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REVIEW ARTICLE

Nanoparticles: Emerging carriers for drug delivery

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Abstract The core objective of nanoparticles is to control and manipulate biomacromolecular constructs and supramolecular assemblies that are critical to living cells in order to improve the quality of human health. By definition, these constructs and assemblies are nanoscale and include entities such as drugs, proteins, DNA/RNA, viruses, cellular lipid bilayers, cellular receptor sites and antibody variable regions critical for immunology and are involved in events of nanoscale proportions. The emergence of such nanotherapeutics/diagnostics will allow a deeper understanding of human longevity and human ills that include cancer, cardiovascular disease and genetic disorders. A technology platform that provides a wide range of synthetic nanostructures that may be controlled as a function of size, shape and surface chemistry and scale to these nanotechnical dimensions will be a critical first step in developing appropriate tools and a scientific basis for understanding nanoparticles.

Contents

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1. Nanoparticles

Conventional preparations like solution, suspension or emulsion suffer from certain limitations like high dose and low availability, first pass effect, intolerance, instability, and they exhibit fluctuations in plasma drug levels and do not provide sustained effect, therefore there is a need for some novel carriers which could meet ideal requirement of drug delivery system. Recently nanoparticles delivery system has been proposed as colloidal drug carriers. Nanoparticles (NP) are a type of colloidal drug delivery system comprising particles with a size range from 10 to 1000 nm in diameter. Nanoparticles may or may not exhibit size-related properties that differ significantly from those observed in fine particles or bulk materials (Buzea et al., 2007). The key advantages of nanoparticles are (1) improved bioavailability by enhancing aqueous solubility, (2) increasing resistance time in the body (increasing half life for clearance/increasing specificity for its cognate receptors and (3) targeting drug to specific location in the body (its site of action). This results in concomitant reduction in quantity of the drug required and dosage toxicity, enabling the safe delivery of toxic therapeutic drugs and protection of non target tissues and cells from severe side effects (Irving, 2007). It is increasingly used in different applications, including drug carrier systems and to pass organ barriers such as the blood-brain barrier, cell membrane etc (Abhilash, 2010). They are based on biocompatible lipid and provide sustained effect by either diffusion or dissolution (Cavalli et al., 1995; Müller et al., 2000; Yang et al., 1999; zur Mühlen and Mehnert, 1998).

2. Drug release from nanoparticles

The nanoparticle is coated by polymer, which releases the drug by controlled diffusion or erosion from the core across the polymeric membrane or matrix. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes the determining factor in drug release. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxillary ingredients. When the drug is involved in interaction with auxillary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect (Chen et al., 1994).

To develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on (1) solubility of drug, (2) desorption of the surface bound/ adsorbed drug, (3) drug diffusion through the nanoparticle matrix, (4) nanoparticle matrix erosion/degradation and (5) combination of erosion/diffusion process (Mohanraj and Chen, 2006). Thus solubility, diffusion and biodegradation of the matrix materials govern the release process.

3. Types of nanoparticles

Extensive libraries of nanoparticles, composed of an assortment of different sizes, shapes, and materials, and with various chemical and surface properties, have already been constructed. The field of nanotechnology is under constant and rapid growth and new additions continue to supplement these libraries. The classes of nanoparticles listed below are all very general and multi-functional; however, some of their basic properties and current known uses in nanomedicine are described here.

3.1. Fullerenes

A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called buckyballs, and cylindrical ones are called carbon nanotubes or buckytubes. Fullerenes are similar in structure to the graphite, which is composed of stacked grapheme sheets of linked hexagonal rings, additionally they may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules (Holister et al., 2003). Buckyball clusters or buckyballs composed of less than 300 carbon atoms are commonly known as endohedral fullerenes and include the most common fullerene, buckminsterfullerene, C_{60}. Megatubes are larger in diameter than nanotubes and prepared with walls of different thickness which is potentially used for the transport of a variety of molecules of different sizes (Mitchell et al., 2001). Nano "onions" are spherical particles based on multiple carbon layers surrounding a buckyball core which are proposed for lubricants (Sano et al., 2001). These properties of fullerenes hold great promise in health and personal care application. The versatile biomedical applications are enlisted in Table 1.

