Nanocarriers in Drug and Gene Delivery

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6.1 Introduction

Nanotechnology and nanoscience are widely seen as having a tremendous promise to revolutionize the scientific landscape in terms of research and applications. Among various approaches, nanocarriers as a tool of nanotechnology offer great advantages for biomedical applications, viz., drug delivery, sensing, and imaging (Singh and Lillard 2009). Concurrently, the applications of nanotechnology in target-specific delivery of drug and gene have opened up new areas of research in nanomedicine.

Nanotechnology is the design of objects with dimensions conveniently described in units of nanometers (10^{-9} m) (Thassu et al. 2007). The dimensions of nanoparticles (NPs) lie between 10 and 1000 nm. Objects in the nanometer size range often exhibit properties that are not found in bulk materials of the same composition. However, particles >200 nm are not widely used, and nanomedicine holds interest in particles <200 nm as physicochemical properties of the particles in this range make them attractive for commercial and medical development (Singh and Lillard 2009). Nanocarriers for drug and gene delivery can be classified as lipid-based (solid lipid NPs, liposomes), polymer-based (polymeric micelles, dendrimers or polymeric NPs), and inorganic NPs (metallic NPs, silica NPs (SiNPs), carbon nanotubes (CNTs)) (Estanqueiro et al. 2015). The selection of material for development of nanocarrier is highly dependent on encapsulated payload/bioactives, therapeutic or diagnostic goal, and route of administration (Jabr-Milane et al. 2008).

Nowadays nanosystems focus primarily on the development of target-specific and slow but controlled drug release systems. A major milestone has been achieved in drug delivery systems with the development of technologies that can mask the

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nanocarriers from the immune system. Specific decoration of nanocarriers has significantly increased the half-life of the drug. The introduction of synthetic lipid derivatives of polyethylene glycol (PEG) confers "stealth" capability on nanocarrier system, due to the hydrophilicity of the PEG chains. This PEG stealth avoids opsonization and reduces fast blood clearance by immune recognition, hence helping in passive accumulation in the tumors via an enhanced permeation and retention (EPR) effect (Gref et al. 1995, 2000; Mosqueira et al. 1999). The first generation of nanosystems was nanometric liposomes. They are able to encapsulate both hydrophilic and hydrophobic drugs (Patel et al. 2015). The next generation were polymeric NPs precipitated with drug molecules and surface functionalized that prevented the immune recognition and nowadays even having targeting moieties in form of antibodies or folic acid. They have potential to enhance therapeutic benefit while reducing side effects as compared to free drug. Furthermore, inorganic NPs are being widely explored because of their chemical, physical and structural characteristics. This chapter considers current status and possible future directions of conventional and engineered pharmaceutical nanocarriers used for drug and gene delivery.

6.2 Lipid-Based Nanoparticles

Among the group of several nanoformulations, lipid nanoformulations have received much attention due to its biocompatible and biodegradable nature. They have huge potential for delivery of drugs and genes in several diseases. In the field of nanomedicine, they offer interesting benefits, viz., enhancing drug efficacy and providing controlled and convenient drug release. The performance of lipid nanoformulations greatly depends upon the composition and structure of formulations. Lipid-based nanocarriers may be further categorized as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) (Lim et al. 2012) (Fig. 6.1). Several lipid-based formulations have already entered in the market, and others are in preclinical and clinical phase (Table 6.1).

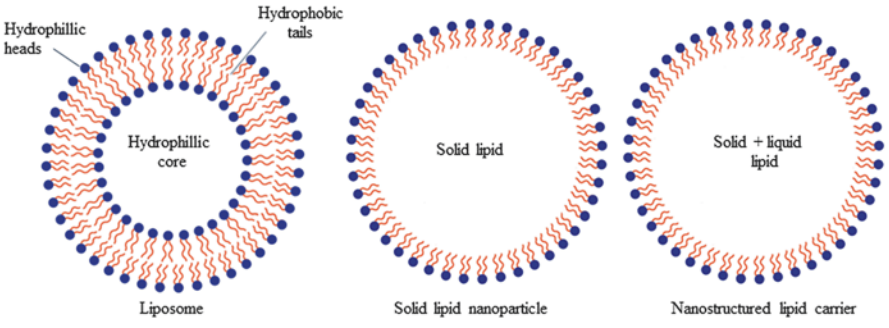

Fig. 6.1 Structure of lipid-based nanocarriers

Table 6.1 Clinical status of liposomal formulations

Brand name	Drug	Indication	Status	References
Mepact® [Takeda]	Mifamurtide MTE-PE	Osteosarcoma	Marketed	Venkatakrishnan et al. (2014)
AmBisome™ [Astellas Pharma/ Gilead Sciences]	Amphotericin B	Serious fungal infections	Marketed	Pagano et al. (2013)
Marqibo® [Talon Therapeutics, Inc.]	Vincristine sulfate	Acute lymphoblastic leukemia	Marketed	Rodriguez et al. (2009)
Doxisome®/ Lipo-Dox® [Taiwan Liposome Company, Ltd]	Doxorubicin	Kaposi's sarcoma, ovarian cancer, breast cancer	Marketed	Rivera (2003)
Myocet®50 [Cephalon]	Doxorubicin	Metastatic breast cancer	Marketed	Batist et al. (2001)
Visudyne® [Novartis AG/QLT Inc.]	Verteporfin	Age-related macular degeneration	Marketed	Huber and Levy (2001)
DepoCyt ® [Pacira Pharmaceuticals, Inc.]	Cytarabine	Lymphomatous meningitis	Marketed	Glantz et al. (1999)
Doxil®/Caelyx® [Sequus Pharmaceutical, Inc./ Schering-Plough]	Doxorubicin	Kaposi's sarcoma, ovarian cancer, breast cancer	Marketed	Muggia et al. (1997)
LEP-ETU [Liposomal Insys Therapeutics]	Paclitaxel	Metastatic pancreatic cancer	Phase II	Slingerland et al. (2013)
EndoTAG®-1 [MediGene AG]	Paclitaxel	HER2-negative breast cancer	Phase II	Fasol et al. (2012)
OSI-211 [Astellas Pharma Inc.]	Lurtotecan	Metastatic or recurrent head and neck cancer	Phase II	Duffaud et al. (2004)
L-Annamycin [Callisto Pharmaceutical, Inc.]	Annamycin	Acute lymphoblastic leukemia	Phase II	Booser et al. (2002)
MBP-426 [Mebiopharm Co., Ltd.]	Oxaliplatin	Gastric, gastroesophageal, esophageal adenocarcinomas	Phase II	Higashihara et al. (1991)
TKM-PLK1 [Tekmira Pharmaceuticals]	siRNA	Gastrointestinal neuroendocrine tumors, adrenocortical carcinoma, hepatocellular carcinoma	Phase II	Stevens et al. (1991)

(continued)

Table 6.1 (continued)

Brand name	Drug	Indication	Status	References
NL CPT-11 [University of California, San Francisco]	Irinotecan	Solid tumor	Phase I/ II	Prados et al. (2006)
ATI-1123[Azaya Therapeutics]	Docetaxel	Advanced solid tumors	Phase I	Mahalingam et al. (2014)
ALN-VSP02[Alnylam Pharmaceuticals]	Liposomal RNAi	Solid tumors with liver involvement	Phase I	Tabernero et al. (2013)
ALN-TTRsc [Alnylam Pharmaceuticals]	Liposomal RNAi	Subcutaneous, TTR-mediated amyloidosis	Phase I	Kanasty et al. (2013)
Anti-EGFR immunoliposome [University Hospital, Switzerland]	Doxorubicin	Solid tumor	Phase I	Mamot et al. (2012)
BikDD nanoparticles [MD Anderson Cancer Center]	Proapoptotic Bik gene (BikDD)	Pancreatic cancer	Phase I	Xie et al. (2007)

6.2.1 Liposomes

Almost from the time of their first report in the 1960s by Bangham and coworkers, liposomes have been extensively used by researchers as prospective carriers for various bioactive molecules. Liposomes are self-closed spherical phospholipid vesicular system having size ranges of 20–200 nm. These lipid vesicles are derived by the dispersion of phospholipids in an aqueous media. Various techniques pursued to disperse the lipids into the aqueous media include thin lipid film hydration, extrusion, sonication, etc. The basic component of liposome is formed by phospholipids or any similar amphipathic lipids (having both hydrophilic head and hydrophobic tail) (Onyuksel et al. 2006; Rawat et al. 2008). The phospholipid molecules used are either naturally occurring and/or derived from synthetic sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, polyethylene glycol, cholesterol, distearoyl-sn-glycero-3-phosphoglycerol, and dipalmitoyl-sn-glycero-3-phosphothioethanol (Arias 2013).

Liposomes have been broadly classified on the basis of their size, number of bilayers, composition, and method of preparation employed, viz., multilamellar vesicles (MLV), large unilamellar vesicles (LUV), small unilamellar vesicles (SUV), conventional liposomes (CL), pH-sensitive liposomes, cationic liposomes, long circulating liposomes (LCL), reverse phase evaporation vesicles (REV), French press vesicles (FPV), ether injection vesicles (EIV), etc. (Samad et al. 2007; Pattni et al. 2015; Matougui et al. 2016).

Liposomes possess superior capability of delivering drugs to target site and thus overcomes the adverse effect and resistance of drug due to reduced non-targeted circulation of the drug. Zhang et al. (2016a) prepared oxaliplatin and irinotecan hydrochloride co-loaded liposomes for the treatment of colorectal cancer. In vitro cytotoxicity results demonstrated that co-loaded liposomes showed higher cytotoxicity as compared to single loaded liposomes in both CT-26 and HCT-116 cells. Also, co-loaded liposomes exhibited greater antitumor therapeutic activity in CT-26-bearing BALB/c mice. In vivo safety evaluation showed that liposomes had less toxicity as compared to free drug solution (Zhang et al. 2016a). Recently, a liposome-based theranostic system was developed for delivery of docetaxel and quantum dots (QD) simultaneously. In this study, liposomes were conjugated with arginine-glycine-aspartic acid (RGD) to target them effectively in brain for theranostic applications. Brain distribution study confirmed higher accumulation of targeted liposomes in comparison to Docel™ and free QD. Results of brain histopathology were also in concordance to above results (Sonali et al. 2016). More recently, the effectiveness and safety profile of trastuzumab and liposome-loaded doxorubicin and paclitaxel combination was evaluated for early or locally advanced breast cancer therapy, clinically. The study was carried out on 30 breast cancer patients, and treatment was found to be well tolerated with very few adverse effects suggesting good therapeutic option for treatment of cancer patients (Uriarte-Pinto et al. 2016). Owing to the several beneficial properties, several liposome-based formulations has been approved by the FDA for various anticancer agents such as daunorubicin (DaunoXome®, Doxil®/Caelyx®), cytarabine (DepoCyt®), vincristine (Marqibo®), etc. (Lian and Ho 2001).

Liposome-mediated gene transfer has also been found as a promising approach not only in the treatment of diseases with genetic disorders but also in the development of strategies for treatment of several fatal diseases, viz., cancer, degenerative disorders, and AIDS. For instance, Landen et al. (2005) developed 1, 2-dioleoylsn-glycero-3-phosphatidylcholine (DOPC)-encapsulated siRNA liposomes using tertiary-butanol and nonionic detergent Tween 20. Developed system was found to be effective in reducing EphA2 expression 48 h after administration of a single dose in an orthotopic model of ovarian carcinoma suggesting its applicability (Landen et al. 2005). Bubble liposomes (containing perfluoropropane gas) possess specific advantage of high gene loading with improved intracellular penetration. Sugii and coworkers formulated the plasmid DNA-loaded bubble liposomes. The developed system was specifically targeted to neovessels via conjugating cyclic RGD peptides on their surface and exhibited high gene transfection efficiency to human umbilical vein endothelial cells (HUVECs) (Sugii et al. 2016). Similarly, folic acid modified liposomes were also loaded with plasmid DNA and binding affinity of gene was modified by agarose gel electrophoresis assays. Gene transfection efficiency was studied against NCI-H460 cells. The results showed improvement in gene transfection efficiency after attaching the targeting moieties (Cui et al. 2016).

6.2.2 Solid lipid Nanoparticles

SLNs were first developed in 1991 and are used as alternative carrier systems to traditional colloidal carriers, such as emulsions, liposomes, and polymeric NPs (Muller et al. 2002). SLNs consist of 0.1–30% (w/w) lipid, dispersed in an aqueous solution of 0.5–5% (w/w) of surfactant and are solid at both room and body temperature (Rawat et al. 2008). These particles are prepared by using number of solid lipid materials such as mono-, di-, and triglycerides; fatty acids; waxes; and steroids. The lipid materials employed should possess favorable properties such as biocompatibility, biodegradability, and low toxicity. Various surfactants employed for steric stabilization includes phospholipids, poloxamers, and polysorbates. Most commonly, SLNs are fabricated using hot or cold homogenization technique. The average diameter of the SLNs ranges from approximately 40–1000 nm (Mehnert and Mader 2001).

