J Nanopart Res (2020) 22: 245
https://doi.org/10.1007/s11051-020-04959-8

REVIEW

Application of nano-based systems for drug delivery and targeting: a review

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Received: 19 December 2019 / Accepted: 16 July 2020 / Published online: 12 August 2020

Abstract Over the last decades, magnificent progress in the field of nanopharmaceuticals mostly with sizes smaller than 100 nm has led to the development of novel delivery systems and brightened the hope of finding new approaches to combat threatening diseases including cancer. So far, numerous efforts have been made to develop appropriate delivery systems with favorable features such as acceptable toxicity profile, high cellular uptake, low immunogenicity, and stable physicochemical properties along with distribution of the therapeutic molecule specifically to the site of action, without affecting healthy organs and tissues. Non-viral delivery systems have always been suitable options for delivery purposes. Polymers, liposomes, and inorganic delivery systems are all of the available choices in non-viral delivery systems, with each possessing their own advantages and pitfalls. This current review presents the recent advances about the application of various non-viral nanocarriers in the delivery of diverse therapeutic agents especially in cancer treatment. Targeting ligands as an important part of designing targeted nanocarriers to the site of interest or intra-cellular environment and opportunities and challenges of nano-based systems for drug and gene delivery are also discussed.

Keywords Nanopharmaceuticals · Polymeric nanocarriers · Lipid-based delivery systems · Inorganic delivery systems · Targeting ligands · Intra-cellular delivery

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Introduction

The odyssey of transferring from the macro-sized world to the nano-sized world has been one of the most important events of recent decades. The journey reveals the surprising features of substances and their creating units: molecules/atoms. Supported by thousands of papers and studies, more than ever, this expedition seems to change the way we think about treatments and solutions. The rapidly expanding field of nanotechnology offers a great deal of chances and wide range of applications in the fields of engineering, medicine, and life sciences. Focusing on medical applications, nanotechnology has provided the opportunity of designing delivery systems containing the drug of interest to treat cancer in a safer and more effective way. Nanocarriers loaded with anticancer agents have several advantages over the conventional use of their free form: (1) nanocarriers could have the ability to escape from the recognition of the reticuloendothelial system (RES) which results in prolonged

circulation time, increasing the chance of higher drug accumulation at the site of interest; (2) targeted nano-delivery systems can be developed with the aid of targeting moieties, enhancing anti-tumor outcomes as well as reducing off-target effects. This would also result in the need of lower administrated doses of the therapeutic agent; (3) in the case of oral delivery of therapeutic agents prone to degradation within the gastrointestinal tract, nanocarriers enable the oral route of administration and increase the oral bioavailability of the conventional chemotherapeutic agents; (4) nanocarriers can improve the physicochemical properties of drugs with solubility problems; (5) nano-delivery systems can be employed to decrease drug resistance and treat many resistant cancers as most recently, co-delivery systems have been proposed for this aim; (6) and last but not least, the smart design of nanocarriers leads to higher patient compliance (Freimann et al. 2018; Wang et al. 2018; Tezgel et al. 2018; Wong et al. 2017; de Groot et al. 2017; Eftekhari et al. 2019; Baradaran Eftekhari et al. 2020).

Considering the above-mentioned advantages, an ideal drug delivery system must perform 3 functions: (Freimann et al. 2018) (1) it must efficiently load the therapeutic agent; (2) the designed delivery system must protect the incorporated agent from physicochemical or enzymatic degradation, and (3) effectively enter the cells, escape from endosomes, and release the intact cargos to execute their functions. In executing these functions, however, it should be noted that there is no perfect nanocarrier, but the perfect ones each has their own characteristic indicating their empirical, theoretical, and practical advantages while possessing their intrinsic challenges (Eftekhari et al. 2019; Janagam et al. 2017; Lawrence et al. 2003; des Rieux et al. 2013).

In the case of non-viral delivery systems, polymers, liposomes, dendrimers, and inorganic materials can be proposed as four of the most widely used options in delivery systems. Polymers and lipids have played a crucial role in the advancement of drug delivery technology. Natural and synthetic forms of polymers and lipids have been demonstrated in many studies to increase the overall outcome of cancer therapy by either using novel therapeutic anti-cancer agents or providing controlled release of the therapeutic materials, targeted delivery to the site of interest, and significantly reduced side effects (Samimi et al. 2019). Moreover, in recent years, the increasing knowledge of chemical engineering has enabled the rational design of smart polymers and lipids responsive to several stimuli such as temperature, pH, ultrasound, and light (Liu et al. 2016a). Inorganic materials have attracted scientists' interest in the delivery of anti-cancer agents since many of these nano-based systems have promising potentials for both the therapeutic and diagnostic purposes. Regarding the cancer treatment, the possibility of real-time imaging of the nanosystem is of utmost importance as it enables monitoring the whole drug/gene delivery processes within the cancer tissues (Kim et al. 2013; Huang et al. 2011). New advancement in the field of inorganic delivery systems presents inorganic materials with unique features such as magnetic nanosystems resulting in targeted delivery to the cancer cells and improved anti-cancer effects. The newly emerged 3D structures, dendrimers, are also considerable options as nano-based delivery systems due to their interesting properties such as high surface positive charges of free amine groups along with the ease of modifications (Jain et al. 2020).

Many attempts have been devoted to attach the targeting moieties to guide the therapeutic agents to the cells and even organelles in tissues of interest. Targeting moieties provide specific delivery in cells/tissues with some also reduced off-target effects and improving the pharmacokinetic profile of the therapeutic agents. Notably in cancer therapy, these targeting moieties transform the drug/gene delivery system into a *Trojan horse* to be taken up more by the tumor cells (Biffi et al. 2019). In a brief look, structures of nanomaterials used as delivery systems and targeting moieties discussed in the manuscript are described in Fig. 1.

In this review, the overall picture of these numerous attempts in the way of designing the promising drug/gene nano-delivery systems, opportunities, chances, possible clinical uses, and challenges are described and discussed with diverse examples.

Polymers

A polymer is a macromolecule, composed of many repeated subunits forming its unique structure and providing its characteristics. Many important properties of a given polymer are related to the architecture and microstructure feature of the repeating units of the macromolecule possessing different advantages and drawbacks in case of delivery of therapeutic agents. A deep understanding of this concept is crucial for designing a suitable delivery system since it encourages scientists to

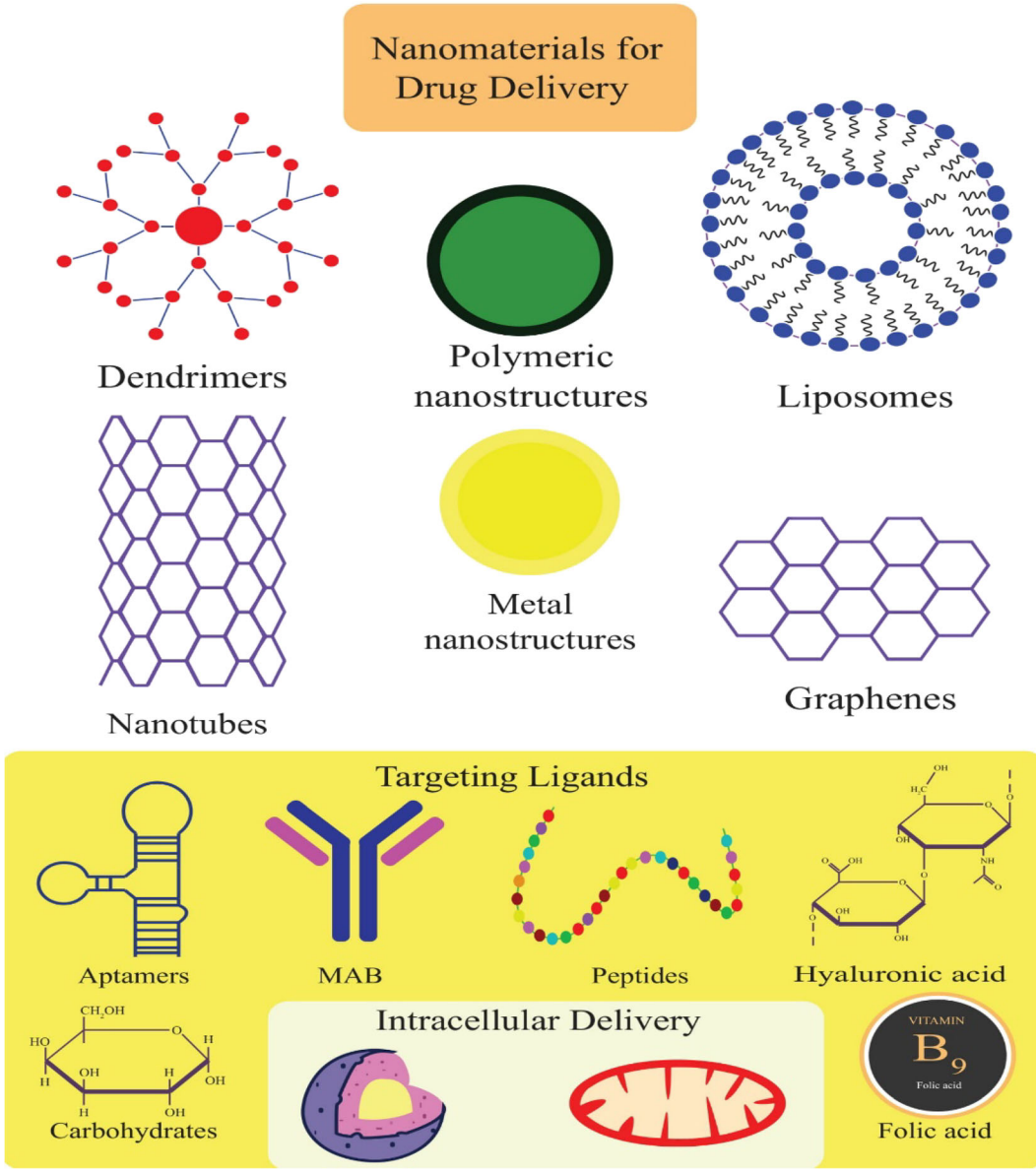

Fig. 1 Schematic structures of nano-delivery systems and targeting moieties

employ different polymers and copolymers as well as searching for synthesis of new ones. In this section, some of the widely used polymers in gene(s)- and drug(s)-loaded delivery systems are summarized in Table 1. Structures of widely used polymers as nanocarriers are described in Fig. 2.

PEI

In light of abundant evidences obtained so far, we have a much better understanding of polyethyleneimine (PEI), a cationic synthetic polymer, and its properties in drug delivery and, more than ever, we understand the high potentials of this *gold standard polymer*, especially in gene delivery. PEI-based systems have been employed to deliver active agents including drugs, nucleic acids, and bioactive molecules, and the feasibility and the possibility of clinical applications of these delivery systems have been explored so far (Vinogradov et al. 2005; Qiu and Bae 2007; Dong et al. 2013; Chen et al. 2015).

Mostly two kinds of PEIs (branched and linear polyethylenimines) have been broadly used to deliver

Table 1 The most recent gene(s)-loaded and drug(s)-loaded nanosystems based on polymeric carriers

Nanosystem	Gene(s) loaded	Result(s)	Ref.
Carbon dots passivation by branched PEI 25 kDa (bPEI25k CD)	Tumor necrosis factor–related apoptosis–inducing ligand (plasmid TRAIL–GFP)	NPs internalized in human mesenchymal stem cell successfully and induced apoptosis in A549 cells. Lower cytotoxicity was seen with bPEI25k CDs than the raw branched PEI25k. After 10 days of treatment on human mesenchymal stem cells, TRAIL concentration was about 60 ng/mL for bPEI25k CDs containing the plasmid as compared with less than 10 ng/mL for plasmid-loaded bPEI25k and the plasmid alone. Cell viability of A549 cells after 10 days of cell treatment was 40% for bPEI25k CD-pTRAIL while more than 80% of cells were alive for both bPEI25k-pTRAIL and free pTRAIL.	(Han and Na 2019)
Polyethyleneimine (PEI)/heparin/Ca2+ nanoparticles (CPH–siH nanoparticles)	AIB1siRNA (targeting the oncogene nuclear receptor coactivator 3 which its high expression in lung cancer is associated with the patient's overall survival)	No toxicity was observed with the blank nanoparticles in cancer cells while more than 60% of the cell population died in the case of treatment with CPH–siH NPs at siRNA concentration of approximate 100 nm. The obtained nanoparticles at the same concentration also induced apoptosis in nearly ~ 35% of cells while as expected, blank nanoparticles did not induce any apoptosis in cancer cells. Reduced AIB1 expression was observed along with induction of apoptosis in non-small cell lung cancer cells.	(Hao et al. 2019)
PEI–PEG–anti-HER2 nanobody (Nb–PEI–PEG) conjugates	Transcriptionally targeted tBid killer gene construct	Transfection efficiencies in HER2-positive cell lines were 1.58 and 1.36 times higher using Nb-modified nanoparticles compared with non-modified nanoparticles in BT-474 and SK-BR-3 cells, respectively. The obtained nanoparticles had lower cytotoxicity than free PEI (32 and 38% using Nb–PEI–PEG and 50 and 55% using PEI in BT-474 and SKBR-3 cells, respectively)	(Saqafi and Rahbarizadeh 2019)
PEGylated PLGA/polyethyleneimine (PEI) nanoparticles	pDNA expressing HSV1–sr39TK–NTR and ganciclovir and CB1954 as the prodrugs	Increased expression of NTR enzyme within the tumor cells could trigger cell death upon the administration of prodrugs in triple-negative breast cancer mice model. In vivo analysis revealed that untreated-control mice and untreated ultrasound-exposed mice had similar amounts of tumor growth, while meaningful reduction in tumor growth was seen in animals treated	(Devulapally et al. 2018)

Table 1 (continued)

		with NP-DNA targeted using ultrasound and microbubble and prodrugs compared with untreated mice (2.3-fold) as well as NP-DNA- and prodrug-treated mice without ultrasound (1.5-fold).	
Organic–inorganic hybrid nanoparticles composed of stearic acid-modified polyethyleneimine and calcium phosphate	Minicircle DNA encoding anti-IGF1R/CD3 bispecific T cell engagers	Cells treated with PEI600 did not show any green fluorescence signal while in cells treated with stPEI and CaP, 24.27 ± 1.5% and 12.6 ± 5.49% cells were green fluorescence protein (GFP) positive at 48 h, respectively. Obtained nanoparticles containing expressing eGFP reporter gene had a positive rate of 64.87 ± 0.86% after 48 h of treatment. High expression of IGF1R/CD3 antibodies was observed and resulted in enhancement in immune apoptosis.	(Chen et al. 2018a)
PEGylated PEI nanoparticles	miR-221/222 (seems to play an important role in the initiation and progress of prostate cancer)	At an N/P ratio of 10, high transfection efficiency with low carrier cytotoxicity was observed in PC-3 cells in vitro. Viability rates of the cells treated with PEG–PEI containing a scrambled miRNA sequence (miR--scr), PEG–PEI/miR-221, and PEG–PEI/miR-222 polyplexes were 95.49 ± 4.77%, 67.83 ± 3.39%, and 61.49 ± 3.07%, respectively. SIRT1 expression was increased due to the function of miR-221/222, which resulted in cell death in PC-3 cells. Prepared nanoparticles even showed better function in terms of miR-221 and miR-222 transfection than the positive control lipo2000 with SIRT1 expression of 70.85. ± 3.54% vs 46.37. ± 2.32% and 55.58. ± 2.78% vs 44.2. ± .2.21%, respectively.	(Chen et al. 2018b)
Linear PEI-coated siRNA–PLGA hybrid micelles	Glypican-3 specific siRNA	The designed hybrid micelles effectively inhibited GPC3 expression in vitro in HM-1 cells compared to free siRNA solution. Cell viability rate of treatment groups is as follows: control (100.0 ± 1.2%), siRNA Gpc3 (99.7 ± 0.5%), siRNA–PLGA hybrid micelles (86.5 ± 0.9%), linear PEI 25k-coated siRNA–PLGA hybrid micelles (58.5 ± 2.5% and 56.2 ± 5.4 at N/P = 20 and 40, respectively) and linear PEI 2.5k-coated siRNA–PLGA hybrid micelles (74.7 ± 1.9% and 70.6 ± 0.3% at N/P = 20 and 40, respectively). In vivo studies demonstrated decreased number of tumor nodes in the mesentery in intraperitoneal	(Hazekawa et al. 2019)

