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REVIEW

Advanced drug delivery systems: Nanotechnology of health design A review

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Abstract Nanotechnology has finally and firmly entered the realm of drug delivery. Performances of intelligent drug delivery systems are continuously improved with the purpose to maximize therapeutic activity and to minimize undesirable side-effects. This review describes the advanced drug delivery systems based on micelles, polymeric nanoparticles, and dendrimers. Polymeric carbon nanotubes and many others demonstrate a broad variety of useful properties. This review emphasizes the main requirements for developing new nanotech-nology-based drug delivery systems.

1. Introduction

Nanotechnology is increasingly considered to be the technology of the future, With nanotechnology, scientists are acquiring abilities to understand and manipulate materials at the scale of atoms and molecules, with having the following key properties:

- Nanostructures have at least one dimension of about 1–100 nm.
- They are designed through methodologies that exhibit fundamental control over the physical and chemical attributes of molecular-scale structures.
- They can be combined to form larger structures (Rocco, 2001):

"There's plenty of room at the bottom" is the title of a lecture in 1959 by Richard Feynman, that introduced the concept of nanotechnology as an important field for future scientific researches (Feynman, 1960). Nanotechnology research can be developed to advances in communications, engineering, chemistry, physics, robotics, biology, and medicine. Nanotechnology has been utilized in medicine for therapeutic drug delivery and the development of treatments for a variety of diseases and disorders. So, there are very significant advances in these disciplines.

Since emerging in the early 1970s, Controlled drug delivery systems (DDS), which are aimed to deliver drugs at predetermined rates and predefined periods of time, have attracted increasing attention (Qiu and Park, 2001; Jeong et al., 2002). On the other hand, drug delivery is an emerging field focused on targeting drugs or genes to a desirable group of cells. The goal of this targeted delivery is to transport proper amounts of drugs to the desirable sites (such as tumors, diseased tissues,

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etc.) while minimizing unwanted side effects of the drugs on other tissues (Tran et al., 2009).

In recent years, numerous proteinic and other drugs designed to target various cellular processes have emerged, creating a demand for the development of intelligent drug delivery systems that can sense and respond directly to pathophysiological conditions. Micro- and nano-scale intelligent systems can maximize the efficacy of therapeutic treatments in numerous ways because they have the ability to rapidly detect and respond to disease states directly at the site, sparing physiologically healthy cells and tissues and thereby improving a patient's quality of life. This new class of "intelligent therapeutics" refers to intelligent and responsive delivery systems that are designed to perform various functions like detection, isolation and/or release of therapeutic agents for the treatment of diseased conditions. To meet these requirements, researchers must be able to interface synthetic and hybrid materials with dynamic biological systems on the micro- and nano-length scale. Stimuli responsive biomaterials are very promising carriers for the development of advanced intelligent therapeutics (Moore and Peppas, 2009).

In this review, we discuss the use of nanotechnology for medical applications with focus on its use for drug delivery. Specifically, we discuss about various intelligent drug delivery systems such as inorganic nanoparticles, polymeric based drug delivery and many others. Use of smart drug delivery systems is a promising approach for developing intelligent therapeutic systems.

2. Inorganic nanoparticles

Inorganic nanoparticles can be defined as particles of metal oxide or metallic composition possessing at least one length scale in the nanometer range. These nanostructures exhibit significantly novel and distinct chemical, physical, and biological properties, and functionality due to their nanoscale size, have elicited much interest. The preparation of inorganic nanoparticles offers several challenges. There is not a one-fits-all type of production process for nanoparticles and most procedures will differ considerably between different research institutions and industrial scale laboratories (Brinker and Scherer, 1990; Lee et al., 2006).

The most traditional preparation method for nanoparticle synthesis is the sol–gel route (Brinker and Scherer, 1990) which the preparation of a solution of inorganic precursor, and the control of its particle growth though thermal or pH conditions of the solution. Typical inorganic precursors including metal salts, metal halides, and inorganic alkoxides are synthesized by hydrolysis and condensation reactions into the relevant metal oxide species. The use of mineralizers (acids or bases) allows for control of the rates of hydrolysis and condensation independently, switching from kinetic-based to equilibrium-based particle growth mechanisms, and ultimately allowing for control of the growth speeds of various facets versus others (Lee et al., 2006).