3.2. Solid lipid nanoparticles (SLNs)

SLNs mainly comprise lipids that are in solid phase at the room temperature and surfactants for emulsification, the mean

Table 1 Biomedical application of fullerenes.

Fullerenes composition	Application	References
Fullerene (C_{60})	HIV proteases	Friedman et al. (1993) and Sijbesma et al. (1993)
Fulleropyrrolidines	HIV-1 and HIV-2	Marchesan et al. (2005)
Dendrofullerene 1	HIV-1 replication	Brettreich and Hirsch (1998) and Schuster et al. (2000)
Amino acid derivatives of fullerene C60 (ADF)	HIV and human cytomegalovirus replication	Kotelnikova et al. (2003)
Buckminsterfullerene	Semliki forest virus (SFV, Toga*viridae*) or vesicular stomatitis virus (VSV, Rhabdo*viridae*)	Kaesermann and Kempf (1997)
Cationic, anionic and amino acid type fullerene	HIV-reverse transcriptase and hepatitis C virus replication	Mashino et al. (2005)
Fullerene (C_{60}) 34 methyl radicals	Free radicals and oxidative stress	Krusic et al. (1991)
Fullerene (C_{60})	Liver toxicity and diminished lipid peroxidation	Slater et al. (1985)
C3-Fullero-tris-methanodicarboxylic acid	Apoptosis of neuronal cells	Dugan et al. (1997)
Carboxyfullerene	Apoptosis of hepatoma cells	Huang et al. (1998)
Carboxyfullerenes	Neurological disease including Parkinson's disease	Dugan et al. (1997)
Fullerene (C_{60}) with organic cationic compounds, viral carriers, recombinant proteins and inorganic nanoparticles	Gene transfer	Azzam and Domb (2004)
Metallofullerol	Leukemia and bone cancer	Thrash et al. (1999)

diameters of which range from 50 nm to 1000 nm for colloid drug delivery applications (zur Mühlen et al., 1998). SLNs offer unique properties such as small size, large surface area, high drug loading, the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials (Cavalli et al., 1993). The typical methods of preparing SLNs include spray drying (Freitas and Müller, 1998), high shear mixing (Domb, 1993), ultra-sonication (zur Mühlen, 1996; Eldem et al, 1991), and high pressure homogenization (HPH) (Müller et al., 1996; Speiser, 1990). Solid lipids utilized in SLN formulations include fatty acids (e.g. palmitic acid, decanoic acid, and behenic acid), triglycerides (e.g. trilaurin, trimyristin, and tripalmitin), steroids (e.g. cholesterol), partial glycerides (e.g. glyceryl monostearate and gylceryl behenate) and waxes (e.g. cetyl palmitate). Several types of surfactants are commonly used as emulsifiers to stabilize lipid dispersion, including soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate (Zhang et al., 2010).

Advantages of these solid lipid nanoparticles (SLN) are the use of physiological lipids, the avoidance of organic solvents in the preparation process, and a wide potential application spectrum (dermal, oral, intravenous). Additionally, improved bioavailability, protection of sensitive drug molecules from the environment (water, light) and controlled and/or targeted drug release (Mehnert and Mäder, 2001; Müller et al., 2002; Müller et al., 2000), improved stability of pharmaceuticals, feasibilities of carrying both lipophilic and hydrophilic drugs and most lipids being biodegradable (Müller and Runge, 1998; Jenning et al., 2000).

SLNs possess a better stability and ease of upgradability to production scale as compared to liposomes. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year. There are several potential applications of SLNs some of which are given in Table 2.

