Environmental Chemistry Letters
https://doi.org/10.1007/s10311-018-00841-1

REVIEW

Nanocarriers for drug delivery applications

Munusamy Chamundeeswari[1] · John Jeslin[1] · Madan Lal Verma[2]

Received: 8 November 2018 / Accepted: 14 November 2018

Abstract
Nanobiotechnology research has recently provided numerous basic and applied advances in the health sector. Nanocarriers have been developed for efficient drug delivery and diagnostic tools. Nanocarrier enables an effective, targeted biomolecular interaction in order to lower side effects caused during the treatment. Here, we review the problems associated with the conventional drug development and its delivery system. The efficacy of the treatment can be improved by the usage of efficient nanocarriers such as polymeric nanocarriers, superparamagnetic nanoparticles, quantum dot, dendrimers and lipid nanoparticles. We discuss the mechanisms of delivery. This review may aid in providing better solutions for unsolved problems that prevails with the day-to-day in silico, in vitro and in vivo drug delivery model development.

Keywords Nanocarrier · Drug delivery · Superparamagnetism · Biomedical applications

Introduction

Nanotechnology finds applications in various fields such as medicine, cosmetics, environmental and nutraceutical research areas (Baskar et al. 2017a, b; Muthukumar et al. 2014; Chamundeeswari et al. 2010). There are different forms of nanostructures such as nanofibers, nanocomposites, nanoparticles and nanotubes that effectively serve in the diagnosis and treatment of various diseases (Verma 2017; Baskar et al. 2017a, b; Chamundeeswari et al. 2013). These nanostructures are also employed as a carrier molecule or transporting agent for vaccines, drugs, genes, proteins and enzymes (Verma et al. 2013a, b, c, 2016; Baskar et al. 2018). The peculiar quantum properties associated with these nanostructures also enable them to be applied in the field of agri-food industry (Baskar et al. 2018).

Drug delivery is the process of transportation of a therapeutic agent into the body with appropriate pharmacokinetics, thereby creating the desired impact (Allen and Cullis 2004). The drug administered into the body is generally delivered through the gastrointestinal tract or through other routes than the gastrointestinal tract. The enteral and parenteral route is the conventional mode of drug administration. The enteral route of drug administration is through oral, rectal or sublingual, involving gastrointestinal tract for the drug delivery, while parenteral route of drug administration is through intravenous, intramuscular or subcutaneous. This involves routes other than the gastrointestinal tract (Bardal et al. 2011). The enteral route of administration is the highly preferable one due to its noninvasive nature. But, it reduces the bioavailability of the drug as the drug undergoes first-pass metabolism and incomplete drug absorption (Sala et al. 2018; Chowdary and Rao 2004).

Surgery, chemotherapy and radiation therapy have served as a major solution for treating deadly diseases such as cancer. This has resulted in various side effects due to the inverse action of the drug to the healthy cells and burst release. Therefore, it is necessary to develop an organized structure which could enable a sustained release of drug overcoming the first-pass metabolism and drug side effects. In recent years, the sustained release of the drug is achieved through nanostructures that could deliver drug at the desired site with reduced side effects and with potent pharmacological response (Zhang et al. 2013). However, cancer cells attain a defense mechanism by the efflux pump overexpression, self-repairing capacity, altered targets or by increased metabolism of the drug (Gottesman 2002; Bradshaw and Arceci 1998). These may affect the treatment process which

✉ Madan Lal Verma
madanverma@gmail.com

[1] St. Joseph's College of Engineering, Sholinganallur, Chennai 600 119, India

[2] Centre for Chemistry and Biotechnology, Deakin University, Victoria 3216, Australia

Published online: 21 November 2018

increases the value of specialized nanocarriers which can overcome all its defense mechanism.

The present review article discusses the different forms of nanocarriers and their mechanism of drug delivery. The emerging issues and future challenges in nanocarrier-mediated drug delivery are also addressed in order to design a novel high drug-loaded nanocarrier.

Research and development on nanocarriers

Nanocarriers are simply colloidal nanoparticles widely used for the transportation of a therapeutic agent or any other substances to a target site (Qian et al. 2012). The size of the nanocarriers lies between 1 and 100 nanometer (nm) in diameter (Peer et al. 2007), while the nanocarriers in the therapeutic application have to be less than 200 nm as the microcapillaries of the body are 200 nm (Singh and Lillard 2009). These nanocarriers provide good biocompatibility as they are inactive generally regarded as safe medium. These nanocarriers will have a long-term circulation period with the sustained release of drug overcoming the endosome–lysosome mechanism (Kingsley et al. 2006). The modification of the physiochemical properties of nanocarriers such as surface, composition as well as its shape can enhance their activity with decreased secondary effects (Sun et al. 2014). Thus, it creates a plethora of impact in the field of drug delivery. Though there is a wide range of nanocarriers developed, only a few possess remarkable ability to transport the drug to the targeted site. Some of the unique features of nanocarriers include (Mishra et al. 2010; How et al. 2013):

- Enhanced biodistribution and pharmacokinetics
- Enhanced stability
- Enhanced solubility
- Reduction in toxicity
- Sustained and targeted drug delivery

Types of nanocarriers

Nanocarriers with high surface-to-volume ratio majorly form three types such as organic nanocarriers, inorganic nanocarriers and hybrid nanocarriers. The structure and characteristics of different forms of nanocarrier are presented in Fig. 1 and Table 1, respectively.

Organic nanocarriers

Organic nanocarriers include nanoparticles such as solid lipid nanocarriers, liposomes, dendrimer, polymeric nanocarriers, micelles and viral nanocarriers. These organic nanocarriers are very versatile in nature with less toxicity and have the ability to conjugate a variety of drugs as well as ligands for drug delivery. Among organic nanocarriers, micelles and liposome mediated drug delivery has the ability to accumulate at the desired site by enhanced permeability and retention effect (Lopez-Davila and Loizidou 2012). Polymeric nanocarriers and liposome mediated drug delivery are the first generation nanocarriers as they are simple excipient (Bhatia 2016).

Solid lipid nanocarriers From the early 1990's, solid lipid nanocarriers are utilized as a suitable carrier for delivering lipophilic drugs. The solid lipid nanocarriers are prepared by the dispersion of melted solid lipids in water and stabilized by adding emulsifiers through micro-emulsification or through high pressure homogenization (Malam et al. 2009; Muller 2000). The solid form of lipids at room temperature like free fatty alcohol or acids; steroids or waxes; mono, di, or triglycerides are commonly used for the preparation of solid lipid nanocarriers (Üner and Yener 2007). Based on the production condition and composition, the drug molecules can be incorporated into the matrix, shell or core of the solid lipid. This solid lipid nanocarrier can overcome the drawbacks of conventional chemotherapy due to its versatile nature. The conventional solid lipid nanocarrier can be easily eliminated by Reticule Endothelial System and also offer a challenge in sustained drug release, incorporating ionic and hydrophilic drug molecules. Recently, the solid lipid nanocarrier can be used to incorporate ionic and hydrophilic anticancer drugs along with the lipophilic drug. For example, polymer-lipid hybrid nanocarrier has been explored as an effective source for oral drug delivery (Hallan et al. 2014). Certain new generation nanocarriers such as nanostructured lipid carrier (the mixture of liquid lipid and solid lipid) and lipid drug conjugates (water insoluble carrier molecule) are found to overcome the drawbacks of conventional solid lipid nanocarrier. This nanocarrier can be used for drug delivery through topical application, parenteral and oral administration. The solid lipid nanocarrier can act as an 'ideal tailor made carrier' to deliver any drug molecule at specified site. Various researches in solid lipid nanocarrier has been carried out to act as a vehicle to deliver genes (Yoo et al. 2005) and nucleic acids, to treat ophthalmic diseases, for controlled release of active agents (Muller 2000) and for targeted drug delivery of antitumor agents (Bondi et al. 2007; Stella et al. 2018).

Liposome Liposomes are lipid bilayers enclosing an aqueous core which forms a spherical vesicle that can be used to deliver both lipophilic and hydrophilic drugs at target site. The bilayer can differentiate it into unilamellar vesicle (one bilayer) or multilamellar vesicle (more than one bilayer). This vesicle serves as an agent to transport biologically active molecules at the specific site. However, these molecules have less half-life period in the systemic circulation.

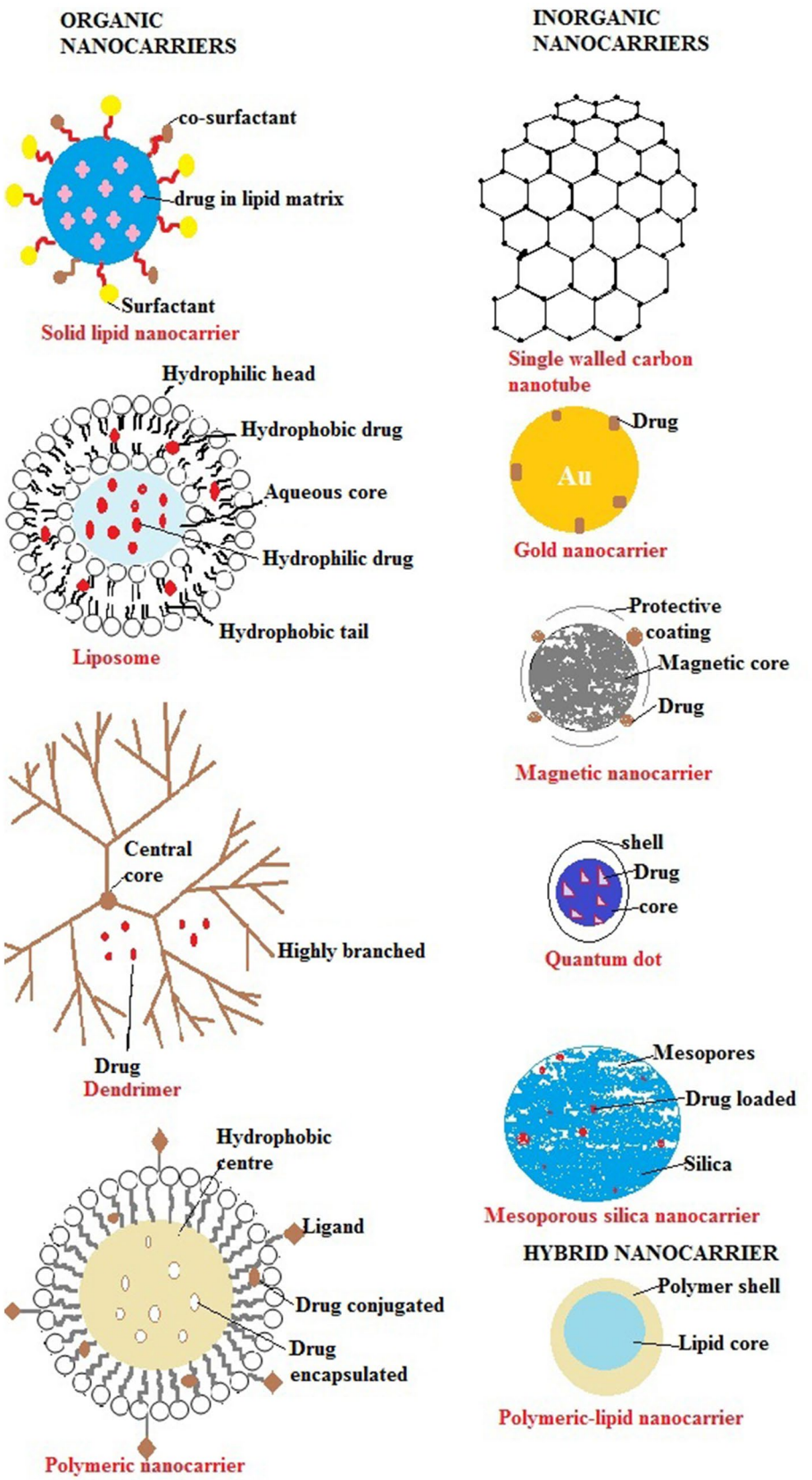

Fig. 1 Examples of nanocarriers. Different types of nanocarriers are employed to carry hydrophilic/hydrophobic drugs to the target site, such as inorganic nanocarriers: single walled carbon nanotube, gold nanocarrier, magnetic nanocarrier, quantum dot, mesoporous silica nanocarrier; organic nanocarriers: solid lipid nanocarrier, liposome, dendrimer, polymeric nanocarrier; and hybrid nanocarrier: polymeric-lipid nanocarrier

