



Nanocarriers for drug delivery applications

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Received: 8 November 2018 / Accepted: 14 November 2018 / Published online: 21 November 2018
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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

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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 nano-carriers. 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 nano-carriers: solid lipid nanocarrier, liposome, dendrimer, polymeric nanocarrier; and hybrid nanocarrier: polymeric-lipid nanocarrier

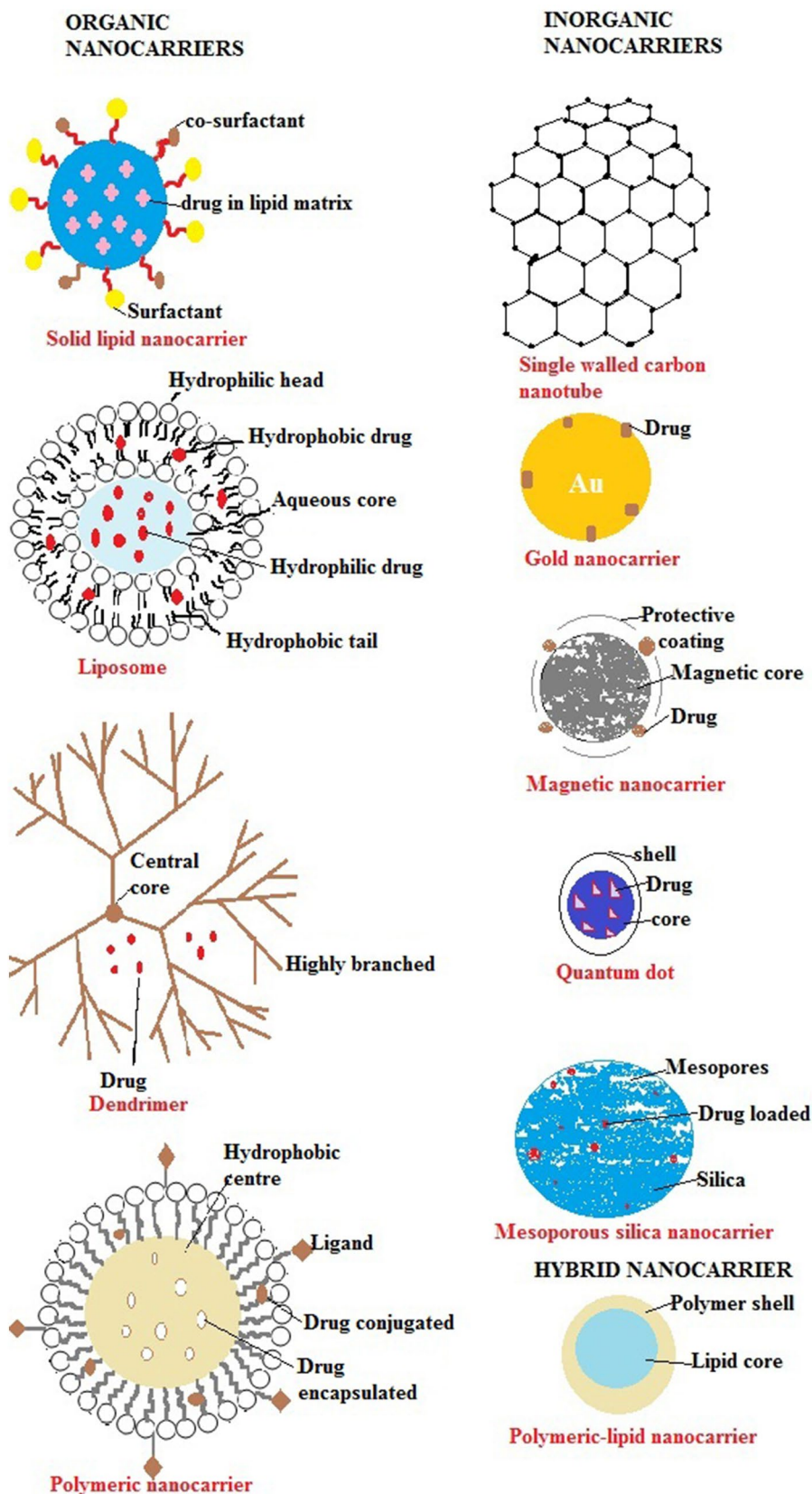


Table 1 Characteristics of different nanocarriers. Different nanocarriers are being prepared with different physicochemical methods. Such nanocarriers possess unique properties, most sought for drug delivery such as drug loading capacity, compatibility, stability and degradability. Nanocarriers have 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 upgradability, 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	Bio stability, 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 polymeric 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, fluorescently 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, fluorophores, 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 retention 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 (polyethylene 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 recruit 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 over-expressed 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 glycyaspartic 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