3.3. Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids. Phospholipids are GRAS (generally recognised as safe) ingredients, therefore minimizing the potential for adverse effects. Solutes, such as drugs, in the core cannot pass through the hydrophobic bilayer however hydrophobic molecules can be absorbed into the bilayer, enabling the liposome to carry both hydrophilic and hydrophobic molecules. The lipid bilayer of liposomes can fuse with other bilayers such as the cell membrane, which promotes release of its contents, making them useful for drug delivery and cosmetic delivery applications. Liposomes that have vesicles in the range of nanometers are also called nanoliposomes (Zhang and Granick, 2006; Cevc, 1996). Liposomes can vary in size, from 15 nm up to several μm and can have either a single layer (unilamellar) or multiple phospholipid bilayer membranes (multilamellar) structure. Unilamellar vesicles (ULVs) can be further classified into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) depending on their size range (Vemuri and Rhodes, 1995).

The unique structure of liposomes, a lipid membrane surrounding an aqueous cavity, enables them to carry both hydrophobic and hydrophilic compounds without chemical modification. In addition, the liposome surface can be easily functionalized with 'stealth' material to enhance their in vivo stability or targeting ligands to enable preferential delivery of liposomes. These versatile properties of liposomes made them to be used as potent carrier for various drugs like antibacterials, antivirals, insulin, antineoplastics and plasmid DNA (Table 3).

Table 2 Biomedical application of solid lipid nanoparticles.

SLN composition	Drug	Application	References
Stearic acid	Rifampicin, isoniazid, pyrazinamide	*Mycobacterium tuberculosis*	Pandey and Khuller (2005)
Stearic acid, soya phosphatidylcholine, and Sodium taurocholate	Ciprofloxacin hydrochloride, tobramycin	Gram-negative bacteria, grampositive bacteria and mycoplasma	Jain and Banerjee (2008)
Glyceryl tripalmitate and tyloxapol	Clotrimazole	Fungi (e.g. yeast, aspergilli, dermatophytes)	Souto et al. (2004)
Glyceryl behenate and sodium deoxycholate	Ketoconazole	Fungi	Souto and Müller (2005)
Glyceryl behenate, propylene glycol, tween 80, and Glyceryl monostearate	Miconazole nitrate	Fungi	Bhalekar et al. (2009)
Glycerol palmitostearate	Econazole nitrate	Fungi	Sanna et al. (2007)
Cetyl palmitate	Insulin	Type 1 diabetes	Sarmento et al. (2007)
Lecithin, SODIUM taurocholate	Nimesulide	Inflammation	Jain et al. (2009a,b)
Oleic acid	Ibuprofen	Inflammation	Panga et al. (2009)
Poly(lactide) (PLA), poly(lactideco-glycolide) (PLGA), poly-ε-caprolactone (PCL) and poly(ortho esters)	Bacterial and viral antigens	Immunity	Tamber et al. (2005), Storni et al. (2005) and Yuki and Kiyono (2003)
Stearic acid, soya phosphatidylcholine, and sodium taurocholate	Tobramycin	*Pseudomonas aeruginosa*	Cavalli et al. (2002)
Soyabean-oil	Doxorubicin	Breast cancer	Wong et al. (2006)
Hyaluronic acid–coupled chitosan	Oxaliplatin	Colorectal cancer	Jain et al. (2009a,b)
Cholesteryl butyrate	Doxorubicin, paclitaxel	Colorectal cancer	Serpe et al. (2004)
SLN	Tamoxifen,	Breast cancer	Fontana et al. (2005)
SLN	Methotrexate and camptothecin	Carcinoma	Ruckmani et al. (2006) and Yang et al. (1999)

3.4. Nanostructured lipid carriers (NLC)

Nanostructured Lipid Carriers are produced from blend of solid and liquid lipids, but particles are in solid state at body temperature. Lipids are versatile molecules that may form differently structured solid matrices, such as the nanostructured lipid carriers (NLC) and the lipid drug conjugate nanoparticles (LDC), that have been created to improve drug loading capacity (Wissing et al., 2004). The NLC production is based on solidified emulsion (dispersed phase) technologies. NLC can present an insufficient loading capacity due to drug expulsion after polymorphic transition during storage, particularly if the lipid matrix consists of similar molecules.

Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally this release should be triggered by an impulse when the particles are administered. NLCs accommodate the drug because of their highly unordered lipid structures. A desired burst drug release can be initiated by applying the trigger impulse to the matrix to convert in a more ordered structure. NLCs of certain structures can be triggered this way (Radtke and Müller, 2001). NLCs can generally be applied where solid nanoparticles possess advantages for the delivery of drugs. Major application areas in pharmaceutics are topical drug delivery, oral and parenteral (subcutaneous or intramuscular and intravenous) route. LDC nanoparticles have proved particularly useful for targeting water-soluble drug administration. They also have applications in cosmetics, food and agricultural products. These have been utilized in the delivery of anti-inflammatory compounds, cosmetic preparation, topical cortico therapy and also increases bioavailability and drug loading capacity. Few biomedical applications of NLCs are enlisted in Table 4.

3.5. Nanoshells

Nanoshells are also notorious as core-shells, nanoshells are spherical cores of a particular compound (concentric particles) surrounded by a shell or outer coating of thin layer of another material, which is a few 1–20 nm nanometers thick (Liz-Marzan et al., 2001; Davies et al., 1998; Templeton et al., 2000; Xia et al., 2000). Nanoshell particles are highly functional materials show modified and improved properties than their single component counterparts or nanoparticles of the same size. Their properties can be modified by changing either the constituting materials or core-to-shell ratio (Oldenberg et al., 1998). Nanoshell materials can be synthesized from semiconductors (dielectric materials such as silica and polystyrene), metals and insulators. Usually dielectric materials such as silica and polystyrene are commonly used as core because they are highly stable (Kalele et al., 2006a,b).

Metal nanoshells are a novel type of composite spherical nanoparticles consisting of a dielectric core covered by a thin

Table 3 Biomedical application of liposomes.

Liposome composition	Drug	Application	References
Hydrogenated soya, phosphatidylcholine, cholesterol and distearoylphosphatidylglycerol (DSPG)	Amphotericin B	*Aspergillus fumigatus*	Takemoto et al. (2004)
1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol	Polymyxin B	*Pseudomonas aeruginosa*	Omri et al. (2002)
Hydrogenated Soya phosphatidylcholine (PC) and cholesterol	Ampillicin	*Micrococcus luteus* and *Salmonella typhimurium*	Schumacher and Margalit (1997)
Dipalmitoyl-phosphatidylcholine, dipalmitoyl-phosphatidylglycerol and cholesterol	Ciprofloxacin	*Salmonella dublin*	Magallanes et al. (1993)
Dipalmitoyl-phosphatidylcholine (DPPC), cholesterol and dimethylammonium ethane carbamoyl cholesterol (DC-chol)	Benzyl penicillin	*Staphylococcus aureus*	Kim and Jones (2004)
Phosphatidylcholine, cholesterol and phosphatidylinositol	Netilmicin	*Bacillus subtilis* and *Escherichia coli*	Mimoso et al. (1997)
Partially hydrogenated egg phosphatidylcholine (PHEPC), cholesterol and 1,2-distearoylsn-glycero-3-phosphoethanolamine-N-(polyethylene glycol-2000) (PEGDSPE)	Gentamicin	*Klebsiella pneumoniae*	Schiffelers et al. (2001)
Phosphatidyl glycerol, phosphatidyl choline and cholesterol	Streptomycin	*Mycobacterium avium*	Gangadharam et al. (1991)
Hydrogenated soy phosphatidylcholine, cholesterol and distearoylphosphatidylglycerol (DSPG)	Amikacin	Gram-negative bacteria	Fielding et al. (1998)
Stearylamine (SA) and dicetyl phosphate	Zidovudine	Human immunodeficiency virus	Kaur et al. (2008)
Egg phosphatidylcholine, diacetylphosphate and cholesterol	Vancomycin or teicoplanin	methicillin-resistant *Staphylococcus aureus* (MRSA)	Onyeji et al. (1994)
DC-Chol liposome	Plasmid DNA	Gene transfer in subcutaneous tumor	Whitemore et al. (2001)
Liposome	Daunorubicin and doxorubicin	Breast cancer	Park (2002)
Liposome	Anti-GD_2 immunoliposomes, Liposomes Entrapping Fenretinide (HPR), Gold-Containing Liposomes	Neuroblastoma	Di Paolo et al. (2009)
Hepatically targeted liposomes	Insulin	Diabetes mellitus	Spangler (1990)