The use of the spray-drying process is a more scale-up friendly technique (Vasiliev et al., 2008). This method entails spraying a homogenized precursor solution composed of the inorganic compounds and relevant additives within a specially designed chamber at temperatures at or above the boiling point of the solvent. The precursor solution is atomized through a nozzle into droplets using flowing gas. The droplet is sprayed into a chamber through which a flow of hot air or nitrogen is introduced leading to the quick evaporation of the droplets and the formation of the nanoparticle. The droplet size determines to a large extent the particle size and hence the type of nozzle and atomizer unit determines the possibilities of using this technique for the production of nanometer particles (Trommelen and Crosby, 2004). Furthermore, an effective route is the use of gas-phase methods, which include the use of a combustion flame, laser ablation, chemical vapor deposition, and spray-pyrolysis (Zachariah and Joklik, 1990).

Another method for the preparation of nanoparticles is microemulsion processing. Microemulsions have been used for the production of metallic nanoparticles (Kishida et al., 1995) as well as magnetic and superconductor nanoparticles (Pileni and Fendler, 1998). Microemulsions are produced spontaneously without the need for significant mechanical agitation making it a rather simple technique. The technique is simple and uses inexpensive equipment that results in high yields with homogeneous particle sizes (Vestal and Zhang, 2002). Among, inorganic nanoparticles, we focus on metallic nanoparticles and mesoporous silica nanoparticles.

Although inorganic nanoparticles are attracting great interest in the field of nanomedicine the long-term, effects of these nanoparticles needs have not been investigated in detail. Concerns associated with long-term tissue damage, toxicity, immunogenicity, carcinogenesis, and inflammation need to be elucidated. It will be necessary to design inorganic nanoparticles whose stability, circulation times, and localization can be modulated without compromizing theranostic efficacies in order to optimize the demands of short-term therapeutic and potential adverse effects due to long-term exposure (Huang et al., 2011).

2.1. Metal nanoparticles

Applications of metal nanoparticles have been dominated by the use of nanobioconjugates that started in 1971 after the discovery of immune gold labeling by Faulk and Taylor (Hayat, 1989). Metal nanoparticles have been used in various biomedical applications including probes for electron microscopy to visualize cellular components, drug delivery (vehicle for delivering drugs, proteins, peptides, plasmids, DNAs, etc.), detection, diagnosis and therapy (targeted and non-targeted) (Bhattacharya and Mukherjee, 2008; Goldman et al., 2004; Alivisatos and Gu, 2005; Adeli et al., 2011).

Metallic nanoparticles such as gold or silver have many optical and electronic properties, derived from their size and composition (Jana et al., 2001). These nanomaterials have found important applications as chemical sensors, when coupled to affinity ligands, For example, gold nanoparticles conjugated with specific oligonucleotides can sense complementary DNA strands, detectable by color changes (Mirkin et al., 1996). Furthermore, gold nanoparticles can be readily functionalized with probe molecules such as antibodies, enzymes, nucleotides, etc. These hybrid nanostructures are the active elements of a number of biosensor assays, drug and gene delivery systems, laser confocal microscopy diagnostic tools, and other biomaterial-based imaging systems (Loo et al., 2005).

Silver has been known since ancient times as a very effective antimicrobial agent. Silver particles in the nanometer range have been routinely used to prevent the attack of a broad spectrum of microorganisms on prostheses, catheters, vascular

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grafts, and human skin, also used in medicine to reduce infection in burn treatment, arthroplasty, etc. However, they exhibit low toxicity to mammalian cells (Mahapatra and Karak, 2008).

Currently, magnetic nanoparticles (MNPs) have attracted considerable interest in recent years, as they possess unique magnetic properties and the ability to function at the cellular and molecular level of biological interactions making them an attractive platform as contrast agents for magnetic resonance imaging (MRI) (Corot et al., 2006) and as carriers for drug delivery (Chang et al., 2011). Recent advances in nanotechnology have improved the ability to specifically tailor the features and properties of MNPs for these biomedical applications (Jiang et al., 2011).

However, the safety and efficacy of using metal nanoparticles is debatable among scientists. Wherever appropriate, studies that report the toxicity of metal nanoparticles are included. Mu et al. have researched about the relationship between biocompatibility and surface chemistry of carbon coated iron NPs (Fe@CNPs). The results are shown that biocompatibility of Fe@CNPs is dependent on both cell type and nanoparticles' surface chemistry (Mu et al., 2010).

