorophores are engineered to inherit these properties. For example, the cyanine dye family has profound applications in surgical oncology and for imaging vascular networks (Polom et al. 2011; Alander et al. 2012; Sevick-Muraca 2012). The introduction of vinylene functional units on cyanine dyes has led to the development of fine-tuneable cyanine dyes within the spectral range of 400–850 nm. These dyes are popularly known as Cy3, Cy5, Cy7, etc. Cy7 dyes are extensively used for labeling peptides and other organelles for in vivo imaging (Merian et al. 2012; Te Velde et al. 2010; Fernandez-Suarez and Ting 2008). As far as clinical applications are concerned, indo-cyanine green is used for intravenous administration for angiography and mapping lymph nodes. Another class of potential markers is those for which the emission predominantly lies in the near infrared (NIR) region (600–1,000 nm). NIR markers are synthesized by conjugation with cancer-specific ligands such as, cRGD peptides, folate, and other antibodies. These dyes (IR-783 and IR-808) favor accumulation in the tumor both with and without conjugation to tumor-specific ligands (Tan et al. 2012; Zhang et al. 2010). Within the visible range, commonly used organic dyes for clinical applications are Rhodamine B and FITC because of their brightness and high quantum efficiency. They are routinely used for blood flow examination and angiography (Koc et al. 2008; Fenton 1965). However, uses of these dye molecules have been successful only when they were injected locally at or near the diseased tissues due to limited biodistribution issue. Moreover, local injection success rate is minimal due to tissue specific morphological barriers such as size, shape, and location of target tissue (Wang et al. 2013). Therefore, the prime focus of nanoparticles as drug carriers should be to encourage enhanced tissue accumulation. Systemic injection of cyanine-loaded polymeric nanoparticles and liposomes has shown an improved in vivo fluorescent imaging of target organ due to its enhanced accumulation at the target site (Puvanakrishnan et al. 2009).

Polymeric fluorescent nanoparticles are promising candidates for both in vitro and in vivo imaging, because of their multiple advantages over dye molecules. Due to its multi-valency and nanometric size, these nanoparticles have shown enhanced target site accumulation, better distribution, and significant increase in the retention time. The fluorescence is greater because a few hundred dye molecules can be encaged within a single nanoparticle. This entrapment helps in protecting the dye from interacting with the biochemical environment thereby significantly reducing photo-bleaching.

Perspective for tailoring particle with optimal drug delivery and fitting imaging agent

It is a challenge for nanoscientists to engineer particles that possess all the essential criteria (e.g., efficient

target delivery; non-specific accumulation and toxic side effects) in order to develop a potential nano-system for drug delivery. Moreover, when developing the ideal system for the specific disease, all discussed points in this review need to be fully considered.

Nanomaterials for cancer treatment are designed mainly for targeting the specific characteristics of cancerous tissues, such as hyperthermia or low pH environment. Therefore, it is useful to design the model in terms of those characteristics of cancerous tissues. The prime criterion to enhance active targeting of nanoparticles is to promote prolonged retention in the blood and to achieve efficient elimination from the body. For hydrophobic drug delivery (as most of the cancer drugs are hydrophobic), a nanoparticle carrier with a hydrophobic core, such as liposome or micelle should be preferred. However, size-wise micelles are the better choice compared to liposomes as they (90–150 nm) are slightly larger than the other conventional nanoparticles (Wang et al. 2013). Among the spherical worm-like and vesicles-shaped micelles, the former one is favored over the latter because this increases their systemic retention time (Cai et al. 2007). If micelle area is held constant for a given mass of polymer in solution, then filomicelles $[(\pi r2l)/(2\pi rl) = r/2]$ are expected to carry more hydrophobic drugs than spherical ones $[(4/3\pi r3)/(4\pi r2) = r/3]$ by a ratio of $(r/2 - r/3)/(r/3) = 50$ %, where, r = radius and l = length. Additionally, filomicelle with positively charged particles can easily be internalized in the target organ. Surface modification of this particle with PEG (polyethylene glycol) can further increase the blood circulation retention period. Consequently, for hydrophobic cancer drug, <5 nm size of filomicelle with a positive charge is an ideal candidate for drug delivery.