SLNs have gained popularity as these combine advantages of various "soft" drug carriers such as emulsions, liposomes, and polymeric NPs and at the same time avoid or minimize some of their drawbacks. They have progressively been explored for the encapsulation of labile hydrophilic and hydrophobic drugs protecting them from degradation in the body and for sustained release. Some of the drug classes that are being investigated with this system includes antibacterial, antiparasitic, antioxidant, anticancer, antiviral, antiandrogenic, antihypertensive, anti-inflammatory, antipsychotic agents, vitamins, and various bioactive compounds having multipotential (polyphenols, flavonoids, carotenoids). Numerous studies have shown that bioavailability of drugs loaded in SLNs can be extensively improved and also provide site specificity. For example, Bhandari and Kaur prepared isoniazid-loaded SLNs to improve its oral bioavailability. The study showed 6 and 4 times higher relative bioavailability of the drug in plasma and brain, respectively, when compared to the free drug solution at the same dose in rats. The high plasma drug concentration reported was attributed to the lipidic transport of SLNs through lymphatics and thus bypassing first pass metabolism of isoniazid (Bhandari and Kaur 2013). Pandita et al. successfully developed resveratrol loaded stearic acid-based SLNs using a mixture of surfactants (lecithin/poloxamer 188) as stabilizers. Pharmacokinetic results demonstrated that oral bioavailability of resveratrol was 8.035-fold high in male Wistar rats when compared to its pure suspension (Pandita et al. 2014). Also, in a study, paclitaxel loaded SLNs when administered orally in male Swiss albino mice exhibited tenfold high bioavailability as compared to paclitaxel solution, and the toxicity studies confirmed the relatively safe nature of the SLNs carrier systems with or without drug (Pandita et al. 2011). In another study, curcumin-loaded SLNs prepared with liquid lipid Sefsol-218® showed higher bioavailability and prolonged inhibitory activity in cancer cells. After the i.v. administration to rat, SLNs were capable of enhancing the bioavailability of curcumin to 1.25-fold compared to free drug (Sun et al. 2013).

Although, exhilarating results have been obtained with SLNs as mentioned above, various biological barriers, viz., rapid clearance, serum instability, and nonspecific uptake by the mononuclear phagocytic system, are associated with

conventional SLNs. PEGylation was introduced for surface functionalization of SLNs to provide a hydrophilic layer resulting in increased circulation time via overcoming of opsonization process (Uner and Yener 2007). In a study, Madan and colleagues prepared noscapine-loaded SLNs and noscapine-loaded PEG conjugated SLNs. After i.v. administration to mice, the plasma half-life was significantly enhanced up to ~11-fold and ~5-fold in case of noscapine-PEG-SLNs and noscapine-SLN, respectively, in comparison to free drug suggesting applicability of surface modification (Madan et al. 2013).

Since early 2000, SLNs have been investigated for delivery of genetic material in several disease treatments (Olbrich et al. 2001). Radaic et al. formulated SLNs for gene delivery using factorial design approach wherein different formulation parameters were varied w.r.t. DNA load, colloidal stability, in vitro cytotoxicity, and transfection efficiency in prostate cancer cells. Results suggested that the concentration of lipids and surfactant employed affected the size, stability, and transfection efficiency (Radaic et al. 2015). Yu et al. prepared paclitaxel-loaded cationic SLNs and fabricated its complex with human MCL1-specific siRNA. They showed that co-delivery of paclitaxel and MCL1-specific siRNA using cationic SLNs enhanced anticancer efficacy both in vitro and in vivo when compared to each agent alone (Yu et al. 2012). In spite of several beneficial properties as drug-carrier, SLNs have lots of drawbacks such as limited drug loading and leakage of drug during storage. Further, NLCs were developed as next generation of lipid drug carrier systems at the end of 1990s to overcome the drawbacks of SLNs.

6.2.3 Nanostructured Lipid Carriers

NLCs may overcome the limitations associated with SLNs such as low drug payloads, leakage of drug during storage, and stability (Weber et al. 2014). They are mainly produced by mixing of different lipids, i.e., solid lipids (glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate/monostearin, cetyl palmitate, and stearic acid) with liquid a lipid (caprylic and capric fatty acids with a minor level of caproic, lauric, myristic, corn oil, coconut or palm kernel oils, etc.) which remains solid at room temperature (Naseri et al. 2015). NLCs show higher entrapment efficiency because solid lipids provide higher space for hold of drug and higher solubility of drugs in liquid lipids in comparison to solid lipids (Poonia et al. 2016). NLCs have been investigated for parenteral, oral, pulmonary, and topical delivery of drugs and have also presented good potential in gene delivery.

The attractive properties of NLCs on skin offer increase in drug penetration mainly through occlusion effect. They transfer drugs into deeper layers of the skin with reservoir action and provide sustained release (Muller et al. 2007). Sweety and coworkers formulated NLCs of an anti-acne drug, azelaic acid, using solvent diffusion-solvent evaporation method for enhancing its dermal retention and overcoming its adverse effects. Results of skin retention study showed high retention of azelaic acid from NLCs gel (63.96 ± 4.45%) followed by plain azelaic acid gel (15.12 ± 3.2%) and drug solution (4.78 ± 1.1%) in rat skin (Sweety et al. 2015).

NLCs are also employed for the treatment of the damaged or inflamed skin due to nonirritant and nontoxic properties of NLCs. Valdecoxib-loaded NLC carbopol gel demonstrated no skin irritation while the marketed gel of valdecoxib caused slight irritation after 48 h (Joshi and Patravale 2006). NLC-based gel also showed prolonged release activity as compared to market gel. Further, chitosan-coated NLCs showed 7.7-fold higher flurbiprofen residence time on the cornea when compared to uncoated NLCs. Also, transcorneal penetrations were increased up to 2.4-fold compared to uncoated NLCs (Luo et al. 2011). In a short period of time, NLC technology has come out as a big boon for topical delivery and two NLC-based products are available in the market (Cutanova Nanorepair Q10 and FloraGLO®).

Another widely employed route of administration for NLCs is the oral route. Due to the increased drug loading capacity of NLCs, most of these studies have focused on the ability of NLCs to improve the oral bioavailability of poorly water-soluble drugs. For example, lovastatin-loaded NLCs made from mixtures of precirol and squalene were able to promote the oral absorption and led to increased bioavailability of lovastatin. More than 70% of lovastatin was entrapped in the NLCs, which was significantly higher compared to the SLNs. Results of in vivo studies on rats showed that NLCs produced a significant improvement in the bioavailability compared to the free solution (Chen et al. 2010). In another study, saquinavir, a P-gp substrate, loaded NLCs were prepared and transport mechanisms across Caco-2 cells were studied. A 3.5-fold increase in drug permeability was reported in case of NLCs than the drug suspension (Beloqui et al. 2013). In another study, a ~2.5- and ~3-fold higher bioavailability was achieved with silymarin-loaded NLCs than the marketed formulation (Legalon®) and free drug (Zhai and Zhai 2014). Yang et al. (2013) prepared hyaluronic acid-coated NLCs using electrostatic attraction for targeted delivery of paclitaxel at tumors' site and investigated the in vitro cytotoxicity and in vivo antitumor efficacy against three CD44-overexpressing cell lines. The result of hyaluronic-coated NLCs showed better antitumor efficacy in B16-bearing Kunming mice when compared to Taxol®. Further, hyaluronic-coated NLCs showed higher accumulation in tumor and enhanced the circulation time of paclitaxel in blood.

NLCs as gene carriers can easily penetrate through the biological membranes effectively because lipids are the main components of cell membranes boosting the uptake of genetic compounds (Pathak et al. 2009). In a study, Zhang and coworkers prepared a novel system by modifying NLCs using cetylated polyethylenimine (PNLC). PNLCs showed high transfection efficiency in human lung adenocarcinoma cell line SPC-A1 and Chinese hamster ovary (CHO) cells as compared to free drug. The transfection efficiency of the optimized PNLC was similar to marketed formulation (Lipofectamine™2000) (Zhang et al. 2008). More recently, Han and coworkers (2016) developed a modified plasmid-containing enhanced green fluorescence protein (pEGFP)-loaded NLCs with transferrin (Tf) as an excellent active targeting ligand for improving the A549 cell targeting ability of the carriers. Tf-NLC/pEGFP showed higher gene expression efficiency in cancer cells both in vitro and in vivo than unmodified NLC/pEGFP suggesting enhanced activity after loading into targeted NLCs.

6.3 Polymer-Based Nanoparticles

A long chain that is made up with a repeated subunit by joining together larger macromolecules or micromolecules is called a polymer. Mainly two types of polymers have been used for the development of polymer-based nanocarriers, i.e., natural and synthetic. Some examples of natural and synthetic polymers include albumin, dextran, hyaluronate, chitosan, and poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), poly(cyanoacrylate) (PCA), poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA), PEG, polyethyleneimine (PEI), etc., respectively (Haag and Kratz 2006). On the basis of method of preparation, various types of polymeric-based nanoformulations have been obtained such as polymeric NPs, nanospheres or nanocapsules, micelles, polymer drug conjugates, etc. (Fig. 6.2). The average size ranges of such nanocarriers are from 10 to 1000 nm (Peer et al. 2007).

6.3.1 Polymeric Micelles

Polymeric micelles are spherical, colloidal, and nanoscopic core/shell structures and usually have narrow size distributions with diameters ranging from 10 to 100 nm (Jhaveri and Torchilin 2014). They are formed via self-assembly of amphiphilic copolymer chain in aqueous milieu. They present a core and shell architecture; the inner core is hydrophobic part which serves as a microenvironment for poorly water-soluble drugs, whereas the outer hydrophilic corona protects drug from aqueous environment and stabilizes interface between the core and the external medium (Kedar et al. 2010). This self-assembly monomer provides the main driving force behind the micellization process. Polyion complex micelles are subclass of polymeric micelles and are obtained from electrostatic interactions between oppositely charged copolymer (one is charged segment and other is neutral polymer chain) and drug followed by self-assembly of charge-neutralized blocks (Harada and Kataoka 1995; Kataoka et al. 1996). Both polymeric micelles and polyion complex micelles can serve as reservoir for drugs, which may be loaded by different methods, i.e., chemically, physically, or electrostatically, depending on the chemistry of drug and core forming block.

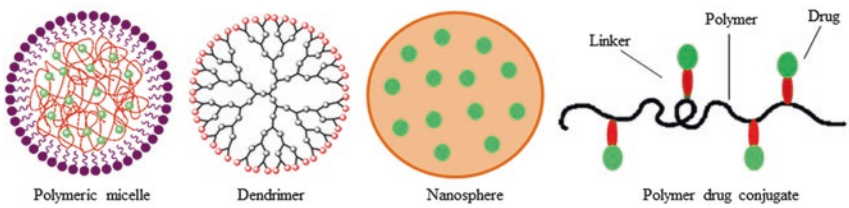

Fig. 6.2 Structure of polymer-based nanocarriers

Many drugs present low aqueous solubility and poor accumulation at their target site which lower their efficacy and can promote systemic adverse effects. In addition, macromolecular drugs such as peptides, DNA, and RNA suffer from premature degradation upon administration, low bioavailability, and inefficient cellular entry, compromising their therapeutic outcome. The versatile attributes of polymeric micelles make these systems an attractive nanocarrier for the delivery of these therapeutics. Due to the nonionic hydrophilic corona, polymeric micelles can prevent the adsorption of opsonins, thereby limiting the rapid uptake by the mononuclear phagocyte system (MPS) and prolonging the circulation half-life of the encapsulated drug (Jones and Leroux 1999). Hamaguchi et al. (2005) showed that the incorporation of paclitaxel in PEG-*b*-P(Asp) polymeric micelle resulted in about 90- and 25-fold increase in plasma concentration and tumor area, respectively, compared to the free drug. This remarkable increase in the AUC, in spite of using equivalent doses, can be ascribed to the greater stability conferred by the micelles which permits long circulation and minimizes the drug leakage (four to six times longer elimination half-life vs. the free drug) and thus allow the passage and accumulation of the drug in the tumor. Polymeric micelles can be functionalized with targeting ligands in order to achieve active targeting. Perche et al. (2012) demonstrated superior cellular uptake and cytotoxicity of doxorubicin when loaded in antibody-conjugated (anti-nucleosome 2C5) poly(ethylene)glycol-phosphatidylethanolamine micelles in comparison to free drug and conjugated micelle system. Also, developed system was found to be efficient in drug-resistant ovarian cancer cells.

