Chapter 5
Nanomaterials for Drug Delivery

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Abstract Nanotechnology in medicine and drug delivery are currently investigating many nanomaterials for drug delivery. Several nanomaterials have been approved for medicinal use and treatment of life threatening diseases. Nanomaterials have applications from binding to the right target to the delivery of drug molecules at the target site. Nanomaterials are the potential candidates in site specific delivery due to their unique properties, size and shape. There versatile use brings an attention to know more about their size, shape and different chemical behavior. The detailed study can direct the ongoing research in a manner to know the potential hazards of nanoparticles (NPs). Several formulations include size and surface characteristics, chemical and physical interactions, increase in permeability, retention effect and other major influencers have been taken into account in development strategies of drug delivery methods. Nano materials may or may not be soluble in biological matrices and can lead to toxicity, thus cell toxicity majorly influence the potential exposure to biological systems. For NPs, the small size allow access to thin and very narrow cellular components such as a need of potential NPs to cross the blood brain barrier. A multitude of substances are recently under study for drug delivery applications such as liposomes, gene based conjugated materials, polymers micelles etc. Various research efforts have been safe and efficient in using NPs drug delivery methods. This chapter provides recent research protocols used along with different conjugation methods. Chemically modified nanomaterials and their derivatives used in drug delivery research are also discussed to evaluate the usefulness of these systems in delivering the bioactive molecules.

Keywords Nanostructures • Biomedical Applications • Drug delivery

1 Introduction

Nanoparticle (NPs)-based platforms for gene therapy and drug delivery are gaining popularity for treatment of various life threatening diseases. Cutting edge research and limitless efforts in development of drug delivery systems have gained

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success from conventional chemotherapy to the most recent research methods. There were times when only a fraction of the administered drug was reaching the tumor site or cancer cells and several other limitations such as nonspecific biodistribution and site specific targeting, lack of water solubility, poor oral bioavailability and low therapeutic indices. All these limitations have been addressed for rapid progressing and improvement due to novel drug delivery methods. For successful translation of developed formulations, it was imperative to evaluate the design and properties of these NPs. There have been many research studies done to improve circulation time, retention effect, reduce cell toxicity and enhance biocompatibility [1].

The "theranostic properties" associated with NPs have shown enhanced delivery of therapeutic drugs with superior imaging capabilities, minimal toxicities, enhanced drug delivery, efficient tumor targeting, treatment monitoring, and diagnostics. Such methods were categorized under passive mode of drug delivery systems. Other than passive methods, active targeting strategies involve other therapeutic chemical compounds and antibodies in conjugation with nano particles to increase drug loading capacity and efficiency in drug delivery without altering properties of therapeutic agents. Certain drugs on administration are always challenged and often encountered by the body defense mechanism. Certain limitations such as cell toxicity are always remain a challenge in not only conventional methods but also for the newer molecularly targeted therapeutics [2].

NPs with the help of combined active and passive strategies i.e. conjugation of drug with other chemical carriers resulted into multifunctional benefits, facilitated personalized and tailored many treatment. Chemical therapeutic agents have been able to distinguish between normal to diseased cell with the help of these conjugated methods. These conjugated NPs can increase retention time and also avoid increasing cell toxicity. Encapsulation is another effecting strategy of drug delivery in which NPs are encapsulated under the endosomes via receptor mediated endocytosis to avoid recognition and elimination by body defense mechanism. In this chapter, we will discuss recent novel NPs in drug delivery methods and there characteristics with some applications in improving therapeutic efficiency and function in life threatening diseases treatments [1, 2].

Nanomaterials are biomaterials used in tissue engineering and as a drug delivery channels. Developing surface engineered materials can enhance major properties which can favor the interaction of biological system with the biomaterial. Nanomaterials are categorized into nano-structured and nano-crystalline materials. Nano-structured materials are shaped raw nanomaterials with their unique functionalities for example, quantum dots, dendrimers, fullerenes and carbon nanotubes. In contrast, nano-crystalline materials are non-polymer materials which are highly demanded for their small size and wide surface area with biocompatible characteristics. Nanostructure materials are further distinguished into Polymer and Non-polymer forms [3].

Transferring genetic materials into the affected cells for treatment through inducing artificial expression of associated proteins is fast gaining acceptance in drug

delivery systems. Nucleic acid based therapies use DNA and RNA as a drug. However, issues with cellular uptake, quick biodegradation and escape, poor stability associated with these biomolecules can limit the use in clinical trials. Though recent research efforts have combine the viral and non-viral vectors to overcome these limitations [4].

2 Inorganic-NPs

2.1 Carbon Nanotubes

Carbon based tubular structures with benzene ring are main constituent for biological application applied in sensors for detecting DNA, RNA and other biomolecules. They are hexagonally shaped branched network of carbon atoms varying from the size 1 to 100 nm. These branched networks are made of layer of graphite which are rolled into cylindrical form. Carbon natures are of two types-single walled nanotubes (SWNTs) and multi walled nanotubes (MWNTs). The size, geometry and surface features increase their demand for carrying different proteins from serum samples and delivery [5]. CNTs are completely insoluble in all solvent. They are also needed to treat for reducing cell toxicity. They are directed by endocytosis for cellular uptake or by insertion through the cell membrane. In the recent novel study, PEGylated multi wall carbon nanotubes (MWNTs) based drug delivery method was developed using both physical and chemical method. This method was applied for loading of Ibuprofen drug. Further, surface was modified with the use of several acylated groups. Cytotoxicity of PEGylated MWNTS were examined by MTT assay. The results showed improvement in drug loading by both physical and chemical based methods, though chemical loaded MWNTs showed more clear release of drug in comparison to the physically loaded one and could be used as a controlled release system for various drugs [6].