Design of nanoparticles in the case of imaging involves the following important parameters: (1) Size: nanoparticles with a size <1 μm is preferred for better circulation. EPR is known to be far better for particles in the range of few tens to few hundreds of a nanometer. More precisely, the nanoparticles of ~30 nm size are considered to be the most easily endocytosed (Albanese et al. 2012) and thus show prolonged EPR in the tumors (Maeda et al. 2009). (2) Aspect ratio: recent studies show that the aspect ratio plays a prominent role as far as internalization is concerned. For example, rod-like nanoparticles with a large aspect ratio are internalized faster in the cellular environment as compared to spherical nanoparticles (Wang et al. 2011b). As a result, cellular uptake increases thereby prolonging the circulation time. (3) Surface change in the cellular environment, the cell membrane is negatively charged, and thus the cellular uptake of positively charged nanoparticles is enhanced. The other mode of targeting nanoparticles is by conjugation. The commonest way of active targeting is using antibodies, nucleic acids, and other small molecules (Gullotti and Yeo 2009). Unique parts of cell lines such as antigens bind highly in a selective manner with specific antibodies. For example, in breast cancer imaging, selectivity of HER2/neu antigen with the antibody Trastuzumab (humanized antibody) is well-known (Mortimer et al. 2014). In tumor cells, folic acid shows a high selectivity to folate receptors that are over expressed (Kularatne and Low 2010). At the cellular environment, the properties such as, hydrophobicity and specific functionalization of nanoparticles further significantly boost their interaction with target proteins.

There are also a few pre-requisites on the nanoparticles as far as image-guided surgery is concerned. Nanoparticles must be highly target specific and must have superior colloidal stability to avoid aggregation and degradation. Finally, complete clearance from the biological system must be ensured after imaging is done. As an example, PLGA is one of the most extensively and reliably used nanoparticles for imaging and drug delivery (Makadia and Siegel 2011) having the added advantage of excellent biocompatibility. PMMA is another example of a nanoparticle that has good stability and biocompatibility but is non-biodegradable (Pavlov et al. 2011; Wang et al. 2011b).

Due to its uniqueness and efficiency, various imaging nano-probes such as Combidex (active agent: iron oxide nanoparticles- used as MRI and PET contrasting agent), Resovist (active agent: super paramagnetic iron oxide- used as MRI contrasting agent), and Feridex (active agent: super paramagnetic iron oxide- used as MRI contrasting agent) are FDA approved contrasting agents used for tumor detection (Gindy and Prud'homme 2009; Wang 2011). The clinical successes of above mentioned nano-probes are not only due to their better biodistribution and proper targeting ability, but most importantly due to their lower toxicity. Thus, one of the major concerns and causes of clinical failure of materials are their toxicity issues. Therefore, toxicity issues of nanomaterials

need special attention, while designing, enabling, and promoting drugs to be available on the market.

Exit point

Excretion criteria for nanoparticles

The route of administration determines the fate of a nanoparticle's accumulation and elimination. If the particle is injected orally, then there is greater likelihood of accumulation in intestinal organs (e.g., liver and spleen), whereas after parenteral or intravenous application, molecules are mostly eliminated via the kidney while traveling through the blood. This is known for fullerene particles applied through the oral and intravenous route. Particles administered through the former route can easily be eliminated through feces, whereas those administered through the latter pathway can be retained in the body for 1-week. The intravenously injected fullerene particles are mainly (91.7 % of dose) distributed in the liver (Shinohara et al. 2011).