Table 1 Characteristics of different nanocarriers. Different nanocarriers are being prepared with different physicochemical methods. Such nanocarriers possess unique properties, most sought for drug delivery such as drug loading capacity, compatibility, stability and degradability. Nanocarriers have broader applications such as diagnosis of disease, targeted drug release, drug delivery and biosensing

Nanocarrier	Mode of synthesis	Size of nanocarriers (nm)	Properties of nanocarriers	Applications
Solid lipid nanocarriers (Kingsley et al. 2006)	High shear homogenization, hot homogenization, cold homogenization, ultrasonication, solvent emulsification, microemulsion, spray drying	50–100	Colloidal carrier, better stability, ease of upgradeability, biodegradable Low drug loading capacity, burst release	Drug delivery to liver cells both in vivo and in vitro, gene vector carrier, topical use, targeted drug delivery to solid tumors, antitubercular chemotherapy
Liposome (Sun et al. 2014; Mishra et al. 2010)	Mechanical dispersion, Solvent dispersion, detergent removal method	50–100	Phospholipid bilayer vesicle, Biocompatible, biodegradable, less toxicity	Trap hydrophilic and hydrophobic drug, optimal delivery of biologically active agent
Dendrimer (How et al. 2013)	Cascade reaction, either convergent or divergent approach, self-assembly	1–10	Radially symmetric, homogeneous, well defined, monodisperse hyperbranched molecules	Drug delivery, liver targeting, photodynamic therapy, neutron capture therapy, imaging, gene delivery
Polymeric nanocarriers (Lopez-Davila and Loizidou 2012)	Solvent evaporation, Emulsification/solvent diffusion, nanoprecipitation, salting out, supercritical fluid technology, dialysis, polymerization	10–100	Effective cell membrane permeation, stability in blood stream, biodegradable	High concentration of drug delivery, active and passive drug delivery, maintains stability of volatile pharmaceutical agent
Micelle (Bhatia 2016; Malam et al. 2009)	Supramolecular self-assembly, solvent/mechanical dispersion	10–100	Biostability, dynamic system, colloidal aggregate of amphiphilic molecule	Encapsulate either hydrophobic or hydrophilic drug
Carbon nanotubes (Muller 2000)	Chemical vapor deposition, laser ablation, carbon arc discharge	0.4–3	Hexagonal pattern, crystalline, third allotropic carbon sheet, single or multi-layer, dynamic strength, unique electrical and elastic property	Gene and drug delivery, peptide delivery, artificial implants, tissue engineering, cancer cell identification
Gold (Üner and Yener 2007)	Two phase synthesis, biphasic reduction	1–100	Multi-surface functionality, versatile, excellent biocompatibility, less toxicity, surface plasmon resonance property, Fluorescence resonance energy transfer phenomenon	Biosensing, functionalized AuNP improve drug delivery, imaging
Magnetic nanocarriers (Hallan et al. 2014)	Metal alkoxide hydrolysis, coprecipitation in microemulsion hydroxide coprecipitation, glycothermal synthesis, citrate gel process, glass crystallization	1–100	Superparamagnetism, chemical stability, high colloidal stability, magnetic moment	Magnetic separation, Magnetic Resonance Imaging, targeted drug delivery, hyperthermia, magnetic fluid, biosensing, thermoablation
Quantum dot (Geißler et al. 2010; Freeman et al. 2011)	X-ray lithography, molecular beam epitaxy, e-beam lithography, ion implantation, self-assembly followed by chemical reduction	2–10	Unique electronic properties, luminescence characteristics, narrow emission spectra, continuous absorption spectra, high light stability	Tracking macromolecules in tissue and cell, labeling cells and organelles, bioimaging, Biomarker detection

Table 1 (continued)

Nanocarrier	Mode of synthesis	Size of nanocarriers (nm)	Properties of nanocarriers	Applications
Mesoporous silica (Yoo et al. 2005)	Sol–gel method, self-assembly, hard and soft templating, aerogel approach, dissolving-reconstruction method	1–100	Hundreds of pores with honey-comb structure, good biocompatibility, high loading capacity, good thermal and chemical stability, controllable pore, high drug payload, versatility for drug loaded with hydrophilic and lipophilic characteristics	Sustained drug delivery, peptides and protein delivery
Hybrid nanocarriers (Qian et al. 2012)	Miniemulsion copolymerization, nanoencapsulation, hydrolysis and condensation, spray pyrolysis, supercritical fluid-assisted method	1–100	Enhanced chemical and physical properties based on nanostructure and spatial distribution of components	Synergetic therapy, targeted drug delivery, biosensing, imaging

Therefore, liposomes can be coated with polymeric molecules like polyethylene glycol to form PEGylated liposomes or stealth liposomes. This stealth liposome has high stability and long half-life period in the blood by escaping from the Reticule Endothelial System elimination producing a sustained drug release (Torchilin 2005). The drug molecules incorporated in the liposomes improves the pharmacokinetics and biodistribution of the incorporated drug molecules. For instance, the drug molecule, doxorubicin in stealth liposome reduces the distribution of drug in the plasma and its concentration in the healthy cells (Wang et al. 2012) than the drug in solution. The controllable switch nanocarriers like temperature response liposomes are reported to enhance the drug release locally (Rosenblum et al. 2018).

Dendrimers Dendrimers are branched macromolecules consisting of a central core (initiator core) giving rise to various arms (terminal active groups) (Kresge et al. 2001). Dendrimers can be produced from nucleotides, sugar molecules as well as amino acids. They are multivalent, highly branched with diverse peripheral groups and have a distinct molecular weight serving it as a unique source for drug delivery. The stepwise synthesis of dendrimer can yield an irregular well-arranged branching pattern of dendrimer (Basu et al. 2004). The branch level added to the core is known as a generation which on further extension gives a bulk external group. The drugs molecules can be encapsulated within the core cavities through hydrophobic bonds, chemical interaction or through hydrogen bonds with improved surface functionality. The drug molecules can also be attached to terminal active groups through covalent bonds. These dendrimers possess a well defined structure which can be finely tuned to encapsulate various drugs like anti-Tuberculosis drug, rifampicin (Mignani et al. 2018). However, dendrimers with single generation can cause disassociation of the attached molecules (de Groot et al. 2003). The major mechanism in drug–dendrimer interaction is through physical and chemical bond formation. This dendrimer can be used in magnetic resonance imaging scanning, gene delivery, drug delivery, antiviral and vaccine delivery (Stiriba et al. 2002). It is also found useful in linking with prodrugs. Different anticancer drugs such as cisplatin, doxorubicin are extensively linked with the dendrimer to produce enhanced anticancerous activity (Lai et al. 2007; Zhuo et al. 1999; Malik et al. 1999; Bhadra et al. 2003; Lee et al. 2006).

Polymeric nanocarriers Polymeric nanoparticles are colloidal, solid nanoparticles produced from any biodegradable polymers (Bamrungsap et al. 2012). It can be a reservoir type (nanocapsules) dissolving/dispersing the drug molecules in the core of polymer or matrix type (nanospheres) that entraps drug molecules within the polymer matrix. Both the type can also chemically conjugate or adsorb the

drug on its surface (Prabhu et al. 2015). Inside the human body, biodegradation of the polymeric nanocarriers produce monomers that can be easily degraded by the metabolic pathways (Mishra et al. 2010). The polymeric nanocarriers can be produced from both natural (such as chitosan, gelatin, albumin, collagen, alginate etc.) and synthetic polymers (such as poly(lactic-co-glycolic acid, polyethylene glycol, polyglutamic acid and polycaprolactone) (Wang et al. 2009). This polymeric nanocarrier possess advantages over other nanocarriers in terms of higher stability, drug payload, half-life time in systemic circulation and sustained drug release. The anticancer drug like doxorubicin is entrapped within the polymeric nanocarriers to target cancerous cells. The controlled release of drug can be enhanced by changing the physiochemical properties of the polymeric source. It is also possible to produce multifunctional polymeric nanocarriers which enable incorporation of multiple drugs in it (Zhu and Liao 2015). There is also advancement in the polymeric nanoparticle synthesis for targeted drug delivery through stimuli sensitive polymers (smart polymers). These smart polymers release drug on internal (low pH, redox, enzyme) and external environmental stimulus (temperature, light, ultrasound, magnetic and electric field). The design challenges in smart polymers include scalability, toxicity/biocompatibility, stimuli sensitivity. However, intrinsic stimuli have a challenge of variation between clinical and preclinical models as well as extrinsic stimuli involve challenges like stimuli providing compliance and tissue penetration and localization (Rosenblum et al. 2018). Apart from these challenges, a polymeric nanocarrier stands as a promising nanocarrier for targeted drug delivery.

Micelles McBain introduced the term 'micelle' in 1913 which is the colloidal aggregates formed by mixing detergent in water (liquid colloid). They are amphiphilic molecules with nonpolar tail (hydrophobic) facing the centre and polar head (hydrophilic) having contact with the external solvent (Wennerström and Linman 1979). Likewise, inverse micelle can be obtained by amphiphilic or detergent molecule in nonpolar solvent which produces micelle with head facing centre and tail facing outside. The solution condition (temperature, ionic strength and pH) and nature of amphiphilic molecule determine the size and shape of the produced micelle nanoparticles. Critical micellar concentration (surfactant concentration) determines the proper micelle formation. Below the critical micellar concentration, proper micelle formation will not occur. Along with amphiphilic molecules, polymeric micelles are formed in certain solvents by means of two copolymers. One copolymer is soluble in the solvent while other insoluble in the solvent. The insoluble copolymer forms the core and soluble copolymer forms the shell in which the copolymer form the chain or micellar aggregate (Riess 2003). This polymeric micelle offers themselves in the industrial and drug delivery applications (Zhang et al. 2009; AL-Sabagh et al. 2007). In case of disease associated with hair follicle, these polyemeric micellar nanocarriers that finely target pilosebaceous unit. For example, adapalene encapsulated in micellar nanocarrier increased its targeting efficiency to 4.5 as well as 3.3-fold higher with finite dose (Kandekar et al. 2018). In terms of oligonucleotide delivery, fluroscently labeled aptamer based on anti-human epidermal growth factor receptor encapsulated in pH-responsive micellar nanocarriers has a potential to effectively delivering nucleic acids to the target cancer sites (Shen et al. 2018).

Inorganic nanocarriers

Inorganic nanocarriers include gold, magnetic nanocarriers, quantum dots, and mesoporous silica etc. The inorganic nanocarriers take the advantage of tractable properties. Inorganic nanocarriers can be effectively used in biosensing, cell labeling, targeting, imaging and as well as in diagnostics. These inorganic nanocarriers also possess synergetic therapeutic effect (Santos et al. 2014). Furthermore, altering the composition or size of the inorganic nanocarriers enables remarkable magnetic, plasmonic and optical properties. However, use of heavy metals as inorganic nanocarrier would result in the long-term health issues (Ma et al. 2015).