Table 1 (continued)

		administration of micelles.	
PEI-RRRRRRRR(R8)-heparin (HPR) nanogel	Heparin and phTRAIL pDNA (encoding human TNF-related apoptosis inducing ligand)	Cytotoxicity of carrier was significantly decreased due to the shielding effect of heparin. R8 peptide resulted in enhanced cellular uptake. Transfection efficiency of more than 64.3 ± 1.5% was observed with HPR/pGFP (20:1, mass ratio) complex at 24 h compared with PEI25K/pGFP (1:1, mass ratio) with less than 37.8 ± 1.6%. pDNA induced significant cell apoptosis in HCT-116 cells (42.5 ± 1.8% for HPR/phTRAIL complex versus 18.9 ± 2.1% for PEI25K/phTRAIL).	(Song et al. 2018)
Dehydroascorbic acid (DHA)–PEG–disulfide bonded PEI (pOEI)-modified anti-miR21 nanopompons	Anti-miR21(it is well established that the inhibition of function of this oncogenic miRNA is associated with the tumor suppression through different pathways)	DHA modification resulted in significant accumulation at the tumor site. Injection of nanopompons resulted in noticeable tumor growth inhibition compared with control group in mice. Tumor volume as biomarker of treatment response was recorded less than 300 mm^3 for DHA-targeting mice group while non-targeting and control group had tumor volumes of approximately 1000 mm^3 and more than 2000 mm^3, respectively.	(Guo et al. 2019)
Arginine–glycine–aspartate (RGD)-targeted PEGylated chitosan-poly (ethyleneimine) hybrid nanoparticles	Dicer substrate 25/27-mer siRNA targeting GFP (DsiRNA GFP)	About 90% EGFP inhibition was observed at 150 nM DsiRNA concentration with RGD-targeted nanoparticles while non-targeted nanoparticles induced less than 50% inhibition into human non-small cell lung carcinoma cell line H1299.	(Ragelle et al. 2015)
Nanosystem	Drug(s) loaded	Result(s)	Ref.
HA/PEI nanoparticles	Docetaxel (DTX) and α-napthtoflavone (ANF, a CYP1B1 inhibitor)	NPs downregulated the expression of CYP1B1 resulting in reversing the multidrug resistance in breast cancer. Apoptotic rates of treatment groups were as follows: DTX group (40.40%), DTX + ANF (45.42%), PLGA NPs (54.73%), HA/PEI NPs (60.02%). The IC50 of DTX on MCF-7/1B1 cells (2.89 ± 0.21 μg/mL) was decreased with addition of ANF (1.77 ± 0.17 μg/mL on MCF-7/1B1 cells) with a further decline to 0.81 ± 0.11 μg/mL with the aid of HA/PEI NP.	(Zhang et al. 2019)
RGD peptide targeted-PEGylated PLGA NPs	Paclitaxel	PEGylated PLGA NPs could efficiently deliver the drug to tumor endothelium cells. Cell viability was significantly lower for PTX-loaded nanoparticles group than for Taxol® group with IC50 values of 5.5 vs 15.5 μg/mL, respectively.	(Danhier et al. 2009)

Table 1 (continued)

AuNPs–PLA–PEG–PLA nanoconjugates (AuNPs-Pol)	Caffeine	Caffeine–AuNPs–PLA–PEG–PLA nanoconjugates showed a significantly higher anti-inflammatory response than caffeine alone in fresh human blood samples. Inhibition rate of protein denaturation was recorded 55% at 200 μg/mL for the caffeine group, 18–63% at 5–200 μg/mL for caffeine-loaded AuNP nanoconjugates, and 22–69% at 5–200 μg/mL for caffeine-loaded AuNPs-Pol nanoconjugates.	(Kamalakannan et al. 2017)
PLGA NPs loaded with antigen	Ovalbumin	The obtained NPs were capable of inducing potent and specific humoral and cellular immune responses in BALB/c mice. The cells treated with the prepared nanoparticles containing ovalbumin had considerably lower dextran uptake, while cells treated with ovalbumin alone possessed a high antigen uptake ability. Significant production of IFN-g from the T cells was observed with the cells treated with ovalbumin-loaded nanoparticles (> 150 pg/mL) compared with the control group, ovalbumin alone group and mixture of blank nanoparticles and ovalbumin (all less than 50 pg/mL).	(Wang et al. 2008)
N-(2-Hydroxypropyl)methacrylamide copolymer) (HPMA) coated trymethylchitosan nanoparticles	Insulin	HPMA copolymer-coated NPs showed a 9.6-fold higher mucus diffusion rate than the non-coated nanoparticles. Both coated and non-coated NPs significantly enhanced the cellular uptake of insulin compared with the free insulin solution and it was 1.4-fold higher than non-coated NPs with HPMA copolymer coated NPs.	(Liu et al. 2016b)
HA-IR-780 nanoparticles	IR imaging agent (IR-780)	The NPs could well accumulate in the tumor cells and due to their high photothermal effect were able to effectively destroy orthotopic bladder cancer cells. Mice with orthotopic bladder cancer were subjected to treatment with injection and laser therapy. 6 min of 808 nm laser (1 W/cm^2) was applied to animals after 48 h of injection of PBS or HA-IR-780 NPs (5 mg/kg of IR-780). The tumor sizes in the PBS alone, PBS plus laser irradiation, and IR-780-loaded NP-treated groups were about 784.75 mm^3, 707.5 mm^3, and 711.37 mm^3, respectively.	(Lin et al. 2017)
PEGylated HA NPs	DOX (doxorubicin)	The NPs demonstrated effective tumor suppression effects along with their low toxicity. In vivo studies demonstrated that after 16 days of treatment, mice group treated with	(Han et al. 2013)

Table 1 (continued)

		DOX-loaded M-PEG-HANPs had tumor volume of less than 2000 mm^3, while those treated with DOX alone (at the same concentration) had tumor volume of around 5000 mm^3.	
PEG–PCL–HA nanoparticles	DOX (doxorubicin)	As compared with free DOX, the NPs could reduce the tumor size 2.6 times higher in 20 days in Ehrlich ascites tumor (EAT)–bearing mice.	(Grossen et al. 2017)
Self-assembled PCL–PEG micelles	Dexamethasone	The NPs showed a better anti-rheumatoid response than free dexamethasone in arthritis rats, indicating that employment of safe and human-friendly systems with more curative effects could be a better option in treatment of rheumatism.	(Wang et al. 2016a)

nucleic acids both in vitro and in vivo. Because of the high cationic charge, the branched polymers exhibit high transfection efficiency; PEIs especially with molecular weight (MW) of 25 kDa perform excellently in gene delivery (Ansari et al. 2017).

The highly cationic charge of PEI makes it a suitable carrier for gene delivery. Endocytosis is the dominant mechanism responsible for nanoparticles entering a cell, during which the introduced nanoparticles become surrounded by an area of the cell membranes, forming endosomes, to be further joined with lysosomes for destruction and enzymatic degradation. Therefore, the introduced nanoparticles must escape from the endosomes in order to perform their functions (Gormally et al. 2009; Wang et al. 2014a; Hu et al. 2007). One of the unique features of PEI is a phenomenon called proton sponge effect in which upon the acidification of the endosomes, PEI absorbs H+ from the cytoplasm causing osmotic pressure, absorption of water, swelling of the endosome, and its eruption and, eventually, releasing the trapped nanoparticles (Ishida et al. 2006; Nosova et al. 2019). In addition, the high cationic charge also leads to interaction with negatively charged molecules, drugs, and nucleic acids such as small interfering RNAs (siRNAs), microRNAs (miRNAs), and DNAs which results in electrostatic interaction to either absorb them onto the PEI surface or entrap them into the PEI complexes. PEI nanocarriers can perfectly interact with the proteoglycan of cell membranes and consequently increase the uptake of the drug by endocytosis pathway (Ginn et al. 2013; Kievit et al. 2009). Nevertheless, the high positive surface charge is well established to be related to higher toxicity in vivo since negatively charged components in blood could form aggregates with PEI (Sajid et al. 2016). It is reported that a lower positive surface charge contributes to increased safety of the delivery system, but decreases the intracellular transfection and the overall delivery efficiency. Thus, a balance between efficiency and toxicity might be a solution to the problem. In the case of DNA delivery in one study, an optimal PEI concentration was defined at which successful transfection and toxicity were in balance. The study concludes that the lower PEI concentration is attributed to the lower transfection efficiency when at decreased PEI concentration, the zeta potential measurements show a net negative charge, resulting in poor complexation and protection of DNA against nucleases and overall gene transfection efficiency (Florea et al. 2002).

Another solution for the toxicity problem is surface coating of free amine groups which are strongly correlated with PEI toxicity. Several materials can be used for this aim such as albumin, polyethylene glycol (PEG), folate (Iannazzo et al. 2017; Shi et al. 2013), hyaluronic acid (HA) (Ito et al. 2008), chitosan (Kievit et al. 2009), cellulose (Zhao et al. 2015), and cholesterol (Furgeson et al. 2004).

PEGylated PEI is one the most used modified forms of PEI. Several mechanisms have been proposed for the impact of PEGylation on PEI toxicity: (Freimann et al. 2018) PEGylation of PEI complexes provides an aqueous shield around the complexes which can reduce the

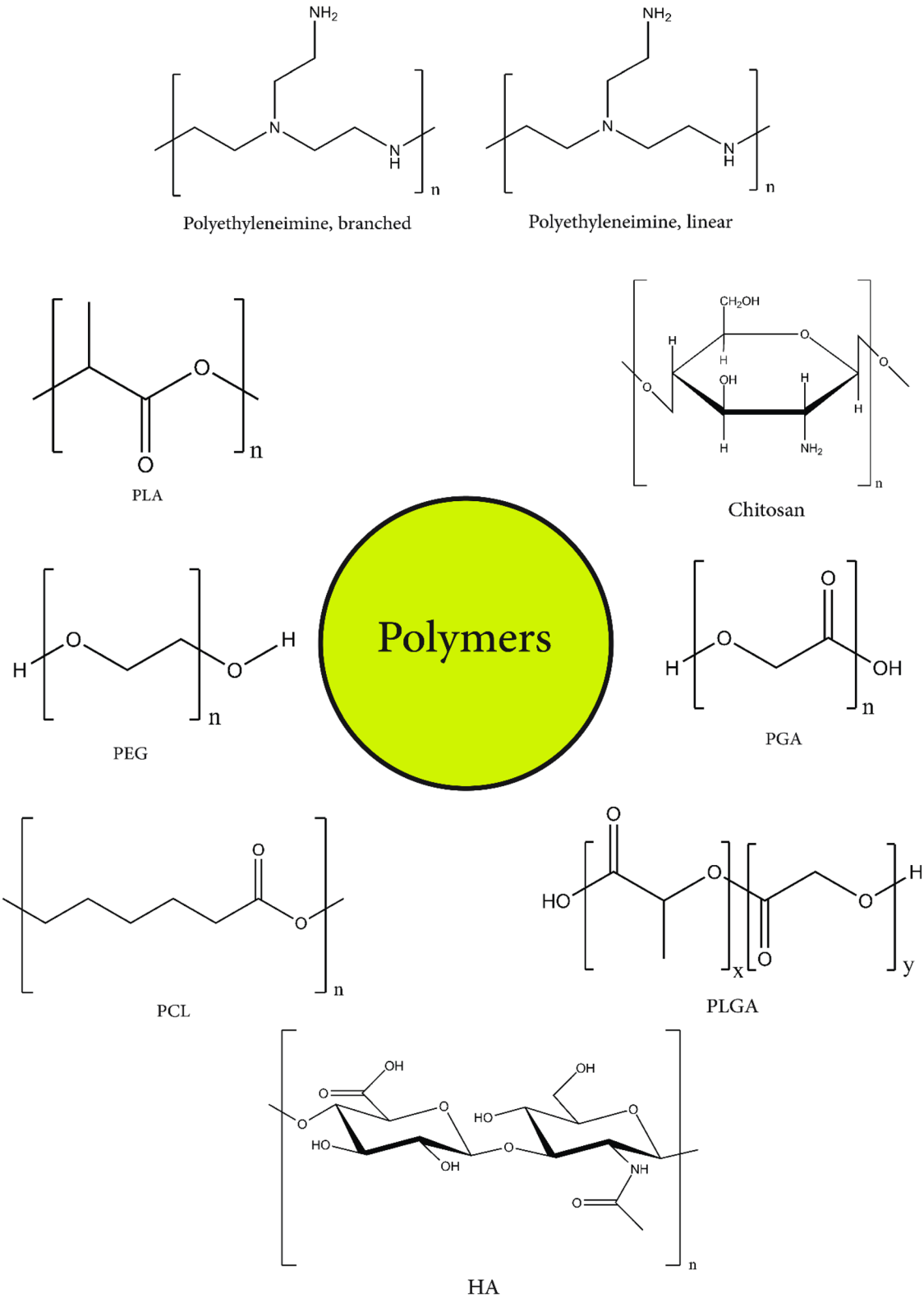

Fig. 2 Chemical structures of widely used polymers in nano-delivery systems

detection of the obtained complexes by immune systems and thus avoiding RES (Wang et al. 2018), and incorporation of hydrophilic PEG can decrease the surface charge of the PEI and thus reducing the interaction of PEI complexes with negatively charged blood components (Liang et al. 2008). Nevertheless, excessive PEGylation leads to reduced transfection efficiency mostly due to the fact that a longer PEG side chain can strongly decrease the surface potential resulting in poor interaction with cell membranes. This problem can be addressed by taking a balance between toxicity and transfection either using a lower proportion of PEG or employing a combination of modifications. In the case of the latter, branched polyethylenimine modified with HA via a PEG spacer was designed and examined for the delivery of doxorubicin. Modified PEG chains (NH_2–PEG–COOH) play a connective role in bringing the high drug delivery properties of PEI and targeting feature of HA, while benefiting from unique features of PEG. The PEI–PEG–HA/DOX complexes could differentially target CD44 receptor expressing on cancer cells (Almalik et al. 2013) (Fahmy et al. 2005).