SWNTs have advantage over metallic NPs as they include high drug loading capacity, intrinsic stability, easy surface modification which can enhance circulation time and also bioavailability of the drug molecules [7]. They have been successful in delivery of nucleic acid [8–10], proteins [11, 12] and drug molecules [9, 13–15]. On conjugation with antibodies and low molecular weight targeting agents, they have high efficiency for nanotube internalization into cells. They also have higher loading capacity and allow incorporation of targeting agents in such a way that they can deceive the evading system of body [16, 17].

CNTs are usually needed in gene and other biomolecules delivery. A technique of molecular dynamics made it more convenient by inducing small molecule transportation with the help of flowing water and surface—functionalized carbon nanotubes. It has become an important tool in gene therapy. The antibody linked to the nanotubes are easily encapsulated into mammalian cells without producing any

toxic effects in comparison to the naked antibody delivery methods [18]. The most recent research used polyethylenimine (PEI) with polyethylene glycol (PEG) linker to the carboxylated single-walled carbon nanotubes (SWNT) to facilitate delivery of shRNA. This whole molecule was attached with an aptamer AS1411 along with DOX to test targeted tumor cells. These tumor cells showed strong selectivity towards the whole conjugation and inhibited growth of nucleolin-abundant gastric cancer cells. Also, they found very less amount of DOX which is favorable condition for cells as the toxicity is reduced [19].

Drug loading can be external and internal or can be active or passive. Active targeting requires functionalization with tumor specific binding sites to selectivity bind to tumor cells. Passive targeting depends on the inertness and physical size of the macromolecule. Van der Waals forces hold internalized or encapsulated for insertion into the CNT. This is the best way to keep the drugs protected from the external environment [20]. CNTs have major advantages in reducing cell toxicity, increased circulation time, active targeting circulation and reduced side effects. There are many applications on different drugs which were administered in conjugation with other molecules such as PEG and Folate (Table 5.1)

Table 5.1 Drugs delivered using CNTs

Name of drug	Modification/Functionalization	CNTs	Advantage
Doxorubicin	PEG conjugation	SWCNT	Reduced toxicity
Mitoxantorne	PEG conjugation	SWCNT	Reduced toxicity
Paclitaxel	PEG conugation	SWCNT	Increased circulation time
Carboplastin		SWCNT	
Cisplatin	Non functialized	SWCNT	Decreased toxicity
Doxorubicin	Conjugated with folate	MWCNT	Active targeting
Paclitaxel	Folate conjugate	MWCNT	Increased circulation period
Methotrexate	PEGylated	MWCNT	Controlled toxicity
Quercitin	PEGylated	SWCNT	Reduced side effect
Folic acid	PEGylated	MWCNT	Active targeting circulation period
Gamicitabine	NA	SWCNTs	NA
HCPT(10-hydroxycamptothecin)	NA	MWCNT	NA

2.2 Gold NPs

Gold (Au) NPs provide novel platform for site specific drug delivery. They possess unique chemical and physical properties for releasing and loading drugs [21]. Such unique properties lead to different yet unique applications in medical field. AuNPs are found in different forms among which, bulk is a yellow solid and less reactive form otherwise they are wine red solution and are anti-oxidant in nature. These distinct characteristics of these AuNPs are due to their internal interactions [22]. The AuNPs can be easily prepared and are of size between 1 nm and 8 μm. The commonly used shapes are spherical, decahedral, icosahedral multiple twined, irregular shape, tetrahedral, nano-triangle, nano-prisms and hexagonal platelets and nano-rods (Table 5.2).

Various techniques have been employed to increase optical properties and purification of GNPS to enhance their medicinal properties (Fig. 5.1). The AuNPs are also widely used as a contrast agent in site specific delivery [25]. These particles have various applications such as biomolecules ultra-sensitive detention, cancer cells treatment, labeling of cells and proteins and delivering drugs. Surface Plasmon resonance (SPR) has been very effective method in identification of pathogens in clinical field [26]. Conjugated assemblies of GNPs with biomolecules improved loaded capabilities and make them most efficient method in gene delivery [27]. Gene used as a biomolecule in conjugation with AuNPs are used in epidermal delivery of DNA vaccines and this method is one of the most recognized in delivery of DNA based vaccines. The latest research in gene or drug laden near-infrared (NIR) absorbing Au-NPs in complex with NIR light showed special mechanism of DNA release. Researchers used plasmonic NPs complexes with continuous wave (CW) and femtosecond pulsed lasers which excited dehybridized single-stranded DNA whereas pulsed-laser excitation resulted in double stranded DNA release by cleavage of the Au–S bond. This study showed that different type of laser excitations can cause wide difference in characteristic of DNA which is bounded with the same DNA-NPs complex [23]. The vascular endothelial growth factor (VEGF) were also seen as a primary factor in preventing skin injury progression but delivery of it at injury site is challenging due to various skin barriers. By modifying surface of AuNPs and conjugate with negative surface VEGF resulted in site specific transdermal delivery [24].