metallic shell which is typically gold. Nanoshells possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications. Nanoshells offer other advantages over conventional organic dyes including improved optical properties and reduced susceptibility to chemical/thermal denaturation. Furthermore, the same conjugation protocols used to bind biomolecules to gold colloid are easily modified for nanoshells (Loo et al., 2004). When a nanoshell and polymer matrix is illuminated with resonant wavelength, nanoshells absorb heat and transfer to the local environment. This causes collapse of the network and release of the drug. In core shell particles-based drug delivery systems either the drug can be encapsulated or adsorbed onto the shell surface (Sparnacci et al., 2002). The shell interacts with the drug via a specific functional group or by electrostatic stabilization method. When it comes in contact with the biological system, it directs the drug. In imaging applications, nanoshells can be tagged with specific antibodies for diseased tissues or tumors. Nanoshell materials have received considerable attention in recent years because of potential applications associated with them. A few applications in the area of imaging and diagnostics are discussed in Table 5.

3.6. Quantum dots (QD)

The quantum dots are semiconductor nanocrystals and core-shell nanocrystals containing interface between different semiconductor materials. The size of quantum dots can be continuously tuned from 2 to 10 nm, which, after polymer encapsulation, generally increases to 5–20 nm in diameter. Particles smaller than 5 nm are quickly cleared by renal filtration (Choi et al., 2007a,b). Semiconductor nanocrystals have unique and fascinating optical properties, become an indispensable tool in biomedical research, especially for multiplexed, quantitative and long-term fluorescence imaging and detection (Michalet et al., 2005; Medintz et al., 2005; Alivisatos, 2004; Smith et al., 2006). QD core can serve as the structural scaffold, and the imaging contrast agent and small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Hydrophilic therapeutic agents including small interfering RNA (siRNA) and antisense oligodeoxynucleotide (ODN)) and targeting biomolecules such as antibodies, peptides and aptamers can be immobilized onto the hydrophilic side of the amphiphilic polymer via either covalent or non-covalent bonds. This fully integrated nanostructure

Table 4 Biomedical application of nonstructured lipid carriers (NLC).

Nanostructured lipid carrier's composition	Application	References
Phosphatidylcholine, dynasan and flurbiprofen	Sustained release of anti-inflammatory drug	Bhaskar et al. (2009)
Stearic acid, oleic acid, carbapol and minoxidil	Pharmaceutical, cosmetic and biochemical purposes	Silva et al. (2009)
Fluticasone propionate, glyceryl palmito-stearate and PEG	Topical corticotherapy	Doktorovová et al. (2010)
Beta-carotene loaded Propylene glycol monostearate	Evaluate the feasibility	Hentschel et al. (2008)
Monostearin and caprylic and capric triglycerides	Improved drug loading capacity and controled release properties	Hu et al. (2006)
Clozapine, triglycerides (trimyristin, tripalmitin and tristearin), soylecithin 95% and poloxamer 188)	Improved bioavailability	Venkateswarlu and Manjunath (2004)

Table 5 Biomedical application of nanoshells.