Other studies use different biocompatible materials for this matter. Polyethylenimine–graft–chitosan (PEI–g–chitosan) was reported to have much lower toxicity than free PEI. MTT assay was carried out to determine the cytotoxicity of PEI–g–chitosan, and it demonstrated that PEI–g–chitosan complexes had a significantly lower cytotoxicity as compared to PEI (25 K) in HeLa cells (Pandey and Sawant 2016). In a study done by Sahiner et al., 25 kDa PEI–cholesterol showed reduced cytotoxicity reflecting the role of the incorporation of natural organic molecules found within human blood (Gusachenko Simonova et al. 2009). PEI–HA complexes also demonstrated lower toxicity when compared with unmodified PEI (Sahiner et al. 2017). Zhao et al. designed polyethyleneimine-grafted cellulose nanofibrils (CNFs-PEI) for the delivery of water-soluble sodium salicylate as a model drug. The designed nanofibrils demonstrated excellent biodegradability and biocompatibility along with the release profile dependent on pH and temperature allowing the controlled release at the site of interest (Zhao et al. 2015). Compared to PEI (25 kDa), conjugation of dextran to linear 800 Da PEI enhanced the transfection ability of nanoparticles (NPs) (Sun et al. 2008). A different approach to modify the surface charge of PEI complexes was developed by Johal et al.; they used polystyrene sulfonate (PSS), a polyanion layer, on the surface of PEI complexes that resulted in diminished toxicity compared with PEI nanoparticles (Gormally et al. 2009). Pullulan–PEI–folate was reported to be a promising candidate for gene delivery into the cancer cells while demonstrating much lower toxicity compared to PEI (Wang et al. 2014a).

PEG

Polyethylene glycol has a long history of use in drug delivery fields. This synthetic polymer is widely employed to cover the surface of the main delivery system, the process called *PEGylation*, to modify the properties of the designed carrier. The so-called PEGylation process can significantly reduce the toxicity of the delivery system, especially in the case of highly cationic polymers since, as mentioned previously, cationic charges interact with blood components. It also prolongs blood circulation time providing more chance of the drug/gene accumulation at the tumor site.

However, drug delivery systems coated with PEG polymers might have some obstacles. Wang et al. argued that cellular uptake of NPs can be notably affected by PEGylation (Hu et al. 2007). They discussed this view by some previous confirmatory evidences which suggest that particle size and surface charge play essential roles in cellular uptake of designed delivery systems.

PEGylated delivery systems demonstrated lower cellular uptake and endosomal escape. Therefore, there should be a balance between extending the blood circulation time and reduction of cellular uptake or endosomal escape. The rational design of the PEGylated delivery systems using mild modifications might be the easily achievable solution along with more innovative approaches such as using cleavable PEGylated liposomes which PEG moieties dissociate upon penetration into tumor tissues and surrounding extracellular area due to the abnormal properties existing in the tumor site. Lower pH values within the tumor environment or hyperthermia induced by pyrogen action can act as stimuli for the cleavable PEG moieties to dissociate from the nanosystem, and thus, endosomal escape might be reserved to the previous optimum level. Moreover, it is reported that PEG polymers might induce immunogenicity differed from direct interaction with blood component. It results from anti-PEG IgM production produced in the spleen as a consequence of the first injected dose which activates the complement system and further serum factor binding to PEG moieties and the

subsequent capture by Kupffer cells in the next exposures (Ishida et al. 2006). Cleavable PEG chains can also address the anti-PEG IgM-induced immunogenicity as reported by studies; the distribution in the liver and spleen of cleavable PEG nanosystems remained at a consistent level after repeated administration (Nosova et al. 2019).

Chitosan

Chitosan, a linear natural polysaccharide, possesses interesting features. The current literature on this polymer abounds with a great deal of examples in many fields such as agriculture, water filtration, weight loss products, wine making, food preservation, bio-printing, and biomedical uses. The employment of chitosan in drug delivery fields actually has been reported in many researches; thus, we have a way deeper understanding on this polymer more than ever. Chitosan is a highly biocompatible and biodegradable polymer with a very low toxicity both in vitro and in vivo (Ali and Ahmed 2018; Baradaran Eftekhari et al. 2019). Chitosan polymers seem to have high affinity to cell membranes. Along with permeation-enhancing properties, this polymer might be the first choice in drug delivery fields. Data yielded by some studies provide some evidences that chitosan polymer has a sort of mucoadhesive property which makes it a promising candidate in mucosal drug delivery (Howard et al. 2006; Ways et al. 2018). Moreover, as appeared in many studies, chitosan seems to have high endosomal escape indicating it is a favorable carrier in drug/gene delivery (Van Woensel et al. 2016). At physiologic pH, chitosan polymers are positively charged and they are able to highly load negatively charged molecules as nucleic acids. Presenting of both hydroxyl and primary amine group in chitosan units allow generating diverse chitosan derivatives to take advantage of intended features in other ligands (Dmour and Taha 2017). In an interesting design of carrier, chitosan chains were incorporated to the surface of lipid vesicles to investigate their cellular uptake which demonstrated these novel carriers actually had higher stability in extreme pH (pH 1 or 11), and also, rate of penetration and the retention time in biological tissues were increased by employing chitosan which most possibly was due to mucus-adhesive and permeation-enhancing features (Bugnicourt and Ladaviere 2017). Due to biocompatibility and biodegradability properties, chitosan nanoparticles could be applied as a potential carrier for different therapeutic agents such as anticancer agents, proteins/peptides, growth factors, antibiotics, and anti-inflammatory and other drugs, as well as in both vaccine delivery and gene delivery (Ahmed and Aljaeid 2016).

With these fascinating features in mind, on the other hand, there is a notable drawback in the use of chitosan in drug/gene delivery which is its poor solubility due to its low protonation percent at the physiologic pH. This limitation should be considered especially in industrial scope (Elgadir et al. 2015). One of the important issues in drug delivery by chitosan carriers is the molecular weight as some studies focused on this issue and found significant differences between diverse MW of chitosan and their interaction with biomaterials (Almalik et al. 2013). Taking everything together, the results from various studies suggest that there seems to be a big advantage in use of chitosan as a carrier in drug/gene delivery.

PLA, PGA, PLGA

Poly (D, L-lactic acid) (PLA), poly (glycolic acid) (PGA), and poly (lactic-co-glycolic acid) (PLGA) seem to have some similar properties that a number of studies have decided to argue about them and treat them as they are in a united group. Indeed, the key properties that have been seen in these three synthetic polymers are their high biocompatibility, biodegradability, and nontoxic features on which a lot of research have been made and which also brightened the hope of more clinical trials with these polymers. Thanks to their old history of application, a massive data is now available in the use of these polymers in drug delivery systems (Fahmy et al. 2005; Kapoor et al. 2015). PLGA has versatile degradation kinetics, and due to the high flexibility of PLGA, the physical properties of the obtained nanoparticles can be easily controlled by adjusting the suitable *L*:*G* ratio (lactate to glycolic acid ratio) (Kapoor et al. 2015). PLGA NPs have been successfully proven to be efficient carriers of large biomolecules such as vaccines and proteins (Chereddy et al. 2014). An active pharmaceutical ingredient (API) appears to be dispersed homogeneously within the PLA matrix (Lee et al. 2016). In a comparison between PLGA and PGA, PGA polymers possess amide groups which make modification with biologically active moieties possible and easier (Jaimes-Aguirre et al. 2017).

Considering the advantages of using PLGA, PLA, and PGA in the delivery of therapeutic molecules, it seems fair enough to conclude that there is a high potential lying in these polymers as they have some interesting features desirable in a given drug/gene carrier. However, like any polymers, the limitations in the way of employing them should be also taken into account as for instance one of the notable drawbacks observed by PLA is its high initial burst release that could make it hard to get the repeatable results from the pharmacokinetic-related tests (Lee et al. 2016).

Hyaluronic acid

Hyaluronic acid (HA) is a linear high molecular weight natural biopolymer which consists of repeating d-glucuronic acid and N-acetyl-d-glucosamine disaccharide units. This natural polymer actually exists in the human body mainly found in the extracellular matrix of connective tissues, indicating the possible non-toxic features that can be expected from hyaluronic acid-based NPs (Quiñones et al. 2017). HA is highly biocompatible and biodegradable and is gradually degraded by enzymes such as hyaluronidases in the body. This unique polymer has been widely applied in medicine for tissue engineering, drug delivery, and molecular imaging, indicating a massive data is available on it and the toxicity profile of the polymer has been well studied (Yadav et al. 2008). It is well established by many studies that tumor cells overexpress CD44 receptors on them which is actually a potent receptor for HA (Lin et al. 2017).

Wrapping everything up, HA possesses some interesting features to encourage designing HA-based carriers. Along with a perfect toxicity profile, the tumor-targeting properties of this polymer make it a promising drug/gene carrier.

PCL

Polycaprolactone (PCL) is a synthetic biodegradable polyester approved by the Food and Drug Administration (FDA) as a drug delivery system. The application of PCL as a device in biomedical implants has almost an old history of use, but the use of this polymer as a compartment of a drug delivery system has attracted a great deal of attention, recently. Indeed, the acceptable toxicity profile of PCL encourages the attempts for clinical applications. The presence of ester linkage groups in PCL structure opens the ways of hydrolysis in the human body resulting in such biodegradability which is favorable in a given drug/gene carrier. PCL-based NPs appear to have a prolonged circulation property, bringing more chances for the medicine to reach the action site. They also seem to have a high drug–loading capacity which widens the choices of selected drugs/genes (Wang et al. 2016a). PEG–PCL NPs were reported to have high biocompatibility and biodegradability and long circulation time in the delivery of a wide range of therapeutic agents (Wang et al., 2016b).

Other polymers

Several other polymers also have been synthesized and used in some studies. Though a few of them showed acceptable properties and potentials in drug/gene delivery, still the literature on them is not sufficient enough to draw firm conclusions about their features, advantages, and limitations. In this part, some of these polymers and the designed delivery systems will be discussed.

Polyorthoester (POE)

POE with the general structure $–[–R–O–C(R_1, OR_2)–O–R_3–]_n–$ is a synthetic biodegradable and highly hydrophobic polymer that follows a zero-order drug release kinetics in the physiological environment. The release profile of POE can be adjusted by choosing the appropriate molar ratio of latent acid in the polymer chains as well as lipophilicity of the diol and polymer molecular weight, indicating the degradation time of POE-based polymers can be easily controlled (Einmahl et al. 2000).

Monica M. Jablonski et al. designed POE nanoparticles to investigate their drug delivery potentials to the human eye. They encapsulated various molecules such as epinephrine and rhodamine 6G. They also investigated the encapsulation ability of bovine serum albumin (BSA) as a representation for large molecules. They found that POE-based NPs could efficiently improve the intraocular bioavailability and decrease the dosing frequency, consequently minimizing the dose-dependent adverse effects (Palamoor and Jablonski 2013).

Poly (methyl methacrylate) (PMMA)

PMMA is the synthetic polymer of methyl methacrylate approved by the Food and Drug Administration (FDA)

for medical applications. The highlighting feature of PMMA is its biocompatibility. To take advantage of this feature in one study, PEI–PMMA were synthetized for gene delivery and the obtained NPs efficiently delivered DNA into HeLa cells (Feng et al. 2006). In another report, cellulose–graft–poly (methyl methacrylate) nanoparticles loaded with betulinic acid (BA) demonstrated perfect biocompatibility in vitro and in vivo and better anti-tumor efficiency with reduced side effects (Dai and Si 2017).

Polyvinylpyrrolidone (PVP)

PVP with synthetic origin has been also used in some studies to investigate its drug delivery features. In a study, Praseetha et al. coated magnetic nanoparticles with PVP polymer and then coated the whole carrier with folic acid (FA) for specific targeting of an anticancer drug (epirubicin hydrochloride) to cancer cells. They revealed that PVP-coated NPs had a better anti-tumor response than PVP uncoated NPs (Rose et al. 2013).

Dendrimers

Dendrimers are synthetic 3D hyperbranched globular and monodispersed nanopolymeric architectures with multivalent functional end groups. They are typically used as well-defined scaffolding or nanocontainers to conjugate, complex or encapsulate therapeutic drugs or imaging moieties.

Innovation in polymer synthesis and advances in the design of biodegradable polymeric macromolecules have made dendrimers as new applications for nanodrug delivery systems. The attractive features of dendrimers such as nanoscopic size, narrow polydispersity index, excellent control over molecular structure, availability of multiple functional groups at the periphery and cavities in the interior, high branching points, three-dimensional globular shape, and well-defined molecular weight have characterized them as new nanoagents in drug delivery. The structure of dendrimers consists of three distinct domains: a core at the center of the dendrimer consisting of an atom or a molecule having at least two identical chemical functions, branches consisting of repeat units having at least one branch junction that results in a series of concentric layers called "generations," and terminal functional groups located at the surface of dendrimers that determine the properties of dendritic macromolecules and provide a platform for covalent conjugation of the drugs and targeting moieties through biodegradable linkers suggesting controlled release of the drugs.

Bioactive agents and drugs can be also encapsulated into the interior cavities of dendrimers. The maximum amount of entrapped guest molecules is directly proportional to the shape and the size of the guest molecules, as well as to the amount, shape, and size of the internal cavities of dendrimers (Tomalia 1990). The diameter of dendrimers increases systematically at a rate of approximately 1 nm per generation with the range of 10 to 130 Å from generation 0 through generation 10 (Jonathan et al. 2000). The structure of lower generations (0.5–4.0G) is planner and asymmetric shape with fewer inner pockets and high polarity range whereas higher generations (5.0–10.0G) show the densely packed shape and star-like pattern (Kaur et al. 2016).

Dendrimers have been studied from gene delivery to magnetic resonance imaging. They are used in drug delivery systems because they have some excellent features such as increasing bioavailability, cellular uptake and therapeutic efficacy, and reducing the systemic toxicity (Yavuz et al. 2016). In this wide range of using dendrimers, PAMAM and PPI are the most available agents in drug delivery systems.

PAMAM dendrimers

The first synthesis and characterization of polyamidoamine dendrimers (PAMAM) using ammonium (NH3) or ethylenediamine (EDA) as the core were reported by Tomalia et al. in 1985 (Tomalia et al. 1984).

PAMAM dendrimers are generally available in generations ranging from 0.5 to 10G (Kaur et al. 2016). There are primary amine groups (positively charged at physiological pH) as poly amide branches (pKa = 6.85) on the PAMAM dendrimer surface and tertiary amine groups within the core (pKa = 3.86) (Sadekar and Ghandehari 2012). Therefore, PAMAM dendrimers have a high buffer capacity owing to protonable amine groups that enable them to act as a weak base and retarding degradation caused by acidification within the endosome–lysosome called as "protone sponge effect" (Jonathan et al. 2000). Drug delivery by PAMAM dendrimers could be achieved through simple encapsulation, electrostatic interactions, and covalent conjugations to the surface groups suggesting controlled drug release systems (Ma et al. 2015). Encapsulation in the interior cavities of PAMAM dendrimers can improve

the water solubility and bioavailability of hydrophobic drugs and permeability of poorly absorbable drugs acting as penetration enhancers (Zhong et al. 2016).

PAMAM dendrimers are non-immunogenic and exhibit low mammalian toxicity especially when their surface contains anionic or neutral groups such as carboxylic or hydroxylic functionalities (Cea 1996).

Toxic behavior of PAMAM dendrimers is due to the presence of surface amine groups depending on concentration and generation. Cationic generations cause toxicity in lower concentrations compared with negative-charged dendrimers (Kaur et al. 2016). Anionic dendrimers have exhibited lower liver concentrations and higher circulation time in the blood than the cationic ones that resulted from studies on the in vivo intravenous administration of 125I-labeled-PAMAM dendrimers in rats (Sadekar and Ghandehari 2012). In general, PAMAM dendrimers represent lower toxicity as compared to linear polymers due to lower attachment to the cellular surfaces (Kaur et al. 2016). The toxicity profile of PAMAM dendrimers can be improved by surface modifications such as PEGylations, acetylations, or hydroxylation (Duncan and Izzo 2005).