Excretion and internalization are integral phenomena in the physiology of nanoparticles. If the particles are <20 nm, they can easily be cleared up by the normal drainage organs, such as the kidney (<5 nm) or the liver (10–20 nm) (Longmire et al. 2008). However, if particle size is between 20 and 200 nm, it then starts to accumulate in the spleen, bone marrow, and other reticulo-endothelial system (RES) and eventually, these cause damage to the whole system to which they are being introduced (Petros and DeSimone 2010). It is not only size that matters in the excretion criteria, but also the shape and surface properties (i.e., charge on the particle and surface chirality). Before looking into more detail of the ideal nanoparticle structure composition, it is essential to describe the cellular structures of the drainage organs, in order to understand their natural sieving mechanism for the excretion of nanoparticles from the body.

The kidney is the most potent sewage system for excretion. There are three steps for the elimination of nanoparticles through the kidney: glomerular filtration, tubular secretion, and tubular reabsorption. The major cellular structures involved in the first step of sieving (which mainly determines the renal clearance capability) are the glomerular basement membrane (average thickness 200–400 nm), the fenestrated endothelium (diameter 80–100 nm), and the podocytes (width 30–40 nm and pore size of 4–5 nm between podocytes). Thus, nanoparticles of ~5 nm (Fig. 5a) can be excreted. Ultimately, this filtering is very much size, shape, molecular weight and charge-selective. Studies with quantum dots have been shown that nanoparticles <5 nm and positively charged are easily excreted by the kidney (Choi et al. 2007). Conventionally, molecular weight cut-off of nanoparticles for glomerular filtration is considered to be ~70 kDa (Choi et al. 2011). The charged particles above this size limit (<20 nm) thus lead to their excretion through the liver (Fig. 5c). This sieving organ mainly consists of phagocytic kupffer cells and hepatocytes for eliminating particles through them. Pore size of fenestrations of hepatic sinusoid in between kupffer cells and hepatocytes is 100–200 nm. Hence, particles smaller than this size limit can pass through the fenestrations and enter into lymphatic circulation or hepatocytes. Recent studies have revealed the presence of polystyrene nanoparticles (size of 20 nm) within the bile system indicating possible elimination through this system (Johnston et al. 2010) (Fig. 5c). Finally, the particles passing through hepatic kupffer cells are digested by lysosomal enzymes present there.

One of the non-traditional drainage organs for aerosol-based nanoparticles is the lung (Fig. 5b). Phagocytic uptake by alveolar macrophages and mucociliary transporters are the main mode of excretion through the lungs (He et al. 2010). This macrophage-mediated clearance is size, geometry, and surface property selective. Particles or agglomeration of these <100 nm is quite inefficient to traverse through and even materials coated with surfactant (e.g., albumin) cannot be easily taken up by alveolar macrophages (Zhu et al. 2009) (Fig. 5b).

Finally, when these nanomaterials bypass all the standard drainage system, then they tend to accumulate in RES, namely in the liver and spleen monocytes and macrophages (Fig. 5c, d). Rapid clearance from the blood circulation with an insufficient delivery of the particles to the target organs and a consequent over-accumulation in RES organs are regarded as the major causes of nanomaterial adverse effects (Petros and DeSimone 2010). Until now, most in vivo studies hint at the tendency of accumulating these particles in RES organs for extended periods of time and finally degrade there slowly or excrete from the body. This