Table 5.2 Shapes of Au-NPs and their applications

Shape	Size	Application
Nano rod	2–5 nm	Drug Delivery and photo thermal therapy [12].
Triangular particle	3.85–7.13 nm	Used effectively again *E.coli* strains and K.pneumonia [20]
Nano cage	50 nm	Highly effective contrast agent in endomicroscopy imaging [16] and in vivo medical applications [23].
Hollow particle	25 nm	Photo-electronics, catalysis and cancer therapy [9].
Branched particle	90 nm	Surface enhanced Raman Spectroscopy based imaging of Kidney cells [24].

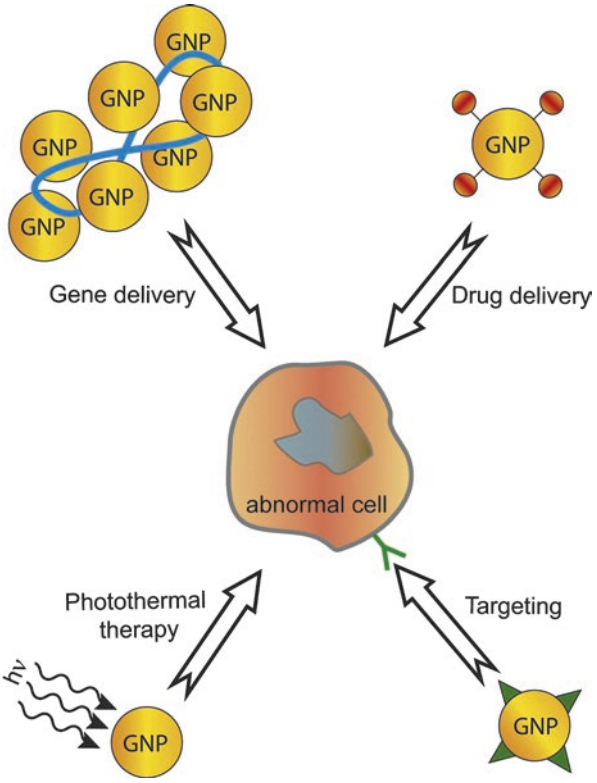

Fig. 5.1 Various biomedical applications of AuNPs

Coated Au nano-cages with temperature sensitive polymer in conjugation with near-infrared radiations further improved drug releasing capacity [28]. Colloidal AuNPs have been used tremendously due to their easy preparation and can be easily incorporated into tissues and cells due to their small size [29]. GNPs are also used in conjugation with organic molecules which drastically reduced cell toxicity. Also, on conjugation with organic molecules, the physical and chemical properties are very tunable and surface can be modified based on the requirements. GNPs are also used in analytical chemistry laboratories specifically in the tests where the native structure and enzymatic activity of attached proteins or enzymes need to be unchanged [30].

Drug delivery systems are mainly in demand due to favorable solubility, in-vivo stability and bio-distribution. The GNPs also favor unfavorable bio-distribution of some free drugs [31, 32]. Anti-tumor agents and antibiotics are the most commonly used in targeted drug delivery. The GNPs conjugated with anti-tumor drugs are paclitaxel [33], methotrexate [34], daunorubicine [35], hemcytabin [36], 6-mercaptopurine [37], dodecylcysteine [38], sulfonamide [39], 5-fluorouracil [40], platinum complexes [41], kahalalide [42], tamoxifen [43], herceptin [44], doxorubicin [45], and prospidin [46]. These conjugations were developed using simple adsorption of the drugs onto GNPs and in some cases, by using alkanthiol linkers

with drug-GNPS. The validation of these conjugated agents was done in vitro models and in vivo, in mice suffering from different types of cancer cells. The focus is never limited to therapeutic agents but also to the targeting cells in order to avoid complications and challenges after administration of the drug. Many side effects are observed of these commonly used drugs in Cancer (Table 5.3). So this drawback brought necessary focus on improvement in developmental strategies for providing better support and binding with the target cells. The target modifications also enhanced reactivity with several therapeutic agents (hydrophilic, hydrophobic and auxiliary agents etc. [47].

2.3 Silica NPs

Silica NPs due to their small size and tunable surface modification are good candidates for carrying drugs and better dispersion. Mesoporous silica (Table 5.4), such as MCM-41 and SBA-15 are solid materials which are comprised of porous structure with hundreds of empty pores (mesopores). These pores are able to encapsulate large amount of biological molecules. Silica NPs have high surface area, large pore volume, adjustable pore size, good chemical, and thermal stability. These properties

Table 5.3 Commonly used drugs with their side effects

Drugs	Cancer type	Short term possible side effects
Carboplatin (Paraplatin)	Cancers of the ovary, head and neck, and lungs	Low blood counts, confusion, nausea and hair loss
Cisplatin	Bladder, ovary and testicales	Low blood counts, allergy reaction, ringing in ears and hearing loss, fluctuations in blood erythrocytes and kidney damage.
Flururacil	Cancers of the colon, breast , stomach, head and neck	Low blood counts, diarrhea, mouth ulcers and photosensitivity
Doxorobucin	Breast cancer, lymphoma and multiplemyeloma.	Low blood counts, ulcers in mouth, nausea and heart damage.
Paclitaxel	Cancers of the breast, ovary and lung	Low blood count, allergic reactions, nausea, joint pain and numbness in fingers or toes.