Nanoshell's composition	Applications	References
Silica coating of silver colloids	Stability of colloids	Ung et al. (1998)
Gold nanoshell	Detection of DNA	Thaxton et al. (2005)
Gold nanoshell	Immunoassay to detect analytes	Hirsch et al. (2003a)
Nanoshell	To detect cancer cells	Loo et al. (2004)
Nanoshell	To detect tumors	Hirsch et al. (2003b)
Silica-silver core-shell particles	To detect antibodies	Kalele et al. (2005)
Silver nanoshell	To detect microorganisms	Kalele et al. (2006b)
Silver nanoshells	Detection of toxic ions such as Cd, Hg and Pb present in water	Kalele et al. (2006a)
Gold nanoshells particles conjugated with enzymes and antibodies embedded in the polymer like Nisopropylacrylamide and acrylamide	Imaging of the diseases	Sparnacci et al. (2002)

may behave like magic bullets that will not only identify, but bind to diseased cells and treat it. It will also emit detectable signals for real-time monitoring of its trajectory (Qi and Gao, 2008). These benefits enable applications of QDs in medical imaging and disease detection (Table 6).

3.7. Superparamagnetic nanoparticles

Superparamagnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5–100 nm range have been used for selective magnetic bioseparations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix.

The main advantages of superparamagnetic nanoparticles are that they can be visualized in magnetic resonance imaging (MRI) due to their paramagnetic properties; they can be guided to a location by the use of magnetic field and heated by magnetic field to trigger the drug release (Irving, 2007).

Superparamagnetic nanoparticles belong to the class of inorganic based particles having an iron oxide core coated by either inorganic materials (silica, gold) and organic (phospholipids, fatty acids, polysaccharides, peptides or other surfactants and polymers) (Gupta and Curtis, 2004; Babic et al., 2008; Euliss et al., 2003). In contrast to other nanoparticles, superparamagnetic nanoparticles based on their inducible magnetization, their magnetic properties allow them to be directed to a defined location or heated in the presence of an externally applied AC magnetic field. These characteristics make them attractive for many applications, ranging from various separation techniques and contrast enhancing agents for MRI to drug delivery systems, magnetic hyperthermia (local heat source in the case of tumor therapy), and magnetically assisted transfection of cells (Horák, 2005; Gupta and Gupta, 2005; Jordan et al., 2001; Neuberger et al., 2005).

Already marketable products, so-called beads, are micron sized polymer particles loaded with SPIONs. Such beads can be functionalized with molecules that allow a specific adsorption of proteins or other biomolecules and subsequent separation in a magnetic field gradient for diagnostic purposes. More interesting applications, like imaging of single cells or tumors, delivery of drugs or genes, local heating and separation of peptides, signaling molecules or organelles from a single living cell or from a living (human) body are still subjects of intensive research. The transdisciplinarity of basic and translational research carried out in superparamagnetic nanoparticles during the last decades lead to a broad field of novel applications for superparamagnetic nanoparticles. There are several potential applications of superparamagnetic nanoparticles

Table 6 Biomedical application of quantum dots.

Quantum dot's composition	Applications	References
Quantum dots	For measuring protein conformational changes, monitoring protein interactions, assaying of enzyme activity, in Fluorescence resonance energy transfer (FRET) technologies, particularly when conjugated to biological molecules, including antibodies, for use in immunoassays	Heyduk (2002), Day et al. (2001), Li and Bugg (2004), Kagan et al. (1996), Willard et al. (2001), Wang et al. (2002) Hohng and Ha (2005)
QD-conjugated oligonucleotide sequences (attached via surface carboxylic acid groups)	Gene technology	Pathak et al. (2001) and Gerion et al. (2002)
Conjugation of quantum dot with Tat protein, and by encapsulation in cholesterol-bearing pullulan (CHP) modified with amine groups coating with a silica shell	Fluorescent labeling of cellular proteins and different intracellular structures	Hasegawa et al. (2005) and Derfus et al. (2004)
QDs encapsulated in phospholipid micelles	Cell tracking and color imaging of live cells	Dubertret et al. (2002) and Jaiswal et al. (2003)
Transferrin-bound QDs, wheat germ agglutinin and transferrin-bound QDs,p53 conjugated with QDs	Pathogen and toxin detection such as *Cryptosporidium parvum* and *Giardia lamblia*, *Escherichia coli* 0157:H7 and *Salmonella typhi*, Hepatitis B and C viruses and *Listeria monocytogenes*	Lee et al. (2004), Zhu et al. (2004), Yang and Li (2006), Gerion et al. (2003), Agrawal et al. (2005), Goldman et al. (2002)
PEG-encapsulated QDs	In vivo animal imaging, Lymph node mapping	Gao et al. (2004), Jakub et al. (2003), Lim et al. (2003)
Quantum dots	Barriers to use in vivo	Akerman et al. (2002)
Combination of QD imaging with second-harmonic generation (SHG), CdTe bound QDs	Tumor biology investigation, Cell motility and metastatic potential, measurement of different cancer antigens	Choi et al. (2007), Parak et al. (2002), Ghazani et al. (2006), Williams et al. (2001)