PAMAM dendrimers have been the most appreciably studied dendritic polymers for oral delivery purposes. They can permeate across the gut epithelial barrier by a combination of paracellular and transcellular routes due to their especial structure. In the paracellular route, PAMAM dendrimers can internalize by opening the tight junctions of epithelial cells. In transcellular transport, they can permeate into the cells by a variety of endocytic mechanisms. Higher generations of cationic dendrimers show more intestinal membrane damage than lower generations and anionic ones (Sadekar and Ghandehari 2012). The reason for this difference may be the strong interaction between the negatively charged cell membranes and dendrimers resulting in membrane disruption via nanohole formation, membrane thinning, and erosion (Kesharwani et al. 2015).

One of the ways to increase the transepithelial transport of PAMAM dendrimers and reduce their toxicity is surface modification. Lauric acid is a biocompatible molecule that enhances membrane permeability, uptake and transport through the gut (Aungst 2000). Lauroyl chains were conjugated to cationic PAMAM dendrimers generation 2.0 to 4.0 by Jevprasesphant and cytotoxicity and permeability across Caco-2 cell monolayers were measured. The experiment resulted in reducing the toxicity and improving the permeability that was increased with an increase in generation, the number of lipid chains and concentration (Jevprasesphant et al. 2003). The unique globular architecture, large diversity of surface groups, empty internal cavities and high aqueous solubility have made PAMAM dendrimers one of the most available agents in drug delivery systems (Yavuz et al. 2016).

DNA transfection is enhanced with application of amine terminated PAMAM dendrimers as non-viral gene transfer agents due to their well-defined features (Kaur et al. 2016). PAMAM dendrimers can make complexes with genes by electrostatic interactions between negatively charged phosphate groups of the nucleic acid and protonated (positively charged) primary amino groups on the dendrimer surface. It has been shown that PAMAM dendrimers are more efficient than other cationic polymers (such as PEI, PLL,…) or cationic liposomes for gene delivery in a wide array of primary cells of various origins including human fibroblasts (HF1) and human lung epithelial cells (Jonathan et al. 2000). Higher generations of dendrimers (G5 or above) have higher transfection activity in gene delivery, and the extent of in vitro transfection depends on cell specificity in combination with the dendrimer and DNA concentrations used to form the complex. It has been studied that complexes consisting of G5-PAMAM dendrimers and DNA expression plasmids were more efficient in transfection than over naked plasmid DNA in many cells particularly cell lines derived from monkey and human neoplasms (Haensler JaS Jr 1993). PAMAM dendrimers have been also studied as a new promise in siRNA delivery. Perez et al. identified various polymeric nanocarriers for anti-TNF-α siRNA with optimal efficacy and minimal off-target effects in vitro. Among these nanocarriers, PAMAM dendrimers showed high gene silencing with minor toxicity and were recognized to be suitable for siRNA delivery systems (Jensen et al. 2012).

Examining the features, advantages, and challenges of PAMAM dendrimers, it seems fair enough to say that these carriers are just on their first steps in the development road. Due to their interesting properties, PAMAM dendrimers might be one of the promising candidates in the field of drug/gene delivery. Future studies of these delivery systems would reveal the chances of PAMAM-based NPs for clinical trials.

PPI dendrimers

Polypropyleneimine dendrimers (PPI) have two types of nitrogen atoms: nitrogen of primary amines and nitrogen

of tertiary amines of which the primary amines are more basic having a pKa around 10 (Kesharwani et al. 2014).

Lower generations of PPI dendrimers like 0.0, 1.0, and 2.0G have an open structure and show a high polarity range. PPI dendrimers are more hydrophobic in nature and larger than PAMAM dendrimers (Kaur et al. 2016). The maximum amount of entrapped molecules into PPI dendrimers depends on the shape and the size of the molecules, as well as on the amount, shape, and size of the internal cavities of PPI dendrimers (Esfand and Tomalia 2001).

PPI dendrimers exhibit charge-based, generation and concentration-dependent cytotoxicity effects similarly as PAMAM dendrimers (Svenson 2009). Masking could reduce the cytotoxicity. Modification of peripheral amines with various biocompatible molecules such as glycine, phenylalanine, mannose, and lactose significantly improves the toxicity profile of PPI dendrimers, making them biocompatible drug vehicles for controlled and targeted drug and gene delivery (Agashe et al. 2006). Dufes et al. indicated that intravenous administration of G3-PPI dendrimers gene complexes could result in intratumoral transgene expression and decrease of the established tumors in all the experimental animals (Nanjwade et al. 2009).

PLL dendrimers

Poly-L-lysine dendrimers (PLL) have several carborane moieties on the periphery and a peptide spacer at the core including cysteine residue with a reactive thiol for selective coupling to targeting molecules. They are used as vaccine, antiviral, and antibacterial candidates by suitable peripheral modifications (Gillies and Frechet 2005). For example, poly (L-lysine)-PLL dendrimers surface modified with mannosyl groups have demonstrated antibacterial effects (Svenson and Tomalia 2012).

Improvement in the biocompatibility properties of PLL dendrimers could be achieved by surface modifying with molecules such as PEG and polyoxazolines (POZ). One major benefit of POZ over PEG is main-chain ester functionalities that can be deprotonated to give carboxyl groups (England et al. 2016).

PLL dendrimers due to the excellent features of dendrimers and biodegradable property unlike PAMAM and PPI dendrimers could be used in drug and gene delivery systems.

Various applications of dendrimers as drug and gene delivery systems are exhibited in Table 2, and FDA-approved polymeric nanosystems are reviewed in Table 3.

Liposomes

Traditional and stealth liposomes

Liposomes are vesicles formed through spherical assembly of phospholipid bilayers. Categorization is commonly based on size, number of lamellae, and charge (Patil and Jadhav 2014). Liposome properties such as biocompatibility, biodegradability, and low toxicity have led to their widespread usage as a pharmaceutical drug delivery system (DDS) (Samimi et al. 2019; Xu et al. 2012). The ability to carry both hydrophilic and lipophilic molecules simultaneously, DNA molecules, proteins, and peptides is another feature which has put these structures in the spotlight (Torchilin 2005). Surface modification by poly-(ethylene glycol) (PEG) has yielded to stealth liposomes showing longer circulation time due to lesser phagocytosis. PEGylated liposomal doxorubicin (PLD) (DOXIL/Caelyx) was the first stealth liposome to be approved by the FDA (Food and Drug Administration). Modification of the aforementioned polymer chain can be employed to obtain targeted liposomes. PEG-lipids are considered as the most dominant material in formulating stealth liposomes. Vinyl-based lipopolymers, poly (2-oxazoline)-based lipopolymers, poly (amino acid)-based lipopolymers, and zwitterionic lipopolymers are alternatives to PEG-lipids. These surface modifications can be achieved through pre-insertion, post-insertion, post-modification by chemical reaction, or physical adsorption methods (Nag and Awasthi 2013). FDA-approved liposome formulations have been mentioned in Table 4.

Targeted liposomes

Immunoliposomes (antibody-mediated liposome targeting)

Immunoliposomes prepared via attachment of immunoglobulins to vesicles' lipids have been used as a targeted DDS. Furthermore, use of immunoliposomes as immunodiagnostic agents has been investigated. Classic methods for obtaining these systems include crosslinking techniques and

Table 2 The most recent gene(s)-loaded and drug(s)-loaded nanosystems based on dendrimers

Nanosystem	Gene(s) loaded	Result(s)	Ref.
PAMAM dendrimers	Luciferase receptor gene	The expression levels of luciferase were one or two orders of magnitude higher than commercial lipid preparations such as Lipofectamine.	(Jonathan et al. 2000)
α-Cyclodextrin-conjugated G3 PAMAM dendrimer	siRNA	It showed higher siRNA specific gene silencing effects than commercial transfection reagents such as Lipofectamine 2000 TransFast, and Lipofectin in various cells. The inhibition ratio (pGL2/pGL3) was 6.6, 1.3, 2.5, and 0.2 for dendrimer, Lipofectamine™ 2000, TransFast™, and Lipofectin™, respectively.	(Tsutsumi et al. 2006)
Internally quaternized and surface-acetylated G4--PAMAM dendrimer (QPAMAMNHAc)	siRNA	QPAMAMNHAc dendrimer showed lower cytotoxicity and enhanced cellular internalization. Quaternization of inside the dendrimer protected siRNA from degradation.	(Patil et al. 2008)
Triblock poly (amidoamine)-poly (ethylene glycol)-polyLlysine(PAMAM–PEG–PLL)	siRNA	The complexes between siRNA and this triblock were stable in human plasma and taken up effectively by cancer cells and made the knockdown of the target BCL-2 gene (down to 20% from the control value).	(Patil et al. 2011)
Modified G5/G6 PAMAM dendrimer with MPEG5000	GFP-siRNA	The results were knockdown of adenovirus-mediated GFP expression in both transiently adenovirus-infected C57BL/6 mice and GFP transgenic mice.	(Liu et al. 2012)
G5-TEA-core PAMAM dendrimer	siRNA	The results were achieving gene silencing of Hsp27 efficiently in prostate cancer. Hsp27 mRNA expression was reduced to less than 50% than its control amount following treatment in the PC-3 cell xenografted nude mice. Similar reduction in Hsp27 protein level was observed indicating the efficiency of the NPs in siRNA transfection.	(Wu et al. 2013)
Nanosystem	Drug(s) loaded	Result(s)	Ref.
Dexamethasone (DEX)–PAMAM conjugates for retinal delivery	Dexamethasone	The ocular permeability and ocular tissue levels of DEX were enhanced by DEX–PAMAM conjugates. The conjugates also prolonged the drug presence in retina and the duration of DEX release. Release rate was less than 8% after 6 days of incubation in cornea. Following 1 mg/mL intravitreal conjugate injection, DEX-loaded dendrimers were present in vitreous for 24 h while previous works reported that about half of the drug is cleared within the first 3 h following intravitreal DEX injection.	(Yavuz et al. 2016)
Lauroyl chain-modified PAMAM G0.0–naproxen conjugates	Naproxen	Naproxen transport was significantly enhanced resulting from permeability groups on the dendrimer surface significantly contributing to the cellular uptake. Moreover, measurements of the transepithelial electrical resistance values showed a value of around 70% for the PAMAM G0.0–naproxen conjugates while less than 10% decrease in the value was observed with naproxen alone. This observation is justified by the fact of high presence of amines in dendrimer.	(Najlah et al. 2007)
Propranolol–PAMAM G3 conjugates	Propranolol	Conjugation of the drug showed the increasing of its solubility and bypassing P-gp-mediated secretory efflux.	(Menjoge et al. 2010)
Carboxylate-terminated PAMAM dendrimers	Cisplatin		

Table 2 (continued)

		The results showed sustained release behavior of the drug due to hydrolysis from the dendrimers (< 1% after 80 h), higher accumulation in solid tumors, and lower side effects compared to free cisplatin.	(Noriega-Luna et al. 2014)
Fifth-generation PPI dendrimers, t-Boc–glycine-conjugated (TPPI) and mannose-conjugated dendrimers (MPPI) for targeted delivery to macrophages	Efavirenz (EFV)	The toxicity of t-Boc–glycine-conjugated dendrimers and mannose-conjugated dendrimers was found to be negligible, and the hemolytic activity was reduced due to masking of cationic terminal amino groups responsible for the hemolytic activity of PPI dendrimers. Moreover, use of dendrimer systems resulted in significant cellular uptake of the drug (12 and 5.5 times higher than that of free drug with MPPI and TPPI, respectively).	(Dutta et al. 2007)
Mannosylated fifth-generation PPI dendrimers (MPPI)	Lamivudine (3TC)	The results indicated that 3TC-loaded PPI and MPPI formulations possess higher anti-HIV activity due to the enhanced cellular uptake of 3TC in formulation and prolonged drug delivery as compared to that of free drug. The proposed carrier was suggested to increase the efficacy and reduce the toxicity of antiretroviral therapy.	(Dutta and Jain 2007)
Folate-modified PPI dendrimers	Docetaxel (DTX)	Engineered PPI dendrimers could be used as a controlled and targeted delivery system for the delivery of anticancer drugs like DTX.	(Thakur et al. 2013)
Apolipoprotein B (ApoB)-specific siRNA-PLL-G6 dendrimers conjugate	Apolipoprotein B (ApoB)--specific siRNA	Later knockdown of ApoB in healthy mice without hepatotoxicity resulted from intravenous delivery of apolipoprotein B (ApoB)-specific siRNA-PLL G6 dendrimer conjugate.	(Watanabe et al. 2009)
G3-[PEG-RGD peptide]-[DOX] nanoglobular PLL dendrimers conjugate complexed with siRNA	Doxorubicin (DOX)	These PLL/siRNA complexes exhibited much higher gene silencing efficiency in U87-Luc cells than those of control conjugates including G3-[PEG-RGD] and G3-[DOX].	(Wu et al. 2013)
Sixth-generation cationic poly-L-lysine dendrimers	Doxorubicin (DOX)	Doxorubicin–dendrimer (DOX–DM) complexes achieved a significantly higher cytotoxicity in DU145 multicellular tumor spheroid (MTS) system compared to the free drug, and the penetration of DOX into MTS was increased due to making complexes with DM in vivo solid tumors.	(Khuloud et al. 2013)
PEGylated poly-L-lysine dendrimers	Methotrexate (MTX)	Methotrexate (MTX) conjugated to PEGylated poly-L-lysine dendrimers has been reported to accumulate in solid Walker 256 and HT1080 tumors in rats and mice and reduce accumulation in RES organs with extended circulation times.	(Khuloud et al. 2013)

antibody derivatization (Jenkins et al. 2016). Anti-HER2 immunoliposomes were developed for co-delivery of paclitaxel and rapamycin to HER2 (+) breast cancer cells (Eloy et al. 2017). Use of more than one ligand would lead to multi specific systems. The anti-transferrin receptor monoclonal antibody (OX26MAb) and the anti-amyloid beta peptide antibody (19B8MAb) conjugation to PEG-liposomes are investigated as a dual ligand system for delivery across blood brain barrier (BBB) (Loureiro et al. 2015). It has been showed that a new drug-loaded immunoliposome using a polyclonal antibody against plasmodium falciparum-parasitized red blood cells (pRBCs) had been more successful in treatment of severe malaria in vitro (Moles et al. 2016). Endoglin (CD105) and fibroblast activation

Table 3 Most recent FDA-approved polymeric nanosystems (Patra et al. 2018)

Nanosystem	Description	Indications	Year approved
Cimzia®/certolizumab pegol (UCB)	PEGylated antibody fragment (certolizumab)	Crohn's disease	2008
		Rheumatoid arthritis	2009
		Psoriatic arthritis	2013
		Ankylosing spondylitis	2013
Krystexxa®/pegloticase (Horizon)	Polymer–protein conjugate (PEGylated porcine-like uricase)	Chronic gout	2010
Plegridy® (Biogen)	Polymer–protein conjugate (PEGylated IFN beta-1a)	Multiple sclerosis	2014
Adynovate® (Baxalta)	Polymer–protein conjugate (PEGylated factor VIII)	Hemophilia	2015
Zilretta®	Triamcinolone acetonide with a poly lactic-*co*-glycolic acid (PLGA) matrix microspheres	Osteoarthritis (OA) of the knee	2017
Rebinyn®	Coagulation fator IX (recombinant) glyco-PEGylated	Control and prevention of bleeding episodes and prevention of bleeding in the perioperative setting for hemophilia B patients	2017

protein (FAP) have been hired in creation of doxorubicin loaded immunoliposomes providing an increase in cytotoxicity against target tissue in comparison with mono specific liposomes (Rabenhold et al. 2015).