In addition to modifying the pharmacokinetics and biodistribution, and decreasing the systemic toxicity of drugs, polymeric micelles have been also found to stabilize their incorporated drug, as in the case of amphotericin B. Amphotericin B is a membrane disruptive drug used to treat systemic fungal diseases in its monomeric form. Its direct administration, however, is associated with self-aggregation, leading to loss of selectivity and systemic toxicity. Adams et al. have shown that when amphotericin B was incorporated into the core of PEG-*b*-poly(*N*-hexyl-laspartamide-stearic acid) micelles, it was stabilized in its monomeric form, preventing the non-selective hemolysis of mammalian red blood cells in vitro (Adams et al. 2003). Moreover, the drug-loaded polymeric micelle retained in vivo antifungal activity as compared to the standard clinical Fungizone® formulation (Barratt and Bretagne 2007). In another study, Ge et al. formulated polyplex micelle modified with PEG-polycation block copolymer for gene delivery. Furthermore, in order to enhance targeted delivery and to promote cellular uptake, cyclic RGD peptide was attached at distal end of PEG. It was found that circulation time was successfully increased through PEG conjugation. Thus, constructed cyclic RGD conjugated polyplex micelle with the prominent PEG shielding resulted in both improved accumulation at tumor site and provided efficient gene expression of antiangiogenic protein (sFlt-1) through intracellular trafficking (Ge et al. 2014).

6.3.2 Dendrimers

Dendrimers are highly branched, three-dimensional polymeric architecture with many arms originating from a central core (Gillies and Frechet 2005). They have an internal cavity, in which drug can be incorporated and also large number of functional groups present on the outer surface can be used to bind variety of drugs and other functional groups. Dendrimers can be prepared by iterative synthetic methodology, i.e., divergent synthesis or convergent synthesis (Nanjwade et al. 2009). The void area within dendrimer and its ease of modification makes it applicable for drug and gene delivery, imaging, and boron neutron capture therapy. Dendrimers generally have a uniform structure, with the prospective to create an isolated "active site" core area through chemical functionalization. Modification of branching may allow for incorporation of molecule within this system. For example, dendrimers may become water soluble when outer surface is functionalized with hydrophilic groups, such as carboxylic acids (Faraji and Wipf 2009). Cytotoxicity of dendrimers strongly depends on its surface modification and core material. For example, cytotoxicity can be reduced by changing the surface amine groups with hydroxyl groups (Wilczewska and Niemirowicz 2012). It was found by Singh et al. that doxorubicin dendrimers conjugated with biodegradable polymer were ten times less toxic than free doxorubicin toward colon carcinoma cells (Singh and Lillard 2009).

Among many different types of dendrimers, poly(amidoamine) (PAMAM) has been one of the commonly used systems and shown significant applications in pharmaceutical and biomedical fields (Madaan et al. 2014). Although it has many advantages in drug delivery, it has several issues which limit its clinical applications. PAMAM is cytotoxic and rapidly removed from systemic circulation due to presence of amine groups on the surface. This drawback is one of the key barriers for the clinical use of dendrimers. PAMAM surface has been modified using different techniques such as PEGylation, carbohydrate conjugation, acetylation, and amino acid or peptide conjugation for enhancing the biocompatibility and drug encapsulation as well as targeting ability. Various studies have been investigated w.r.t. the low cytotoxicity and enhanced transfection efficiency of modified PAMAM dendrimers (Bae et al. 2016; Luong et al. 2016). Yu et al. developed PAMAM dendrimers modified with histidine and arginine, which resulted in higher gene transfection efficiency when compared to unmodified PAMAM dendrimers. They also found that histidine unit attached with PAMAM dendrimers improved its proton buffering capacity in the range of 3.5–6. The histidine and arginine modified dendrimers also showed less cytotoxicity as compared to PEI modified dendrimers. This proves that PAMAM dendrimers modified with histidine and arginine may provide a promising gene carrier system (Yu et al. 2011). Dutta et al. studied toxicity profile of conventional and surface engineered fifth generation poly(propyleneimine) (PPI) dendrimers. They were evaluated after administering 2.5 mg/kg, 25 mg/kg, and 250 mg/kg doses via i.v. route to Wister rats. Hemolytic studies depicted a decrease in RBCs

and hemoglobin content in conventional PPI dendrimers. Biochemical analysis also showed an increase in level of serum biochemical parameters indicative of the hepatotoxic effect of PPI. However, functionalized PPI dendrimers showed no signs of toxicity suggesting reduction of toxicity followed by functionalization (Dutta et al. 2008). In another study, fifth generation PAMAM dendrimer was functionalized with hydrophobic chains (12–16 C-alkyl chain) for delivery of plasmid DNA in mesenchymal stem cells. In vitro results demonstrated that functionalized dendrimers had low level of cytotoxicity due to presence of alkyl group on the outer surface. Further, it was found that smallest carbon chain of alkyl group showed higher efficiency for gene delivery (Santos et al. 2010).

6.3.3 Polymeric Nanoparticles

Polymeric NPs have great potential to enhance therapeutic benefit while reducing side effects of the free drug. These NPs are generally aqueous dispersions or dry powders obtained by freeze/spray drying. They overcome the stability and premature drug release issues associated with liposomes and emulsions and also facilitate prolonged drug release (Kumari et al. 2010). Polymeric NPs are prepared from PLA, PLGA, etc., possess excellent biodegradability and low toxicity, and consist of drug dispersed in an amorphous form within a polymer matrix; such particles could be prepared as nanosphere, wherein the drug is dispersed uniformly throughout the matrix of the particle or as nanocapsules. They have been studied for localized as well as controlled drug delivery. For example, carmustine-loaded polymeric implant disc made by polyanhydride polymer was used for the treatment of brain cancer. Such disc is placed into the brain to follow controlled release pattern while preventing tumor regrowth (Domb et al. 1999).

6.3.3.1 PLGA Nanoparticles

Among various polymeric NPs, PLGA-based NPs are particularly attractive in biomedical applications. PLGA is a frequently used biodegradable polymer as its hydrolytic degradation produces the original monomers, lactic acid, and glycolic acid which are side-products of various metabolic pathways. The degradation time of PLGA is controlled by the ratio of lactic acid and glycolic acid: the higher the content of glycolide units, the less is the time required. However, the copolymer with 50:50 monomers ratio reveals the fastest degradation. Because of its minimal toxicity and ability for providing greater control over the drug release profile, PLGA is suitable for drug delivery (Astete and Sabliov 2006). PLGA NPs are versatile among various polymeric NPs systems because of their biocompatibility for drug targeting at the cellular level (Mohamed and van der Walle 2008). Mathew et al. (2012) developed curcumin-loaded PLGA NPs conjugated with Tet-1 peptide for the treatment of Alzheimer's disease. Due to antioxidant and anti-amyloid activity of curcumin, curcumin-loaded NPs were successfully used in the treatment of

Alzheimer's disease. In vitro cytotoxicity studies toward LAG cell lines demonstrated that Tet-1 conjugated or unconjugated NPs showed no cytotoxicity while exhibiting antioxidant property. Furthermore, cell uptake was performed by using GI-1 glioma cells for Tet-1 conjugated and unconjugated NPs. It was found that Tet-1-conjugated PLGA NPs showed multiple-fold increased uptake than the unconjugated NPs. Moreover, confocal microscopy studies showed that Tet-1 targeted NPs distributed more around the cell soma and nucleus compared to unconjugated NPs. These results demonstrated that Tet-1 conjugated PLGA NPs were proved to have great potential as therapeutic carrier of curcumin for Alzheimer's disease treatment (Mathew et al. 2012). Yu et al. (2015) developed paclitaxel-loaded PLGA NPs complexed with PEI conjugated with Herceptin onto the surface of NPs through electrostatic interaction. In vitro cell line study toward HER-2 cancer cells showed that Herceptin-loaded polymeric NPs have high degree of cytotoxicity when compared with unmodified polymeric NPs. Furthermore, they also fabricated Herceptin-loaded polymeric NPs through chemical conjugation. It was found that chemically conjugated Herceptin polymeric NPs showed less cytotoxicity and cellular uptake efficiency in comparison with electrostatically bound Herceptin. These results demonstrated that electrostatic interaction provided an appropriate method for the synthesis of protein-loaded NPs (Yu et al. 2015).

6.3.3.2 PLA Nanoparticles

PLA is linear aliphatic polyester derived from lactic acid monomers and is widely used in micro- and nanoparticulate drug delivery systems because of its biocompatibility and biodegradation properties. It possesses the Generally Recognized as Safe (GRAS) status of the FDA (Kumari et al. 2010; Athanasiou et al. 1996). Among all biopolymers, PLA has been widely investigated in drug delivery systems since the 1980s due to its extensive biodegradability nature. For instance, Zhu et al. successfully developed D-alpha-tocopherol polyethylene glycol 1000 succinate (TPGS)-PLA NPs modified with polydopamine for the treatment of liver cancer. In this study, docetaxel was used as a model drug and galactosamine was conjugated on the surface of modified polymeric NPs to enhance the targeted delivery of drug to cancer cells. In vitro cellular uptake and cytotoxicity studies showed that galactosamine-conjugated polymeric NPs target HepG2 cells and inhibit the growth of cancer cells in comparison to Taxotere®. Furthermore, in vivo results demonstrated that drug-loaded polymeric NPs reduced the tumor size most extensively on hepatoma-bearing mice (Zhu et al. 2015). In another study, Tan et al. (2014) fabricated PLA-TPGS NPs to reduce the antagonist effect of docetaxel and tamoxifen. It was found that co-delivery of both anticancer drugs in PLA-TPGS NPs can significantly enhance the cytotoxicity toward MCF7 cancer cells. Moreover, decrease in IC_{50} in MCF7 cell line showed that polymeric NPs have the potential to enhance the synergistic effects by reducing antagonistic effect.

In gene delivery studies, DNA is coupled to NPs to create non-viral vectors protecting the DNA in body conditions. A size of around 100 nm and the positive charge of the particles facilitate the delivery and interactions with the cell membrane, respectively. Qian et al. (2014) developed different shaped PLA-polydimethylaminoethyl methacrylate (PDMAEMA) nanoarchitectures for the co-delivery of miR-21 and doxorubicin to treat glioma. It was found that star-shaped copolymer formed nanosized micelles and had positive charge and low cytotoxicity toward GES-1 cells in comparison to control PEI 25 kDa. Also, they had higher gene transfection efficiency (2.5 times) than the control PEI. The results depicted that star-shaped copolymers are promising candidate for the gene delivery and hydrophobic therapeutics.

6.3.3.3 Chitosan Nanoparticles

Chitosan NPs are also one of the most accepted polymer-based NPs used in drug delivery and targeting applications. Due to its hydroxyl and amine functional groups, the chemical modifications of chitosan have been extensively investigated in literature in order to improve its physicochemical properties, without changing its fundamental skeleton. The main goals of chemically modifying chitosan are to provide derivatives that are soluble at neutral and basic pH values, to control hydrophobic, cationic, and anionic properties as well as to attach various functional groups and ligands and optimize the process of drug release. Furthermore, the hydrophobic modification of cationic polymers has shown facilitated dissociation of polymer/DNA, enhancing the release of DNA to cytoplasm that would otherwise remain strongly bound through ionic interactions between phosphate groups of DNA and cationic units of polymers (Maximilien et al. 2015). The chemical modification of this cationic natural polymer, without changing its main properties, could be a huge approach for enhancing the efficiency of transfection. Recently, Rudzinski et al. (2016) formulated PEGylated chitosan NPs for delivery of siRNA with improved transfection efficacy in colon cancer cells. Confocal studies depicted high level of fluorescent tagged RNAs into cells showing better effect in treatment of colon cancer.

Hybrid lipid-based polymeric NPs provide several opportunities in drug delivery and gene delivery due to their physicochemical properties in terms of drug encapsulation, size as well as low immunogenicity, and no risk of transmission of infectious diseases (Pandita et al. 2015a). The versatility of this lipid-polymer hybrid NP platform allows for surface chemistry modifications. Ewe and Aiqner (2016) used cationic lipids in their hybrid NPs in order to form a DNA complex for gene delivery. In a study by Morales et al. (2009), the end group on the PEG that makes up the corona can be changed from a carboxyl group to an amine or a methoxy group in order to change the surface zeta potential. It was also shown that the surface chemistry of the hybrid NPs affects human plasma and serum absorption patterns by inducing different levels of compliment activation. The compliment and coagulant

activation studies exhibited the potential for the lipid-polymer hybrid NPs to be a viable immunocompatible delivery option. Another type of surface chemistry modification is the addition of targeting ligands, which are used to increase cellular uptake and accumulation in the tumor sites. Different types of ligands are used to target hybrid NPs to cancer cells such as antibodies, proteins, small molecules, aptamers, and peptides (Wang and Thanou 2010). Zhao et al. (2015) synthesized lipid-polymer hybrid NPs to co-deliver HIF1α and gemcitabine for the treatment of pancreatic cancer. It was found that lipid-polymer hybrid NPs have higher stability and longer circulation time than polymer NPs. Furthermore, drug-loaded lipid-polymer hybrid NPs exhibited synergistic antitumor effect in vivo than drug-loaded polymer NPs.