Table 5.4 Types of mesoporous Silica NPs with their internal structure and pore diameter

Type	Internal Structure	Pore Diameter	References
MCM-41	2D hexagonal	1.5–3.5	[11]
MCM-41	Hexagonal structure with unidirectional	3.70′	[12]
SBA-15	2D hexagonal	6.0–10.0	[11]
SBA-15	3D cubic cage like	4.0–9.0	[13]
SBA-15	2D hexagonal	7.80	[12]
MCM-48	3D cubic	2.5–3.5	[14]

Table 5.5 List of various types of drugs delivered through mesoporous silica NPs

Classes	Drugs	Delivery agents	References
Anti-inflammatory	Ibuprofen	SBA-14	[10, 46]
	Naproxen	SBA-15	[46]
	Naproxen	MCM-4	[46]
	Naproxen	Amine-modified MCM-41	[49]
Chemotherapy	DOX	Folic-acid conjugate MSN	[47]
	DOX	DOX-hydrozone MSN-FA	[23]
	Camptothecin	Galactose-functionalized MSN	[29]
Estrogenic	Alendronate	SBA 15 with phosphorous	[48, 49]
	Alendronate	Amine modified MCM-41	[48, 49]
	Alendronate	MCM-41	[53, 54]
Antibiotics	Erythromycin	Octadecyl-functionalized SBA-15	[10]
	Erythromycin	SBA-15	[10]
	Vancomycin	CDS-capped MCM-41	[57]

make them ideal candidate for control release of drug at targeted sites as presented in Table 5.5 [48].

Mesoporous silica microspheres of micrometer was synthesized based on the Stober reaction [49]. The reaction involved the co-hydrolysis and condensation of tetraethoxysilane (TESO) and an alkyltrialkoxysilane in a mixture of ethanol, water and aqueous ammonia [50]. This resulted into micrometer-sized mesoporous silica spheres with a narrow size distribution [51]. Later, mesoporous silica nanosphere (MSN) were discovered which were more suitable for biotechnological and biomedical applications. MSN particle size is very compatible with biological agents such as bacteria which can make them efficient carriers for gene transfection or in intracellular drug delivery. It was synthesized using MCM-41 type of mesoporous silica, where TEOS was used as a silica source, a cationic surfactant cetyltrimethylammonium bromide (CTAB). MSN has an average particle dimeter of around 100 nm, surface areas around 900.2/g, pore sizes around 2 nm, pore volumes around 0.9 cm^3/g, abundant surface silanol groups (around 30 mol %), and a hexagonal porous channel structure [52].

The following unique properties of MSN have increased tremendous use in controlled release delivery applications

1. Tunable particle size—Size of the particle can be adjusted from 50 to 300 nm allowing an endocytosis without any considerable cytotoxicity [48].
2. Stable and rigid framework—MSN is more resistant to pH change, mechanical stress, heat and hydrolysis-induced degradations [45].
3. Uniform and tunable pore size—The pore size can be tuned between 2 and 6 nm [48].
4. High surface area and large pore volume—Due to high surface area (N 900 m^2/g) and large volume (N 0.9 cm^3/g), they have high loading capacities for drug molecules. The general total surface area and pore volume [48].
5. Two functional surfaces—MSN has an internal and external surface properties. These characteristics let them carry different moieties [48].

6. Unique porous structure-Many drug delivery materials have interconnecting porous structure such as dendrimers with branching porous structures and liposomes with a large void core and a porous shell [48].

MSN has been used in various shapes. Spheres, ellipsoids, rods and tubes have been seen as a good carriers for drugs delivery. Further, improvement of surface enhanced binding capacity of MSN with many drugs which also improved drug loading capacity. There are three methods: co-condensation, grafting and imprint coating method [53, 54].

The NPs prepared by microemulsion method provided inner hydrophobic core and the outer hydrophilic region. The hydrophobic core carries drug docetaxel, a chemotherapy drug while the outer hydrophilic region binds with water molecules to increase distribution of drug—NPS conjugates. Docetaxel is known to have radio sensitizing properties which makes it popular theranostic NPs in prostate cancer [28]. It is well defined that an efficient delivery system should have good loading capacity to transport the desired candidate drug without any loss of therapeutic characteristics. Any premature leakage of drug is a major challenge along with other considerable issues such as hydrolysis induced erosion of the carrier structure and require of organic solvents for drug loading that can induce undeniable modifications of the structure. Use go mesoporous silica materials offer several convenient features such as stable mesoporous structures, large surface areas, easily modified pore sizes with varying volumes and well defined surface properties for site specific drug delivery and for carrying molecules of various sizes, shapes, and functionalities [29, 30]. Recent research used hydrophobic interactions to attach lipid membrane to the surface of chlorodimethyloctadecylsilan -e-modified hollow mesoporous silica NPs. The main characteristics were uniform structure, comparable drug loading efficiency, desirable stability and strengthened controlled release. The prepared nano-vehicles Arg-Gly-Asp (RGD)-conjugated liposome showed good compatibility and low toxicity on HepG2, MCF-7 and LO2 cells. In comparison of RGD-LP-CHMSN ATO group to the free ATO, prolongation in half time and increase area under curve (AUC) were observed [55]. Another study used large-pore mesoporous silica NPs were utilized due to high loading capacity for [PtCl(en)(*N*-[acridin-9-ylaminoethyl]-*N*-methylpropionamidine)] dinitrate salt (P1A1). P1A1 is a dicationic and hydrophilic carrier for platinum-acridimide (PA) anticancer agents. This conjugation created artificial favorable pH inside the cells lysosomes and coating in phopholipd bilayers resulted in better colloidal stability. This method also caused S phase arrest and inhibited cell proliferation in pancreatic cancer. The most attractive result was that this conjugation withstand acidic environment of lysosomes vesicles into the cytoplasm [56].