Table 7 Biomedical application of superparamagnetic nanoparticles.

Superparamagnetic nanoparticle's composition	Applications	References
SPIONs coated with organic molecules showing an overall median diameter of less than 50–160 nm	MRI contrast agents for detecting liver tumors	Smith et al. (2007)
Superparamagnetic iron oxide nanoparticles	Identify dangerous arteriosclerotic plaques by MRI	Zur Mühlen et al. (2007) and Smith et al. (2007)
Superparamagnetic Iron oxide nanoparticles (SPIONs) coated with polyvinylbenzyl-*O*-β-D-galactopyranosyl-D-gluconamide (PVLA) with galactose moieties	Liver-targeting MRI contrast agent	Yoo et al. (2007)
Superparamagnetic iron oxide nanoparticles conjugated to luteinizing hormone releasing hormone (LHRH–SPIONs),	Enhanced MRI contrast in breast cancer xenografts and metastases in the lungs	Meng et al. (2009)
Superparamagnetic iron oxide nanoparticles	Magnetic particle imaging	Minard (2009)
Combidex a ultrasmall superparamagnetic iron oxide (USPIO) covered covered dextran	Molecular imaging agent during contrast-enhanced MRI	McIlwain (2008)
Monocrystalline iron oxide nanoparticles-47 [MION-47]	Measures macrophage burden in atherosclerosis	Morishige et al. (2010)
Colloidal dispersions of superparamagnetic (subdomain) iron oxide nanoparticles	Magnetic fluid hyperthermia (MFH) in cancer treatment	Jordan et al. (1999)
Nanosized superparamagnetic nanoparticles (Fe_3O_4) coated with the multivalent cationic agent, polyethylenimine (PEI)	Purification of plasmid DNA from bacterial cells	Chiang et al. (2005)

some of which are given in Table 7. The following issues are not yet fully understood such as (1) the mechanisms utilized by cells to take up multifunctional SPIONs in human cells in culture, (2) are there membrane molecules involved?, (3) specific adsorption of SPIONs to targeted subcellular components after uptake, transport of drugs, plasmids or other substances to specific cells followed by controlled release, (4) separation of SPIONs from the cells after cell-uptake and specific adsorption

Table 8 Biomedical application of dendrimers.