Carbon nanotubes The peculiar biological and physicochemical properties of carbon nanotubes make it an ideal and a promising source for drug delivery. Carbon nanotube is formerly found by Iijima (1991). These are tube like hollow structure containing sheets of graphene rolled together at discrete and specific angles (Bianco 2004; Iijima 1991). The carbon nanotubes can be single walled or multi-walled carbon nanotubes based on the number of graphene sheets rolled together. The cross section of these tubes can be 0.4–100 nm in diameter while the length of the tube elongates thousand times the diameter. In drug delivery process, this carbon nanotubes has a wide applications through its distinct characteristics such as high aspect ratio, ultralight weight with high surface area, nanosized needle structure, distinguished chemical, thermal, mechanical and electrical properties (Ng et al. 2016; Madani et al. 2011). The endocytosis process occurs readily through its needle-penetration enabling it to cross the barriers or cell membrane (Pérez-Herrero and Fernández-Medarde 2015). The functionalized nanotubes are water soluble with long circulation period in the serum. However, non-functionalized carbon nanotubes are toxic and water insoluble in nature. The structural stability, flexibility and surface modification enable it as a suitable agent to target the cancer cells. In that concept, functionalized carbon nanotubes are widely used to encapsulate or link with anticancer drugs like Paclitaxel (Lay et al. 2010),

Mitomycin C (Levi-Polyachenko et al. 2009), Doxorubicin, Methotrexate (Das et al. 2013), etc. for targeted drug delivery. Apart from the biomedical application, carbon nanotubes form an ideal source for many industrial applications due to its inevitable properties. Graphene is another important carbon based nanocarrier which is efficient in drug delivery.

Gold nanocarriers Noble metal, gold has influenced the nanotechnology to built gold nanoparticles to serve as effective agent to serve different applications such as photoacoustic imaging (Wang et al. 2004), chemotherapy, surface enhanced resonance spectroscopy (Qian et al. 2008; Garcia 2011), gene therapy (Cao et al. 2002) and photothermal therapy (Lu et al. 2010). Both top down and bottom up approaches can be employed for synthesizing of gold nanoparticles. There are different anisotropes of gold nanoparticles like nanostar, nanorod, nanocage, nanoshell, nanoprism etc. Among the distinguishable properties of gold nanocarriers, optical property is the foremost one which attracts it to the biomedical field. It enables different biomolecules such as enzymes, carbohydrates, flurophores, peptides, proteins and genes to get attached to the gold nanoparticles. This enables molecules to be effectively transported within the cell overcoming the barriers associated in it. The major application of gold nanocarriers enables imaging of tumor cells efficiently (Loo et al. 2005; Huang et al. 2006a, b). The nanoshell with optical coherence tomography agents enables to obtain potential three dimensional images of tissues (Chen et al. 2005; Gobin et al. 2007). Gold nanocarriers are also used for positron emission tomography, single photon emission computed tomography and computed tomography analysis (von Maltzahn et al. 2009).

Magnetic nanocarriers The magnetic nanocarrier typically consists of a magnetic core. Generally, metal nanoparticles are magnetic in nature than the metal oxide nanoparticles. This magnetic property and its modified properties enable it to be employed for the biosensing application (Koo et al. 2011; Berry 2009). The superparamagnetic nanoparticles are found to have high susceptibility to magnetic field than the paramagnetic nanoparticles. The polymer coated superparamagnetic iron oxide nanoparticle has been widely opted for molecular imaging due to its magnetic resonance hence used as a contrast agent in the imaging purpose (Huang et al. 2011). Also, it enhanced the internalization in cell and particle clearance. The magnetic field removal sways the paramagnetism. Superparamagnetic iron oxides are also used to target cancer cells through passive targeting (Barry 2008). The surface functionalization of magnetic nanoparticles enables it to be used as a magnetic resonance imaging dependent sensor in implant components (Toma et al. 2005). Examples of magnetic nanoparticles are haematite, maghemite, nanoferrites and magnetite. The unique property of magnetic nanoparticle enables it to be utilized for targeted drug and gene therapy, hyperthermia mediators (Van Landeghem et al. 2009; Kim et al. 2008; Tang et al. 2008) and contrast agents (Babincova et al. 2004). An attempt is done to link Epirubicin drug in ferrofluid resulted in the drug accumulation at the desired site (Lubbe et al. 2000). However, there lies a problem in deep penetration of magnetic field in the animal models. Therefore, it provides a drawback to use magnetic nanocarriers only on the targets close to the body (Grief and Richardson 2005). Magnetofection is another term which employs magnetic nanocarrier in gene and antisense therapy (Mykhaylyk et al. 2007). Size changeable nanocarrier, Trojan Horse containing paclitaxel showed greater penetration into tumor cells and controlled drug release into it with higher cytotoxicity (Lai et al. 2018).

Quantum dot Quantum dots include atoms in the II–VI (Se, Zn, Te, Cd) or III–V (In, As, P) element groups in the periodic table. They are colloidal nanocrystals and energy donors (Alivisatos 1996). The size of the quantum dot varies the light emission between UV-near IR regions, i.e., the smaller quantum dots (~2 nm) emit blue fluorescence and larger quantum dots (~5 nm) emit red fluorescence (Bruchez et al. 1988). This optic property along with prolonged light emission and less photobleaching makes it superior over other organic dyes. This enables it to be used in the cell imaging purposes. For example, quantum dot—peptide conjugate is employed for in vivo tumor vasculature targeting in mice (Mkerman et al. 2002). Generally, the toxic cadmium in CdSe quantum dot is enclosed within ZnS shell to protect from toxicity. This enhanced the accumulation of nanoparticles in the desired vascular site. These quantum dots are also known to be efficient as delivery system and reporter system. For instance, surface modification of quantum dots by homing tumor peptide effectively attach to the nucleolin on the cancerous cells which also enhanced the cellular uptake (Christian et al. 2003). Similarly, small interfering RNA bound quantum dots are also found enhance the gene knockdown (Derfus et al. 2007). Quantum dots are also used as energy transfer quencher in charge transfer process (Medintz et al. 2009), quantum dot-fluorescence resonance energy transfer system (Geißler et al. 2010), chemiluminescence-resonance-energy transfer acceptors (Huang et al. 2006a, b; Freeman et al. 2011) etc.

Mesoporous silica Mesoporous silica possesses a large porous honey-comb structure that enables incorporation of more drug molecules into it. Due to its simplicity and availability, it has a tremendous application in the biomedical field. It can encapsulate both the hydrophobic and hydrophilic drugs which can be attached to a ligand molecule for targeted drug delivery (Li et al. 2017). The characteristics

of mesoporous silica include large pore volume with high surface area, biocompatibility, high drug loading capacity and thermochemical stability. In cancer treatment, both active and passive targeting can be successfully carried out through this mesoporous silica (Wang et al. 2015). For example, camptothecin and methotrexate anticancer drugs are efficiently delivered by using mesoporous silica (Rosenholm et al. 2010; Lebold et al. 2009).

Hybrid nanocarriers

Hybrid nanocarriers are nanocarriers combining two or more organic and inorganic nanocarriers together or individually. It includes organic–inorganic, inorganic–inorganic, multi components. Some of the examples for hybrid nanocarriers are a lipid-polymer hybrid; ceramic-polymer hybrid etc. incorporating two nanoparticles together will possess the dual nature of both the nanoparticles enhancing its properties many folds (Qian et al. 2012). In the case of organic nanocarriers like liposomes, it suffers from internal solution leakage as well as less stability. This makes it to be removed easily from the circulating blood. Therefore, additional stabilization makes it suitable for drug delivery. Hybrid nanocarrier system serves for that disadvantages (Peer et al. 2007).

The selection of nanocarriers depends on the site of action, type of drug to be conjugated, physiological barriers during the drug delivery, stability and solubility of the nanocarriers. The utmost goal of selecting suitable nanocarriers for drug delivery is to increase the bioavailability of the therapeutic agent with minimum or no side effects.

There is different research works carried out in these hybrid nanocarriers. The mesoporous silica nanoparticle-lipid bilayer hybrid nanocarrier system has showed a distinguished intracellularly delivery of zoledronic acid in the breast cancer with high retension rate (Han et al. 2015; Desai et al. 2017). This system enables a stimuli-response release of drug preventing the premature release of drug into the body. Novel albumin hybrid nanocapsules are found to be efficient in encapsulating the hydrophilic peptides or other small drug molecules for targeting cancer cells. It enables an even distribution on the microenvironment of the tumor cells and reduced toxicity (Zhou et al. 2013). Similarly, ferritin involving in the drug delivery application finds an impressive advantage in encapsulating therapeutic agents and the stimuli-response release for drug enables sustained release of drug into the target site (Khoshnejad et al. 2018). There are also many researches carried out for the in vivo delivery of small interfering RNA by means of core/shell lipid/cholesterol-grafted poly(amidoamine) hybrid nanocarriers (polyethyelene glycol-Liposome/small interfering RNA nanoparticles and peptide HAIYPRH, named as T7-Liposome/small interfering RNA nanoparticles). This system has the benefit of long stability with high cellular uptake and is efficient in the theranostic application for gene silencing (Gao et al. 2014).

Functionalization of nanocarriers

The process of adding functional groups to the surface of the nanocarrier system is termed as functionalization. It is necessary to control the nanocarriers–biosystem interaction during the drug delivery process and its targeting capacity (Chou et al. 2011). For instance, intracellular drug delivery specifically tailored nanoparticles will possess enhanced payload with binding capacity, specific cytotoxicity and cellular internalization (Saha et al. 2011). Different methods are strategically employed for the surface functionalization of nanoparticles with different ligands like small molecules, biomolecules, surfactants, polymers, dendrimers etc. The multivalent surface enables covalently or non-covalently conjugating multiple bioactive agents or biological macromolecules to achieve target-specific interaction and biocompatibility (Moyano and Rotello 2011).

Functionalization of nanocarriers by polymer

The coating of nanoparticles with the polymer is a versatile process that has the tendency to impart macromolecular properties to the nanoparticles thus making it a target-specific. The polymer coating enables the passive targeting of tumor cells and sustained release of therapeutic agent (Yavuz et al. 2009). For example, polyethylene glycol makes the nanoparticles target-specific through enhanced permeability and retention effect (Matsumura and Maeda 1986; Petros and DeSimone 2010). The stealth nanocarriers provide increased circulation time, enhanced particle permeation probability into the tumor cells, and also reduced the adsorption of serum proteins in the blood (Peer et al. 2007; Kommareddy and Amiji 2004; Niidome et al. 2006). The attachment of targeting molecules on stealth nanoparticles serves the purpose of targeting tumor cells effectively (Wang et al. 2011a, b). This PEGylation process also improves the stabilization of the nanoparticles than the unmodified nanoparticles. An example of functionalized nanocarrier with polymer includes a cooperative nanosystem which is used for passive targeting of murine tumor tissues. The cooperative nanocarrier system consists of gold nanorod coated with polyethylene glycol and liposomes loaded with doxorubicin or a magnetic nanoworm. When the first component gold nanorod was irradiated by infrared, it acts as a photothermal antenna to heat up the tumor tissues. This, in turn, will recruits the second component, targeting cyclic peptide species binds to the upregulated p32 stress related protein in the tumor cells. This thermal treatment reduced the tumor

volume efficiently (Zhao and Karp 2009; von Maltzahn et al. 2011).

Functionalization by tagging ligand molecules

The binding of nanocarriers with ligands like green fluorescent protein enables them to be used for biosensing and diagnosis of diseases (You et al. 2007; Jiang et al. 2010; El-Boubbou et al. 2010). The nanocarriers complexed electrostatically with green fluorescent protein is found to be an efficient nanosystem to discriminate metastatic cells, tumor cells as well as healthy cells in the murine and human cell lines (Bajaj et al. 2010). The sensing property of green fluorescent protein complexed gold nanocarriers is found to be controlled by the ligand headgroup change and also by the cell-nanoparticle affinity (Moyano et al. 2011). The cellular uptake and internalization are the necessary aspect for drug delivery that depends on the surface charge of the functionalized nanocarriers, i.e., the negatively charged cell can be easily internalized by positively charged functionalized nanocarriers. For example, functionalization of magnetic iron oxide nanoparticle is carried out by guanidine headgroup. It is also found that the negatively charged functional groups on the surface of the nanocarrier (carboxylate on iron oxide nanocarrier) can interact with the cell membrane by means of diffusion or through pinocytosis. Moreover, the neutral surface charge of functionalized nanocarrier can exhibit a specific cellular interaction (Kim et al. 2010; Shi et al. 2007).