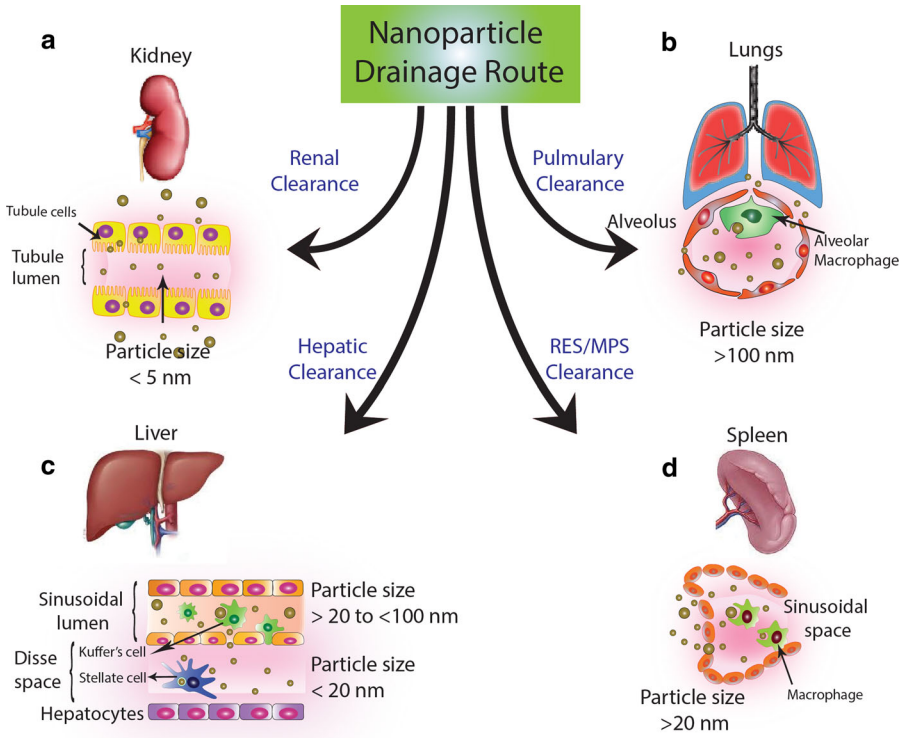

Fig. 5 Drainage of nanoparticles through different organs according to their properties: The Kidney is the most traditional drainage system eliminating the particles <5 nm (**a**) and the particles <5 nm are easily eliminated from the blood. Although the lungs (**b**) is not a conventional eliminatory system, it can help in filtering aerosolic nanoparticle elimination with sizes >100 nm. A second level of elimination is done through the liver (**c**) where particles of size 20–100 nm can pass through. The *larger particles* (<200 nm) which are not eliminated through the kidney or liver are eventually eliminated by the RES e.g., Lymph node and spleen (**d**)

unwanted accumulation of particles can be exemplified by a study which observed that intravenous or intraperitoneal administration of gold nanoparticles (40 nm) remained in the liver, up to 6 months after their application (Sadauskas et al. 2009).

Perspective for custom-designing particle with optimal accumulation and excretion criteria

In relation to all that have been previously discussed, we have aimed to pinpoint the ideal structure and composition of a particle for elimination. In terms of shape, cylindrical nanoparticles with high aspect ratio can easily be internalized compared to spherical particles (Wang et al. 2013). In terms of the charge on surface, particles with a negative or neutral charge have more blood circulation time and less internalization rate compared to positively charged particles (Alexis et al. 2008). Thus, in terms of better removal from the body, cylindrical-shaped nanomaterials with size <5 nm and positive charge would be the ideal nanoparticle structure compared to spherical particles. Additionally, chirality of the molecules attached to the nanomaterials (e.g., QDs) can also affect cellular processes (e.g., autophagy). It has been reported that L-GSH (Glutathione tripeptide) QDs have profound effects on autophagy (Li et al. 2011b). Thus, presumably an R-type of chirality with cylindrical shape, positive charge, and smaller size (<5 nm) in a particle can affect the cells to a lesser extent and are ideal for excretion. This hypothesis has already been validated by a pharmacokinetic model comparing different kinds of nanoparticles (Kadam et al. 2012). In summary, attention should be given for minimizing the toxicity, while delivering a drug or imaging agent circumventing the problem of non-target specific accumulation and retention, which can ultimately lead to harmful effects.

Toxicity issues

While discussing the excretion criteria of nanoparticles, it is clear that these engineered particles can sometimes turn out to be malice for the target organs (due to unspecific aggregation while reaching to their destinations) in contrary to their functions. The toxicity of nanoparticles, when applied to the target body system, is the Achilles' heel in the nanomedicine world. Several organs such as the liver, lung, kidney

brain, heart, testis, and even ovary (at developmental stage) can be affected by diverse amounts of nanomaterials. Here, we will discuss examples of these toxicity effects. As the kidney, liver, lung, and spleen are the major sites of exit of these particles, it is quite evident that they accumulate in these organs. It is true that the manipulated nanoparticles increase delivery range from 2 to 40-fold, has increased over the years of their development, but still only 5 % of the drug's needed amount are delivered and the rest traverses through the other organs (Medina et al. 2007).