Folate-mediated liposome targeting

Due to overexpression of folate receptors (FRs) on tumor cells, folate derivatives have been used as a targeting ligand for nanoparticles. FR mediated endocytosis is used to bypass multidrug resistance. Folate–polyethylene glycol–cholesterol hemisuccinate (F–PEG–CHEMS), folate–PEG–cholesterol (F–PEG–Chol), and F–PEG–DSPE (distearoylphosphatidylethanolamine) have been successfully used for enhancing the cytotoxicity at tumor site of melanoma and lung cancer. Although folate conjugated liposomes exhibit higher uptake by macrophages (Xiang et al. 2008).

Transferrin-mediated liposome targeting

Transferrin (Tf) receptors are another common overexpressed receptors on tumor cells (Torchilin 2005). The Tf–PEG–liposomes had been used for delivery of oxaliplatin (Suzuki et al. 2008) and doxorubicin (Li et al. 2009). Tf-modified liposomes encapsulating mastoparan developed with a pH-sensitive fusogenic peptide (GALA) has shown effective internalization and endosomal escape (Yamada et al. 2005).

Miscellaneous targeting strategies

Vitamin E d-α-tocopherol acid–polyethylene glycol 1000-succinate (TPGS) has been hired for enhanced tumor accumulation of hydrophobic drugs such as luteolin (Li et al. 2016). A formulation of RGD conjugated TPGS (RGD–TPGS) liposome containing docetaxel (DTX) and quantum dots (QDs) was investigated for theranostic application in brain tumors and showed promising results regarding targeted delivery to cancer cells across BBB (Sonali et al. 2016).

Coating liposomes with hyaluronic acid through electrostatic adsorption has yielded a promising carrier for specific drug delivery to tumor tissues, e.g., paclitaxel for breast cancer (Ravar et al. 2016).

Stimuli-responsive (stimuli-sensitive) liposomes

pH-sensitive liposomes (PSLs)

PSLs are one of the most investigated stimuli-sensitive formulations with the main purpose of cancer drug delivery. These liposomes are more stable in

Table 4 Most recent FDA-approved liposome systems (Patra et al. 2018)

Nanosystem	Description	Indications	Year approved
Doxil®/Caelyx™ (Janssen)	Liposomal doxorubicin	Karposi's sarcoma	1995
		Ovarian cancer	2005
		Multiple myeloma	2008
Marqibo® (Onco TCS)	Liposomal vincristine	Acute lymphoblastic leukemia	2012
Onivyde® (Merrimack)	Liposomal irinotecan	Pancreatic cancer	2015
Vyxeos (Jazz Pharma)	Liposomal combination of daunorubicin and cytarabine	Acute myeloid leukemia (AML) or AML with myelodysplasia-related changes (AML-MRC)	2017

physiological pH (pH = 7.4) compared to sub-acidic pH that exists at tumor sites (pH = 5). Materials used in pH-sensitive liposomes have the property to be changed in conformation when delivering in acidic environment (pH = 5) (Fan et al. 2017; Wang et al. 2014b). Methods of obtaining PSLs include:

1. Using a combination of polymorphic lipids: unsaturated phosphatidylethanolamine (PE), such as diacetylenic-phosphatidyl-ethanolamine (DAPE), palmitoyl-oleoyl-phosphatidyl-ethanolamine (POPE), and dioleoyl-phosphatidyl-ethanolamine (DOPE) with oleic acid (OA), linoleic acid (LA), and cholesteryl hemisuccinate (CHEMS) which are amphiphilic molecules acting as stabilizers (Fan et al. 2017; Liu and Huang 2013).
2. Using "cage" lipid derivatives: e.g., N-citraconyl-dioleoyl-phosphatidyl- ethanolamine (C-DOPE), N-citraconyl-dioleoyl-phosphatidylserine (C-DOPS), and poly(ethylene-glycol)-N-distearolyphosphatidyl-ethanolamine (PEG-DSPE) that are able to reversibly form a non-bilayer phase which promotes delivery by release in acidic pH and/or fusion with cell membrane (Liu and Huang 2013).
3. Using synthetic fusogenic pH-sensitive peptides/proteins: such as GALA, N-terminus of hemaglutinin (INF peptides from influenza), or listeriolysin O. These peptides are inactive when liposomes are in the neutral pH environment. However, in the acidic environment, the change in conformation of said materials will increase the leakage and liposome–cell membrane fusion resulting in release of pH-sensitive liposome contents to the cell environment. For instance, this issue could be taking place in pH = 5 for GALA peptide as its repeat unit (EALA) undergoes a pH-dependent conformational change from random coil at pH = 7.5 to an amphipatic helix at pH = 5 (Liu and Huang 2013).
4. Using pH-sensitive polymers: materials including poly (alkyl acrylic acid)s, succinylated PEG, N-isopropylacrylamide (NIPAM) copolymers, and hyperbranched poly (glycidol) (HPG) derivatives are used to enhance the fusogenic properties of liposomes (Liu and Huang 2013).
5. Newer formulations have been prepared using structures such as octylamine-graft-PASP (PASP-g-C8)-modified liposomes (OPLPs) and glucosylated pH-sensitive amphiphile moieties acting as both targeting agent and pH-sensitive agents simultaneously, thus creating a multifunctional system against cancerous tissues (Wang et al. 2014b; Giansanti et al. 2016).

Redox-sensitive liposomes

These systems operate via reduction with high concentrations of glutathione (GSH)—a reducing agent found in high concentration (1–10 mM) in cytosol of normal cells and 4 times more than the mentioned amount in tumor cells—destabilizing the liposome structure (Araujo et al. 2017). A novel cationic liposome formulation using PEG_{2000}–Chol conjugation by means of bio-reducible disulfide linker (Chol-SS-mPEG) and HA coating (for CD-44 targeting) has been employed for delivery of DOX. The results in rats showed a more than ten fold increase in half-life while mouse models showed minimal hepatocyte uptake, better tumor

suppression, and a higher overall survivability compared to free drug (Chi et al. 2017).

Thermosensitive liposomes (TSLs)

TSLs were first introduced by Yatvin et al. in 1978 (Mannaris et al. 2013). These formulations are based on enhanced permeability of lipid bilayers at temperatures above the average transition temperature of mixture of lipids leading to rapid drug release. Thermo-DOX is the only thermo-sensitive liposome that has reached clinical phase. The lysolipid 1-stearoyl-2-hydroxy-sn-glycero-3-phosphatidylcholine (MSPC or S-lyso-PC) used in this formulation will lead to pore formation at above transition temperature (42 °C which is achieved by means of radiofrequency ablation (RFA)) resulting in an 80% drug release within 20 s. To have a sharp transition temperature, Thermo-DOX is a Chol-free liposome (Dou et al. 2017).

Multi-modal thermo-sensitive polymer-modified liposomes (MTPLs) compounded by application of 2-(2-ethoxy) ethoxyethyl vinyl ether (EOEOVE) in the lipid mixture as the thermo responsive moiety has been investigated for theranostic purposes. EOEOVE, a hydrophilic molecule, turns hydrophobic upon reaching lower critical solution temperature (LCST). In this case, magnetic resonance from MRI machine was recruited for triggering the release of drugs and contrast materials (Kokuryo et al. 2015).

High intensity focused ultrasound (HIFU) and alternating magnetic fields (AMF) are common TSL's triggers (Tai et al. 2010). TSLs are used in delivery of variety of pharmaceuticals such as DOX (Mannaris et al. 2013; Dou et al. 2017; Kokuryo et al. 2015), manganese sulfate (MnSO4) (Kokuryo et al. 2015), and zwitterionic diazeniumdiolate, a precursor of nitric oxide (Tai et al. 2010).

Ultrasound-responsive liposomes

Low-frequency ultrasound (LFUS) and HIFU have been used in the control of drug release from liposomes. LFUS acts in a non-thermal manner and induces transient pore formation in liposomes. Also, it promotes ion permeation through the lipid bilayer due to disruption of lipids' hydrophobic ends (Schroeder et al. 2009). An ultrasound-responsive liposome formulation including HSPC, DSPC, Chol, and DSPE-PEG2000 was investigated for control release of poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs) and exhibited promising results as a new anti-cancer delivery system (Xin et al. 2017).

Magnetically responsive liposomes

Incorporation of magnetic nanoparticles (mostly iron oxides) has yielded novel liposome formulations that can be manipulated by external magnetic fields to enhance localization in target tissues. Moreover, they can be used as contrast media in MRI and to enhance transfection efficacy by increasing liposome temperature using alternative magnetic fields (Movahedi et al. 2015). Dextran-magnetic layered double hydroxide-fluorouracil liposomes (DMFLs) have been developed as a targeted delivery system deploying ferrous chloride and ferric chloride as magnetic agents (Huang et al. 2013). Manganese ferrite-based magnetic liposomes displayed auspicious result in the field of thermo-chemotherapy (Pradhan et al. 2007). Thermo-sensitive magnetic liposomes (TML) were prepared using Fe_3O_4-NPs as magnetic agent. TML magnetic properties come handy for targeted delivery while its thermal response acts as the trigger for controlled drug release (Hsu and Chen 2017).

Photosensitive liposomes

Use of near-infrared (NIR)-absorbing inorganic nanomaterials leads to a hybrid class of liposomes triggered via NIR. Gold nanoparticles (AuNPs) entrapped in a liposome can produce heat if exposed to NIR, thus disrupting the said liposome's bilayer membrane. Furthermore, hollow gold nanoshells (HGNs) can be tethered or encapsulated in liposomes leading to a photoresponsive system in the same way. HGNs' ultrasonic cavitation effect can be employed to control the release of liposome contents (Cho et al. 2015).

Liposomes can be used in the delivery of photosensitizers such as m-THPC (Foscan) used in photodynamic therapy (PDT). Specific wavelengths of visible light can trigger a reaction leading to production of reacting oxygen species (ROS) and cell death (Shah et al. 2016). Poly (vinylalcohol) with a malachite green moiety (PVAMG) has been used to trigger liposomes with UV light exposure. PVAMG-positive sites (formed upon exposure) disrupt and destabilize anionic surfaced liposomes with no sign of lipid solubilization (Uda et al. 2016).

Enzyme-responsive liposomes

This triggering mechanism is based on the enzyme localization, e.g., extracellular enzymes such as cathepsin (exuded by neutrophils) can be found in inflammation sites. Cell-associated proteases can mediate fusogenicity through different mechanisms such as proteolytic cleavage. N-Acetylated alanyl alanine DOPE (N-Ac-AA–DOPE) and N-methoxysuccinylalanylalanylprolylvalyl–DOPE (MeO-suc-AAPV–DOPE) can be cleaved by elastase leaving only DOPE that leads to liposomal fusion. Phospholipase C, phospholipase-A, trypsin, alkaline phosphatase, cathepsin B, and other enzymes have been investigated as triggers for these systems (Rose et al. 2013). Phospholipase A2 (PLA2) has been found in high concentrations in tumor cells and during inflammations and infections. Polymer-coated liposomes having a 1-O-phospholipid formation can be substrate of PLA2. (R)-1-O-Hexadecyl-2-palmitoyl-sn-glycero-3 phosphocholine (1-O-DPPC) and PEG tethered phospholipids (1-O-DPPE-PEG) have been investigated as materials for composition of such liposomes (de la Rica et al. 2012). Poly (hydroxyethyl l-glutamine)–N-succinyl-dioctadecylamine (PHEG–DODASuc) was also used for enhancing the circulation time and being triggered by protease (Romberg et al. 2008).

Niosomes and proniosomes

Niosomes are vesicles formed by self-assembly of non-ionic surfactants. Hydrophilic–lipophilic balance (HLB) and molecule geometrical characteristics, i.e., the critical packing parameter (CPP), are principal factors in niosome formation. A typical niosome formulation includes non-ionic surfactants (polyglycerol monoalkyl ethers, polyoxylate, etc.), cholesterol, and charged molecules (negatively charged such as dicetyl phosphate (DCP) and phosphatidic acid molecules, and positively charged such as stearylamine (SA) and cetylpyridinium chloride) which are employed to prevent aggregation and stabilize the system (Marianecci et al. 2014). Niosome application has been investigated as a DDS for a variety of molecules such as peptides, vaccines, and genes. The more stable structure of niosomes in comparison to liposomal vesicles regarding encapsulation of macromolecules and hydrophobic agents has made them viable systems. Proniosomes—the dry (hence more stable) formulation of a surfactant-coated water-soluble core—can be reconstituted to niosomes simply by adding water above mean phase transition temperature of system and agitating the system for a short time period (Mahale et al. 2012). Span, Tween, and Brij are among the most common surfactants used in preparation of niosomes (Moghassemi and Hadjizadeh 2014).

Cationic liposomes

Cationic liposomes have been investigated as gene delivery systems due to their ability to stabilize negatively charged nucleic acids. Cationic lipids—with a positively charged head—such as N′, N′-dioctadecyl-N-4,8-diaza-10-aminodecanoyl glycine amide has been recruited for production of such structures. Neutral helper lipids, e.g., DOPE and Chol, are commonly used beside cationic lipids for enhanced transfection (Shim et al. 2013). The DNA/cationic liposome complexes also known as lipoplexes have been first introduced in 1987. 1,2-Dioleoyl-3-trimethylammoniumpropane (DOTAP), 2,3-dioleyloxypropyl-1-trimethylammoniumbromide (DOTMA), and 3β(N(N′,Ndimethylaminoethane)carbamoyl)cholesterol (DC-CHOL) are among the most common cationic lipids (Madeira et al. 2011). Lipoplexes has been used for a variety of purposes; as an example, the production of mRNA lipoplex vaccines can be mentioned (De Beuckelaer et al. 2016).

Inorganic-based delivery systems

Metal-based nanostructures

Functionalization of inorganic nanoparticles (INPs) and their role in drug and gene delivery, molecular diagnostics, and biomedical engineering due to their unique features has made INPs as suitable candidates in pharmaceutical products. Some of the more studied metals recruited in delivery systems are as follows:

Au-based nanoparticles

Au-NP synthesis occurs through reduction (via agents such as $NaBH_4$ and citrate) of gold salts (e.g., AuCl(PPh_3) and $HAuCl_4$) in attendance of suited stabilizing

agents (for instance phosphine, alkanethiol, and citrate). Reduction of AuCl (PPh_3) with $NaBH_4$ alongside phosphine as stabilizer yields to NPs in the vicinity of 1 to 2 nm. These particles can be applied in fields such as gene (through electrostatic absorption of DNA leading to stabilization of nucleic acids) and drug delivery, targeting, photothermal and radiation therapy, and diagnostic imaging. The conjugation of just one gold nanoparticle (with 2 nm core diameter) to about a hundred molecules can be hired for controlled release of molecules. Promoting the hydrophobicity of these particles can lead to higher transfection efficacy and cellular internalization (Ghosh et al. 2008; Her et al. 2017; Papasani et al. 2012).