Functionalization of nanocarriers by biomolecules

Biomolecules such as monoclonal antibodies, oligonucleotides, proteins and small interfering RNA can be used for functionalization of nanoparticles. This biomolecules conjugated nanocarriers can reduce the cytotoxicity and enable targeted drug delivery as they can specifically bind to the cell surface receptors delivering an effective therapeutic effect (Verma and Stellacci 2010). These biomolecules can be covalently conjugated to the nanocarriers through alkyl thiol groups or through glycol spacer molecule (Jiang et al. 2008). This bio-inspired nanocarrier system is widely applicable for biosensing, bioimaging, and targeted drug delivery as they are biocompatible in nature (Giljohann et al. 2009). The cell-mimicking characteristic of this bio-inspired nanocarrier enables a long-term circulation within the biosystem. It can overcome the reticulo endothelial system. For example, a biomimetic nanocarrier comprising of a luminescence centre (persistent luminescence nanophosphors) and loading surface (mesoporous silica). The doxorubicin loaded in the erythrocyte bioinspired membrane nanoprobe is analyzed as the vital therapeutic and diagnostic agent (Balmert and Little 2012).

Drug loading in nanocarriers and release strategy

The drug loading and drug release occur effectively because of the presence of functional groups on its surface. There are three major strategies enables the efficient loading of the therapeutic agent within the nanocarrier system (Verma et al. 2013b, c; Puri et al. 2013; Verma et al. 2012). They are:

- Conjugation through covalent bonding
- Encapsulation
- Electrostatic interaction

Covalent bonding

A nanocarrier system can incorporate a high concentration of therapeutic agent by the presence of appropriate functional groups on its surface. The drug conjugates covalently with the nanocarrier due to the presence of a vast number of a functional group on its surface (Liu et al. 2018). The drug release after the conjugation occurs through enzymatic cleavage or through the chemical breakage of liable hydrolytic bonds. The nanocarrier-drug conjugate diffuses slowly to the cell membrane enabling specific controlled drug release into the target site. This covalent conjugation enables stable nanocarrier system for targeted drug delivery (Chang et al. 2012).

Encapsulation

The encapsulation is another strategy to load therapeutic drug into the nanocarrier system. The hollow space within the nanocarrier enables sufficient encapsulation of drug molecules. Nanocarriers like polymeric nanocarriers, nanocapsules, dendrimers etc. can encapsulate the drug efficiently within its hollow cavities (Alvarez-Román et al. 2004; Arpicco et al. 2015). The hydrophobic nature of the inner cavities enables to incorporate more hydrophobic drug within the nanocarrier by means of hydrophobic interaction or through hydrogen bonding. This encapsulation can also occur through physical interactions. In the case of liposomes, the encapsulation occurs through active and passive drug loading. The drug release occurs through pH prone neutralization or hydrolysis, thiolysis and through thermolysis mechanism (Patil et al. 2016).

Electrostatic interactions

The nanocarriers with functional groups such as carboxyl and amine groups increase the solubility of the hydrophobic drug. These high density functional groups make the

drug molecules to electrostatically interact with the nanocarrier system. Certain nonsteroidal anti-inflammatory drugs like indomethacin, ciprofloxacin, diflunisal, ibuprofen etc. are incorporated efficiently within the nanocarrier through electrostatic interaction (Kumari et al. 2014). Liposomes generally possess electrostatic charges on the surface due to its double electrical layer.

Nanocarriers-strategies of the targeting mechanism

The major challenges in clinical research include finding a correct target for disease diagnosis, finding an appropriate drug for disease treatment and also finding the best targeting strategy for drug delivery at the specific site. In 1906, Paul Ehrlich postulated using a magic bullet, that the targeted drug delivery is very important for disease treatment. It increases the therapeutic efficacy by reducing non-specific drug distribution and its side effects (Imae 2012). The extensive approach of drug delivery depends on the physiological characteristics of the target area. The major strategies for targeting nanocarriers to the specific site include (Davis et al. 2008):

- Administration of nanocarriers at the target site directly
- Directing magnetic nanocarriers using magnetic fields to the target site
- Active targeting
- Passive targeting

The administration of nanocarriers with a therapeutic drug directly to the target site technically sounds difficult. This is due to the fact of systemic spreading of disease all over the cells or tissues in the body. The localized disease site is rare to occur (Torchilin 2000). The second approach of directing magnetic nanocarriers to the target site with the application of a magnetic field is a noninvasive technique. This technique has been verified both in vitro and in vivo tests. Though this approach has many advantages like increased cellular uptake of magnetic nanocarriers at the diseased site, it also possesses certain limitations. The drug delivery efficiency depends on the field strength, the physicochemical properties of the particles, vascular supply, the depth of the target tissue, and the rate of blood flow (Torchilin 2010; Barakat 2009). This approach also affects the blood flow rate in the blood vessels. The other two approaches like active and passive targeting are the widely used techniques up to date.

Active targeting

The active targeting strategy possesses small ligand molecules on the surface of the nanocarriers that actively binds to the specific receptor, retains at the target site and can be actively uptaken by the diseased cells. This approach is the widely accepted one and has high selectivity in binding the target site with high affinity. The binding ligand should have specificity in determining the protein receptors overexpressed in the diseased cells which are absent the healthy one (Nacev et al. 2010). For example, cancer or tumor cells have overexpressed proteins on their surface. This active targeting enables increased intracellular uptake of the drug by the diseased cells. The targeting ligands include the small molecules, lectins, antibodies and its fragments, lipoproteins, peptides (arginyl glycylaspartic acid), hormones, glycoproteins (transferrin), polysaccharides, low molecular weight vitamins (folic acid), nucleic acids and growth factors (Danhier et al. 2010;Pérez-Herrero and Fernández-Medarde 2015). The nanocarriers can also be modified to target multiple moieties as they have a high surface-to-volume ratio. The active targeting is advantageous over passive targeting as it prevents the off-site drug delivery and has the ability to reduce multi-drug resistance (Sun et al. 2014). The internalization or endocytosis with reduced tumor accumulation due to the ligand–receptor interaction has attracted active targeting in the cancer treatment. This is due to the specific receptors that are expressed only in the cancer cells (Patil et al. 2009). For instance, Transferrin receptor in breast cancer cells, epidermal growth factor receptor, folate receptors in ovarian or lung cancer cells, aptamer etc. (Pirollo and Chang 2008). The use of folate ligands has the advantage of its small size with molecular weight ~ 441 kDa than the antibodies with molecular weight ~ 160,000 kDa (Deshpande et al. 2013). The smaller size molecule penetrates more easily to the distant target site than the larger one.

In the case of the blood–brain barrier, the endothelial cell surface expresses transferrin receptors which enable the use of transferrin ligands as the targeting agent for the antitumor drug delivery (Sega and Low 2008). An alternative approach in active targeting mechanism is targeting the leaky vasculature of tumor vessel. This would break the nutrient and oxygen supply to the tumor vessels thereby destroying the tumor cells (Gan and Feng 2010). The vascular active targeting can also target its moieties such as vascular cell adhesion molecule, vascular endothelial growth factors, $\alpha_v\beta_3$ integrins and matrix metalloproteases (Neri and Bicknell 2005; Martinez-Carmona et al. 2015; Zhou 2009; Byrne et al. 2008). This vascular targeting also prevents tissue penetration and drug resistance can be prevented as the markers in the endothelial cell are more stable than in the tumor cells (Linkous and Yazlovitskaya 2012). Active targeting of caveolar markers in the endothelial cell is another strategy for bypassing

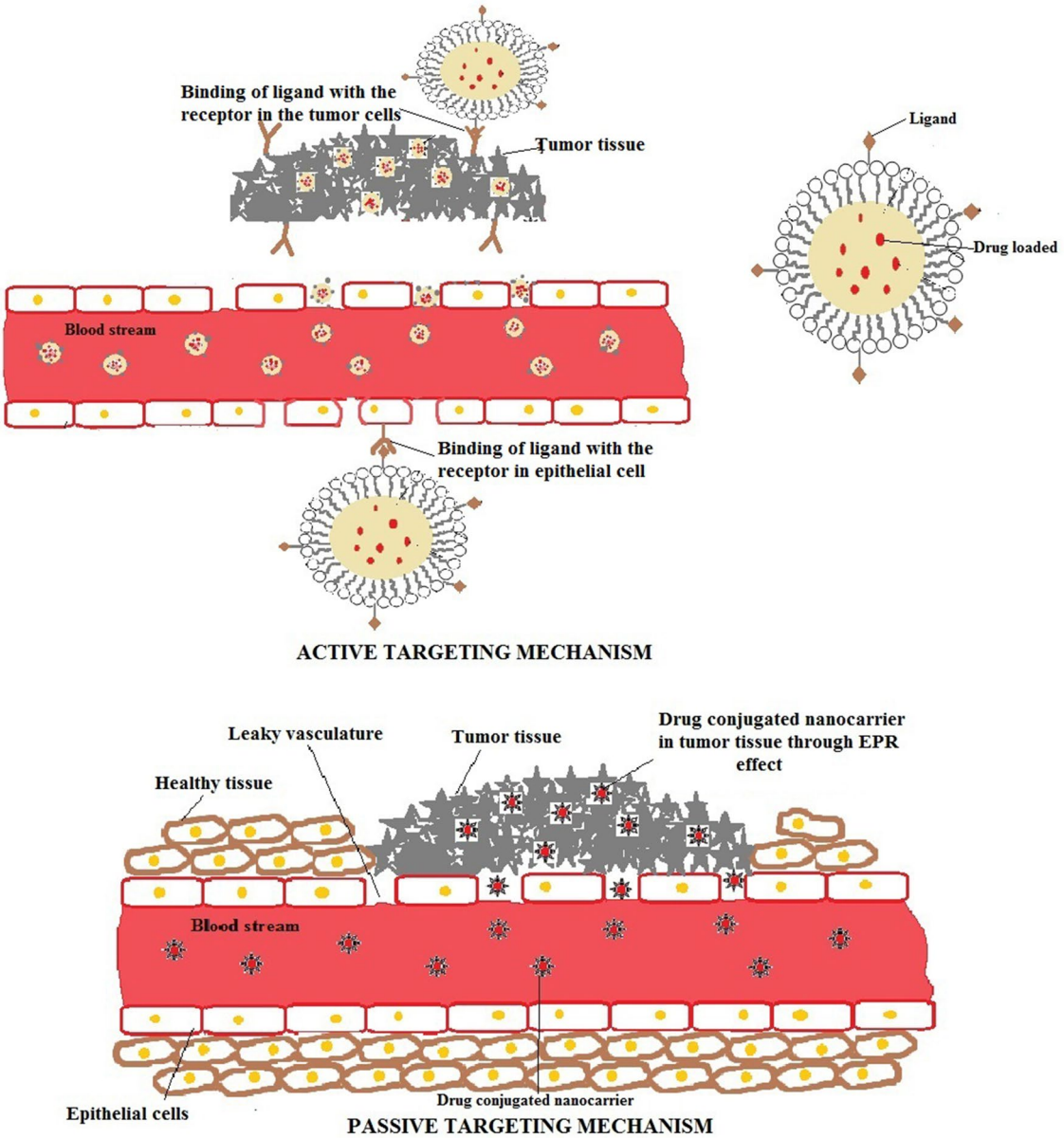

Fig. 2 Mechanism of nanocarrier targeting. In active targeting, the drug-loaded nanocarriers with receptor specific ligands circulates in the blood stream and release the drug at the target tumor site. While, in passive targeting, the enhanced permeability and retention effect enables the drug conjugated nanocarriers to penetrate deep into the tumor site)

endothelial barrier (Gosk et al. 2008; Wang et al. 2011a, b). Figure 2 explains the active targeting of polymeric nanocarrier in which the ligand binds to the receptors of epithelial cell and also to the tumor cell.