6.3.4 Polymer-Drug Conjugates

Ringsdorf proposed the idea of polymer-drug conjugates in the mid-1970 that could enhance the delivery of an anticancer drug to a tumor. Polymer-drug conjugate is a drug delivery technology in which a drug is covalently attached to a polymeric carrier, mostly via biodegradable linker (Haag and Kratz 2006). These linkages might be cleaved to release the pharmacologically active moieties in a particular condition such as pH, temperature, and osmolality around the tumor. Polymers such as PEG, poly-styrene-maleic anhydride copolymer (SMA), *N*-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), and poly(a, L-glutamic acid) (PG) have been investigated with different cytotoxic drugs (doxorubicin, paclitaxel, gemcitabine, camptothecin, irinotecan, cisplatin, etc.). More than 15 polymer-drug conjugates have entered in clinical trials till now (Table 6.2). The main benefits of polymer-drug conjugates compared to the free drug include EPR effect, reduced toxicity, improved solubility in biological fluids, ability to overpass some mechanisms of drug resistance, and increased half-life of the drug (Duncan 2006). For instance, Vasey et al. (1999) reported the conjugation of HPMA copolymer with doxorubicin (PK1). They found that PK1 demonstrated antitumor activity with significantly lower cardiotoxicity and alopecia when compared to unconjugated doxorubicin. Chytil et al. (2006) developed water-soluble polymer-drug conjugate for cancer therapy. This agent consisted of anticancer drug doxorubicin conjugated to a HPMA copolymer through the hydrolytically degradable hydrazone bond. The system was incubated at pH 7.4 and 5.0 in order to enable pH-controlled release of the drug. At pH 7.4 conjugates were found to be stable and sustain the drug release while at pH 5.0 burst release of drug was observed. Moreover, in vitro cell line study showed higher cytotoxicity of polymer-drug conjugate system when compared to the free drug suspension.

Table 6.2 Clinical status of polymer-based nanocarriers

Product (company)	Nanoplatform	Drug	Indication	Status	References
Genexol-PM® [Samyang Biopharm]	PEG-PLA polymeric micelle	Paclitaxel	Breast cancer, lung cancer	Approved	Lee et al. (2008)
Paclical [Oasmia Pharmaceutical]	Polymeric micelle	Paclitaxel	Ovarian cancer	Phase III	Oasmia Pharmaceutical (2014)
NKTR-102 [Nektar]	PEG drug conjugate	Irinotecan	Breast cancer, ovarian cancer	Phase III	Awada et al. (2013)
Nanotax [CritiTech]	Polymeric micelle	Paclitaxel	Peritoneal neoplasms	Phase III	Roby et al. (2008)
Transdrug BA-003 [BioAlliance Pharma]	Polymeric micelle	Doxorubicin	Hepatocellular carcinoma	Phase III	Barraud et al. (2005)
Xyotax, Opaxio (CT-2103) [Cell Therapeutics]	Polyglutamic acid (polyglumex) drug conjugate	Paclitaxel	Lung cancer, ovarian cancer	Phase III	Sabbatini et al. (2004)
NK-105 [Nanocarrier Nippon Kayaku]	PEG-PAA polymeric micelle	Paclitaxel	Gastric cancer, breast cancer	Phase II/III	Kato et al. (2012)
NC-6004 [Nanocarrier]	PEG-PGA polymeric micelle	Cisplatin	Pancreas cancer	Phase II/III	Plummer et al. (2011)
Taxoprexin [Protagra]	Docosahexaenoic acid drug conjugate	Paclitaxel	Melanoma, liver cancer, kidney cancer	Phase II/III	Bedikian et al. (2011)
SP1049C [Supratek Pharma]	Polymeric micelle	Doxorubicin	Advanced adenocarcinoma	Phase II/III	Morris (2003
PEG-SN38 [Belrose Pharma/Enzone]	PEG drug conjugate	SN 38 (irinotecan derivative)	Solid tumors, breast cancer, colorectal cancer	Phase II	Patnaik et al. (2013)
Pegasys [Genentech]/ PegIntron [Merck]	PEG drug conjugate	IFNα2a/-IFNα2b	Melanoma, leukemia	Phase II	Egusquiaguirre et al. (2012)
NK-012 [Nippon Kayaku]	PEG-PAA polymeric micelle	SN-38 (active metabolite of irinotecan)	Solid tumors, small cell lung cancer, breast cancer	Phase II	Hamaguchi et al. (2010)
Pegamotecan [Enzon]	PEG drug conjugate	Camptothecin	Gastric cancer	Phase II	Scott et al. (2009)
DHAD-PBCA-NP	Polymeric micelle	Mitoxantrone	Hepatocellular carcinoma	Phase II	Zhou et al. (2009)
PK 2 (FCE28069) [UK Cancer Research/Pfizer]	HPMA drug conjugate	Doxorubicin	Hepatocellular carcinoma	Phase II	Seymour et al. (2002)

PK 1 (FCE28068) [UK Cancer Research/Pfizer]	HPMA drug conjugate	Doxorubicin	Hepatocellular carcinoma	Phase II	Vasey et al. (1999)
Lipotecan [Taiwan liposome]	Polymeric micelle	TLC388 (Camptothecin derivative)	Liver cancer, renal cancer	Phase I/II	Ghamande et al. (2014)
NKTR-105 [Nektar]	PEG drug conjugate	Docetaxel	Solid tumors, ovarian cancer	Phase I/II	Awada et al. (2013)
CT-2106 [CTI Biopharma]	Polyglutamic acid drug conjugate	Camptothecin	Colon cancer, ovarian cancer	Phase I/II	Homsi et al. (2007)
AP5280 [Access Pharmaceutical]	HPMA drug conjugate	Platinum	Solid tumors	Phase I/II	Rademaker-Lakhai et al. (2004)
NC-4016 [Nanocarrier]	Polymeric micelle	Oxaliplatin	Solid tumors, lymphoma	Phase I	Ueno et al. (2014)
Nanoxel [Fresenius Kabi Oncology]	Polymeric micelle	Paclitaxel	Advanced breast cancer	Phase I	Madaan et al. (2013)
Docetaxel-PNP [Samyang Biopharm]	Polymeric micelle	Docetaxel	Solid tumors	Phase I	Jung et al. (2012)
NC-6300 [Nanocarrier]	pH-sensitive polymeric micelle	Epirubicin	Solid tumors	Phase I (Japan)	Harada et al. (2011)
XMT-1001 [Mersana]	Fleximer drug conjugate	Camptothecin	Gastric cancer, lung cancer	Phase I	Yurkovetskiy and Fram (2009)
DE-310 [Daiichi Pharmaceutical]	Carboxymethyldextran polyalcohol drug conjugate	DX-8951 (camptothecin derivative)	Solid tumors	Phase I	Soepenberg et al. (2005)
NK-911 [National Cancer Institute Japan/Nippon Kayaku]	PEG-PAA polymeric micelle	Doxorubicin	Solid tumors	Phase I	Matsumura et al. (2004)
MAG-CPT [Pfizer]	HPMA drug conjugate	Camptothecin	Solid tumors	Phase I	Bissett et al. (2004)
PNU166945 [Pfizer]	HPMA drug conjugate	Paclitaxel	Solid tumors	Phase I	Meerum et al. (2001)

6.4 Inorganic Nanocarriers

Inorganic nanocarriers are emerging nanosystems utilizing inorganic nanomaterials to achieve medical breakthroughs in therapeutics and advanced diagnostics (Sekhon and Kamboj 2014; Huang et al. 2011; Malmsten 2013). These include metallic NPs, SiNPs, CNTs, QD, etc. (Fig. 6.3). Due to large size and anionic nature, these systems can reduce problems associated with chemical stability and poor gene transfection efficacy (Malmsten 2013). By varying size and surface composition, smart engineered nanocarriers can avoid the RES and can improve drug targeting to the specific area of the body. These nanocarriers have strong affinity to thiol, amine, and carboxyl groups. Such affinity enables surface-modified nanocarriers as promising material for targeting drugs and/or chemotherapeutics. For example, gold nanoparticles modified with albumin do not show any hemolytic response and are used as a carrier for drug release in systemic circulation (Khullar et al. 2012).

6.4.1 Metallic Nanoparticles

Numerous efforts have been made to fabricate various noble metal NPs and to investigate their optical properties. The use of gold (Au) and silver (Ag) NPs has been explored broadly in biological imaging and gene and drug delivery owing to their unique dimensions, tunable functionalities, and controlled drug release (Yang et al. 2012)

The strong plasmon resonance, surface-enhanced Raman scattering, and photothermal conversion of metallic AuNPs have been exploited for imaging and therapy of cancerous cells (Sekhon and Kamboj 2014). The scattering from a single AuNP or AgNPs has been found to be of many orders of magnitude than the signal from single fluorophores or QD. AuNPs are good candidates for drug and gene delivery. Andres and coworkers synthesized AuNPs and grafted them with thioctic acid-PEG-folic acid. The resulting folate-PEG-coated NPs were soluble in aqueous solution over pH range 2–12 and at electrolyte concentration of up to 0.5 M NaCl. They also demonstrated the specific uptake of folate-conjugated AuNPs by folate-receptor positive tumor cells (Dixit et al. 2006). Brown et al. (2010) functionalized gold NPs

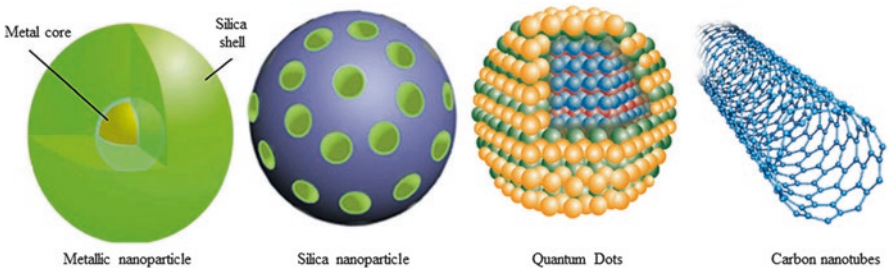

Fig. 6.3 Structure of inorganic nanocarriers

with a thiolated PEG capped with a carboxylate group for improved drug delivery of oxaliplatin anticancer drug (Brown et al. 2010). In an another attempt, doxorubicin-loaded PEGylated AuNPs were successfully delivered for overcoming multidrug resistance of MCF-7/ADR cancer cells (Wang et al. 2011). Recently, Manivasagan et al. (2016) synthesized fucoidan (Fu)-capped AuNPs for delivery of doxorubicin and photoacoustic imaging. Fu was used as a capping and reducing agent. The in vitro cytotoxicity effect of Fu, Fu AuNPs, and DOX-Fu AuNPs were studied on human breast cancer cells (MDA-MB-231). It was found that in vitro cytotoxicity of DOX-Fu AuNPs can be recognized to the greater uptake potential of Fu AuNPs, thus establishing the role of AuNPs as capable carriers for the delivery of anticancer drugs (Manivasagan et al. 2016). AuNPs have been used in gene therapy by using viral and non-viral vectors to transport foreign genes to somatic cells. Mirkin and coworkers demonstrated functionalized AuNPs with single-stranded thiolated oligonucleotide for gene therapy. They found that modified AuNPs have higher binding affinity for complementary nucleic acids and exhibited greater cellular uptake than unmodified NPs (Rosi et al. 2006). Niidome et al. (2006) synthesized spherical AuNPs to investigate the release of plasmid DNA through pulsed-laser-induced fragmentation and dissociation. The result indicated that laser power could release plasmid DNA without significant degradation. Braun et al. (2009) reported novel lipid-based gold NPs for delivery of siRNA that provided temporally and spatially controlled cellular delivery for gene silencing, with the help of direct endosomal release mechanism activated via pulsed laser treatment.

6.4.2 Silica Nanoparticles

Humans are introduced to silica, the most generous substance on earth surface and widely used in our daily life from various sources such as clays, rocks, and sand (Barik et al. 2008). Fumed silica, colloidal silica, etc. are industrial silica extensively used in microelectronics, optical communication, and food additives. SiNPs have attracted key attention for tumor-targeted drug delivery due to their enormous biomedical applications. There are two major types of SiNPs for tumor-targeted drug delivery, i.e., core/shell SiNPs (C/S-SiNPs) and mesoporous silica nanoparticles (MSNs) (Vallet-Regi et al. 2007; Vivero-Escoto et al. 2010; Malmsten 2013). But MSNs have served its groundbreaking potential in drug and gene delivery due to good physical and chemical stability, high loading capacity, zero premature release, and controlled release of drug molecules with proper rate of release to achieve an effective local concentration. MSNs possess unique features of tunable particle size/pore size/morphology, high surface area and pore volume, biocompatibility, and facile surface functionalization (Yang et al. 2012; Malmsten 2013; Pandita et al. 2015b). Recently, researchers have made several efforts to synthesize hybrid MSNs (AuNPs and magnetic NPs as functional components) loaded with drug molecules (Sekhon and Kamboj 2014). These multifunctional nanosystems have potential applications like targeted drug delivery, in vivo imaging, and theranostic applications (Pandita and Lather 2015). For example, researchers

successfully loaded camptothecin in fluorescent MSNs and confirmed the release of drug to various types of human cancer cells to induce cell death (Lu et al. 2007). MSNs are promising vehicle for drug delivery, on account of their successful encapsulation and delivery to the target sites, for drugs such as quercetin, paclitaxel, and doxorubicin (Sarkar et al. 2016; Jia et al. 2013; Fu et al. 2016; Zhang et al. 2016b). Suwalski and coworkers developed a MSN-based gene transfer system that allows an acceleration of tendon regeneration by PDGF-B gene transfer. The MSNs were modified with amino and carboxyl group and in vitro and in vivo transfection efficiency were evaluated. The result showed that modified MSNs did not have signs of inflammation or necrosis in the tendon, kidney heart, and liver of rat during a period of 1.5 months (Suwalski et al. 2010). Roy et al. (2005) used organically modified MSNs to deliver the non-viral DNA sequence for gene delivery. Pan et al. (2012) synthesized peptide-MSN conjugates for targeting cell nuclei and delivering the anticancer drug doxorubicin into targeted nucleus, killing cancer cells with high efficiency. This study provided an effective strategy for design and development of cell-nuclear-targeted drug delivery systems.