2.4 Quantum Dots

Quantum dots (QDs) are semiconducting materials of size between 10 and 100 Å with other chemical characteristics such as fluorescence and narrow emission (Table 5.6). They show broad spectrum of excitation on exposure to UV rays and

Table 5.6 List of various QDs type and coating

Quantum Dot type and coating	Core/shell shape	Core/shell diameter (nm)	Expected surface charge
QD 565-PEG	Spherical	4.6	Neutral/uncharged
QD 565-amine	Spherical	4.6	Positive
QD 565-carboxylic acid	Spherical	4.6	Negative
QD 655-PEG	Ellipsoid	6 nm	Neutral/uncharged
QD-655-PEGamine	Ellipsoid	6 nm	Positive
QD 655-carboxylic acid	Ellipsoid	6 nm	Negative

also possess high photo stability. Quantum dots are nano crystals of semiconducting materials consisting of semiconductor inorganic core (CdSe) and organic coated shell (ZnS) to improve optical properties. They are heterogeneous NPs that consist of a colloidal core surrounded by one or more surface coatings. Surface coatings in single or multiple layers are applied to modify QDs as needed for experiments. Hydrophilic coatings increase solubility in a biological medium. This prevents leaking of metals from the core and bounded molecules such as receptor–ligands, antibodies, therapeutic and diagnostic macromolecules [58, 59]. The size of QDs are highly adjustable from 2–10 nm to 5–20 nm on polymerization. Particles small in size can be wiped out by renal filtration where as large size can be engulfed by the reticuloendothelial cellular system before reaching to the targeted site [60]. The recent improvement has lead drastic applications due to highly tunable sizes of QDs. Further, high surface-to-volume ratio of nanomaterials, it is possible to link multiple functional groups on single QDs while keeping the surface-volume constant. Hydrophilic materials fit well with QD such as siRNA, aptamers and can be immobilized on to hydrophilic side or amphiphilic polymer [61, 62].

They are successfully integrated in receptor mediated endocytosis, as a cancer marker, DNA hybridization, immunoassays and multiple color imaging. The outer surface of shell involves in interaction whereas core determine the color emission. These features can be modified based on the targeting biomarkers [63]. Current applications of QDs in drug delivery are focused on two major areas: QDs as carriers and labeling therapeutics or drug carriers QDs. The majority of drug carriers are Poly(lactic-co-glycolic acid) and polyethyleneimine (PEI). The QDs with LipofectamineTM 2000 was used for siRNA delivery [64]. Researchers found that amount of QD should 1:1 rations as excess of QDs can reduce the silencing efficiency whereas lower concentration can fail to detect fluorescence [57]. For antisense OD delivery, highly uniform QD-doped chitosan nano-beads for traceable siRNA delivery [65] and PEI-coated carbon nanotubes with QDs were used [66]. They improved quantification of proteins of interest by detecting their differential expression levels. They co-related their expressions with fluorescence and can be isolated using florescence-activated cell sorting and if multicolor QDs are used for screening of siRNA sequences. The potential application of QDs in drug delivery are shown in Fig. 5.2.

Most recently, for synergistic therapy, controlled drug release, magnetic hyperthermia and photo thermal therapy, combined approach using magnetic mesoporous