In concise, actively targeting nanocarriers has the advantage of targeting sites disseminated all over the body without involving the enhanced permeability and retention effect. But the reduction in the manufacturing cost of actively targeting nanocarriers is essential for the development of economically valuable therapeutics for disease treatment. Recently, for treating genitourinary tumors, a suppressor gene RB94 is encapsulated in the anti-transferrin receptor decorated cationic liposomes under low cost good manufacturing practices scale-up techniques (Pirollo et al. 2008).

Passive targeting

Enhanced permeability and retention effect is the basic route for passive targeting. The deadly disease like cancer leads to leaky vasculature with endothelial cell dimension many folds (50–70fold) more than that of the healthy blood vessels (Chrastina et al. 2011). This also has lymphatic drainage

with inner vascular growth providing irregular angiogenesis. Therefore, nanocarrier with molecular weight more than 40 kDa can extravasate through the leaky vasculature of inflamed area, tumor tissue or ischemic tissue. Passive targeting of this leaky vasculature can enable the nanocarrier to enter through the interstitial space in the endothelial barrier enhancing the drug conjugated nanocarrier to accumulate at the disease site. This effect is known as the enhanced permeability and retention effect explained by Matsumura and Maeda in 1986 (Haley and Frenkel 2008; Torchilin 2011). This enhanced permeability and retention effect prevents the undesired side effects by the target-specific accumulation of drug at the diseased site. The targeting of nanocarrier with low molecular weight drug has the drawback of diffusing away from the target site and re-entering the blood circulation. The accumulation of nanocarrier at the target site depends on its charge due to the functional group and its size (Matsumura and Maeda 1986). The nanocarriers with hydrophilic surface and size less than 200 nm are found to have enhanced permeability and retention effect as their blood circulation time is higher (Fang et al. 2011). Thus, targeting tumor based on its immunochemical and patho-physiological characteristics overcome the above drawback (Acharya and Sahoo 2011).

Though the enhanced permeability and retention effect has a greater impact on the passive targeting of tumor cells, this enhanced permeability and retention effect is not found in every tumor cells. This size dependent enhanced permeability and retention effect is heterogeneous for different tumor and for different patient (Haley and Frenkel 2008; Ruoslahti et al. 2010). Enhanced permeability and retention effect is also affected due to the high fluid pressure at its interstitial space, relative hypoxia; complexity in the extracellular matrix, endosomal escape and due to its difficulty in tumor penetration as endothelial gaps varies (Lee et al. 2010). Therefore, the study of enhanced permeability and retention effect in different tumor is essential to produce nanocarriers with improved efficacy and target-specific therapeutic effect.

In passive targeting, only 15 nanocarriers (Doxil™, Marqibo™, Abraxane™, Onivyde™, DaunoXome™-US; Genexol-PM™-Korea; Mepact™, Myocet™-Europe; SMANCS™-Japan) have been successful in the preclinical studies and recommended for clinical use (Shi et al. 2017). However, no nanocarriers have been approved for the clinical use through active targeting. This is due to the difficulties in the regulatory and scale-up process of actively targeting nanocarriers. The foremost passively targeting nanocarrier reaching the clinical use is DOXIL™ which is doxorubicin in PEGylated liposome (Barenholz 2012). Liposomal nanocarrier containing two drugs cytarabinee and daunorubicin [CPX-351 (Vyxeos™)] is proved to be an efficient treating acute myeloid leukemia (Lancet 2016). The diagrammatic representation in Fig. 2 describes the accumulation of nanocarriers with the therapeutic agent at the tumor site through the leaky vasculature.

Precisely, the passively targeting nanocarriers solely depend majorly on the enhanced permeability and retention effect but the above drawbacks limit its use in the diagnostic and therapeutic process. Currently, various strategies and tools to evaluate nanocarrier interactions have been developed to cut off the limitations. For example, the use of multilayered passively targeting nanocarriers for diagnostics and therapeutics (Poon et al. 2011; Tasciotti 2008); ionisable lipids in case of endosomal escape (Mi 2016; Ramishetti et al. 2016; Semple 2010; Tam et al. 2013).

Conclusion

Thus, these nanocarriers have tremendous exploration in the drug delivery application than the conventional treatment. Therefore, there lies a large concern to produce economically valuable nanocarriers with proper good laboratory practice techniques which fits all the standards needed to serve as a potential agent for the drug delivery application.

The future decade in drug delivery would witness deep involvement of nanocarrier in diagnosis and treatment of various diseases. The main challenge lies will be on the expansion of novel nanocarriers for the biomedical purposes and the barriers associated with target drug delivery. The ability of tumor localization and imaging will further brings out the unexplored nanocarriers successfully to the clinical trials. The future researches can be extended to the stimuli-response drug release by non-toxic, biocompactable, biodegradable nanocarriers. This can prolong the drug release strategy and reduce the side effects associated with the unnecessary cell damage. Also, for circulating tumor cells, it is possible to design a stimuli-response surface modified (antibody bound) nanocarriers to target the tumor cells with a long half-life circulation reducing the premature release. The inorganic nanocarriers possess large benefits than the organic nanocarriers as they can be easily prepared and are controllable in nature. The development of hybrid nanocarriers or composite nanocarriers or multifunctional inorganic nanocarriers can enhance the therapeutic and diagnostic efficiency of the single nanocarrier.

Acknowledgements Authors would like to thank Director, Centre for Chemistry and Biotechnology, Deakin University Australia for providing research facility to carry out this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Acharya S, Sahoo SK (2011) PLGA nanoparticles containing various anticancer agents and tumour delivery by EPR effect. Adv Drug Deliv Rev 63:170–183. https://doi.org/10.1016/j.addr.2010.10.008

Alivisatos AP (1996) Semiconductor clusters, nanocrystals, and quantum dots. Science 271:933–937. https://doi.org/10.1126/science.271.5251.933

Allen TM, Cullis PR (2004) Drug delivery systems: entering the mainstream. Science 303:1818–1822. https://doi.org/10.1126/science.1095833

AL-Sabagh AM, Maysour NE, El-Din MRN (2007) Investigate the demulsification efficiency of some novel demulsifiers in relation to their surface active properties. J Dispers Sci Technol 28:547–555. https://doi.org/10.1080/01932690701277237

Alvarez-Román R, Naik A, Kalia YN, Guy RH, Fessi H (2004) Skin penetration and distribution of polymeric nanoparticles. J Control Release 99:53–62. https://doi.org/10.1016/j.jconrel.2004.06.015

Arpicco S, Battaglia L, Brusa P, Cavalli R, Chirio D, Dosio F, Gallarate M, Milla P, Peira E, Rocco F, Sapino S, Stella B, Ugazio E, Ceruti M (2015) Recent studies on the delivery of hydrophilic drugs in nanoparticulate systems. J Drug Deliv Sci Technol 1:15. https://doi.org/10.1016/j.jddst.2015.09.004

Babincova M, Altanerova V, Altaner C, Cicmanex P, Babinec P (2004) In vivo heating of magnetic nanoparticles in an alternating magnetic field. Med Phys 31:2219–2221. https://doi.org/10.1118/1.1767101

Bajaj A, Rana S, Miranda OR, Yawe JC, Jerry DJ, Bunz UHF, Rotello VM (2010) Cell surface-based differentiation of cell types and cancer states using a gold nanoparticle-GFP based sensing array. Chem Sci 1:134–138. https://doi.org/10.1039/C0SC00165A

Balmert SC, Little SR (2012) Biomimetic delivery with micro- and nanoparticles. Adv Mater 24:3757–3778. https://doi.org/10.1002/adma.201200224

Bamrungsap S, Zhao Z, Chen T (2012) Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system. Nanomedicine 7:1253–1271. https://doi.org/10.2217/nnm.12.87

Barakat NS (2009) Magnetically modulated nanosystems: a unique drug-delivery platform. Nanomedicine 4:799–812. https://doi.org/10.2217/nnm.09.66

Bardal SK, Waechter JE, Martin DS (2011) Chapter 2-pharmacokinetics. Appl Pharmacol 17–34. https://www.elsevier.com/books/applied-pharmacology/9781437703108. Accessed 30 Aug 2018

Barenholz Y (2012) Doxil®—the first FDA-approved nano-drug: lessons learned. J Control Release 160:117–134. https://doi.org/10.1016/j.jconrel.2012.03.020

Barry SE (2008) Challenges in the development of magnetic particles for therapeutic applications. Int J Hyperth 24:451–566. https://doi.org/10.1080/02656730802093679

Baskar G, George GB, Chamundeeswari M (2017a) Synthesis and characterization of asparaginase bound silver nanocomposite against ovarian cancer cell line A2780 and lung cancer cell line A549. J Inorg Organomet Polym Mater 27:87–94. https://doi.org/10.1007/s10904-016-0448-x

Baskar G, Lalitha K, Garrick BG, Chamundeeswari M (2017b) Conjugation, labeling and characterization of asparaginase bound silver nanoparticles for anticancer applications. Indian J Exp Biol 55:421–426. http://nopr.niscair.res.in/handle/123456789/42354. Accessed 30 Aug 2018

Baskar G, Garrick BG, Lalitha K, Chamundeeswari M (2018) Gold nanoparticle mediated delivery of fungal asparaginase against cancer cells. J Drug Deliv Sci Tec 44:498–504. https://doi.org/10.1016/j.jddst.2018.02.007

Basu S, Sandanaraj BS, Thayumanavan S (2004) Molecular recognition in dendrimers. In: Mark HF (ed) Encyclopedia of polymer science and technology, 4th edn. Wiley, New York, pp 385–424. https://doi.org/10.1002/0471440264

Berry CC (2009) Progress in functionalization of magnetic nanoparticles for applications in biomedicine. J Phys D Appl Phys 42:R198–R206. https://doi.org/10.1088/0022-3727/42/22/224003

Bhadra D, Bhadra S, Jain S, Jain N (2003) A PEGylated dendritic nanoparticulate carrier of florouracil. Int J Pharm 257:111–124. https://doi.org/10.1039/C39940000801:801

Bhatia S (2016) Chapter 2 nanoparticles types, classification, characterization, fabrication methods and drug delivery applications. In: Natural polymer drug delivery systems. Springer, Switzerland, pp 33–93. https://www.springer.com/cda/content/document/cda_downloaddocument/9783319411286-c1. Accessed 30 Aug 2018

Bianco A (2004) Carbon nanotubes for the delivery of therapeutic molecules. Expert Opin Drug Deliv 1:57–65. https://doi.org/10.1517/17425247.1.1.57

Bondi ML, Craparo EF, Giammona G (2007) Nanostructured lipid carriers-containing anticancer compounds: preparation, characterization, and cytotoxicity studies. Drug Dev 14:61–67. https://doi.org/10.1080/10717540600739914

Bradshaw DM, Arceci RJ (1998) Clinical relevance of transmembrane drug efflux as a mechanism of multidrug resistance. J Clin Oncol 16:3674–3690. https://doi.org/10.1200/JCO.1998.16.11.3674

Bruchez M, Moronne M, Gin P, Weiss S, Alivisatos AP (1988) Semiconductor nanocrystals as fluorescent biological labels. Science 281:2013–2016. https://doi.org/10.1126/science.281.5385.2013