The first level of toxicity of any drug is tested in the heart. One such example of a nano-drug delivery system which has been tested on heart is the liposomal formulation of the drug promising chemotherapeutic drug Dox called Doxil. Although overall toxicity of this nanoparticle-based Dox formulation was much less than the drug itself, there were still profound morphological changes that occurred in the muscles of the heart (myocardium) such as cytoplasm vacuolation, atrophy of myocytes, pycnosis of nuclei, loss of myofibrils, and lymphoid infiltrations (Pereverzeva et al. 2007). In general, the kidney and liver are the organs responsible for the accumulation of any kind of environmental toxic substance or the particles generated by excessive smoking exposure (Trabelsi et al. 2013). The kidney is the major organ of xenobiotic particle removal, thus they tend to accumulate there to a great extent. As shown in many studies, the kidney is identified as the primary clearance route for carbon nanotubes, fullerenes, and dendrimers. Temozolomide is widely used in various kinds of malignant tumors in the nervous system with a gamut of side effects in the kidney, brain, bone marrow, and the mouth. The liposomal formulations of this drug have less toxicity ($\leq$28.4 %) than the use of only the drug, but still Temozolomide-SLN mainly accumulates in the kidney and other RES organs (Huang et al. 2008). As mentioned, liver is the other organ where the foreign particles can accumulate. In the case of liver, we present here, the example of gold nanoparticles, whose primary site of accumulation is mostly there (Sadauskas et al. 2007). This is why, they are thought to be used for targeting hepatocellular carcinoma; however, chemotherapeutic drug conjugated with gold nanoparticles can cause severe cytotoxicity in the hepatic cells even at lower concentrations (Paino et al. 2012). As mentioned previously in the excrition criteria for nanoparticles section, the geno- and cyto-toxicity of nanomaterial is mainly size and surface charge-dependent. Gold nanoparticles <18 nm can easily diffuse through the cellular systems and smaller size of particles can easily penetrate through the cellular microenvironment such as the nucleus and mitochondria. In the context of surface charge, the toxicity of cationic nanobubbles (i.e., particles with acoustical activity are used both as a diagnostic and therapeutic carrier for detecting and treating diseases) should also be considered. Nanobubbles with a cationic surfactant (e.g., commercial product: FluoroGene) exhibit greater toxicity than anionic ones (Pan et al. 2012). In general, nanoparticles with cationic surfactants show more toxicity than anionic surfactants. Moreover, neutral particles with no charge are non-toxic. Additionally, the respiratory system poses as a unique target for potential toxicity of gold nanoparticles, as it is the portal entry of inhaled particles and also receives entire cardiac output (Liu et al. 2009). This is exemplified by C_{60}fullerene, which is also considered an environmental pollutant (Baker et al. 2008). Exposure to these nanoparticles does not lead to any significant cardiac or hepatic changes, but changes in the lung physiology if exposed for a long duration. Another example to be mentioned in this issue are the PAMAM dendrimers which are efficiently used as a nanocarrier for drug delivery. This drug carrier system can cause acute lung injury by autophagic cell death. Lastly and importantly, the use of Cy5.5 conjugated super paramagnetic iron oxide particles in optical imaging should be considered due to their pulmonary toxicity (Cho et al. 2009).