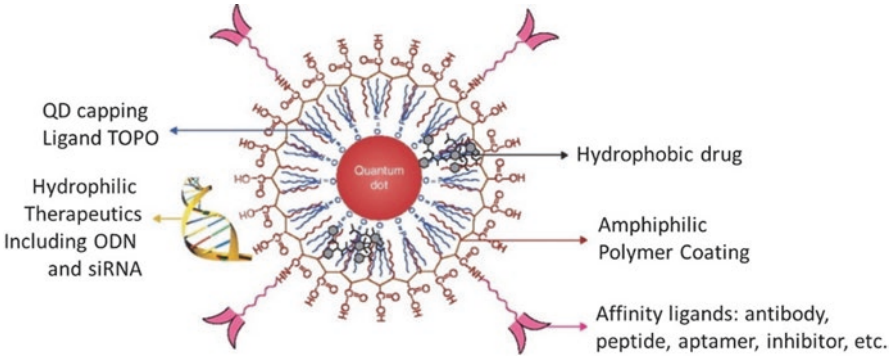

Fig. 5.2 QDs for drug delivery and therapy

silica NPs (MMSN) as drug carriers, magnetic thermos-seeds, local photo thermal generators and graphene quantum dots has been proposed. The results show that in low pH doxorubicin release can be triggered and loading of the drug can also be increased using 100 nm particle. Further, generated hyper-thermal temperature improved chemotherapy of 4T1 cells. Researchers also compared chemotherapy, magnetic hyperthermia or photo-thermal therapy when used alone, the combined chemo-magnetic hyperthermia therapy or chemo-photo-thermal therapy with the DOX-loaded MMSN/GQDs nano-system, resulted in a higher efficacy to kill cancer cells. Therefore, the MMSN/GQDs multifunctional platform has important application in cancer therapy for enhancing the therapeutic efficiency [67].

2.5 Magnetic NPs

Nano scale dimension particles, their magnetic properties and their capacity of carryon active biomolecules for specific tasks. Due to small size, such nano particles easily pass through the narrowest blood vessels and also penetrate through cell membranes if required [68]. If these particles are ferromagnetic or superparamagnetic, they can be manipulated by an external magnetic field which can further enhance efficiency in drug delivery [69, 70]. So the magnetic NPs are composed of number of components the magnetic core, the protective coating and the modified surface based on functionality. The challenge in using magnetic NPs is to bring all of these components into one system which can fit best for required therapeutic characteristics.

The magnetic core materials are Magnetite Fe_3O_4, Maghemite γ-Fe_2O_3, Iron-based metal oxides, Iron alloys and some rare earth metal alloys and transition metal clusters. The magnetite exhibits ferro (ferri) magnetic properties which has strong magnetization properties. Maghemite has the same lattice structure but all iron atoms in third oxidation states. It has 100 time stronger magnetization properties

than hematite and ferrihydrite. It is most suitable materials as it is least likely to cause health hazardous side effects. It is likely acceptable in biomedical applications [71].

The iron based NPs possess strong magnetic properties. With oxide NPs and non-permeable coatings to prevent leaching of these metals, they have been taken into a large account in biomedical applications. In conjugation with coating materials, they become highly reactive due to high surface-volume ratio. This coating also prevents leakage of toxic components into the body during in-vivo administration. Coating with natural polymers is very common [72].

Most recent formulations have administered the dry powder nano-in-microparticles (NIMs) in in-vivo targeted pulmonary drug delivery. The dry powder NIMs containing fluorescent NPs and magnetically-responsive superparamagnetic iron oxide NPs were more efficient in targeting left lung of mice [73]. Superparamagnetic magnetite NPs with temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAm) hydrogel core were prepared to enhance binding with targeting ligand. This system was further integrated with folic acid (Fig. 5.3) for targeting cervical cancer cell line (HeLa) which shown good capacity of intracellular uptake due to both magnetic properties and receptor mediate endocytosis [74]. The various linker used to modified surface of magnetic nanostructures and polymers to improve applications of magnetic NPs are shown in Tables 5.7 and 5.8, respectively.

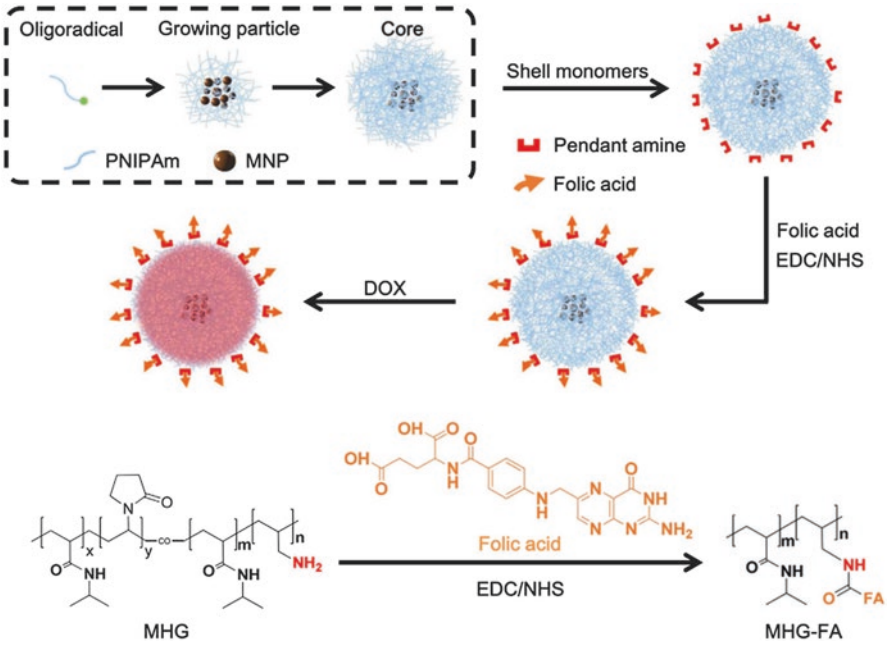

Fig. 5.3 Illustration of MHG-FA hydrogel synthesis

Table 5.7 List of various linkers used with Magnetic NPs

Linkers	Property	Target biomolecules	Examples
Amine	Positively charged	Drugs	Ibuprofen Aspirin DNA
Carboxylic acid	Negatively charged Can form amide bond with $-NH_2$ Can form ester bond with -OH	Proteins	Lysozyme Antibodies
Aldehyde	Form imide bond with $-NH_2$	Proteins	Enzymes
Thiol	-SH	Proteins	Cytochrome C Trypsin Lipase

Table 5.8 Polymer of magnetic NPs.