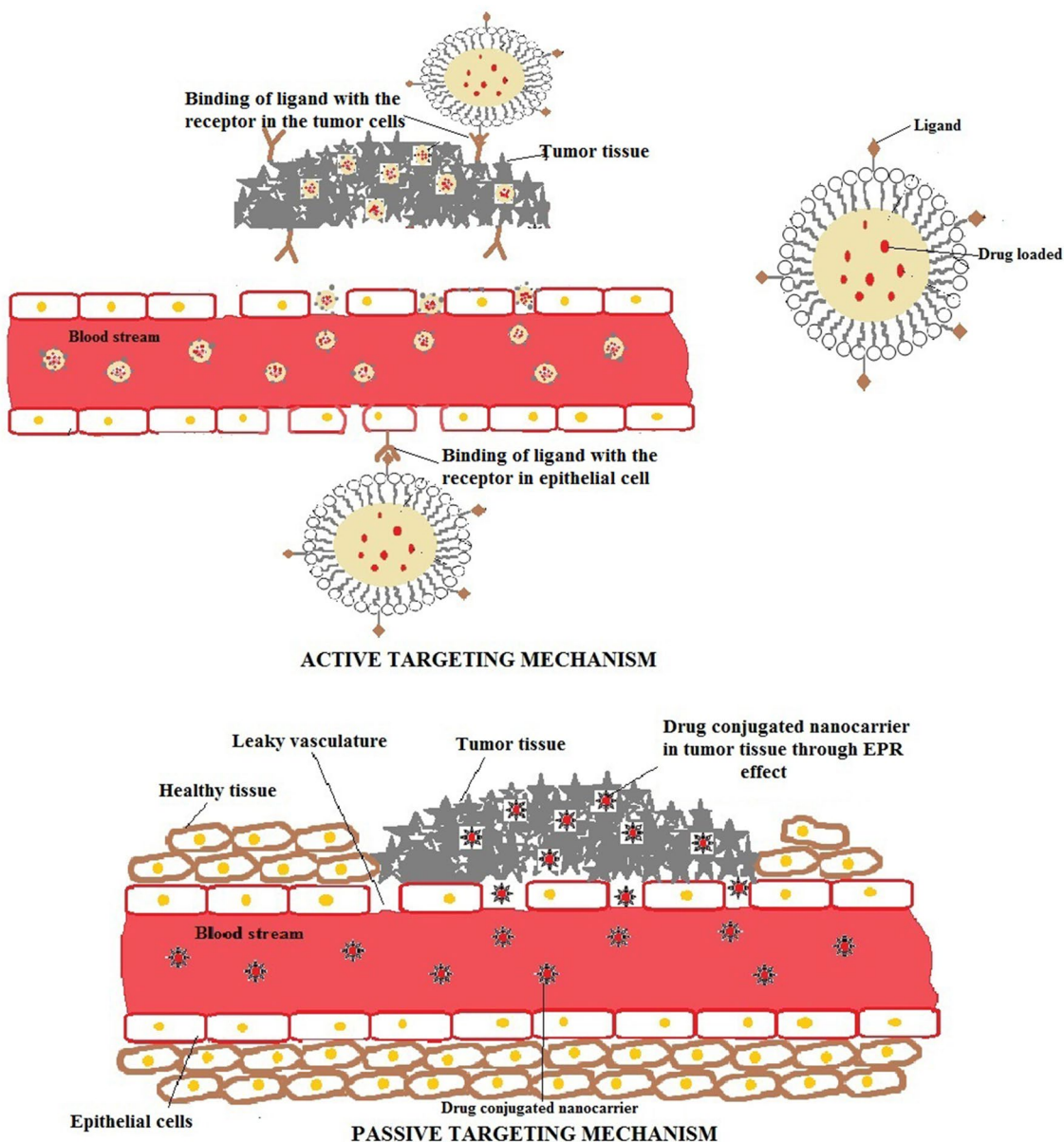


Fig. 2 Mechanism of nanocarrier targeting. In active targeting, the drug-loaded nanocarriers with receptor specific ligands circulates in the blood stream and release the drug at the target tumor site. While,

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 cytarabine 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 multi-layered 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, biocompatible, 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.

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