6.4.3 Quantum Dots

QD are semiconductor nanocrystals whose optical and electronic properties are strongly size-dependent (Alivisatos 1996). Larger QD have a smaller bandgap and emit lower energy photons (toward the red side of the spectrum) and smaller QD have a larger bandgap and emit higher energy photons (toward the blue side of the spectrum). QD of various semiconductor compositions, such as ZnS, CdS, ZnSe, CdTe, and PbS, have size-tunable fluorescence emission that range between the UV and infrared range (Medintz et al. 2005). QD can replace organic dyes in many applications and offer several advantages over organic dyes, such as photo stability, long fluorescence lifetime, broad absorption, and narrow, tunable emission spectra (Chan et al. 2002). These properties make QD well suited for applications such as single molecule tracking (Dahan et al. 2003), time-gated imaging (Dahan et al. 2001), and multiplexed imaging where organic dyes would be of limited use due to their photo bleaching, short fluorescence lifetime, and narrow absorption spectra (Ghazani et al. 2006). Their photo stability and tunable emission spectra also enable long-term multicolor imaging, which can offer real-time insights into how cells and proteins interact (Jaiswal et al. 2003). They have also been used to track metastasis. The ability to tune their fluorescence into the near infrared window has also enabled their use in optically guided surgery and in vivo cancer imaging (Gao et al. 2004). The surface of QD can be coated or conjugated with polymers in order to enhance its biocompatibility and extend stability against biochemical reactions. Gao et al. (2004) successfully coated triblock amphiphilic copolymer over CdSe/ZnS QD which protected QD from hydrolysis and enzymatic degradation. They also found that in vivo imaging results of QD probes can be targeted to tumor site through active and passive mechanisms but active targeting is much efficient than passive targeting (Gao et al. 2004). In another study, Johari-Ahar et al. (2016) synthesized L-cysteine-capped CdSe QD conjugated with methotrexate (MTX) and evaluated

their internalization and cytotoxicity in the KB cells. Based on cytotoxicity assessment results, drug-QD conjugate was found to efficiently internalize into cancer cells and eradicate MTX-resistant KB cells with IC_{50} of 12.0 μg/ml as compared to free drug molecules, i.e., 105.0 μg/ml. These findings proposed MTX-QD as promising material for targeted therapy of MTX-resistant cells (Johari-Ahar et al. 2016). Further, QD has been found as promising approache in gene delivery. For example, Yang et al. (2014) functionalized PEI on QD to study the effect of particle size and PEI coating on the efficiency of gene delivery into human mesenchymal stem cells. QD of several sizes (5, 10, 15, and 20 nm) were used in the study. It was found that PEI-coated QD exhibited high gene transfection efficacy as compared to unmodified QD. Particularly, QD with largest particle size (20 nm) exhibited much higher uptake capability and greater gene transfection efficacy.

6.4.4 Carbon Nanotubes

The rapid development of carbon nanotube (CNT)-based technology in many different fields rendered this material not as much unknown as few years ago for scientific community. CNTs are classified into single-walled carbon nanotubes (SWNTs) and multiwalled carbon nanotubes (MWNTs). These exhibit unique physicochemical properties like high aseptic ratio, high mechanical strength, ultralight weight, and high electrical and thermal conductivity (Yang et al. 2012). They have been demonstrated to be potential carriers for a wide variety of agents such as drugs, DNA, proteins, and genes. Functionalization of CNTs is receiving attention in biomedical applications. With the help of covalent functionalization of CNTs through side-walls and tips, these can be soluble in wide range of solvents (Madani et al. 2011). Also, functionalization of CNTs is responsible to determine its biocompatibility and cytotoxic effect. It was reported that the higher the degree of CNTs functionalization, the safer the material is, thus offering the potential exploitation of nanotubes for drug administration (Prato et al. 2008). Although the clearance mechanism of CNTs is still not clear, numerous studies have reported that accumulation of functionalized CNTs takes place in the RES after i.v. administration. Kang et al. (2010) reported that endocytosis of larger SWNTs (100–200 nm) takes place mainly through clathrin-mediated pathway, whereas smaller SWNTs having size 50–100 nm are internalized employing both clathrin- and caveolae-mediated pathway.

Although amine functionalized CNTs have good binding efficiency for DNA, their transfection efficiency is low (Singh et al. 2005). PEI was reported to be employed on the surface of CNTs to enhance DNA binding and cell uptake (Liu et al. 2005). Later, Liu et al. (2008) developed SWNTs functionalized with phospholipid branched PEG via a cleavable ester bond to deliver the paclitaxel drug at tumor site. They found that functionalized SWNTs owing to prolong blood circulation and tenfold higher tumor PTX uptake by SWNTs through EPR presented higher tumor suppression efficacy compared to clinical Taxol in a murine 4T1 breast cancer model. They also found that drug molecules were excreted via biliary pathway without causing toxic effect to normal cells. The clinical status of different inorganic nanocarriers is listed in Table 6.3.

Table 6.3 Clinical status of inorganic nanocarriers

Product (company)	Nanoplatform	Application	Indication	Status	References
Feridex i.v. [AMAG]	Iron oxide nanoparticles	Magnetic resonance imaging	Liver cancer	FDA approved	Wang (2011)
Resovist [Bayer]	Iron oxide nanoparticles	Magnetic resonance imaging	Liver cancer	FDA approved	Wang (2011)
Ferumoxtran-10 [Guerbet/AMAG]	Iron oxide nanoparticles	Magnetic resonance imaging	Prostate cancer	Phase III	Fortuin et al. (2013)
Aurimune (CYT-6091) [Cytimmune Sciences]	Colloidal gold	Tumor necrosis factor delivery	Solid tumors	Phase I/II	Libutti et al. (2010)
Ferumoxytol [MD Anderson/AMAG]	Iron oxide nanoparticles	Magnetic resonance imaging	Head and neck cancer, lymph node cancer	Phase I	Hedgire et al. (2014)
AuroLase [Nanospectra]	Gold-coated silica nanoparticles	Photothermal ablation	Head and neck cancer	Phase I	Li et al. (2013)
Targeted SNP [Memorial Sloan Kettering cancer Centre]	Silica nanoparticles	Lymph node imaging	Head and neck cancer	Phase 0	Benezra et al. (2011)

6.5 Conclusion

A variety of nanocarriers are being investigated for the drug and gene delivery. The size of these nanocarriers is responsible for the wide range of promising properties. The ideal nanocarrier can be used to achieve the suitable kinetic properties such as long circulation time, excellent biocompatibility, selective targeting to tumor sites, etc. Nanocarriers are developed to enhance the pharmacological effect and therapeutic properties of drugs. Several nanocarriers are being developed and under preclinical stages with few of them already being used in clinical cancer care like liposomal-based formulation Doxil® (doxorubicin), DepoCyt® (cytarabine), Myocet® (doxorubicin), etc. Nanoscale-based delivery strategies have begun to make a significant impact on global pharmaceutical market. NPs in gene therapy have also drawn significant attention as a potential method for treating both acute illnesses and chronic diseases.

The near future may cling to the appearance of new commercial nanocarrier-based products. However, this revolution of technology in terms of NPs is a challenge, since challenges are high in terms of investments, but due to increasing competition and industrial occurrence, the reimbursement can be greater.

References

Adams ML, Andes DR, Kwon GS (2003) Amphotericin B encapsulated in micelles based on poly(ethylene oxide)-block-poly(L-amino acid) derivatives exerts reduced in vitro hemolysis but maintains potent in vivo antifungal activity. Biomacromolecules 4(3):750–757

Alivisatos AP (1996) Semiconductor clusters, nanocrystals, and quantum dots. Science 271(5251):933–937

Arias JL (2013) Liposomes in drug delivery: a patent review (2007–present). Expert Opin Ther Pat 23(11):1399–1414

Astete CE, Sabliov CM (2006) Synthesis and characterization of PLGA nanoparticles. J Biomater Sci Polym Ed 17(3):247–289

Athanasiou KA, Niederauer GG, Agrawal CM (1996) Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers. Biomaterials 17:93–102

Awada A, Garcia AA, Chan S, Jerusalem HM, Coleman RE, Huizing MT, Mehdi A (2013) Two schedules of etirinotecan pegol (NKTR-102) in patients with previously treated metastatic breast cancer: a randomised phase 2 study. Lancet Oncol 14(12):1216–1225

Bae Y, Lee S, Green ES, Park JH, Ko KS, Han J, Choi JS (2016) Characterization of basic amino acids-conjugated PAMAM dendrimers as gene carriers for human adipose-derived mesenchymal stem cells. Int J Pharm 501(1–2):75–86

Barik TK, Sahu B, Swain V (2008) Nanosilica-from medicine to pest control. Parasitol Res 103(2):253–258

Barratt G, Bretagne S (2007) Optimizing efficacy of Amphotericin B through nanomodification. Int J Nanomedicine 2(3):301–313

Barraud L, Merle P, Soma E, Lefrancois L, Guerret S, Chevallier M, Dubernet C, Couvreur P (2005) Increase of doxorubicin sensitivity by doxorubicin-loading into nanoparticles for hepatocellular carcinoma cells in vitro and in vivo. J Hepatol 42(5):736–743

Batist G, Ramakrishnan G, Rao CS, Chandrasekharan A, Gutheil J, Guthrie T, Shah P, Khojasteh A, Nair MK, Hoelzer K, Tkaczuk K, Park YC, Lee LW (2001) Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol 19(5):1444–1454

Bedikian AY, DeConti RC, Conry R, Agarwala S, Papadopoulos N, Kim KB, Ernstoff M (2011) Phase 3 study of docosahexaenoic acid–paclitaxel versus dacarbazine in patients with metastatic malignant melanoma. Ann Oncol 22(4):787–793

Beloqui A, Solinís MÁ, Gascón AR, del Pozo-Rodríguez A, des Rieux A, Préat V (2013) Mechanism of transport of saquinavir-loaded nanostructured lipid carriers across the intestinal barrier. J Control Release 166:115–123

Benezra M, Penate-Medina O, Zanzonico PB, Schaer D, Ow H, Burns A, DeStanchina E, Longo V, Herz E, Iyer S, Wolchok J, Larson SM, Wiesner U, Bradbury MS (2011) Multimodal silica nanoparticles are effective cancer-targeted probes in a model of human melanoma. J Clin Investig 121(7):2768–2780

Bhandari R, Kaur IP (2013) Pharmacokinetics, tissue distribution and relative bioavailability of isoniazid-solid lipid nanoparticles. Int J Pharm 441(1–2):202–212

Bissett D, Cassidy J, de Bono JS, Muirhead F, Main M, Robson L, Fraier D, Magnè ML, Pellizzoni C, Porro MG, Spinelli R, Speed W, Twelves C (2004) Phase I and pharmacokinetic (PK) study of MAG-CPT (PNU 166148): a polymeric derivative of camptothecin (CPT). Br J Cancer 91(1):50–55

Booser DJ, Esteva FJ, Rivera E, Valero V, Esparza-Guerra L, Priebe W, Hortobagyi GN (2002) Phase II study of liposomal annamycin in the treatment of doxorubicin-resistant breast cancer. Cancer Chemother Pharmacol 50(1):6–8

Braun GB, Pallaoro A, Wu G, Missirlis D, Zasadzinski JA, Tirrell M, Reich NO (2009) Laser-activated gene silencing via gold nanoshell-siRNA conjugates. ACS Nano 3(7):2007–2015

Brown SD, Nativo P, Smith JA, Stirling D, Edwards PR, Venugopal B, Flint DJ, Plumb JA, Graham D, Wheate NJ (2010) Gold nanoparticles for the improved anticancer drug delivery of the active component of oxaliplatin. J Am Chem Soc 132(13):4678–4684

Chan WC, Maxwell DJ, Gao X, Bailey RE, Han M, Nie S (2002) Luminescent quantum dots for multiplexed biological detection and imaging. Curr Opin Biotechnol 13(1):40–46

Chen CC, Tsai TH, Huang ZR, Fang JY (2010) Effects of lipophilic emulsifiers on the oral administration of lovastatin from nanostructured lipid carriers: physicochemical characterization and pharmacokinetics. Eur J Pharm Biopharm 74(3):474–482