Au nanorods (Au NR) formed by a variety of methods such as template, electrochemical, or seeded growth method (with/without $AgNO_3$) have unique size- and shape-dependent optical properties. $AgNO_3$ could have effects on the yield and aspect ratio control of AuNR as well as determining crystal structure, morphology, and optical properties (Perezjuste et al. 2005). Au NR can be engineered for maximum optical absorption in wavelengths ~ 700–1200 nm (known as "water window" which is the best region for diagnostic imaging and therapy) and enhanced electric field in the said range due to localized surface plasmon resonance (LSPR) phenomenon. Thermal properties and optical characteristics (extensive light absorption/scattering) of these particles can be used for photothermal therapy (PTT), bio-imaging and chemo-sensing (Alkilany et al. 2012). NR size and volume to size ratio make these particles capable of being targeted by both passive (by means of the enhanced permeation and retention (EPR)) and active (through functionalization with targeting moieties) pathways (Alkilany et al. 2012; Wang et al. 2017a). Although thermal and photothermal properties of these particles are the most common means for controlled drug release, multi-responsive systems (such as pH, redox, and photothermal tri-responsive systems) have been developed for more efficient therapy (Wang et al. 2017a).

Layer-by-layer (LbL) nanoassembly methods have been a pivotal means in the production of nanoshells (de Villiers and Lvov 2011). Studies on novel NIR-triggered gold nanoshell–coated betulinic acid liposomes (AuNS-BA-L) have shown promising results (Liu et al. 2017). Recently, chitosan incorporated AuNP-YIGSR (laminin peptide) dry powder formulation has been developed and studied as a pulmonary DDS for targeted delivery to lung cancer cells (Silva et al. 2017). Other NP shapes such as star, cage, and sphere have been investigated as well (Her et al. 2017).

Fe-based nanoparticles

Iron oxides especially Fe_3O_4 can be used in the synthesis of magnetic nanoparticles (MNPs) which can be recruited for tasks such as magnetic cell and gene therapy, generation of magnetic fluid hyperthermia (MFH), and magnetic targeting of tumor cells (Sekhon and Kamboj 2010; Wang et al. 2016c). The large surface of porous Fe_3O_4 structures facilitates delivery of large number of drugs via surface absorption. Their release controlled with an AC/DC field has been studied (Mustapić et al. 2016). Fe3O4/CS/INH (Fe_3O_4/chitosan/isoniazid) nanoparticles and a mesoporous Fe_3O_4/hydroxyapatite (HA) composite containing DOX were studied as targeted delivery systems for tuberculosis and cancer, respectively (Zhao et al. 2017; Gu et al. 2014).

Ti- and Zn-based nanoparticles

Zinc oxide nanoparticles (ZnO NPs) have been used due to their large surface area, biocompatibility, stability, and low toxicity (much like other metal-based DDSs). ZnO NPs functionalized using 3-mercaptopropionic acids (MPA) have been hired as carriers for curcumin as an anticancer formulation (Ghaffari et al. 2017). A core–shell hybrid of poly diethyl aminoethyl methacrylate (PDEAEMA) as the pH-sensitive shells and modified TiO_2 and ZnO nanoparticles as core has been developed for controlled drug delivery (Ensafi et al. 2017). It has been shown that ZnO NPs have anti-microbial and anti-cancer activities with no virtual cytotoxicity for normal cells. ZnO NPs, nanotubes, nanorods, and nanorings have been exploited for an array of tasks from drug delivery to bio-imaging (Flak et al. 2017). TiO_2 photocytotoxicity resulting from ROS generation upon exposure to UV has been the premise of TiO_2-based PDT. Zinc phthalocyanine deposition on TiO_2 has been applied for development of ZnPc@TiO_2 nanoparticles and nanotubes for a variety of objectives including usage in PDT, bio-imaging, and cancer DDSs by modification via folic acid (FA) for targeted delivery (Awad et al. 2017). Titanium bone implants with TiO_2 NP-modified surface have been investigated for bone-related diseases (Awad et al. 2017). Studies showed better results with FA-conjugated TiO_2 NPs compared to bare TiO_2 NPs

on the human osteosarcoma cell line (MG-63) (Ai et al. 2017). A novel montmorillonite/insulin nanocomposite coated with TiO_2 displayed promising results as an oral DDS (Kamari et al. 2017).

Ag-based nanoparticles

Ag NPs among other functions are famous for their antimicrobial effect (Sekhon and Kamboj 2010). Silver nanoclusters (Ag NCs) encapsulated within porous silica ($pSiO_2$), loaded with N-(2-mercaptopropionyl) glycine (MPG), and capped using Ag NPs which acted as a gatekeeper for this novel redox-responsive nanosphere showed promising GSH-sensitive release, antimicrobial and drug-dependent fluorescence effects (Qiu et al. 2016). Fe_3O_4@C@Ag NPs (~ 200 nm) created by surface modification of Fe3O4@C with Ag NPs exhibited a near gram per gram loading capacity for DOX, NIR-triggered release, and applicability as MRI contrast agents and fluorescent probes (Chen et al. 2013). Ag NP emending of nanocapsules assembled layer by layer has yielded to a new ultrasound-responsive system (Anandhakumar et al. 2012). A functionalized formulation of DOX-loaded Ag NP deposited on graphene oxide (GO) showed about eight to nine fold increase in DOX uptake. Moreover, this designed delivery system showed promising effects as a powerful tumor diagnostic X-ray contrast agent and a strong candidate for photothermal therapy in tumor cells (Shi et al. 2014).

Silicon-based nanostructures

Mesoporous silica nanoparticles (MSNPs) have been investigated for biomedical applications (e.g., drug and gene delivery) due to their special structures. Loading squaraine dyes into MSNP and wrapping the particle with GO nanosheets can be used as a formulation for PDT and bio-imaging process. MSNPs and hollow mesoporous silica nanoparticles (HMSNPs) with different capping can be utilized for drug/gene co-delivery and controlled-release systems via different stimuli based on their capping methods (Ma et al. 2017). Grafting oxidized glutathione (GSSG) into porous SiO_2 capped by pH-sensitive ZnO quantum dots (QDs) was used to develop ZnO-gated $pSiO_2$-GSSG nanospheres responsive to protease/redox/pH as an anticancer DDS (Qiu et al. 2017). Hollow silica nanoshells are of utmost interest due to their capacity for delivering a larger quantity of therapeutic agents. The high surface area, pore volume along with in storage, in vivo stability, and their ability as diagnostic and imaging agents have made them interesting to the scientific community (Mendez et al. 2017). A transferrin-modified MSNP encapsulating DOX which can be triggered by reduction of the disulfide bond through reduction properties of GSH presented new inspiration on the design of MSNPs (Chen et al. 2017a).

An array of redox-responsive biodegradable SiO_2 NPs has been developed using disulfide and tetrasulfide bonds displaying the pivotal role of porosity and core composition in the biodegradation rate of nanoparticles (Hadipour Moghaddam et al. 2017).

Carbon-based nanostructures: nanotubes and graphene

Carbon nanotubes (CNTs) due to their electrical, mechanical, and optical features along with their functionalization ability (which allow them to be soluble in physiological fluids) have been investigated for delivery of a vast range of therapeutics (both macromolecules and small molecules). CNTs can be categorized into single-wall (SWCNTs) or multi-wall (MWCNTs) structures. They need to be functionalized if they are going to be vectors for double-strand DNAs (dsDNAs). Ammonium is commonly used (as positively charged group) for functionalizing oxidized CNTs preparing them for binding to negatively charged nucleic acids (Caoduro et al. 2017). SWCNTs can be used in vaccine delivery systems. SWCNT-PPD (tuberculin purified protein) showed greater Th-1 response in comparison to PPD in Freund's adjuvant which predominantly exhibits Th-2-mediated response. The Wilm's tumor protein (WT1)—a weak immunogenic protein proposed as a cancer vaccine—has been formulated via SWCNT usage for better immunization results (Scheinberg et al. 2013).

Graphene is a 2D sheet of carbon atoms in honeycomb arrangements which are a cornerstone for building other structures, i.e., carbon nanohorns, CNTs, and so on. Graphene-based nanomaterials can be used for a vast number of applications such as bio imaging, drug delivery, and theranostic purposes. Ultra-high surface area, functionalization veritably, and other unique characteristic of these structures have made them interesting candidates. Graphene, graphene oxide (GO), reduced graphene oxide (rGO), and graphene quantum dots (GQDs) have been investigated for bio-imaging and drug delivery purposes. GO composites with metallic compounds and elements such as iron oxide, gold, and

silver can be used for X-ray CT imaging (Lin et al. 2016). Nanographene-based DDSs have been hired for stimuli-responsive delivery of therapeutic agents. For example, light/pH-sensitive GO-PEG or ATP-responsive GO formulation has been investigated as nanocarriers for DOX delivery (Yang et al. 2016). FA-GO@Au-loaded DOX nanocomposites releasing DOX and Au-NPs at the tumor site via NIR mediation were studied as well (Chauhan et al. 2017).

Considering every available aspect of inorganic delivery systems, it seems logical to conclude that like any other strategies for drug/gene delivery, these systems have their fascinating features as well as their limitations, too. Some inorganic targeting devices seem to have dual applications in the human body since they can behave as therapeutic molecules and as imaging/diagnosis tools at the same time. Some also showed perfect cell transfection according to evidences provided by many studies. On the other hand, several inorganic carriers still suffer from their toxicity profile; thereby, modifications should be well employed to arm these systems with sufficient safety for in vivo application. The high potentials of inorganic delivery systems observed in researches have encouraged the scientific society to think up solutions and novel strategies to mask the limitations of these systems.

Targeting ligands

In recent years, nanoparticles have promoted the efficacy of drugs significantly and successfully. Developing nanoparticles to an ideal drug delivery system could be achieved by targeting to the right site that drug must be released. Especially, when it comes to cancer chemotherapy, this matter is more notable because of side effects leading to delay and discontinuance of therapy. Tumor cells overexpress many receptors and biomarkers which can be used as potential targets. Nanocarriers with targeting moieties on their surfaces increase the localization of drugs in sites of interest and reduce the side effects due to the specific delivery not to the whole body. Nanoparticles containing drug/gene should be conjugated to targeting moieties via a suitable linker that must be stable in circulation and be easily cleaved to deliver the drug/gene by incorporation in the interest cells (Jaracz et al. 2005).

Heretofore, the data gathered from a huge number of studies and researches suggest diverse targeting ligands can be used to deliver the drug/gene. Herein, some of the most widely used ones are categorized:

Carbohydrates

Carbohydrate ligands can target endogenous protein receptors such as lectins at the site of localization and have high ability to undergo site-specific modification; therefore, their interactions with receptors are more special than other ligand-binding systems allowing the further enhancement of the targeting efficacy (Kumar 2012).

C-type lectin receptors (CLRs) are a large group of lectin receptor family including lymphocyte lectins, collectins, selectins, and proteoglycans. They have a homologous carbohydrate-recognition domain (CRD) that can bind to carbohydrate structures on pathogens to initiate a protective immune response or they may also have the ability for binding to self-antigens to induce self-tolerance in a Ca^{2+}-dependent manner. Various carbohydrate-based targeting delivery systems such as glyconanoparticles, glycodendrimers, and glycoliposomes have been utilized specifically for a number of CLRs including asialoglycoprotein receptors (ASGPR) in the liver, myeloid CLRs such as DC-SIGN, mannose receptors (MR) and DEC-205 on dendritic cells (DCs), and macrophages. Targeting myeloid CLRs is not only helpful for cell-specific delivery but may also demonstrate as a tool to either stimulate or modulate immune functions (Lepenies et al. 2013). Regulating antigen-presenting cell (APC) functions can be employed by targeting DCs to deliver antigens specifically into APCs (Maglinao et al. 2014). For instance, oligomannose-coated liposomes were employed as antigen-delivery vehicles into DCs and the result was induction of Th1-specific immune response (Kojima et al. 2011). As another example for carbohydrate-targeted delivery, galactose can be used as a targeting moiety against asialoglycoprotein receptor (ASGP-R, C-type lectin receptor) in liver indicating employing galactose on a given drug delivery system could deliver the intended API to the liver tissue (Brannon-Peppas and Blanchette 2012).

Folic acid

The expression of folate receptors is low in normal tissues, but they are differentially overexpressed in cancer tissues including breast, ovary, brain, and

lung malignancies. Therefore, folic acid (FA) can be used as a targeting moiety for anticancer drugs in different formulations such as polymeric nanoparticles, nanotubes, liposomes, micelles, and emulsions. Since today, researches have demonstrated that drug conjugates of folic acid have much lower cytotoxicity in non-cancer cells and a better response in tumor tissues due to the more specific cellular uptake (Jennifer Sudimack et al. 1999). One more unique property of folic acid is its small size that provides favorable pharmacokinetic properties and lower immunogenicity (Wenjin Guo 2001). In a study, Goren et al. attached Doxil (liposomal form of doxurubicin) to folic acid. Confocal fluorescence microscopy of rhodamine-labeled doxorubicin encapsulated inside the liposome showed rapid internalization into folate-receptor-positive cells (Jaracz et al. 2005). Studies have shown that vaccines against the folate receptor also can be used to treat folate-receptor-positive tumors (Brannon-Peppas and Blanchette 2012). Noncovalent complexes of FA and PEI demonstrated better efficiency and more specialty in gene delivery to human oral carcinoma KB cells (Wenjin Guo 2001). Folic acid-conjugated gelatin nanoparticles of cisplatin (Cis–GNs–FA) showed higher delivery in cervical cancer cells (Dixit et al. 2015).

Peptides

Interaction of cell-targeting peptides (CTP) conjugated to a drug carrier with receptors overexpressed in some tumor cells allows tumor-specific targeting of cytotoxic agents and exhibits strong affinity for given targeted cell lines (Vives et al. 2008). Evidences suggest that application of peptides in drug/gene carriers could specifically target the drug/gene to the site of interest, increase cell transfection in the intended cells, and reduce off-target effects. Yet, it should be noted that one of the limitations of using peptides as targeting moieties is their instability in circulation; however, this can be improved by appropriate modifications such as cyclization and multimerization of the peptides(Jaracz et al. 2005). RGD (Arg–Gly–Asp) peptide presents a specific interaction with the αvβ3 integrin receptors which play a notable role in angiogenesis of solid tumors. EGF-R peptide (D4Leu–Ala–Arg–Leu–Leu–Thr) ligand-conjugated liposomes have been shown to bind specifically to EGF-receptor high-expressing cancer cells (Vives et al. 2008). Somatostatin peptide has high binding affinity to SSTR1–5 membrane receptors expressed at significantly elevated levels in GI tumor cells. Some other gastrointestinal peptides such as bombesin (BBN), bombesin-like peptide and gastrin-releasing peptide (GRP) function as growth factors and modulate tumor proliferation. Bombesin-like peptides interact with four different receptors (BBNR1–4) located in different cancer cells such as small cell lung, breast, prostatic and pancreatic cancers. Therefore, bombesin-like peptides and GRP antagonists can be used as potential tumor-targeting anticancer agents (Jaracz et al. 2005). Luteinizing hormone-releasing hormone (LHRH) can be used as a targeting moiety to LHRH receptors which are overexpressed in several types of cancers such as breast, ovarian, and prostate (Dharap et al. 2005). Various cytotoxic drugs (doxorubicin, camptothecin, etc.), cytotoxic genes, small interfering RNA (siRNA), and microRNAs (miRNA) can be conjugated with LHRH peptide in therapeutic nanocarriers for specific delivery to the interest cells (Ghanghoria et al. 2016). In the last decades, using peptides in DDSs as targeting moieties has attracted much attention from researchers that are gathered in Table 5. The most important peptide sequences with their mentioned targets are provided in Table 6 (Vives et al. 2008).