Another organ prone to be affected by these nanoparticles, which has been less explored in research in the nanomedicine world, is the ovary. The liposome type of nanoparticle carrier has been shown to accumulate in ovary (Park 2012). Toxicity, in this case, is also mainly size-dependent, as there is a higher chance of accumulation of the nanocarriers within the 45–350 nm size range (Park 2012). Similarly, the male reproductive organ, the testis, can also be highly affected by the nanoparticles accumulation, although their severity is less than the free drug accumulation (Pereverzeva et al. 2007). The final organ to be addressed here is the brain, as there are many invasive imaging approaches that have had nano-systems developed to get access into this organ. Toxicity of these administered nanoparticles for imaging and loading drug (as a carrier) should also

be considered. The polysorbate 80-coated PBCA (poly n-butylcyanoacrylate) particles and PEGylated PLA-immune nanoparticles can cross the BBB, but cause severe side effects which can affect the brain physiology and BBB function (Zhang et al. 2013). Additionally, nanoparticles possess physical and chemical characteristics that may cause oxidative stress (Batrakova et al. 2007). The brain is particularly vulnerable to many forms of stress (causing Alzheimer's disease, Parkinson's disease, and Huntington's disease) forming easily peroxidizable unsaturated fatty acids, high oxygen consumption rate, and relative scarcity of antioxidant enzymes. Exposure to stress can lead to a chain of events such as increased metabolic activity, change in cell shape and size, cytoplasmic engulfment mediated by microglia, and even alteration in MAPK-signaling events as part of an inflammatory process in CNS (Hu and Gao 2010). Hence, nanoparticle administration in the brain or CNS is still in the nascent stage.

In spite of the various toxicity effects in various organs of human body, these man-made particles are proving to be more promising as a drug carrier and imaging agents compared to other direct drug administration methods for diagnostics/therapeutics. The important point is that toxicity issues need to be considered and nanoscientists need to be more cautious in using them. Their potential is undoubtedly still valid. This issue of toxicity is only raising a yellow card for them, but as yet no red card to exclude them entirely from the therapeutic world (akin to the yellow and red card system as used in soccer).

Future ideas and conclusion

Nanomaterials have proven their potential in the biomedical field. However, proper selection and design are the key criteria to develop a marketable nanomaterial. The present review summarizes the most relevant features of a nanoparticle from their routes of administration to their target organs, their target specific functionality, and finally their elimination from the body. While designing the clinically approvable nano-modules, prime importance has to be given on the route of entry. However, the route of entry is dependent on the tumor target. Therefore, nanoparticles aimed for GI tract-related tumor targets (e.g., colorectal cancer) should be designed for oral route of administration to maximize their accumulation at tumor target. Likewise, for lung cancer, focus should be given to designing an aerosol-based nano-drug delivery system. We have also discussed the nano-module properties for tumor-targeted drug delivery, imaging functions, and the excretion routes. Presently, at the clinical level, polymeric and liposomal nanoparticles are proving to be the most effective system for targeted drug delivery to the tumor target. However, colloidal nanoparticles with polymer coating are proving to be very effective for tumor imaging as well as thermo or radio-therapy.

This review summarizes the necessary views and suggestions that will help nanoscientists to design advanced full-proof target specific nano-drugs and nanodiagnostics to treat chemotherapeutic diseases such as cancer. In this review, we detailed the properties that should be considered and which characteristic of the disease tissues need to be looked into for better prognosis. Keeping in mind the major advantages and disadvantages of nano-system with respect to the oncologic disease, we hereby suggest properties of an ideal nano-system that need to be considered, while designing disease-oriented nano-medicine and diagnostics. Although, there are no clear-cut notions about the long-term complications of using these nano-systems, the efficiency of the nano-system as cancer theranostics is incredibly promising.

Acknowledgments Support was provided in part by Indian National Science Academy (INSA), Bhabha Atomic Research Centre (BRNS), and Department of Science and Technology (DST), India. T.B., P.P.M., and S.M. wrote the manuscript. Present review article was mainly written under the guidance of S.M and P.P.M. D.L., a native English speaker also helped in the structuring and English corrections. The authors declare no conflict of interest. We are thankful to Dr. Sayandip Mukherjee, Bangalore University, India and Dr. Matthew Thomas, Novartis, UK for their valuable suggestions. The funding was provided in part by INSA, BRNS (DAE), and DST, India.

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