Chytil P, Etrych T, Konák C, Sírová M, Mrkvan T, Říhová B, Ulbrich K (2006) Properties of HPMA copolymer-doxorubicin conjugates with pH-controlled activation: effect of polymer chain modification. J Control Release 115(1):26–36

Cui SH, Zhi DF, Zhao YN, Chen HY, Meng Y, Zhang CM, Zhang SB (2016) Cationic lioposomes with folic acid as targeting ligand for gene delivery. Bioorg Med Chem Lett 26(16):4025–4029

Dahan M, Laurence T, Pinaud F, Chemla DS, Alivisatos AP, Sauer M, Weiss S (2001) Time-gated biological imaging by use of colloidal quantum dots. Opt Lett 26(11):825–827

Dahan M, Lévi S, Luccardini C, Rostaing P, Riveau B, Triller A (2003) Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking. Science 302(5644):442–445

Dixit V, Van den Bossche J, Sherman DM, Thompson DH, Andres RP (2006) Synthesis and grafting of thioctic acid-PEG-folate conjugates onto Au nanoparticles for selective targeting of folate receptor-positive tumor cells. Bioconjug Chem 17(3):603–609

Domb AJ, Israel ZH, Elmalak O, Teomim D, Bentolila A (1999) Preparation and characterization of carmustine loaded polyanhydride wafers for treating brain tumors. Pharm Res 16(5):762–765

Duffaud F, Borner M, Chollet P, Vermorken JB, Bloch J, Degardin M, Rolland F, Dittrich C, Baron B, Lacombe D, Fumoleau P (2004) Phase II study of OSI-211 (liposomal lurtotecan) in patients with metastatic or loco-regional recurrent squamous cell carcinoma of the head and neck. An EORTC New Drug Development Group study. Eur J Cancer 40(18):2748–2752

Duncan R (2006) Polymer conjugates as anticancer nanomedicines. Nat Rev Cancer 6(9):688–701

Dutta T, Garg M, Dubey V, Mishra D, Singh K, Pandita D, Singh AK, Ravi AK, Velpandian T, Jain NK (2008) Toxicological investigation of surface engineered fifth generation poly (propyleneimine) dendrimers in vivo. Nanotoxicology 2(2):62–70

Egusquiaguirre SP, Igartua M, Hernández RM, Pedraz JL (2012) Nanoparticle delivery systems for cancer therapy: advances in clinical and preclinical research. Clin Transl Oncol 14(2):83–93

Estanqueiro M, Amaral MH, Conceição J, Sousa Lobo JM (2015) Nanotechnological carriers for cancer chemotherapy: the state of the art. Colloids Surf B Biointerf 126:631–648

Ewe A, Aiqner A (2016) Cationic lipid-coated polyplexes (Lipopolyplexes) for DNA and small RNA delivery. Methods Mol Biol 1445:187–200

Faraji AH, Wipf P (2009) Nanoparticles in cellular drug delivery. Bioorg Med Chem 17(8):2950–2962

Fasol U, Frost A, Büchert M, Arends J, Fiedler U, Scharr D, Scheuenpflug J, Mross K (2012) Vascular and pharmacokinetic effects of EndoTAG-1 in patients with advanced cancer and liver metastasis. Ann Oncol 23(4):1030–1036

Fortuin AS, Meijer H, Thompson LC, Witjes JA, Barentsz JO (2013) Ferumoxtran-10 ultrasmall superparamagnetic iron oxide–enhanced diffusion-weighted imaging magnetic resonance imaging for detection of metastases in normal-sized lymph nodes in patients with bladder and prostate cancer: do we enter the era after extended pelvic lymph node dissection? Eur Urol 64(6):961–963

Fu Q, Hargrove D, Lu X (2016) Improving paclitaxel pharmacokinetics by using tumor-specific mesoporous silica nanoparticles with intraperitoneal delivery. Nanomedicine 12(7):1951–1959

Gao X, Cui Y, Levenson RM, Chung LWK, Nie S (2004) In vivo cancer targeting and imaging with semiconductor quantum dots. Nat Biotechnol 22(8):969–976

Ge Z, Chen Q, Osada K, Liu X, Tockary TA, Uchida S, Dirisala A, Ishii T, Nomoto T, Toh K, Matsumoto Y, Oba M, Kano MR, Itaka K, Kataoka K (2014) Targeted gene delivery by polyplex micelles with crowded PEG palisade and cRGD moiety for systemic treatment of pancreatic tumors. Biomaterials 35(10):3416–3426

Ghamande S, Lin CC, Cho DC, Shapiro GI, Kwak EL, Silverman MH, Tseng Y, Kuo MW, Mach WB, Hsu SC, Coleman T, Yang JC, Cheng AL, Ghalib MH, Chuadhary I, Goel S (2014) A phase 1 open-label, sequential dose-escalation study investigating the safety, tolerability, and pharmacokinetics of intravenous TLC388 administered to patients with advanced solid tumors. Investig New Drug 32(3):445–451

Ghazani AA, Lee JA, Klostranec J, Xiang Q, Dacosta RS, Wilson BC, Tsao MS, Chan WC (2006) High throughput quantification of protein expression of cancer antigens in tissue microarray using quantum dot nanocrystals. Nano Lett 6(12):2881–2886

Gillies ER, Frechet JM (2005) Dendrimers and dendritic polymers in drug delivery. Drug Discov Today 10(1):35–43

Glantz MJ, Jaeckle KA, Chamberlain MC, Phuphanich S, Recht L, Swinnen LJ, Maria B, LaFollette S, Schumann GB, Cole BF, Howell SB (1999) A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 5(11):3394–3402

Gref R, Domb A, Quellec P, Blunk T, Muller RH, Verbavatz JM, Langer VR (1995) The controlled intravenous delivery of drugs using PEG-coated sterically stabilized nanospheres. Adv Drug Deliv Rev 16(2):215–233

Gref R, Lück M, Quellec P, Marchand M, Dellacherie E, Harnisch S, Blunk T, Müller RH (2000) Stealth' corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. Colloids Surf B Biointerf 18(3–4):301–313

Haag R, Kratz F (2006) Polymer therapeutics: concepts and applications. Angew Chem Int Ed Eng 45(8):1198–1215

Hamaguchi T, Matsumura Y, Suzuki M, Shimizu K, Goda R, Nakamura I, Nakatomi I, Yokoyama M, Kataoka K, Kakizoe T (2005) NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumour activity and reduce the neurotoxicity of paclitaxel. Br J Cancer 92(7):1240–1246

Hamaguchi T, Doi T, Eguchi-Nakajima T, Kato K, Yamada Y, Shimada Y, Fuse N, Ohtsu A, Matsumoto S, Takanashi M, Matsumura Y (2010) Phase I study of NK012, a novel SN-38–incorporating micellar nanoparticle, in adult patients with solid tumors. Am Ass Cancer Res 16(20):5058–5066

Han Y, Li Y, Zhang P, Sun J, Li X, Sun X, Kong F (2016) Nanostructured lipid carriers as novel drug delivery system for lung cancer gene therapy. Pharm Dev Technol 21(3):277–281

Harada A, Kataoka K (1995) Formation of polyion complex micelles in an aqueous milieu from a pair of oppositely-charged block copolymers with poly(ethylene glycol) segments. Macromolecules 28(15):5294–5299

Harada M, Bobe I, Saito H, Shibata N, Tanaka R, Hayashi T, Kato Y (2011) Improved anti-tumor activity of stabilized anthracycline polymeric micelle formulation, NC-6300. Cancer Sci 102(1):192–199

Hedgire SS, Mino-Kenudson M, Elmi A, Thayer S, Fernandez-del Castillo C, Harisinghani MG (2014) Enhanced primary tumor delineation in pancreatic adenocarcinoma using ultrasmall super paramagnetic iron oxide nanoparticle-ferumoxytol: an initial experience with histopathologic correlation. Int J Nanomedicine 9:1891–1896

Higashihara M, Kinoshita M, Kume S, Teramoto T, Kurokawa K (1991) Inhibition of platelet function by high-density lipoprotein from a patient with apolipoprotein E deficiency. Biochem Biophys Res Commun 181(3):1331–1336

Homsi J, Simon GR, Garrett CR, Springett G, De Conti R, Chiappori AA, Munster PN, Burton MK, Stromatt S, Allievi C, Angiuli P, Eisenfeld A, Sullivan DM, Daud AI (2007) Phase I trial of poly-l-glutamate camptothecin (CT-2106) administered weekly in patients with advanced solid malignancies. Am Ass Cancer Res 13(19):5855–5861

Huang HC, Barua S, Sharma G, Dey SK, Rege K (2011) Inorganic nanoparticles for cancer imaging and therapy. J Control Release 155(3):344–357

Huber G, Levy J (2001) Development of verteporfin therapy: a collaboration between pharmaceutical companies, device manufacturers and clinical investigators. Semin Ophthalmol 16(4):213–217

Jabr-Milane L, van Vlerken L, Devalapally H, Shenoy D, Komareddy S, Bhavsar M, Amiji M (2008) Multi-functional nanocarriers for targeted delivery of drugs and genes. J Control Release 130(2):121–128

Jaiswal JK, Mattoussi H, Mauro JM, Simon SM (2003) Long-term multiple color imaging of live cells using quantum dot bioconjugates. Nat Biotechnol 21(1):47–51

Jhaveri AM, Torchilin VP (2014) Multifunctional polymeric micelles for delivery of drugs and siRNA. Front Pharmacol 5:77

Jia LJ, Shen J, Li Z, Zhang D, Zhang Q, Liu G, Zheng D, Tian X (2013) In vitro and in vivo evaluation of paclitaxel-loaded mesoporous silica nanoparticles with three pore sizes. Int J Pharm 445(1–2):12–19

Johari-Ahar M, Barar J, Alizadeh AM, Davaran S, Omidi Y, Rashidi MR (2016) Methotrexate-conjugated quantum dots: synthesis, characterisation and cytotoxicity in drug resistant cancer cells. J Drug Target 24(2):120–133

Jones M, Leroux J (1999) Polymeric micelles – a new generation of colloidal drug carriers. Eur J Pharm Biopharm 48(2):101–111

Joshi M, Patravale V (2006) Formulation and evaluation of nanostructured lipid carrier (NLC)-based gel of valdecoxib. Drug Dev Ind Pharm 32(8):911–918

Jung J, Park SJ, Chung HK, Kang HW, Lee SW, Seo MH, Park HJ, Song SY, Jeong SY, Choi EK (2012) Polymeric nanoparticles containing taxanes enhance chemoradiotherapeutic efficacy in non-small cell lung cancer. Int J Radiat Oncol Biol Phys 84(1):77–83

Kanasty R, Dorkin JR, Vegas A, Anderson D (2013) Delivery materials for siRNA therapeutics. Nat Mater 12(11):967–977

Kang B, Chang S, Dai Y, Yu D, Chen D (2010) Cell response to carbon nanotubes: size-dependent intracellular uptake mechanism and subcellular fate. Small 6(21):2362–2366

Kataoka K, Togawa H, Harada A, Yasungi K, Matsumoto T, Katayose S (1996) Spontaneous formation of polyion complex micelles with narrow distribution from antisense oligonucleotide and cationic block copolymer in physiological saline. Macromolecules 29(26):8556–8557

Kato K, Chin K, Yoshikawa T, Yamaguchi K, Tsuji Y, Esaki T, Sakai K, Kimura M, Hamaguchi T, Shimada Y, Matsumura Y, Ikeda R (2012) Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. Investig New Drug 30(4):1621–1627

Kedar U, Phutane P, Shidhaye S, Kadam V (2010) Advances in polymeric micelles for drug delivery and tumor targeting. Nanomed Nanotech Biol Med 6(6):714–729

Khullar P, Singh V, Mahal A, Dave PN, Thakur S, Kaur G, Singh J, Kamboj SS, Bakshi MS (2012) Bovine serum albumin bioconjugated gold nanoparticles: synthesis, hemolysis, and cytotoxicity toward cancer cell lines. J Phys C C 116(15):8834–8843

Kumari A, Yadav SK, Yadav SC (2010) Biodegradable polymeric nanoparticles based drug delivery systems. Colloid Surf B Biointerf 75:1–18

Landen CN, Chavez-Reyes A, Bucana C, Schmandt R, Deavers MT, Lopez-Berestein G, Sood AK (2005) Therapeutic EphA2 gene targeting in vivo using neutral liposomal small interfering RNA delivery. Cancer Res 65(15):6910–6918

Lee KS, Chung HC, Im SA, Park YH, Kim CS, Kim SB, Rha SY, Lee MY, Ro J (2008) Multicenter phase II trial of Genexol-PM, a cremophor-free, polymeric micelle formulation of paclitaxel, in patients with metastatic breast cancer. Breast Cancer Res Treat 108(2):241–250

Li J, Gupta S, Li C (2013) Research perspectives: gold nanoparticles in cancer theranostics. Quant Imaging Med Surg 3(6):284–291