Monoclonal antibodies

Monoclonal antibodies (mAbs) can specifically target the delivery of a cytotoxic agent to the tumor sites by binding to an antigen that is overexpressed on tumor cells but has low expression on normal tissues (Alley et al. 2010). There are many potential targets involved in angiogenesis for mAbs such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, platelet derived growth factor and certain matrix metalloproteinases in cancer cells (Brannon-Peppas and Blanchette 2012). The efficacy of mAbs targeted delivery systems in cancer cells treatment depends on the tumor specificity of monoclonal antibodies (mAbs), the potency of the cytotoxic agents, immunogenicity of the delivery system and determination of the right size of the mAbs targeted systems that can penetrate into tumors but not to be cleared by kidneys too fast (Jaracz et al. 2005). Therapies based on mAbs are now among

Table 5 Nanodrug delivery systems decorated with peptide-targeting moieties

Peptide	Target	Nanosystem	Drugs and/or genes loaded	Result(s)	Ref.
HIV-1 TAT (a nuclear localization signal (NLS) peptide)	Import receptors (importin α and β karyopherin) and nuclear pore complexes (NPCs)	TAT-conjugated mesoporous--silica nanoparticles (MSNs-TAT)	Doxorubicin	MSNs-TAT delivered doxorubicin efficiently into the targeted nucleus.	(Pan et al. 2012)
Peptide-22 (PNP)	LDLR (low-density lipoprotein receptor)	Dual-targeting paclitaxel-loaded nanoparticles (PNP-PTX)	Paclitaxel	PNP–PTX treatment significantly increased the transport ratio of PTX across the BBB and induced more cell apoptosis in C6 glioma cells compared with other treatments.	(Zhang et al. 2013)
Luteinizing hormone--releasing hormone (LHRH)	LHRH receptors	Camptothecin attached to LHRH via PEG as a carrier	Camptothecin	The results showed high accumulation of the drug in ovarian carcinoma cells.	(Dharap et al. 2005)

the most successful and important strategies for cancer treatment but they have some significant disadvantages such as too high cost of production for developing new mAbs and having large size that limits their penetration into tumor cells (Heo et al. 2016).

The topoisomerase-I inhibitor SN-38 incorporated in polymeric nanoparticles (NPs) surface-decorated with the anti-GD2 (a disialoganglioside antigen) mouse mAb 3F8 demonstrated higher amount of tumor localization of SN-38 in mice compared to non-targeted delivery system (Monterrubio et al. 2017). A chemotherapeutic agent, rapamycin, and a photosensitizer, polypyrrole, loaded in trastuzumab-conjugated liposomes (LRPmAb) showed notably enhanced uptake and higher therapeutic efficacy in BT-474 cells, a natural HER2/neu expressing receptors breast cancer cell line compared with cells not overexpressing these receptors (Nguyen et al. 2017).

Hyaluronic acid

A wide range of receptors for HA, a natural anionic polysaccharide, has been established including cell surface glycoprotein CD44, receptor for hyaluronic acid-

Table 6 The most important peptide sequences and their targets used in studies

Peptide sequence	Targeted tissue	Cellular target	Ref.
TSPLNIHNGQKL	Human head and neck solid tumors	Unknown	(Vivès et al. 2008)
CGKRK	Tumor neo-vasculature	Heparan sulfate	(Vivès et al. 2008)
CGNKRTRGC	Breast carcinoma	Unknown	(Vivès et al. 2008)
SMSIARL	Prostate vasculature	Unknown	(Vivès et al. 2008)
FQHPSFI	Hepatocellular carcinoma cell line	Unknown	(Vivès et al. 2008)
NGR	Tumor neo vasculature	Amino peptidase-N	(Vivès et al. 2008)
VHSPNKK	Endothelial VCAM-1-expressing cells	VCAM-1	(Vivès et al. 2008)
RRPYIL	Adenocarcinoma cells	Neurotensin receptor	(Vivès et al. 2008)
EDYELMDLLAYL	Various carcinomas	Unknown	(Vivès et al. 2008)
LTVSPWY	Breast carcinoma	ErbB2	(Vivès et al. 2008)
ATWLPPR	Tumor neo-vasculature	VEGF receptor	(Vivès et al. 2008)

mediated motility (RHAMM), trans-membrane protein layilin, hyaluronic acid receptor for endocytosis (HARE), lymphatic vessel endocytic receptor (LYVE-1), and intracellular HA-binding proteins such as CDC37, RHAMM/IHABP, P-3, and IHABP4. Various tumors such as epithelial, ovarian, colon, stomach, and acute leukemia overexpress HA-binding receptors (CD44 and RHAMM). Therefore, delivering a cytotoxic agent-conjugated HA can provide a non-toxic and tumor-targeting prodrug. The higher concentration of HA in cancer cells form a less dense matrix; thus, the motility of cancer cells enhances achieving the invasive ability into other tissues. HA also provides an immune-protective coat to cancer cells (Jaracz et al. 2005).

Application of HA in drug/gene carrier has its own advantages due to some specific features of HA, such as biocompatibility, biodegradability, non-immunogenicity of HA-conjugated nanoparticles, mediating specific and efficient drug/gene delivery to site of interest (Zhong et al. 2015), enhancing bioavailability by increasing the water solubility of low soluble or insoluble drugs, and protecting drugs from deactivation during circulation (Dosio et al. 2016). The HA-containing DOX liposomes showed better cytotoxicity than the drug alone and more than two orders of magnitude better activity than non-targeting liposomes against B16F10 melanoma cells (Jaracz et al. 2005). Hyaluronic acid electrostatistically attracted to the surface of liposomal formulation of paclitaxel exhibited higher cellular localization (Ravar et al. 2016). Hyaluronic acid (HA)-modified RNase A (RNase A-HA) nanocomplex with cationic lipid-like molecules (lipidoids) carriers resulted in targeted inhibition of cancer proliferation via interaction with overexpressed CD44, increasing the supramolecular interaction with carrier lipidoids and promoting protein encapsulation efficacy due to modification with HA (Wang et al. 2017b).

Aptamers

Aptamers are long single-stranded structured oligonucleotides (DNA or RNA) with three-dimensional conformations that can bind to a wide range of targets (apatopes) with high affinity and specificity. Therefore, aptamers can increase the therapeutic efficacy in cancer treatments as a targeting moiety in nanodelivery systems. The charge of the nanoparticle surface is very important for conjugation to aptamers due to their negative charge. Aptamers also known as "chemical antibodies" have more advantages in comparison with traditional antibodies such as smaller size, low immunogenic potential, easier to synthesize and modify in vitro, higher affinity and specificity, structural flexibility, and stronger stability. The limitation of using aptamers as targeting moieties is their degradation by intracellular nucleases. To overcome this limitation, non-natural bases such as LNA (locked nucleic acid) can be used. Various chimeras such as aptamer–aptamer, aptamer–siRNA, aptamer–miRNA, aptamer–enzyme, aptamer–antibody, and aptamer–drug have been established. All of these chimeras showed better stability and functional capability than the parent molecules. The most characterized chimeras are the aptamer–siRNA chimeras (Kanwar et al. 2011).

PSMA is a cell-surface receptor overexpressed in prostate cancer cells and tumor vascular endothelium. In a research, an aptamer–siRNA chimera was developed. The aptamer portion had affinity for binding to PSMA, and the siRNA portion targeted the expression of tumor survival genes polo-like kinase 1 (Plk1) and BCL-2 (Zhou 2010). In another study, the aptamer targeting PSMA was conjugated to small hairpin RNA (shRNA) against anti-apoptotic factor BCL-XL and doxorubicin into a polyplex of (PEI-PEG) for specific delivery to prostate cancer cells (Kim et al. 2010). Paclitaxel was incorporated into the PLA–PEG copolymer which was then attached to A10 PSMA aptamer, and it showed efficient uptake in human prostate cancer cells (LNCAP and PC3) (Tong et al. 2010). The anti-gp120 aptamer–siRNA chimera was developed in which both aptamer and siRNA had potent anti-HIV activities and provided more potent inhibition of HIV infectivity (Zhou et al. 2008). An RNA aptamer, having binding ability and inhibitor of the tyrosine kinase receptor Axl (GL21.T) expressed on non-small cell lung cancer (NSCLC) cells, was utilized as a means to deliver miR-212 leading to inhibition of anti-apoptotic protein PED/PEA-15 in human NSCL cells. The results demonstrated efficient delivery of miRNA due to the cell-targeting function of GL21.T aptamer (Iaboni et al. 2016).

Intracellular delivery

One of the ways to achieve maximum therapeutic effect and minimum side effects is organelle-specific delivery such as nucleic acids to the nucleus, pro-apoptotic compounds to the mitochondria, or lysosomal drugs and

enzymes to the lysosomes. However, a major challenge is intracellular trafficking of bio-agents to organelles of interest. To overcome this problem, modifying nanocarriers with organelle-specific ligands can improve the intracellular targeting to achieve efficient delivery (Biswas et al. 2012).

Mitochondria-targeted delivery systems

Mitochondria are intracellular organelles that maintain cellular calcium homeostasis, produce ATP for cellular energy via oxidative phosphorylation, play a role in the production of reactive oxygen species, and participate in the intrinsic apoptosis pathway, tricarboxylic acid cycle, and fatty acid metabolism. (Biswas et al. 2012). Mitochondrial dysfunction has been linked to a variety of diseases including neurodegenerative and neuromuscular disorders, cancer, cardiac ischemia–reperfusion injury, metabolic diseases such as diabetes and obesity, and chronic autoimmune inflammatory diseases. Therefore, the ability to target therapeutics to mitochondria may represent new developments for the effective treatment of mitochondrial-related diseases and minimize side effects associated with present therapeutic molecules. As mitochondria are a key regulator in programmed cell death, targeting mitochondria for inducing apoptosis or delivering chemotherapeutic anti-tumor agents can promise a novel treatment in cancer.

Delocalized lipophilic cations (DLC)

Studies have found that DLCs are potential agents capable of localizing in mitochondria. This observed phenomenon is proposed to be grounded on the assumption that DLCs have interactions with highly negatively charged mitochondrial membranes resulting in disturbance in integrity of membranes leading to mitochondrial localization. Conjugation of DLCs with nanocarriers such as liposomes, poylmers and dendrimers develops new drug delivery systems targeted to mitochondria, enhancing the therapeutic effects of drugs in mitochondrial dysfunctions (Chen et al. 2016).

Triphenylphosphonium (TPP) is a common example of DLCs, an amphiphilic cation, which accumulates within the mitochondria at the concentration of a hundred fold greater compared to the cytoplasm. Lipophilic nature and delocalized positive charge allow TPP to accumulate efficiently by permeating through membrane hydrophobic bilayers of mitochondria that have large negative potential (Chen et al. 2016). It has been demonstrated that TPP conjugates have low toxicity and a high level of uptake in vivo even to cross the blood–brain barrier (BBB) (Rin Jean et al. 2014). Dequalinium (DQA) is also a delocalized lipophilic cation that accumulates in mitochondria. In aqueous medium, its amphiphilic nature promotes liposome-like structures known as DQAsomes with a positively charged surface that provides high encapsulation ability of negatively charged APIs (Wen et al. 2016; Yu et al. 2013).

Dendrimers

Poly (amidoamine) (PAMAM) dendrimers are very relevant nanocarrier candidates for mitochondrial delivery due to their large density of surface functional groups with highly positive charge that can interact with mitochondria membranes. TPP can conjugate to PAMAM dendrimers in a direct way or through a flexible linker such as PEG (dendrimer–PEG–TPP). The direct conjugation of anti-cancer drug–TPP to dendrimers has been recently demonstrated as a potential strategy to fight multi-drug-resistant cancers (Wen et al. 2016). In a research, a mitochondria-targeted nanocarrier "PAMAM dendrimer-G (5)-acetylated-TPP" was developed. Conjugation of the TPP molecule with the surface of PAMAM dendrimer-G (5) (de Groot et al. 2017) expressed a mitochondria-targeting property and acetylation of dendrimer neutralized the positive charge on the surface resulting in lower toxicity. This non-toxic nanocarrier exhibited an efficient vehicle for delivery of bioactive agents loading in dendrimer by electrostatic interactions or surface conjugation (Biswas et al. 2012). In another study, PAMAM (G5)-TPP conjugated nanoparticles exhibited mitochondrial localization for microRNA let-7b delivery in NSCLC cells (Maghsoudnia et al. 2020).

Aptamers

Aptamers appear to have the potential to deliver APIs to mitochondria as well. Recent studies provide compelling evidences that RP aptamer is able to target mitochondrial membrane efficiently. Harashima et al. reported a novel dual-ligand liposomal carrier composed of octaarginine (R8) and RP aptamer (RP/R8-modified MITO-Porter) to take advantage of both these ligands

in cell transfection. Since previous efforts for mitochondrial targeting seemed to suggest that employing RP aptamer alone does not meet the need of sufficient intracellular delivery; therefore, octaarginine (R8) was also used to enhance the cellular uptake and also function as a mitochondrial-targeting peptide through electrostatic interactions with negatively charged mitochondria membranes. The obtained NPs seemed to efficiently localize in mitochondria that could be a promising drug delivery system for further studies (Yamada et al. 2016).

Mitochondria-targeting peptides (MTPs) and mitochondria-penetrating peptides (MPPs)

Proteins that are synthesized in cytosol are transported into mitochondria through a cleavable N-terminal targeting sequence known as mitochondrial targeting signal peptide (MTS) that is recognized by the mitochondrial import machinery. Therefore, a variety of molecules including nucleic acids, proteins, and endonucleases can be delivered by the mitochondrial import machinery due to conjugating with MTS effectively (Chen et al. 2016). Combining cell-penetrating peptides as a short cationic oligopeptide composed of histidines and arginines (H3R9) to MTS has demonstrated much facilitated intracellular uptake and localization to mitochondria (Yu et al. 2013). Flierl et al. combined an N-terminal mitochondrial-targeting peptide covalently to a peptide nucleic acid (PNA), encoding a portion of the sequence to be introduced into the mitochondria. This targeting peptide–PNA conjugate then was recombined to an oligonucleotide that was delivered efficiently to mitochondrial matrix both in vitro and in vivo (Chen et al. 2016).

Mitochondria-penetrating peptides (MPPs) possess both lipophilicity and cationic charges due to presence of cationic (lysine and arginine) and hydrophobic (phenylalanine and cyclohexylalanine) amino acids (Lu et al. 2016). Several studies have supported this function of MPPs and have taken advantages of these peptides to deliver anti-cancer drugs within mitochondria, especially the ones that interact with mtDNA such as chlorambucil, doxorubicin, and cisplatin (Fonseca et al. 2011; Wisnovsky et al. 2013; Chamberlain et al. 2013).

Miscellaneous

It is founded on gathered data from some studies that guanidinium-based molecules demonstrate cell permeability ability and a tendency for mitochondrial localization (Lu et al. 2016). In one study, gamitrinib which possesses 1 to 4 tandem repeats of cyclic guanidinium was investigated for its effect on inhabitation of Hsp90 network in mitochondria. It accumulated significantly in the organelle indicating the role of guanidine in localization of APIs in mitochondria (Kang et al. 2009).