Polymer	Surface behavior	Applications
	Natural	polymers
Carbohydrates Dextran	Hydrophilic	Drug delivery Radioimmunoassay MR imaging Hyperthermia Tumor targeting, Mr imaging, Xray imaging
Starch	Hydrophilic	Tumor targeting, MR imaging and X ray imaging.
Proteins Albumin RGD	Hydrophilic Hydrophilic	MR imaging Fluorescent imaging and MR imaging
Lipids	Hydrophobic	Immunoassay
	Synthetic	Polymers
PEG	Hydrophilic	MR imaging Drug delivery
Polyvinyl alcohol (PVA)	Hydrophilic	Drug delivery

3 Liposomes

Liposomes are self-assembling spherical shape colloidal structures composed of lipid bilayers. The outer layer of liposomes surround a central aqueous space. Depending upon their size and number of bilayers they are classified into three basic types

1. Multilamellar vesicles—These are made of several lipid bilayers separated from one another by aqueous spaces.
2. Small unilamellar vesicles—These vesicles are consist of a single bilayer surrounding the entrapped aqueous space. The diameter is less than 100 nm.
3. Large unilamellar vesicles—These vesicles consist of a single bilayer surrounding the entrapped aqueous space with diameters greater than 100 nm.

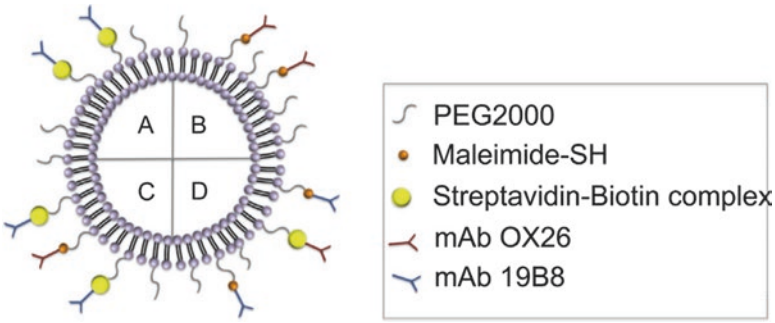

Fig. 5.4 Pegylated liposomes: (**a**) conjugated to 19B8MAb through biotin–streptavidin complex, (**b**) coupled to OX26MAb through maleimide, (**c**) coupled to both OX26MAb and 19B8MAb through, respectively, maleimide and biotin–streptavidin complex, and (**d**) conjugated to OX26MAb and 19B8MAb through, respectively, biotin–streptavidin complex and maleimide. *Colloids Surf B Biointerfaces, 2017*

Several cancer based drugs such as anthracyclines doxorubicin and daunorubicin are used for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma [75–77] with the help of liposomes PEGylated conjugation method. Immunoliposomes are actively in use for treating brain affected areas. Pegylated liposomes functionalized with two antibodies, the anti-transferring receptor monoclonal antibody (OX26MAb) and the anti-amyloid beta peptide antibody (19B8MAb) as nano-carriers of drugs for Alzheimer's disease. Fluorescence spectroscopy showed cellular take of the immunobased liposomes is more efficient if OX26MAb is used in conjugation with streptavidin-biotin complex Fig. 5.4 [78].

4 Polymer Based Nano-materials

The method of preparation for polymers based nano-material utilize entrapment of drug either physically trapped in or covalently bound to the polymer matrix [79]. Polymers used as a drug conjugates are natural and synthetic in nature. This conjugation result into the polymeric NPs (capsules), polymeric micelles (amphiphilic core/shell) or hyper branched macromolecules (dendrimers) and drug-conjugates. Polymeric NPs are biodegradable, biocompatible and well recognized for their protective nature to drug molecules. They are considered as a good source for controlled release and sustained delivery of drugs. They can be easily integrated in active and passive delivery methods of drugs. However, such drugs have always been limited due to cytotoxicity and adverse side effects. To overcome this drawback, an approach called target-specific drug delivery system (DDS) was introduced which can transport a drug to the targeted cells and tissues. To make a general efficient drug delivery system, several perquisites which are required to be incorporated are

1. A biocompatibility of a nanomaterial,
2. High loading capacity of the desirable drug,
3. No leaking or zero premature release of the drug,
4. Cell or tissue specificity and capability for site directing release,
5. Accuracy in controlled release and rate of release to achieve an effective local concentration.

4.1 Micelles

Copolymers dependent micelles are nano-sized core/shell copolymer structure in aqueous media. The hydrophobic core region offers scaffold to hydrophobic drugs and hydrophilic shell stabilizes the hydrophobic core and make association with aqueous medium to enhance drug delivery [80]. The physical and chemical interactions are the most popular reactions seen in such conjugate studies [81, 82].