Byrne JD, Betancourt T, Brannon-Peppas L (2008) Active targeting schemes for nanoparticle systems in cancer therapeutics. Adv Drug Deliv Rev 60:1615–1626. https://doi.org/10.1016/j.addr.2008.08.005

Cao YWC, Jin RC, Mirkin CA (2002) Nanoparticles with raman spectroscopic fingerprints for DNA and RNA detection. Science 297:1536–1540. https://doi.org/10.1126/science.297.5586.1536

Chamundeeswari M, Liji Sobhana SS, Jacob JP, Kumar M, PandimaDevi M, Sastry TP, Mandal AB (2010) Preparation, characterization and evaluation of a biopolymeric gold nanocomposite with antimicrobial activity. Biotechnol Appl Biochem 55:29–35. https://doi.org/10.1042/BA20090198

Chamundeeswari M, Sastry TP, Lakhsmi BS, Senthil V, Agostinelli E (2013) Iron nanoparticles from animal blood for cellular imaging and targeted delivery for cancer treatment. Biochim Biophys Acta 1830:3005–3010. https://doi.org/10.1016/j.bbagen.2012.12.031

Chang Y, Liu N, Chen L, Meng X, Liu Y, Li Y, Wang J (2012) Synthesis and characterization of DOX-conjugated dendrimer-modified magnetic iron oxide conjugates for magnetic resonance imaging, targeting, and drug delivery. J Mater Chem 22:9594–9601. https://doi.org/10.1039/C2JM16792A

Chen J, Saeki F, Wiley BJ, Cang H, Cobb MJ, Li ZY (2005) Gold nanocages: bioconjugation and their potential use as optical imaging contrast agents. Nano Lett 5:473–477. https://doi.org/10.1021/nl047950t

Chou LY, Ming K, Chan WC (2011) Strategies for the intracellular delivery of nanoparticles. Chem Soc Rev 40:233–245. https://doi.org/10.1039/c0cs00003e

Chowdary KPR, Rao YS (2004) Mucoadhesive microspheres for controlled drug release. Biol Pharm Bull 27:1717–1724

Chrastina A, Massey K, Schnitzer JE (2011) Overcoming in vivo barriers to targeted nanodelivery. Wiley Interdiscip Rev Nanomed Nanobiotechnol 3:421–437. https://doi.org/10.1002/wnan.143

Christian S, Pilch J, Akerman ME, Porkka K, Laakkonen P, Ruoslahti E (2003) Nucleolin expressed at the cell surface is a

marker of endothelial cells in angiogenic blood vessels. J Cell Biol 163:871–878. https://doi.org/10.1083/jcb.200304132
Danhier F, Feron O, Préat V (2010) To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. J Control Release 148:135–146. https://doi.org/10.1016/j.jconrel.2010.08.027
Das M, Datir SR, Singh RP, Jain S (2013) Augmented anticancer activity of a targeted, intracellularly activatable, theranostic nanomedicine based on florescent and radiolabeled, methotrexate-folic acid-multiwalled carbon nanotube conjugate. Mol Pharm 10:2543–2557. https://doi.org/10.1021/mp300701e
Davis ME, Chen ZG, Shin DM (2008) Nanoparticle therapeutics: an emerging treatment modality for cancer. Nat Rev Drug Discov 7:771–782. https://doi.org/10.1038/nrd2614
de Groot FM, Albrecht C, Koekkoek R, Beusker PH, Scheeren HW (2003) Cascade-release dendrimers liberate all end groups upon a single triggering event in the dendritic core. Angew Chem Int Ed 42:4490–4494. https://doi.org/10.1002/anie.200351942
Derfus AM, Chen AA, Min DH, Ruoslahti E, Bhatia SN (2007) Targeted quantum dot conjugates for siRNA delivery. Bioconjugate Chem 18:1391–1396. https://doi.org/10.1021/bc060367e
Desai D, Zhang J, Sandholm J (2017) Lipid bilayer-gated mesoporous silica nanocarriers for tumor-targeted delivery of zoledronic acid in vivo. Mol Pharm 14:3218–3227. https://doi.org/10.1021/acs.molpharmaceut.7b00519
Deshpande PP, Biswas S, Torchilin VP (2013) Current trends in the use of liposomes for tumor targeting. Nanomedicine 8:1509–1528. https://doi.org/10.2217/nnm.13.118
El-Boubbou K, Zhu DC, Vasileiou C, Borhan B, Prosperi D, Li W, Huang X (2010) Magnetic glyco-nanoparticles: a tool to detect, differentiate, and unlock the glyco-codes of cancer via magnetic resonance imaging. J Am Chem Soc 132:4490–4499. https://doi.org/10.1021/ja100455c
Fang J, Nakamura H, Maeda H (2011) The EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. Adv Drug Deliv Rev 63:136–151. https://doi.org/10.1016/j.addr.2010.04.009
Freeman R, Liu X, Willner I (2011) Chemiluminescent and chemiluminescence resonance energy transfer (CRET) detection of DNA, metal ions, and aptamer-substrate complexes using hemin/G-quadruplexes and CdSe/ZnS quantum dots. J Am Chem Soc 133:11597–11604. https://doi.org/10.1021/ja202639m
Gan CW, Feng SS (2010) Transferrin-conjugated nanoparticles of Poly(lactide)-d-α-Tocopheryl polyethylene glycol succinate diblock copolymer for targeted drug delivery across the blood–brain barrier. Biomaterials 31:7748–7757. https://doi.org/10.1016/j.biomaterials.2010.06.053
Gao LY, Liu XY, Chen CJ, Wang JC, Feng Q, Yu MZ, Ma XF, Pie XW, Niu YJ, Qiu C, Pang WH, Zhang Q (2014) Core–shell type lipid-rPAA-Chol polymer hybrid nanoparticles for invivo siRNA delivery. Biomat 35:2066–2078. https://doi.org/10.1016/j.biomaterials.2013.11.046
Garcia MA (2011) Surface plasmons in metallic nanoparticles: fundamentals and applications. J Phys D Appl Phys 44:283001. https://doi.org/10.1088/0022-3727/45/38/389501
Geißler D, Charbonnie`re LJ, Ziessel RF, Butlin NG, Lohmannsroben HG, Hildebrandt N (2010) Quantum dot biosensors for ultrasensitive multiplexed diagnostics. Angew Chem Int Ed 49:1396–1401. https://doi.org/10.1002/anie.200906399
Giljohann DA, Seferos DS, Prigodich AE, Patel PC, Mirkin CA (2009) Gene regulation with polyvalent siRNA-nanoparticle conjugates. J Am Chem Soc 131:2072–2073. https://doi.org/10.1021/ja808719p
Gobin AM, Lee MH, Halas NJ, James WD, Drezek RA, West JL (2007) Near-infrared resonant nanoshells for combined optical imaging and photothermal cancer therapy. Nano Lett 7:1929–1934. https://doi.org/10.1021/nl070610y
Gosk S, Moos T, Gottstein C, Bendas G (2008) VCAM-1 directed immunoliposomes selectively target tumor vasculature in vivo. Biochim Biophys Acta 1778:854–863. https://doi.org/10.1016/j.bbamem.2007.12.021
Gottesman MM (2002) Mechanisms of cancer drug resistance. Annu Rev Med 53:615–627. https://doi.org/10.1146/annurev.med.53.082901.103929
Grief AD, Richardson G (2005) Mathematical modelling of magnetically targeted drug delivery. J Magn Magn Mater 293:455–463. https://doi.org/10.1016/j.jmmm.2005.02.040
Haley B, Frenkel E (2008) Nanoparticles for drug delivery in cancer treatment. Urol Oncol Semin Orig Investig 26:57–64. https://doi.org/10.1016/j.urolonc.2007.03.015
Hallan SS, Kaur P, Kaur V, Mishra N, Vaidya B (2014) Lipid polymer hybrid as emerging tool in nanocarriers for oral drug delivery. Artif Cells Nanomed Biotechnol 44:334–349. https://doi.org/10.3109/21691401.2014.951721
Han N, Zhao Q, Wan L (2015) Hybrid lipid-capped mesoporous silica for stimuli-responsive drug release and overcoming multidrug resistance. ACS Appl Mater Interfaces 7:3342–3351. https://doi.org/10.1021/am5082793
How CW, Rasedee A, Manickam S, Rosli R (2013) Tamoxifen-loaded nanostructured lipid carrier as a drug delivery system: characterization, stability assessment and cytotoxicity. Colloids Surf B Biointerfaces 112:393–399. https://doi.org/10.1016/j.colsurfb.2013.08.009
Huang X, El-Sayed IH, Qian W, El-Sayed MA (2006a) Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. J Am Chem Soc 128:2115–2120. https://doi.org/10.1021/ja057254a
Huang XY, Li L, Qian HF, Dong CQ, Ren JC (2006b) A resonance energy transfer between chemiluminescent donors and luminescent quantum-dots as acceptors (CRET). Angew Chem Int Ed 45:5140–5143. https://doi.org/10.1002/anie.200601196
Huang HC, Barua S, Sharma G, Dey SK, Rege K (2011) Inorganic nanoparticles for cancer imaging and therapy. J Control Release 155:344–357. https://doi.org/10.1016/j.jconrel.2011.06.004
Iijima S (1991) Helical microtubules of graphitic carbon. Nature 354:56–58. https://doi.org/10.1038/354056a0
Imae T (2012) Physicochemical properties of dendrimers and dendrimer complexes. In: Cheng Y (ed) Dendrimer-based drug delivery systems. Wiley, Hoboken, pp 55–92. https://doi.org/10.1002/9781118275238.ch2
Jiang W, Kim BY, Rutka JT, Chan WC (2008) Nanoparticle-mediated cellular response is size-dependent. Nat Nanotechnol 3:145–150. https://doi.org/10.1038/nnano.2008.30
Jiang Y, Zhao H, Lin Y, Zhu N, Ma Y, Mao L (2010) Colorimetric assay for determination of lead (ii) based on its incorporation into gold nanoparticles during their synthesis. Angew Chem Int Ed Engl 49:4800–4804. https://doi.org/10.3390/s101211144
Kandekar SG, Río-Sancho S, Lapteva M, Kalia YN (2018) Selective delivery of adapalene to the human hair follicle under finite dose conditions using polymeric micelle nanocarriers. Nanoscale 10:1099–1110. https://doi.org/10.1039/C7NR07706H
Khoshnejad M, Parhiz H, Shuvaev VV, Dmochowski IJ, Muzykantov VR (2018) Ferritin-based drug delivery systems: hybrid nanocarriers for vascular immunotargeting. J Control Release 282:13–24. https://doi.org/10.1016/j.jconrel.2018.02.042
Kim DH, Kim KN, Kim KM, Lee YK (2008) Targeting to carcinoma cells with chitosan and starch coated magnetic nanoparticles for magnetic hyperthermia. J Biomed Mater Res 88:1–11. https://doi.org/10.1002/jbm.a.31775
Kim B, Han G, Toley BJ, Kim CK, Rotello VM, Forbes NS (2010) Tuning payload delivery in tumour cylindroids using gold