Dendrimers composition	Drug	Application	References
PAMAM (polyamidoamine)	Chelated gadolinium	Diagnose certain disorders of the heart, brain and blood vessels	Wiener et al. (1994)
Poly(L-glutamic acid), polyamidoamine and poly(ethyleneimine)	Folic acid	Breast cancer	Wiener et al. (1997) and Kukowska-Latallo et al. (2005)
PAMAM	Antibodies specific to CD14 and PSMA	Cell binding and internalization	Thomas et al. (2004)
PAMAM	Sulfamethoxazole	Strep throat (*Streptococcus*), staph infection (*Staphylococcus aureus*), and flu (*Haemophilus influenza*)	Ma et al. (2007) and Abeylath et al. (2008)
PAMAM (polyamidoamine)	Nadifloxacin, prulifloxacin,	Various bacteria	Cheng et al. (2007b)
PAMAM (Polyamidoamine) PPI (polypropyleneimine generation)	Nystatin and Terbinafine	Antifungal against *Candida albicans*, *Aspergillus niger* and *Sachromyces cerevasae*	Khairnar et al. (2010)
PAMAM (polyamidoamine)	Propranolol	Hypertension	D'Emanuele et al. (2004)
Polyamidoamine (PAMAM) dendrimers	Niclosmide	Tapeworm	Devarakonda et al. (2005)
Pegylated lysine based copolymeric dendrimer	Artemether	*Plasmodium falciparum*	Bhadra et al. (2005)
PAMAM dendrimers with carboxylic or hydroxyl surface groups	Pilocarpine	Glaucoma	Vandamme and Brobeck (2005) and Tolia et al. (2008)
PAMAM	Enoxaparin	Pulmonary embolism	Bai et al. (2007)
PAMAM	Ketoprofen, Diflunisal	Inflammation	Cheng et al. (2007a)
PAMAM	Indomethacin	Inflammation	Chauhan et al. (2003)
Polylysine dendrimer	VivaGel (SPL7013 Gel)	HIV, HSV and sexually transmitted infections	Rupp et al. (2007)
Dendrimer	High resolution X-ray image	Diagnostic tool for arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary	Schumann et al. (2003)
Dendrimer	Gene transfer of cytokine genes (tumor necrosis factor, interleukin-2, granulocyte-macrophage colony-stimulating factor)	Induce a systemic antitumor immune response against residual tumor cells	Culver (1994)
PAMAM	5-Fluorouracil	Tumor	Zhuo et al. (1999)
Dendrimer	Isotope of boron (^{10}B)	Cancer	Hawthorne (1993)

to sub cellular components or to biomolecules like proteins without interfering with cell function, (5) prevention of uncontrolled agglomeration of modified SPIONs in physiological liquids, (6) short and long-term impact on cell functions by loading cells of different phenotypes with such nanoparticles (Hofmann-Amtenbrink et al., 2009).

3.8. Dendrimers

Dendrimers are unimolecular, monodisperse, micellar nanostructures, around 20 nm in size, with a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery. The structure of dendrimers consists of three distinct architectural regions as a focal moiety or a core, layers of branched repeat units emerging from the core, and functional end groups on the outer layer of repeat units. They are known to be robust, covalently fixed, three dimensional structures possessing both a solvent-filled interior core (nanoscale container) as well as a homogenous, mathematically defined, exterior surface functionality (Grayson and Frechet, 2001; Svenson and Tomalia, 2005). Dendrimers are generally prepared using either a divergent method or a convergent one (Hodge, 1993) with an architecture like a tree branching out from a central point.

Dendrimeric vectors are most commonly used as parenteral injections, either directly into the tumor tissue or intravenously for systemic delivery (Tomalia et al. 2007). Dendrimers used in drug delivery studies typically incorporate one or more of the following polymers: polyamidoamine (PAMAM), melamine, poly L-glutamic acid (PG), polyethyleneimine (PEI), polypropyleneimine (PPI), and polyethylene glycol (PEG), Chitin. Dendrimers may be used in two major modalities for targeting vectors for diagnostic imaging, drug delivery, gene transfection also detection and therapeutic treatment of cancer and other diseases, namely by (1) passive targeting-nanodimension mediated via EPR (enhanced permeability retention) effect (Matsumura and Maeda, 1986) involving primary tumor vascularization or organ-specific targeting (Kobayashi and Brechbiel, 2003) and (2) active targeting-receptor-mediated cell-specific targeting involving receptor-specific targeting groups (Hofmann-Amtenbrink et al., 2009). There are several potential applications of dendrimers in the field of imaging,

drug delivery, gene transfection and non-viral gene transfer. Few applications are enrolled in Table 8.

4. Conclusion

There is a wide range of nanoparticulate materials and structures being developed for the delivery of therapeutic compounds. Each has its own particular advantages, but as these nanoparticles become optimized for their specific application, the outcome will be better-controlled therapy as a result of targeted delivery of smaller amounts of effective drugs to the required sites in the body. This is being made possible through the use of advanced material, improved control of particle size, and better understanding of interface between the biological and material surfaces, and their effects in vivo. Some nanoparticle based products are already approved by the US FDA, several others are currently under development and clinical assessment.

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