Most recent research applications have utilized diamond based NPs. The large surface area of biocompatible NDs with different properties is remarkable agent for carrying therapeutic agents. It has a good loading capacity and protects attached molecular entities from disruption. It needs less amount of the carrying agents even to load drug with high concentration. The highly potential agents with good releasing and carrying capacity are in continuous demand of drug delivery methods and research protocols. Diamond NPs have advantageous applications in controlled and sustained-release delivery. They have been explored for improving delivery of therapeutic drugs and several studies showed participating of surfaces in chemical bonding [83, 84] and physical adsorption procedures [84–86]. Such physical interactions avoid the use of complex chemical reactions which are not only cost driving but also alter therapeutic activity. It has been observed that structural alterations due to chemical interactions are often challenging to meet therapeutic requirements which is more strongly handled by physical interactions by NDs. In previous studies, doxorubicin hydrochloride was studied with NDs to find potential capabilities of conjugated molecule as a drug delivery agent. The study was developed based on the interaction between carboxylic and hydroxyl group of detonation NDs which can interact with the basic group of DOX via ionic forces in presence of aqueous medium [83]. Nano diamonds form loose clusters with DOX in such a manner that small amount of absorbed DOX on the NDs surface resides within the cavity of cluster [83]. Further, on adding 1% sodium chloride in aqueous medium increased loading capacity from 0.5 to 10 wt% and removal of salt favored release of DOX molecule [83]. A lower cytotoxicity was also observed in macrophages and human colorectal cancer cells compared with the systems utilized only DOX [83]. Thus, ND based delivery systems could overcome the limitation to the use of high concentrations of chemotherapeutic drugs in cancer treatments. Another study published NDs in conjugation with 10-hydroxycamptothecin (HCPT) which shown good amount of increase in drug loading capacity.

This study also found change in pH from salivation to alkaline [87]. Such multifunctional polymeric micelles are being actively developed for carrying heavy loads and therapeutic agents [88].

4.2 Dendrimers

They are highly branched polymers of size less than 10 nm generated under controlled polymerization process. They are consists of three main components, core, branch and surface. They are very good source for active and passive delivery of bioactive agents such as gene, protein, peptide and others. They are also known for their long sustaining feature in circulatory systems. Dendrimers are made of small monomers and fabricated into converged or diverged step growth polymerization. Such polymerization can be controlled process. These structures carry cavities which are used in drug transportation. The other end of dendrimer can be used for conjugation or attachment with molecules which can tune up with the requirement [89]. Such branches can be tailored into biocompatible compounds with low cytotoxicity and high permeability towards active biomolecules. Dendrimers are good vehicles for drug delivery, gene therapy dendrimer based drug delivery, and immunoassay imaging agent.

4.3 Drug Conjugates

Polymers in drug delivery method are natural and synthetic. Natural forms are albumin, heparin, and chitosan which are very popular form of agents for the delivery of dendrimers and other macromolecules. In treatment of metastatic breast cancer, serum albumin in conjugation with paclitaxel is used [91]. Another component, Abraxen has been explored in treatment of many cancer and advanced non hematologic malignancies [92, 93]. Among synthetic polymers such as *N*-(2-hydroxypropyl)-methacrylamide copolymer, polyethylene glycol (PEG) and poly-l-glutamic acid (PGA) have been extensively utilized as drug delivery channels. PGA is the first biodegradable polymer used in conjugated applications [94]. The outcomes of various studies (Fig. 5.5) confirmed that HPMA and PEG conjugated are most popular non-biodegradable synthetic polymers [95].

5 Conclusions

With continuous demand of novel protocols in drug delivery systems, diagnose and treatments of life threatening disease, the synthesis of nano-material using biological is fast, non-toxic and biocompatible in nature. Various nano-materials have been

Compound	Name	Company	Linker	Status of development
HPMA copolymer–doxorubicin	PK1; FCE28068	CRC/Pharmacia	Amide	Phase II
HPMA copolymer– doxorubicin-galactosamine	PK2; FCE28069	CRC/Pharmacia	Amide	Phase I/II
HPMA copolymer–paclitaxel	PNU166945	Pharmacia	Ester	Phase I
HPMA copolymer–camptothecin	MAG-CPT, PNU166148	Pharmacia	Ester	Phase I
HPMA copolymer–platinate	AP5280	Access Pharmaceuticals	Malonate	Phase I
Polyglutamate–paclitaxel	CT-2103, XYOTAX	Cell Therapeutics	Ester	Phase II/III
Polyglutamate–camptothecin	CT-2106	Cell Therapeutics	Ester	Phase I
PEG–camptothecin	PROTHECAN	Enzon	Ester	Phase II
PEG–aspartic acid-doxorubicin micelle	NK911	National Cancer Institute Japan	Amide/free drug	Phase I

CRC, UK Cancer Research Campaign; HPMA, *N*-(2-hydroxypropyl)methacrylamide; PEG, polyethylene glycol.

Fig. 5.5 Polymer-anticancer-drug-conjugates tested clinically

used to enhance efficiency with the help of favorable, yet different physicochemical parameters. It seems that the nano-enabled drug delivery systems hold great potential to overcome efficient targeting of the affected cells. It is exciting to have progress in facilitating movement of drugs across barriers such as those in the brain. The challenge, to understand the fate of the drugs once delivered in-vitro and the later biological impact is still a major concern.

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