Other studies also have found small molecules with affinity for mitochondria such as sulfonylureas, anthracyclines, benzodiazepines, resveratrol, KLA (KLAKLAKKLAKLAK) and porphyrin-based systems. KLA (KLAKLAKKLAKLAK), mitochondria membrane disrupting peptide, was combined by a cell-penetrating domain R7 (RRRRRRR). This potent cytotoxic peptide (R7-KLA) induced rapid apoptosis and cell death both in vitro and in vivo, therefore it can be potentially used as an anti-tumor agent. In another study, a cell-targeting peptide (RGD) was attached to KlA and growth of breast carcinoma was reduced effectively in vivo. Anti-HER-2 peptide was also attached to KLA in order to target HER-2-overexpressing human breast cancer cells specifically and it showed efficient internalization in mitochondria both in vitro and in vivo (Law et al. 2006).

Recently a liposome-based nanocarrier, designed for delivering therapeutic agents into mitochondria, known as MITO porter, has attracted researchers' attentions. Some additional modifications on it were also investigated to aim higher localization in the organelle. In one study for instance, the conjugation of R8 on the MITO porter led to a better cell uptake and following mitochondrial localization (Yamada et al. 2011). Genistein (Gen) is a soy isoflavone that induces mitochondrial damage by opening mitochondrial permeability transition pore (mPTP) leading to mitochondrial depolarization and influx of solutes resulting in outer membrane damage and activation of intrinsic apoptotic pathway markers including cytochrome c and caspass-9. There are some studies that genistein was incorporated in nanoformulations such as micelles and nanoemulsions for specific delivery to mitochondria and resulted in targeted accumulation in mitochondria and enhanced cancer cell inhibition (Pham et al. 2013).

Mitochondrial targets

Taking everything together, mitochondrial drug/gene delivery seems to be a novel solution to most of our unsolved problems since the functions of mitochondria are diverse to the extent that the footmarks of this organelle can be seen in cancers, neurodegenerative diseases, and metabolic disorders. Mitochondrial targeting offers some advantages such as (Freimann et al. 2018) (1) appropriate drug delivery systems could lead to minimized off-target effects, brightening the hope of killing cancer cells without harming normal cells (Amadou et al. 2010), and (2) providing new approaches to treat diseases, especially when it comes to cancer therapy, various mechanisms of killing tumor cells is a critical issue to prevent drug resistance as mitochondrial delivery is a novel mechanism with possible huge curative responses (Rin Jean et al. 2014).

Mitochondria consists of two bilayer membranes: the inner mitochondria membrane (IMM) and the outer mitochondria membrane (OMM); therefore, two spaces including the inter-membrane space (IMS) and mitochondrial matrix (MM) exist in this unique organelle (Wen et al. 2016).

Outer mitochondria membrane (OMM)

Several targets are presenting on OMM including protein translocators, pore-forming proteins, and fission and fusion proteins of mitochondria encoded by nucleus and produced by cytosolic ribosomes. Voltage-dependent anion channels (VDAC) are protein-based channels in OMM that transport molecules to IMS non-specifically. The roles of VDAC can be summarized as follows: (1) providing a platform for interaction of pro- and anti-apoptotic members of B cell lymphoma-2 (BCl-2) family that are overexpressed in various cancer types, (2) releasing cytochrome c in the apoptosis process, (3) contributing enhanced cholesterol contents in cancer cells compared to normal cells (Wen et al. 2016)), and (4) controlling uptake of Ca^{2+} from cytosol to mitochondria and release of ROS from mitochondria to the cytosol (Luo 2013; Suleiman and Griffiths 2001). Another target on OMM is the BCl-2 family that consists of both pro- and anti-apoptotic proteins controlling permeabilization of mitochondrial membranes, thus indirectly regulating the programmed cell death. Many cancer cells take advantage of anti-apoptotic effects of the BCL-2 protein family by overexpressing them. Therefore, occupying the active site of the BCL-2 protein family might open avenues to a better therapy against cancer (Wen et al. 2016). Based on a theory presented in some reports, one of the mechanisms of atherosclerosis is the disruptive internalization of cholesterol from OMM to IMM. Mitochondrial cholesterol transporter steroidogenic acute regulatory protein also known as StAR is the main player in this process as it binds to cholesterol letting it cross the membranes. Thus, StAR might be a candidate in finding a solution to atherosclerosis (Korytowski et al. 2014).

Inner mitochondria membrane (IMM)

High protein to phospholipid ratio in IMM restricts the entrance of molecules into the matrix which might be an obstacle in mitochondrial delivery (Wen et al. 2016). Considerable attention has been paid to IMM and its compartments including electron transport chain (ETC), metabolite transporters such as the adenine nucleotide translocase (ANT), mitochondrial calcium uniporter (MCU) and ATP synthase which are all critical for cell normal functions. Oxidative damage to electron transport chain (ETC) can be either a cause of a disease or a hope to survive; to more clarify, epileptic seizures as an example, which the abnormal function of complex 1 was reported or cancer as an instant, that the ETC dysfunction may be a way to kill tumor cells (Wen et al. 2016).

Mitochondrial matrix (MM)

MM contains various molecules such as ions, proteins, enzymes of the Krebs and fatty acid cycles, ribosomes, and mtDNA. However, to the authors' best knowledge, very few publications can be found on this subject which makes it hard to reach a precise conclusion. Among these publications, one reported the use of MitoQ to mimic the endogenous antioxidant CoQ10 since it is well established that CoQ10 can accumulate in mitochondrial matrix. Thus, MitoQ can be a mitochondria-targeted antioxidant candidate to deliver the intended APIs and NPs to the mitochondrial matrix (Wen et al. 2016).

Regarding what was mentioned above, mitochondrial drug/gene delivery faces its own challenges such as the following: in order to reach the mitochondrial

matrix, first, the delivery system has to cross the cell membrane which itself alone is an end for many studies. Additionally, the inner membrane of mitochondria is excessively hydrophobic and possesses a strong negative charge (− 180 mv), making the transfection of many drugs tedious entailing specific modifications to overcome the challenge (Yu et al. 2013).

Nucleus-targeted delivery systems

Treatment efficacy of diseases by novel methods would be enhanced greatly by the efficient transport of materials such as drugs or nucleic acids to living cell nuclei where gene transcription and DNA rearrangements take place in the cell (Alexander et al. 2003). Notably, as many anticancer drugs induce cell apoptosis by DNA damage or inhibiting topoisomerase involved in DNA replication, they have to localize in the nucleus but only a very low percentage of drugs can finally reach the nucleus due to many intracellular drug-resistance mechanisms. To overcome this problem, nuclear delivery is an effective approach for enhancing the therapeutic effect of cytotoxic drugs (Zhou et al. 2009). A targeted nuclear delivery system should have a tendency to localize within the nucleus and be small enough (< 30 nm) to cross the nuclear membranes that is a critical limiting step (Alexander et al. 2003). Among various approaches for nuclear targeting, two most widely strategies of nuclear delivery systems are described here as efficient nucleus targeted drug/gene carriers.

NLS-mediated nuclear-targeted delivery

Nuclear-localization signals (NLSs) are basic amino acids that can be used to deliver various molecules (genes/drugs) from the cytosol to the nucleus (Zhou et al. 2009). Many studies since today have provided evidences that NLSs can efficiently localize in the nucleus. PEG-NLS nanoparticles loaded with carboplatin analogues were investigated for anti-tumor responses in wild-type M109 cancer cells. The NPs showed high localization within the nucleus and efficientcytotoxic effects in tumor cells (Olga Aronov et al. 2004). In one study, NLS was conjugated to psoralen in order to non-covalently attach to DNA molecules and the results indicated that conjugation of NLS could significantly increase nuclear localization of DNA molecules (Yoo and Jeong 2007). NLS was also incorporated to PAMAM dendrimers containing DNA molecules. As the obtained NPs (PAMS/DNA/10NLS) enter the cytosol, the NLS particles contact with importins facilitating the efficient accumulation of NPs within the nucleus (Chen et al. 2017b).

However, it should be taken into account that since NLS peptides usually consist of positively charged amino acids such as lysine and arginine, they possess strong non-specific interactions with negatively charged cell membranes resulting in serious side effects in vivo (Sui et al. 2011).

Cationic polymeric-based nuclear-targeted delivery

Cationic polymer nanoparticles such as poly (ethyleneimine) and poly (L-lysine) (PLL) have the ability to localize in the nucleus. However, they also cannot be used in vivo for targeting the nucleus because of non-specific cellular uptake, high interaction with negatively charged blood components, recognition by the immune system, and rapid elimination from the plasma compartment. If there was a smart polymer which can mask its surface charge and regenerate it within the cancer cells, it would be considered as an ideal nuclear delivery system (Zhou et al. 2009). In one attempt for instant to smarten the delivery system, PLL's positive charges were masked by converting them to latent amides. When amidized PLL was transferred to the cell lysosomes, the amines were regenerated by amides' pH-dependent hydrolysis and, thus, the PLL's nuclear-localization ability was recovered (David et al. 1998).

Challenges and opportunities

The advent of nanotechnology has broadened the potential options in the effective treatment of diseases. Modern technologies along with developments in material science offer several approaches, each possessing itself advantages and limitations. Among the available options, polymers, liposomes, dendrimers, and inorganic delivery systems might be exploited to serve multiple functions as improving physicochemical properties of the therapeutic or diagnostic agent, specific targeting of the selected agent to the sites of interest, using lower doses of the drug, and reducing side effects (Eftekhari et al. 2019; Samimi et al. 2019; Pillai 2019). However, as was the case with many new technologies, the

emerging field of drug delivery faces some practical limitations. Regarding safety as an instance, many nanocarriers employed in delivery systems lack an acceptable safety profile to be clinically evaluated while the matter is one of the vital criteria for approval consideration by regulatory bodies. Attempts to reduce intrinsic toxicity of many nanocarries often result in considerable loss of activity of the therapeutic agent against cancer cells. Physical and chemical features of the NPs play a critical role in their toxicity. Among which, size, shape, surface charge, and stability determine a considerable part of the intrinsic toxicity of a given DDS. The surface area and size of the NPs largely affect NP interaction with living systems. In comparison with the cell membrane with thickness of about 10 nm, NPs ranging from 1 to 100 nm can easily enter cells and cell organelles. NPs with sizes less than 10 nm are able to penetrate the cell nucleus intercalating between DNA base pairs (Huo et al. 2014). Moreover, NPs with the same size and cationic nature can interact with the negatively charged DNA backbone and interfere with the natural transcription process (Soenen et al. 2011).

One of the most practical approaches to control toxicity is adjusting the administrated dose. The toxicity profile of many DDS revealed a dose-dependent cytotoxicity and genotoxicity. This strategy might be the perfect one in the case of aluminum-based NPs as reported by one study that aluminum oxide NPs with N/P ratios of 400 or lower had no significant effect on mammalian cells (Radziun et al. 2011). Regarding gold NPs, the toxicity can be controlled using a suitable stabilizer as well as the sequence of the employed cationic/anionic side-chains (Boisselier and Astruc 2009; Goodman et al. 2004). Silver NPs can pose severe risk to human body. Studies have shown that application of silver NPs can result in production of reactive oxygen species and lactate dehydrogenase leakage, both are proposed to damage various organs, including spleen, kidney, lungs, liver, and brain (Tang et al. 2009). However, a dose-dependent toxicity profile of functionalized silver NPs has been reported in the literature. Coating silver NPs with polysaccharides for example, resulted in significant reduction in cytotoxicity (Miao et al. 2009). Zinc oxide and iron oxide NPs also demonstrated a decrease in cell viability on variety of cell lines (Bahadar et al. 2016).

Size of NPs significantly affects pharmacokinetic parameters of the NPs including their distribution and accumulation within the tissues (Zhang et al. 2015). Larger NPs with size of more than 50 nm are largely found in blood, liver, and spleen while smaller NPs can rapidly reach all organs and tissues within the human body. This highlights the role of RES in clearance of larger NPs. Shape of the NPs is also connected with toxicity issues. It is reported that NPs with spherical shape are more dependent on endocytosis for cell entry (Champion and Mitragotri 2006). Compared with spherical fullerenes, carbon nanotubes are found to more specifically block calcium channels (Park et al. 2003). Thus, changes in NP size and shape significantly contribute to the overall efficacy and efficiency of the DDS.

It is well evident that surface charge is directly connected with toxicity, since interaction of NPs with biological systems are highly dependent on surface charge (El Badawy et al. 2011). Dendrimers could target negatively charged cell membranes as they are highly positive charged and induce cell toxicity. Surface charge can be modified by grafting various ligands and polymers such as PEG. NPs modifications can be employed for enhancing physicochemical properties of DDS as well as improving toxicity profile of the NPs.

As per manufacturing process, scaling-up of some delivery systems demand a range of complex expensive processes casting doubts on cost-effectiveness of the designed product. Regulatory challenges associated with drug delivery systems might play as another obstacle in the way of their commercialization. Physicochemical control of drug delivery systems needs establishing sufficient stability data as well as clear determination of final product specifications to cover all the quality aspects, which are critical for clinical outcomes. Currently, pharmaceutical companies, scientific societies, and regulatory bodies are collaborating to define a rational transformation process from the conventional therapy to the almost newly emerged “personalized medicine”; the process might remarkably pave the way for drug delivery systems’ commercialization. Despite these obstacles, a number of currently marketed nano-based medicines such as Abraxane®, Caelyx®, and Myocet® and some other nanosystems currently being investigated in clinical studies suggest the high potential of this field in the treatment of cancer (Jain et al. 2016). As a last remark, it should be taken into account that the superior current position of the conventional medicines over nanomedicines (as not in all, but in many diseases) stems from decades of researches and owes to the numerous attempts by researchers and clinicians; therefore, the continuing efforts in the field of drug delivery might brightens the future of diseases cure.

Conclusion

Nanotechnology indeed has changed significantly the way we think about medicines and, in general, therapeutic agents. Armed with thousands of empirical experiences and a great number of evidences, we are now courageous enough to rationally design the NPs targeting the intended cells and tissues. Not to mention about tedious battlefield patients with cancers are having to fail their disease, it is indeed of great account to think up medicines with specific delivery, lower prescribed dose and much higher efficacy, all the things that nanotechnology seems to be capable to provide us. Studies and researches more than ever appear to suggest that the dream of safe, effective, and targeted delivery systems can be real. Several strategies have been used to date in designing an appropriate delivery system. Biodegradability and biocompatibility are of great importance in the field of drug/gene delivery, since today, many approaches have been proposed to design safer delivery systems, as a simple one is to employ biodegradable and biocompatible carrier and a smarter one is to conjugate several agents to have a combination with acceptable toxicity profile. By attaching biodegradable and biocompatible ligands or coating the core carrier by a safer option, it might be possible to have more feasible NPs.

Moreover, controlling NP properties such as shape, size, surface charge, and stability that have significant effects on toxicity of the desired delivery system could open another way in creating prospered DDS.

Targeting the cells and tissues of interest has huge advantages such as lower needed dose, higher efficacy, reduced toxicity, and improved response to treatment. Drug delivery to inner cellular organelles is of the most novel subject in the field of drug delivery that seems to be a promising way in the treatment of many diseases. Considering aspects of nanotechnology, it seems logical enough to say that this nano-sized world has had a significant effect in medical sciences.

Acknowledgments None declared.

Compliance with ethical standards

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

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