nanoparticles. Nat Nanotechnol 5:465–472. https://doi.org/10.1038/nnano.2010.58
Kingsley JD, Dou H, Morehead J, Rabinow B, Gendelman HE, Destache CJ (2006) Nanotechnology: a focus on nanoparticles as a drug delivery system. J Neuroimmune Pharmacol 1:340–350. https://doi.org/10.1007/s11481-006-9032-4
Kommareddy S, Amiji M (2004) Chapter 10. Targeted drug delivery to tumor cells using colloidal carriers. In: Lu DR, Oie S (eds) Cellular drug delivery: principles and practice. Humana Press, Inc, Totowa, pp 181–215
Koo H, Huh MS, Sun IC, Yuk SH, Choi K, Kim K (2011) In vivo targeted delivery of nanoparticles for theranosis. Acc Chem Res 44:1018–1028. https://doi.org/10.1021/ar2000138
Kresge C, Leonowicz M, Roth W (2001) Dendrimers and dendrons. Concepts, syntheses, applications, vol 12. VCH, Weinheim, pp 7291–7309. https://doi.org/10.3390/molecules21040497
Kumari A, Singla R, Guliani A, Yadav SK (2014) Nanoencapsulation for drug delivery. EXCLI J 13:265–286
Lai PS, Lou PJ, Peng CL (2007) Doxorubicin delivery by polyamidoamine dendrimer conjugation and photochemical internalization for cancer therapy. J Control Release 122:39–46. https://doi.org/10.1016/j.jconrel.2007.06.012
Lai Y, Chiang C, Kao T, Chen S (2018) Dual-drug nanomedicine with hydrophilic F127-modified magnetic nanocarriers assembled in amphiphilic gelatin for enhanced penetration and drug delivery in deep tumor tissue. Int J Nanomedicine 13:3011–3026. https://doi.org/10.2147/IJN.S161314
Lancet JE (2016) Final results of a phase III randomized trial of CPX-351 versus 7 + 3 in older patients with newly diagnosed high risk (secondary) AML. J Clin Oncol 34:7000. https://doi.org/10.1200/JCO.2016.34.15_suppl.7000
Lay CL, Liu HQ, Tan HR, Liu Y (2010) Delivery of paclitaxel by physically loading onto poly (ethylene glycol)(PEG)-graft carbon nanotubes for potent cancer therapeutics. Nanotechnology 21:065101–065111. https://doi.org/10.1088/0957-4484/21/6/065101
Lebold T, Jung C, Michaelis J, Brauchle C (2009) Nanostructured silica materials as drug-delivery systems for doxorubicin: single molecule and cellular studies. Nano Lett 9:2877–2883. https://doi.org/10.1021/nl9011112
Lee CC, Gillies ER, Fox ME (2006) A single dose of doxorubicin functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas. Proc Natl Acad Sci 103:16649–16654. https://doi.org/10.1073/pnas.0607705103
Lee H, Fonge H, Hoang B, Reilly RM, Allen C (2010) The effects of particle size and molecular targeting on the intratumoral and subcellular distribution of polymeric nanoparticles. Mol Pharm 7:1195–1208. https://doi.org/10.1021/mp100038h
Levi-Polyachenko NH, Merkel EJ, Jones BT, Carroll DL, Stewart JH (2009) Rapid photothermal intracellular drug delivery using multiwalled carbon nanotubes. Mol Pharm 6:1092–1099. https://doi.org/10.1021/mp800250e
Li Y, Li N, Pan W, Yu Z, Yang L, Tang B (2017) Hollow mesoporous silica nanoparticles with tunable structures for controlled drug delivery. ACS Appl Mater Interfaces 9:2123–2129. https://doi.org/10.1021/acsami.6b13876
Linkous AG, Yazlovitskaya EM (2012) Novel therapeutic approaches for targeting tumor angiogenesis. Anticancer Res 32:1–12
Liu JM, Zhang DD, Fang GZ, Wang S (2018) Erythrocyte membrane bioinspired near-infrared persistent luminescence nanocarriers for in vivo long-circulating bioimaging and drug delivery. Biomaterials 165:39–47. https://doi.org/10.1016/j.biomaterials.2018.02.042
Loo C, Lowery A, Halas NJ, West J, Drezek R (2005) Immunotargeted nanoshells for integrated cancer imaging and therapy. Nano Lett 5:709–711. https://doi.org/10.1021/nl050127s
Lopez-Davila V, Loizidou M (2012) Organic nanocarriers for drug delivery. Curr Opin Pharmacol 12:414–419. https://doi.org/10.1016/j.coph.2012.02.011
Lu W, Huang Q, Geng KB, Wen XX, Zhou XX, Guzatov D (2010) Photoacoustic imaging of living mouse brain vasculature using hollow gold nanospheres. Biomaterials 31:2617–2626. https://doi.org/10.1016/j.biomaterials.2009.12.007
Lubbe AS, Bergmann C, Brock J, McClure DG (2000) Physiological aspects in magnetic drug targeting. J Magn Magn Mater 19:149–155. https://doi.org/10.1016/S0304-8853(98)00574-5
Ma P, Xiao H, Li C, Dai Y, Cheng Z, Hou Z, Lin J (2015) Inorganic nanocarriers for platinum drug delivery. Mater Today 18:554–564. https://doi.org/10.1016/j.mattod.2015.05.017
Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM (2011) A new era of cancer treatment: carbon nanotubes as drug delivery tools. Int J Nanomedicine 6:2963–2979. https://doi.org/10.2147/IJN.S16923
Malam Y, Loizidou M, Seifalian AM (2009) Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci 30:592–599. https://doi.org/10.1016/j.tips.2009.08.004
Malik N, Evagorou EG, Duncan R (1999) Dendrimer-platinate: a novel approach to cancer chemotherapy. Anticancer Drugs 10:767–776
Martinez-Carmona M, Colilla M, Vallet-Regi M (2015) Smart mesoporous nanomaterials for antitumor therapy. Nanomaterials 5:1906–1937. https://doi.org/10.3390/nano5041906
Matsumura Y, Maeda H (1986) A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent. Cancer Res 46:6387–6392
Medintz IL, Farrell D, Susumu K, Trammell SA, Deschamps JR, Brunel FM (2009) Multiplex charge-transfer interactions between quantum dots and peptide-bridged ruthenium complexes. Anal Chem 81:4831–4839. https://doi.org/10.1021/ac900412j
Mi Y (2016) Enzyme-responsive multistage vector for drug delivery to tumor tissue. Pharmacol Res 113:92–99. https://doi.org/10.1016/j.phrs.2016.08.024
Mignani S, Tripathi RP, Chen L, Caminade A, Shi X, Majoral J (2018) New ways to treat tuberculosis using dendrimers as nanocarriers. Pharmaceutics 10:0105. https://doi.org/10.3390/pharmaceutics10030105
Mishra B, Patel BB, Tiwari S (2010) Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery. Nanomedicine 6:9–24. https://doi.org/10.1016/j.nano.2009.04.008
Mkerman MA, Chan WCW, Laakkonen P, Chatia SN, Ruoslahti E (2002) Nanocrystal targeting in vivo. Proc Natl Acad Sci USA 99:12617–12621. https://doi.org/10.1073/pnas.152463399
Moyano DF, Rotello VM (2011) Nano meets biology: structure and function at the nanoparticle interface. Langmuir 27:10376–10385. https://doi.org/10.1021/la2004535
Moyano DF, Rana S, Bunz UHF, Rotello VM (2011) Gold nanoparticle polymer/biopolymer complexes for protein sensing. Faraday Discuss 152:33–42. https://doi.org/10.1039/c1fd00024a
Muller RH (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. Eur J Pharm Biopharm 50:161–177
Muthukumar T, Chamundeeswari M, Prabhavathi S, Baskar G, Chandhuru J, Sastry TP (2014) Carbon nanoparticle from a natural source fabricated for folate receptor targeting, imaging and drug delivery application in A549 lung cancer cells. Eur J Pharm Biopharm 88:730–736. https://doi.org/10.1016/j.ejpb.2014.09.011
Mykhaylyk O, Antequera YS, Vlaskou D, Plank C (2007) Generation of magnetic nonviral gene transfer agents and magnetofection in vitro. Nat Protoc 2:2391–2411. https://doi.org/10.1038/nprot.2007.352

Nacev A, Beni C, Bruno O, Shapiro B (2010) Magnetic nanoparticle transport within flowing blood and into surrounding tissue. Nanomedicine 5:1459–1466. https://doi.org/10.2217/nnm.10.104

Neri D, Bicknell R (2005) Tumour vascular targeting. Nat Rev Cancer 5:436–446. https://doi.org/10.1038/nrc1627

Ng CM, Loh HS, Muthoosamy K, Sridewi N, Manickam S (2016) Conjugation of insulin onto the sidewalls of single-walled carbon nanotubes through functionalization and diimide-activated amidation. Int J Nanomedicine 11:1607–1614. https://doi.org/10.2147/IJN.S98726

Niidome T, Yamagata M, Okamoto Y, Akiyama Y, Takahashi H, Kawano T, Katayama Y, Niidome Y (2006) Conversion of rod-shaped gold nanoparticles to spherical forms and their effect on biodistribution in tumor-bearing mice. J Control Release 114:343–347. https://doi.org/10.1186/1556-276X-7-565

Patil Y, Sadhukha T, Ma L, Panyam J (2009) Nanoparticle-mediated simultaneous and targeted delivery of paclitaxel and tariquidar overcomes tumor drug resistance. J Control Release 136:21–29. https://doi.org/10.1016/j.jconrel.2009.01.021

Patil H, Tiwari RV, Repka MA (2016) Recent advancements in mucoadhesive floating drug delivery systems: a mini-review. J Drug Deliv Sci Technol 31:65–71. https://doi.org/10.1016/j.jddst.2015.12.002

Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R (2007) Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2:751–760. https://doi.org/10.1038/nnano.2007.387

Pérez-Herrero E, Fernández-Medarde A (2015) Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm 93:52–79. https://doi.org/10.1016/j.ejpb.2015.03.018

Petros RA, DeSimone JM (2010) Strategies in the design of nanoparticles for therapeutic applications. Nat Rev Drug Discov 9:615–627. https://doi.org/10.1038/nrd2591

Pirollo KF, Chang EH (2008) Does a targeting ligand inflence nanoparticle tumor localization or uptake? Trends Biotechnol 26:552–558. https://doi.org/10.1016/j.tibtech.2008.06.007

Pirollo KF, Rait A, Zhou Q, Zhang X, Zhou J, Kim C, Benedict WF, Chang EH (2008) Tumor-targeting nanocomplex delivery of tumor suppressor RB94 chemosensitizes bladder carcinoma cells in vitro and in vivo. Clin Cancer Res 14:2190–2198. https://doi.org/10.1158/1078-0432.CCR-07-1951

Poon Z, Chang D, Zhao X, Hammond PT (2011) Layer-by-layer nanoparticles with a pH sheddable layer for in vivo targeting of tumor hypoxia. ACS Nano 5:4284–4292. https://doi.org/10.1021/nn200876f

Prabhu RH, Patravale VB, Joshi MD (2015) Polymeric nanoparticles for targeted treatment in oncology: current insights. Int J Nanomed 10:1001–1018. https://doi.org/10.2147/IJN.S56932

Puri M, Barrow CJ, Verma ML (2013) Enzyme immobilization on nanomaterials for biofuel production. Trends Biotechnol 31:215–216. https://doi.org/10.1016/j.tibtech.2013.01.002

Qian X, Peng XH, Ansari DO, Yin-Goen Q, Chen GZ, Shin DM (2008) In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. Nat Biotechnol 26:83–90. https://doi.org/10.1038/nbt1377

Qian W, Sun D, Zhu R, Du X, Liu H, Wang S (2012) pH-sensitive strontium carbonate nanoparticles as new anticancer vehicles for controlled etoposide release. Int J Nanomed 7:5781–5792. https://doi.org/10.2147/IJN.S34773

Ramishetti S, Landesman-Milo D, Peer D (2016) Advances in RNAi therapeutic delivery to leukocytes using lipid nanoparticles. J Drug Target 24:780–786. https://doi.org/10.3109/1061186X.2016.1172587

Riess G (2003) Micellization of block copolymers. Prog Polym Sci 28:1107–1170. https://doi.org/10.1016/S0079-6700(03)00015-7

Rosenblum D, Joshi N, Tao W, Karp JM, Peer D (2018) Progress and challenges towards targeted delivery of cancer therapeutics. Nat Commun 9:1410–1415. https://doi.org/10.1038/s41467-018-03705-y