Lian T, Ho RJ (2001) Trends and developments in liposome drug delivery systems. J Pharm Sci 90(6):667–680

Libutti SK, Paciotti GF, Byrnes AA, Alexander HR Jr, Gannon WE, Walker M, Seidel GD, Yuldasheva N, Tamarkin L (2010) Phase I and pharmacokinetic studies of CYT-6091, a novel PEGylated colloidal gold-rhTNF nanomedicine. Am Ass Cancer Res 16(24):6139–6149

Lim SB, Banerjee A, Önyüksel H (2012) Improvement of drug safety by the use of lipid-based nanocarriers. J Control Release 163(1):34–45

Liu Y, Wu DC, Zhang WD, Jiang X, He CB, Chung TS, Goh SH, Leong KW (2005) Polyethylenimine-grafted multiwalled carbon nanotubes for secure noncovalent immobilization and efficient delivery of DNA. Angew Chem Int Ed 44(30):4782–4785

Liu Z, Chen K, Davis C, Sherlock S, Cao Q, Chen X, Dai H (2008) Drug delivery with carbon nanotubes for in vivo cancer treatment. Cancer Res 68(16):6652–6660

Lu J, Liong M, Zink JI, Tamanoi F (2007) Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. Small 3(8):1341–1346

Luo Q, Zhao J, Zhang X, Pan W (2011) Nanostructured lipid carrier (NLC) coated with chitosan oligosaccharides and its potential use in ocular drug delivery system. Int J Pharm 403(1–2):185–191

Luong D, Kesharwani P, Deshmukh R, Mohd Amin MC, Gupta U, Greish K, Iyer AK (2016) PEGylated PAMAM dendrimers: enhancing efficacy and mitigating toxicity for effective anticancer drug and gene delivery. Acta Biomater 43:14–29

Madaan A, Singh P, Awasthi A, Verma R, Singh AT, Jaggi M, Mishra SK, Kulkarni S, Kulkarni H (2013) Efficiency and mechanism of intracellular paclitaxel delivery by novel nanopolymer-based tumor-targeted delivery system Nanoxel TM. Clin Transl Oncol 15(1):26–32

Madaan K, Kumar S, Poonia N, Lather V, Pandita D (2014) Dendrimers in drug delivery and targeting: drug-dendrimer interactions and toxicity issues. J Pharm Bioallied Sci 6(3):139–150

Madan J, Pandey RS, Jain V, Katare OP, Chandra R, Katyal A (2013) Poly (ethylene)-glycol conjugated solid lipid nanoparticles of noscapine improve biological half-life, brain delivery and efficacy in glioblastoma cells. Nanomedicine 9(4):492–503

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

Mahalingam D, Nemunaitis JJ, Malik L, Sarantopoulos J, Weitman S, Sankhala K, Hart J, Kousba A, Gallegos NS, Anderson G, Charles J, Rogers JM, Senzer NN, Mita AC (2014) Phase I study of intravenously administered ATI-1123, a liposomal docetaxel formulation in patients with advanced solid tumors. Cancer Chemother Pharmacol 74(6):1241–1250

Malmsten M (2013) Inorganic nanomaterials as delivery systems for proteins, peptides, DNA, and siRNA. Curr Opin Colloid Interface Sci 18(5):468–480

Mamot C, Ritschard R, Wicki A, Stehle G, Dieterle T, Bubendorf L, Hilker C, Deuster S, Herrmann R, Rochlitz C (2012) Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: a phase 1 dose-escalation study. Lancet Oncol 13(12):1234–1241

Manivasagan P, Bharathiraja S, Bui NQ, Jang B, Oh YO, Lim IG, Oh J (2016) Doxorubicin-loaded fucoidan capped gold nanoparticles for drug delivery and photoacoustic imaging. Int J Biol Macromol 91:578–588

Mathew A, Fukuda T, Nagaoka Y, Hasumura T, Morimoto H, Yoshida Y, Maekawa T, Venugopal K, Kumar DS (2012) Curcumin loaded-PLGA nanoparticles conjugated with Tet-1 peptide for potential use in Alzheimer's disease. PLoS One 7(3):32616

Matougui N, Boge L, Groo AC, Umerska A, Ringstad L, Bysell H, Saulnier P (2016) Lipid-based nanoformulations for peptide delivery. Int J Pharm 502(1–2):80–97

Matsumura Y, Hamaguchi T, Ura T, Muro K, Yamada Y, Shimada Y, Shirao K, Okusaka T, Ueno H, Ikeda M, Watanabe N (2004) Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. Br J Cancer 91(10):1775–1781

Maximilien J, Beyazit S, Rossi C, Bui BTS (2015) Nanoparticles in biomedical applications. In: Wegener J (ed) Bioanalytical reviews. Springer, Cham

Medintz IL, Uyeda HT, Goldman ER, Mattoussi H (2005) Quantum dot bioconjugates for imaging, labelling and sensing. Nat Mater 4(6):435–446

Meerum Terwogt JM, ten Bokkel Huinink WW, Schellens JH, Schot M, Mandjes IA, Zurlo MG, Rocchetti M, Rosing H, Koopman FJ, Beijnen JH (2001) Phase I clinical and pharmacokinetic study of PNU166945, a novel water-soluble polymer-conjugated prodrug of paclitaxel. Anti-Cancer Drugs 12(4):315–323

Mehnert W, Mader K (2001) Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev 47(2–3):165–196
Mohamed F, van der Walle CF (2008) Engineering biodegradable polyester particles with specific drug targeting and drug release properties. J Pharm Sci 97(1):71–87
Morales CS, Zhang L, Langer R, Farokhzad OC (2009) Immunocompatibility properties of lipid-polymer hybrid nanoparticles with heterogeneous surface functional groups. Biomaterials 30:2231–2240
Morris B (2003) The components of the wired spanning forest are recurrent. Probab Theory Relat Fields 125(2):259–265
Mosqueira VC, Legrand P, Gref R, Heurtault B, Appel M, Barratt G (1999) Interactions between a macrophage cell line (J774A1) and surface-modified poly (D, L-lactide) nanocapsules bearing poly(ethylene glycol). J Drug Target 7(1):65–78
Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, Roman L, Uziely B, Muderspach L, Garcia A, Burnett A, Greco FA, Morrow CP, Paradiso LJ, Liang LJ (1997) Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. J Clin Oncol 15(3):987–993
Muller RH, Radtke M, Wissing SA (2002) Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 54(Suppl 1):S131–S155
Muller RH, Petersen RD, Hommoss A, Pardeike J (2007) Nanostructured lipid carriers (NLC) in cosmetic dermal products. Adv Drug Deliv Rev 59(6):522–530
Nanjwade BK, Bechra HM, Derkar GK, Manvi FV, Nanjwade VK (2009) Dendrimers: emerging polymers for drug-delivery systems. Eur J Pharm Sci 38(3):185–196
Naseri N, Valizadeh H, Milani PZ (2015) Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Ad Pharm Bull 5(3):305–313
Niidome Y, Niidome T, Yamada S, Nakashima (2006) Pulsed-laser induced fragmentation and dissociation of DNA immobilized on gold nanoparticles. Mol Cryst Liq Cryst 445(1):201–206
Oasmia Pharmaceutical AB (2014) Study of paclitaxel in patients with ovarian cancer. Retrieved. https://clinicaltrials.gov/ct2/show/NCT00989131
Olbrich C, Bakowsky U, Lehr CM, Müller RH, Kneuer C (2001) Cationic solid-lipid nanoparticles can efficiently bind and transfect plasmid DNA. J Control Release 77(3):345–355
Onyuksel H, Séjourné F, Suzuki H, Rubinstein I (2006) Human VIP-alpha: a long-acting, biocompatible and biodegradable peptide nanomedicine for essential hypertension. Peptides 27(9):2271–2275
Pagano L, Cornely OA, Busca A, Caira M, Cesaro S, Gasbarrino C, Girmenia C, Heinz WJ, Herbrecht R, Florl CL, Nosari A, Potenza L (2013) Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematologic diseases: a report from the SEIFEM and FUNGISCOPE registries. Haematologica 98(10):127–130
Pan L, He Q, Liu J, Chen Y, Ma M, Zhang L, Shi J (2012) Nuclear-targeted drug delivery of TAT peptide-conjugated monodisperse mesoporous silica nanoparticles. J Am Chem Soc 134(13):5722–5725
Pandita D, Lather V (2015) Silica based nanoparticles for theranostic applications. In: Singh B (ed) NanoBioMedicine vol 3 nanotheranostics. Studium Press LLC, Houston
Pandita D, Ahuja A, Lather V, Benjamin B, Dutta T, Velpandian T, Khar RK (2011) Development of lipid-based nanoparticles for enhancing the oral bioavailability of paclitaxel. AAPS PharmSciTech 12(2):712–722
Pandita D, Kumar S, Poonia N, Lather V (2014) Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. Food Res Int 62:1165–1174
Pandita D, Kumar S, Lather V (2015a) Hybrid poly(lactic-co-glycolic acid) nanoparticles: design and delivery prospectives. Drug Discov Today 20(1):95–104
Pandita D, Poonia N, Lather V (2015b) Mesoporous silica nanoparticles in drug delivery and targeting. In: Singh B (ed) NanoBioMedicine vol 1 nanomedicine. Studium Press LLC, Houston

Patel KD, Mahapatra C, Jin GZ, Singh RK, Kim HW (2015) Biocompatible mesoporous nanotubular structured surface to control cell behaviors and deliver bioactive molecules. ACS Appl Mater Interfaces 7(48):26850–26859

Pathak A, Patnaik S, Gupta KC (2009) Recent trends in non-viral vector-mediated gene delivery. Biotechnol J 4(11):1559–1572

Patnaik A, Papadopoulos KP, Tolcher AW, Beeram M, Urien S, Schaaf LJ, Tahiri S, Bekaii-Saab T, Lokiec FM, Rezaï K, Buchbinder A (2013) Phase I dose-escalation study of EZN-2208 (PEG-SN38), a novel conjugate of poly(ethylene) glycol and SN38, administered weekly in patients with advanced cancer. Cancer Chemother Pharmacol 71(6):1499–1506

Pattni BS, Chupin VV, Torchilin VP (2015) New developments in liposomal drug delivery. Chem Rev 115(19):10938–10966

Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R (2007) Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2(12):751–760

Perche F, Patel NR, Torchilin VP (2012) Accumulation and toxicity of antibody-targeted doxorubicin-loaded PEG-PE micelles in ovarian cancer cell spheroid model. J Control Release 164(1):95–102

Plummer R, Wilson RH, Calvert H, Boddy AV, Griffin M, Sludden J, Tilby MJ, Eatock M, Pearson DG, Ottley CJ, Matsumura Y, Kataoka K, Nishiya T (2011) A phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours. Br J Cancer 104(4):593–598

Poonia N, Kharb R, Lather V, Deepti P (2016) Nanostructured lipid carriers: versatile oral delivery vehicle. Future Sci OA 2(3):FSO135

Prados MD, Lamborn K, Yung WK, Jaeckle K, Robins HI, Mehta M, Fine HA, Wen PY, Cloughesy T, Chang S, Nicholas MK, Schiff D, Greenberg H, Junck L, Fink K, Hess K, Kuhn J, North American Brain Tumor Consortium (2006) A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American brain tumor consortium study. Neuro-Oncol 8(2):189–193

Prato M, Kostarelos K, Bianco A (2008) Functionalized carbon nanotubes in drug design and discovery. Acc Chem Res 41(1):60–68

Qian X, Long L, Shi Z, Liu C, Qiu M, Sheng J, Pu P, Yuan X, Ren Y, Kang C (2014) Star-branched amphiphilic PLA-b-PDMAEMA copolymers for co-delivery of miR-21 inhibitor and doxorubicin to treat glioma. Biomaterials 35(2322):2335

Radaic A, de Paula E, de Jesus MB (2015) Factorial design and development of solid lipid nanoparticles (SLN) for gene delivery. J Nanosci Nanotechnol 15(2):1793–1800

Rademaker-Lakhai JM, Terret C, Howell SB, Baud CM, De Boer RF, Pluim D, Beijnen JH, Schellens JH, Droz JP (2004) A phase I and pharmacological study of the platinum polymer AP5280 given as an intravenous infusion once every 3 weeks in patients with solid tumors. Am Ass Cancer Res 10(10):3386–3395

Rawat M, Singh D, Saraf S, Saraf S (2008) Lipid carriers: a versatile delivery vehicle for proteins and peptides. Yakugaku Zasshi 128(2):269–280

Rivera E (2003) Liposomal anthracyclines in metastatic breast cancer: clinical update. Oncologist 8(Suppl 2):3–9

Roby KF, Niu F, Rajewski RA, Terranova PF (2008) In: Coukos G, Berchuck A, Ozols R (eds) Syngeneic mouse model of epithelial ovarian cancer: effects of nanoparticulate paclitaxel, Nanotax®. Ovarian cancer: state of the art and future directions in translational research. Springer New York, New York, pp 169–181

Rodriguez MA, Pytlik R, Kozak T, Chhanabhai M, Gascoyne R, Lu B, Deitcher SR, Winter JN, Marqibo Investigators (2009) Vincristine sulfate liposomes injection (Marqibo) in heavily pretreated patients with refractory aggressive non-Hodgkin lymphoma: report of the pivotal phase 2 study. Cancer 115(15):3475–3482

Rosi NL, Giljohann DA, Thaxton CS, Lytton-Jean AKR, Han MS, Mirkin CA (2006) Oligonucleotide-modified gold nanoparticles for intracellular gene regulation. Science 312(5776):1027–1030

Roy I, Ohulchanskyy TY, Bharali DJ, Pudavar HE, Mistretta RA, Kaur N, Prasad PN (2005) Optical tracking of organically modified silica nanoparticles as DNA carriers: a nonviral, nanomedicine approach for gene delivery. Proc Natl Acad Sci U S A 102(2):279–284

Rudzinski WE, Palacios A, Ahmed A, Lane MA, Aminabhavi TM (2016) Targeted delivery of small interfering RNA to colon cancer cells using chitosan and PEGylated chitosan nanoparticles. Carbohydr Polym 147:323–332

Sabbatini P, Aghajanian C, Dizon D, Anderson S, Dupont J, Brown JV, Peters WA, Jacobs A, Mehdi A, Rivkin S, Eisenfeld AJ, Spriggs D (2004) Phase II study of CT-2103 in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. J Clin Oncol 22(22):4523–4531

Samad A, Sultana Y, Aqil M (2007) Liposomal drug delivery systems: an update review. Curr Drug Deliv 4(4):297–305

Santos JL, Oliveira H, Pandita D, Rodrigues J, Pêgo AP, Granja PL, Tomás H (2010) Functionalization of poly(amidoamine) dendrimers with hydrophobic chains for improved gene delivery in mesenchymal stem cells. J Control Release 144(1):55–64

Sarkar A, Ghosh S, Chowdhury S, Pandey B, Sil PC (2016) Targeted delivery of quercetin loaded mesoporous silica nanoparticles to the breast cancer cells. Biochim Biophys Acta 1860(10):2065–2075

Scott LC, Yao JC, Thomas AL, Falk S, Mena RR, Picus J, Wright J, Mulcahy MF, Ajani JA, Evans TR (2009) A phase II study of pegylated-camptothecin (pegamotecan) in the treatment of locally advanced and metastatic gastric and gastro-oesophageal junction adenocarcinoma. Cancer Chemother Pharmacol 63(2):363–370

Sekhon BS, Kamboj SR (2014) Inorganic nanomedicine-Part 2. Nanomed Nanotechnol Biol Med 6(5):612–618

Seymour LW, Ferry DR, Anderson D, Hesslewood S, Julyan PJ, Poyner R, Doran J, Young AM, Burtles S, Kerr DJ (2002) Hepatic drug targeting: phase I evaluation of polymer-bound doxorubicin. J Clin Oncol 20(6):1668–1676

Singh R, Lillard JW (2009) Nanoparticle-based targeted drug delivery. Exp Mol Pathol 86(3):215–223

Singh R, Pantarotto D, McCarthy D, Chaloin O, Hoebeke J, Partidos CD, Briand JP, Prato M, Bianco A, Kostarelos K (2005) Binding and condensation of plasmid DNA onto functionalized carbon nanotubes: toward the construction of nanotube-based gene delivery vectors. J Am Chem Soc 127(12):4388–4396

Slingerland M, Guchelaar HJ, Rosing H, Scheulen ME, van Warmerdam LJ, Beijnen JH, Gelderblom H (2013) Bioequivalence of Liposome-Entrapped Paclitaxel Easy-To-Use (LEP-ETU) formulation and paclitaxel in polyethoxylated castor oil: a randomized, two-period crossover study in patients with advanced cancer. Clin Ther 35(12):1946–1954

Soepenberg O, de Jonge MJ, Sparreboom A, de Bruin P, Eskens FA, de Heus G, Wanders J, Cheverton P, Ducharme MP, Verweij J (2005) Phase I and pharmacokinetic study of DE-310 in patients with advanced solid tumors. Am Ass Cancer Res 11(2):703–711

Sonali SRP, Sharma G, Kumari L, Koch B, Singh S, Bharti S, Rajinikanth PS, Pandey BL, Muthu MS (2016) RGD-TPGS decorated theranostic liposomes for brain targeted delivery. Colloids Surf B Biointerf 147:129–141

Stevens JM, Auer J, Strong CA, Hughes RT, Oliver DO, Winearls CG, Cotes PM (1991) Stepwise correction of anaemia by subcutaneous administration of human recombinant erythropoietin in patients with chronic renal failure maintained by continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 6(7):487–494

Sugii M, Suzuki R, Oda Y, Unga J, Omata D, Urunga H, Negishi Y, Maruyama K (2016) Development of cell-targeting bubble liposome for effective gene delivery with ultrasound. Asian J Pharm Sci 11(1):146–147

Sun J, Bi C, Chan HM, Sun S, Zhang Q, Zheng Y (2013) Curcumin-loaded solid lipid nanoparticles have prolonged in vitro antitumour activity, cellular uptake and improved in vivo bioavailability. Colloids Surf B Biointerf 111:367–375

Suwalski A, Dabboue H, Delalande A, Bensamoun SF, Canon F, Midoux P, Saillant G, Klatzmann D, Salvetat JP, Pichon C (2010) Accelerated Achilles tendon healing by PDGF gene delivery with mesoporous silica nanoparticles. Biomaterials 31(19):5237–5245

Sweety K, Deepti P, Poonia N, Lather V (2015) Nanostructured lipid carriers for topical delivery of an anti-acne drug: characterization and *ex vivo* evaluation. Pharm Nanotechnol 3(2):122–133

Tabernero J, Shapiro GI, LoRusso PM, Cervantes A, Schwartz GK et al (2013) First-in-humans trial of an RNA interference therapeutic targeting VEGF and KSP in cancer patients with liver involvement. Cancer Discov 3(4):406–417

Tan GR, Fenq SS, Leong DT (2014) The reduction of anti-cancer drug antagonism by the spatial protection of drugs with. PLA-TPGS Nanopart Biomater 35(9):3044–3051

Thassu D, Deleers M, Pathak YV (2007) Nanoparticulate drug delivery systems. CRC Press, Boca Raton

Ueno T, Endo K, Hori K, Ozaki N, Tsuji A, Kondo S, Wakisaka N, Murono S, Kataoka K, Kato Y, Yoshizaki T (2014) Assessment of antitumor activity and acute peripheral neuropathy of 1, 2-diaminocyclohexane platinum (II)-incorporating micelles (NC-4016). Int J Nanomedicine 9:3005–3012

Uner M, Yener G (2007) Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomedicine 2(3):289–300

Uriarte-Pinto MÁ, Escolano-Pueyo Á, Gimeno-Ballester V, Pascual-Martínez O, Abad-Sazatornil MR, Agustín-Ferrández MJ (2016) Trastuzumab, non-pegylated liposomal-encapsulated doxorubicin and paclitaxel in the neoadjuvant setting of HER-2 positive breast cancer. Int J Clin Pharm 38(2):446–453

Vallet-Regi MF, Balas F, Arcos D (2007) Mesoporous materials for drug delivery. Angew Chem Int Ed Eng l46(40):7548–7558

Vasey PA, Kaye SB, Morrison R, Twelves C, Wilson P, Duncan R, Thomson AH, Murray LS, Hilditch TE, Murray T, Burtles S, Fraier D, Frigerio E, Cassidy J (1999) Phase I clinical and pharmacokinetic study of PK1 [N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin]: first member of a new class of chemotherapeutic agents-drug-polymer conjugates. Cancer Research Campaign Phase I/II Committee. Clin Cancer Res 5(1):83–94

Venkatakrishnan K, Liu Y, Noe D, Mertz J, Bargfrede M, Marbury T, Farbakhsh K, Oliva C, Milton A (2014) Pharmacokinetics and pharmacodynamics of liposomal mifamurtide in adult volunteers with mild or moderate hepatic impairment. Br J Clin Pharmacol 77(6):998–1010

Vivero-Escoto JL, Slowing II, Trewyn BG, Lin VS (2010) Mesoporous silica nanoparticles for intracellular controlled drug delivery. Small 6(18):1952–1967

Wang YXJ (2011) Superparamagnetic iron oxide based MRI contrast agents: current status of clinical application. Quant Imaging Med Surg 1(1):35–40

Wang M, Thanou M (2010) Targeting nanoparticles to cancer. Pharmacol Res 62(2):90–99

Wang F, Wang YC, Dou S, Xiong MH, Sun TM, Wang J (2011) Doxorubicin-tethered responsive gold nanoparticles facilitate intracellular drug delivery for overcoming multidrug resistance in cancer cells. ACS Nano 5(5):3679–3692

Weber S, Niemirowicz K, Markiewicz KH, Car H (2014) Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for pulmonary application: a review of the state of the art. Eur J Pharm Biopharm 86(1):7–22

Wilczewska AZ, Niemirowicz K (2012) Nanoparticles as drug delivery systems. Pharmacol Rep 64(5):1020–1037

Xie X, Xia W, Li Z, Kuo HP, Liu Y, Li Z, Ding Q, Zhang S, Spohn B, Yang Y, Wei Y, Lang JY, Evans DB, Chiao PJ, Abbruzzese JL, Hung MC (2007) Targeted expression of BikDD eradicates pancreatic tumors in noninvasive imaging models. Cancer Cell 12(1):52–65

Yang F, Jin C, Subedi S, Lee CL, Wang Q, Jiang Y, Li J, Di Y, Fu D (2012) Emerging inorganic nanomaterials for pancreatic cancer diagnosis and treatment. Cancer Treat Rev 38(6):566–579

Yang XY, Li YX, Li M, Zhang L, Feng LX, Zhang N (2013) Hyaluronic acid-coated nanostructured lipid carriers for targeting paclitaxel to cancer. Cancer Lett 334(2):338–345

Yang HN, Park JS, Jeon SY, Park W, Na K, Park KH (2014) The effect of quantum dot size and poly(ethylenimine) coating on the efficiency of gene delivery into human mesenchymal stem cells. Biomaterials 35(29):8439–8449

Yu GS, Bae YM, Choi H, Kong B, Choi IS, Choi JS (2011) Synthesis of PAMAM dendrimer derivatives with enhanced buffering capacity and remarkable gene transfection efficiency. Bioconjug Chem 22(6):1046–1055

Yu YH, Kim E, Park DE, Shim G, Lee S, Kim YB, Kim CW, Oh YK (2012) Cationic solid lipid nanoparticles for co-delivery of paclitaxel and siRNA. Eur J Pharm Biopharm 80(2):268–273

Yu K, Zhao J, Zunkai Z, Yin G, Yulin Z, Lesheng T, Li Y (2015) Enhanced delivery of paclitaxel using electrostatically-conjugated Herceptin-bearing PEI/PLGA nanoparticles against HER-positive breast cancer cells. Int J Pharm 497(1–2):78–87

Yurkovetskiy AV, Fram RJ (2009) XMT-1001, a novel polymeric camptothecin pro-drug in clinical development for patients with advanced cancer. Adv Drug Deliv Rev 61(13):1193–1202

Zhai Y, Zhai G (2014) Advances in lipid-based colloid systems as drug carrier for topic delivery. J Control Release 193:90–99

Zhang Chen Z, Song X, Si J, Tang G (2008) Low generation polypropylenimine dendrimer graft beta-cyclodextrin: an efficient vector for gene delivery system. Technol Cancer Res Treat 7(2):103–108

Zhang B, Wang T, Yang S, Xiao Y, Song Y, Zhang N, Garg S (2016a) Development and evaluation of oxaliplatin and irinotecan co-loaded liposomes for enhanced colorectal cancer therapy. J Control Release 238:10–21

Zhang J, Sun Y, Tian B, Li K, Wang L, Liang Y, Han J (2016b) Multifunctional mesoporous silica nanoparticles modified with tumor-shedable hyaluronic acid as carriers for doxorubicin. Colloids Surf B Biointerf 144:293–302

Zhao X, Sun X, Zeng L, Liu J, Zhang Z (2015) Co-delivery of HIF1α siRNA and gemcitabine via biocompatible lipidpolymer hybrid nanoparticles for effective treatment of pancreatic cancer. Biomaterials 46:13–25

Zhou Q, Sun X, Zheng L, Liu J, Zhang Z (2009) A randomized multicenter phase II clinical trial of mitoxantrone-loaded nanoparticles in the treatment of 108 patients with unresected hepatocellular carcinoma. Nanomed Nanotechnol Biol Med 5(4):419–423

Zhu D, Tao W, Zhang H, Liu G, Wang T, Zhang L, Zeng X, Mei L (2015) Docetaxel (DTX)-loaded polydopamine-modified TPGS-PLA nanoparticles as a targeted drug delivery system for the treatment of liver cancer. Acta Biomater 30:144–154