Rosenholm JM, Peuhu E, Bate-Eya LT, Eriksson JE, Sahlgren C, Linden M (2010) Cancer-cell-specifi induction of apoptosis using mesoporous silica nanoparticles as drug-delivery vectors. Small 6:1234–1241. https://doi.org/10.1002/smll.200902355

Ruoslahti E, Bhatia SN, Sailor MJ (2010) Targeting of drugs and nanoparticles to tumors. J Cell Biol 188:759–768. https://doi.org/10.1083/jcb.200910104

Saha K, Bajaj A, Duncan B, Rotello VM (2011) Beauty is skin deep: a surface monolayer perspective on nanoparticle interactions with cells and bio-macromolecules. Small 7:1903–1918. https://doi.org/10.1002/smll.201100478

Sala M, Diab R, Elaissari A, Fessi H (2018) Lipid nanocarriers as skin drug delivery systems: properties, mechanisms of skin interactions and medical applications. Int J Pharm 535:1–17. https://doi.org/10.1016/j.ijpharm.2017.10.046

Santos HA, Bimbo LM, Peltonen L, Hirvonen J (2014) Inorganic nanoparticles in targeted drug delivery and imaging. In: Devarajan PV, Jain S (eds) Targeted drug delivery: concepts and design. Springer, Cham, pp 571–613. https://doi.org/10.1007/978-3-319-11355-5_18

Sega EI, Low PS (2008) Tumor detection using folate receptor-targeted imaging agents. Cancer Metastasis Rev 27:655–664. https://doi.org/10.1007/s10555-008-9155-6

Semple SC (2010) Rational design of cationic lipids for siRNA delivery. Nat Biotech 28:172–176. https://doi.org/10.1038/nbt.1602

Shen Y, Zhang J, Hao W, Wang T, Liu J, Xie Y, Xu S, Liu H (2018) Copolymer micelles function as pH-responsive nanocarriers to enhance the cytotoxicity of a HER2 aptamer in HER2-positive breast cancer cells. Int J Nanomed 13:537–553. https://doi.org/10.2147/IJN.S149942

Shi XY, Thomas TP, Myc LA, Kotlyar A, Baker JR (2007) Synthesis, characterization, and intracellular uptake of carboxyl-terminated poly(amidoamine) dendrimer-stabilized iron oxide nanoparticles. Phys Chem Chem Phys 9:5712–5720. https://doi.org/10.1039/b709147h

Shi J, Kantoff PW, Wooster R, Farokhzad OC (2017) Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 17:20–37. https://doi.org/10.1038/nrc.2016.108

Singh R, Lillard JW (2009) Nanoparticle-based targeted drug delivery. Exp Mol Pathol 86:215–223. https://doi.org/10.1016/j.yexmp.2008.12.004

Stella B, Peira E, Dianzani C, Gallarate M, Battaglia L, Gigliotti CL, Boggio E, Dianzani U, Dosio F (2018) Development and characterization of solid lipid nanoparticles loaded with a highly active doxorubicin derivative. Nanomaterials 8:110–118. https://doi.org/10.3390/nano8020110

Stiriba SE, Frey H, Haag R (2002) Dendritic polymers in biomedical applications: from potential to clinical use in diagnostics and therapy. Angew Chem Int Ed 41:1329–1334

Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y (2014) Engineered nanoparticles for drug delivery in cancer therapy. Angew Chem Int Ed 53:12320–12364. https://doi.org/10.1002/anie.201403036

Tam YYC, Chen S, Cullis PR (2013) Advances in lipid nanoparticles for siRNA delivery. Pharmaceutics 5:498–507. https://doi.org/10.3390/pharmaceutics5030498

Tang QS, Zhang DS, Cong XM, Wan ML, Jin LQ (2008) Using thermal energy produced by irradiation of Mn–Zn ferrite magnetic nanoparticles (MZF-NPs) for heat-inducible gene expression. Biomaterials 29:2673–2679. https://doi.org/10.1016/j.biomaterials.2008.01.038

Tasciotti E (2008) Mesoporous silicon particles as a multistage delivery system for imaging and therapeutic applications. Nat Nano 3:151–157. https://doi.org/10.1038/nnano.2008.34

Toma A, Otsuji E, Kuriu Y, Okamoto K, Ichikawa D, Hagiwara A (2005) A Monoclonal antibody A7-superparamagnetic iron oxide as contrast agent of MR imaging of rectal carcinoma. Br J Cancer 93:131–136. https://doi.org/10.1038/sj.bjc.6602668

Torchilin VP (2000) Drug targeting. Eur J Pharm Sci 11:S81–S91. https://doi.org/10.1016/S0928-0987(00)00166-4

Torchilin VP (2005) Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov 4:145–160. https://doi.org/10.1038/nrd1632

Torchilin VP (2010) Drug delivery (handbook of experimental pharmacology 197), vol 68. Springer, Berlin, pp 1521–1524. https://doi.org/10.1007/978-3-642-00477-3_2

Torchilin VP (2011) Tumor delivery of macromolecular drugs based on the EPR effect. Adv Drug Deliv Rev 63:131–135. https://doi.org/10.1016/j.addr.2010.03.011

Üner M, Yener G (2007) Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomed 2:289–300

van Landeghem FKH, Maier-Hauff K, Jordan A, Hoffmann KT, Gneveckow R, Scholz R (2009) Post-mortem studies in glioblastoma patients treated with thermotherapy using magnetic nanoparticles. Biomaterials 30:52–57. https://doi.org/10.1016/j.biomaterials.2008.09.044

Verma ML (2017) Nanobiotechnology advances in enzymatic biosensors for the agri-food industry. Environ Chem Lett 15:555–560. https://doi.org/10.1007/s10311-017-0640-4

Verma A, Stellacci F (2010) Effect of surface properties on nanoparticle–cell interactions. Small 6:12–21. https://doi.org/10.1002/smll.200901158

Verma ML, Barrow CJ, Kennedy JF, Puri M (2012) Immobilization of β-galactosidase from *Kluyveromyces lactis* on functionalized silicon dioxide nanoparticles: characterization and lactose hydrolysis. Int J Biol Macromol 50:432–437. https://doi.org/10.1016/j.ijbiomac.2011.12.029

Verma ML, Barrow CJ, Puri M (2013a) Nanobiotechnology as a novel paradigm for enzyme immobilization and stabilisation with potential applications in biofuel production. Appl Microbiol Biotechnol 97:23–39. https://doi.org/10.1007/s00253-012-4535-9

Verma ML, Chaudhary R, Tsuzuki T, Barrow CJ, Puri M (2013b) Immobilization of β-glucosidase on a magnetic nanoparticle improves thermostability: application in cellobiose hydrolysis. Bioresour Technol 135:2–6. https://doi.org/10.1016/j.biortech.2013.01.047

Verma ML, Naebe M, Barrow CJ, Puri M (2013c) Enzyme immobilisation on amino-functionalised multi-walled carbon nanotubes: structural and biocatalytic characterisation. PLoS ONE 8:e73642–e73642. https://doi.org/10.1371/journal.pone.0073642

Verma ML, Puri M, Barrow CJ (2016) Recent trends in nanomaterials immobilised enzymes for biofuel production. Crit Rev Biotechnol 36:108–119. https://doi.org/10.3109/07388551.2014.928811

von Maltzahn G, Park JH, Agrawal A, Bandaru NK, Das SK, Sailor MJ (2009) Computationally guided photothermal tumor therapy using long-circulating gold nanorod antennas. Cancer Res 69:3892–3900. https://doi.org/10.1158/0008-5472.CAN-08-4242

von Maltzahn G, Park JH, Lin KY, Singh N, Schwöppe C, Mesters R, Berdel WE, Ruoslahti E, Sailor MJ, Bhatia SN (2011) Nanoparticles that communicate in vivo to amplify tumour targeting. Nat Mater 10:545–552. https://doi.org/10.1038/nmat3049

Wang Y, Xie X, Wang X, Ku G, Gill KL, O'Neal DP (2004) Photoacoustic tomography of a nanoshell contrast agent in the in vivo rat brain. Nano Lett 4:1689–1692. https://doi.org/10.1021/nl049126

Wang X, Wang Y, Chen ZG, Shin DM (2009) Advances of cancer therapy by nanotechnology. Cancer Res Treat 41:1–11. https://doi.org/10.4143/crt.2009.41.1.1

Wang Y, Brown P, Xia Y (2011a) Nanomedicine: swarming towards the target. Nat Mater 10:482–483. https://doi.org/10.1038/nmat3060

Wang Z, Tiruppathi C, Cho J, Minshall RD, Malik AB (2011b) Delivery of nanoparticle: complexed drugs across the vascular endothelial barrier via caveolae. IUBMB Life 63:659–667. https://doi.org/10.1002/iub.485

Wang AZ, Langer R, Farokhzad OC (2012) Nanoparticle delivery of cancer drugs. Annu Rev Med 63:185–198. https://doi.org/10.1146/annurev-med-040210-162544

Wang Y, Zhao Q, Han N (2015) Mesoporous silica nanoparticles in drug delivery and biomedical applications. Nanomedicine 11:313–327. https://doi.org/10.1016/j.nano.2014.09.014

Wennerström H, Linman B (1979) Micelles. Physical chemistry of surfactant association. Phys Rep 52:1–86. https://doi.org/10.1016/0370-1573(79)90087-5

Yavuz MS, Cheng Y, Chen J, Cobley CM, Zhang Q, Rycenga M, Xie J, Kim C, Song KH, Schwartz AG, Wang LV, Xia Y (2009) Gold nanocages covered by smart polymers for controlled release with near-infrared light. Nat Mater 8:935–939. https://doi.org/10.1038/nmat2564

Yoo HS, Lee JE, Chung H, Kwon IC, Jeong SY (2005) Self-assembled nanoparticles containing hydrophobically modified glycol chitosan for gene delivery. J Control Release 103:235–243. https://doi.org/10.1016/j.jconrel.2004.11.033

You CC, Miranda OR, Gider B, Ghosh PS, Kim IB, Erdogan B, Krovi SA, Bunz UH, Rotello VM (2007) Detection and identification of proteins using nanoparticle-fluorescent polymer 'chemical nose' sensors. Nat Nanotechnol 2:318–323. https://doi.org/10.1038/nnano.2007.99

Zhang J, Dubay MR, Houtman CJ, Severtson SJ (2009) Sulfonated amphiphilic block copolymers: syntheses, self-assembly in water, and applications as stabilizer in emulsion polymerization. Macromolecules 42:5080–5090. https://doi.org/10.1021/ma900795f

Zhang Z, Tsai PC, Ramezanli T, Michniak-Kohn BB (2013) Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases. Wiley Interdiscip Rev Nanomed Nanobiotechnol 5:205–218. https://doi.org/10.1002/wnan.1211

Zhao W, Karp JM (2009) Multifunctional nanoparticles as coupled contrast agents. Nat Mater 8:453–454. https://doi.org/10.1038/ncomms1042

Zhou Z (2009) Charge-reversal drug conjugate for targeted cancer cell nuclear drug delivery. Adv Funct Mater 19:3580–3589. https://doi.org/10.1002/adfm.200900825

Zhou J, Zhang X, Li M, Wu W, Sun X, Zhang L, Gong T (2013) Novel lipid hybrid albumin nanoparticle greatly lowered toxicity of pirarubicin. Mol Pharm 10:3832–3841. https://doi.org/10.1021/mp400303w

Zhu Y, Liao L (2015) Applications of nanoparticles for anticancer drug delivery: a review. J Nanosci Nanotechnol 15:4753–4773

Zhuo RX, Du B, Lu ZR (1999) In vitro release of 5-florouracil with cyclic core dendritic polymer. J Control Release 57:249–257. https://doi.org/10.1016/s0168-3659(98)00120-5