2.2. Mesoporous silica systems

In the past decade, synthesis and applications of mesoporous solids have received intensive attention due to their highly ordered structures, larger pore size, and high surface area (Scott et al., 2001). Due to stable mesoporous structure and well-defined surface properties, mesoporous materials seem ideal for the encapsulation of pharmaceutical drugs, proteins and other biogenic molecules. Currently, employing mesoporous materials for hosting and further delivering of a variety of molecules of pharmaceutical interest has been appeared (Hartmann, 2005). Several mesoporous materials were used such as M41S, SBA, MSU, and HMS in drug delivery.

The surface area and pore size of the mesoporous silica is important for biotechnological and biomedical applications. For example, microsphere materials cannot serve as efficient agents for gene transfection or carriers for intracellular drug delivery because cells cannot efficiently engulf large particles via endocytosis. Also, mesoporous silica microspheres are within the size window of bacteria and could potentially trigger acute immune response in vivo. To circumvent these problems, researchers have developed a synthetic approach for preparing a series of mesoporous silica nanoparticles (MSN). The following unique properties of MSN have attracted a lot of research attention for various controlled release delivery applications.

1. The tunable particle size of MSN can be tuned from 50 to 300 nm allowing facile endocytosis by living animal and plant cells without any significant cytotoxicity.
2. MSN is more stable to heat, pH, mechanical stress, and hydrolysis-induced degradations, compared to other polymer-based drug carriers.
3. The uniform pore size distribution of MSN is very narrow and the pore diameter can be tuned between 2 and 6 nm. These features allow one to adjust the loading of different drug molecules and to study the kinetics of drug release with high precision.
4. The high surface area ($>900\ m^2/g$) and large pore volume ($>0.9\ cm^3/g$) MSN, allow high loadings of drug molecules (Slowing et al., 2008).
5. MSN have an internal surface (i.e., cylindrical pores) and an external surface (i.e. exterior particle surface). This characteristic allows the selective functionalization of the internal and/or external surfaces of MSN with different moieties.
6. Many drug delivery materials have interconnecting porous structures, such as dendrimers with branching porous structure and liposomes with a large void core and a porous shell. Also, MSN with unique porous structure, is suitable for drug delivery (Slowing et al., 2008; Vallet-Regi et al., 2001).

MCM-41 as one of the importantly synthesized mesoporous materials (Kresge et al., 1992), has been firstly employed as a drug delivery matrix. Other groups of mesoporous materials with larger pore size such as SBA including SBA-15, SBA-16, SBA-1, SBA-3, HMS, and MSU were also used for drug delivery. For drug delivery based on mesoporous materials, several investigations using organic modified mesoporous silica have been reported. Zeng et al. (2005) carried out a study using MCM-41 materials modified by aminopropyl groups as drug-controlled delivery system of aspirin. The results showed that the releasing properties of this delivery system were affected by the amount of aminopropyl groups on the pore wall and the ordered structure of mesoporous materials.

SBA-15 is expected to have less restriction for the delivery of bulky molecules, because the pore size of SBA-15 is usually 6 nm in diameter, larger than the 3 nm pore of MCM-41.

Song et al. (2005) reported mesoporous SBA-15 materials functionalized with amine groups as drug matrixes. Ibuprofen (IBU) and bovine serum albumin (BSA) were selected as model drugs and loaded onto the unmodified and functionalized SBA-15. The release rate of ibuprofen from the SBA-15 functionalized was found to be effectively controlled as compared to that from pure SBA-15. Therefore, introduction of functional groups on the surface of SBA-15 to have specific host–guest interactions with drugs will also be important and good for controlled drug delivery.

Hollow mesoporous spheres (HMS) are another group of important mesostructured materials, which have been used for applications in drug delivery (Zhu et al., 2005). Zhu et al. reported a facile route for the preparation of HMS and employed for drug storage and delivery using ibuprofen. They compared the drug loading with MCM-41 and found that the HMS exhibited much more storage capacity than MCM-41 (Hartmann, 2005). Also, MSU mesoporous silica, has also been employed for drug delivery (Lehto et al., 2005). (Tourne-Peteilh et al. (2003) employed MSU as carriers for the drug pentapeptide. They found that the pentapeptide could be encapsulated in the mesoporous silica and would be released instantly upon solid washing with dimethylformamide.

For mesoporous silica materials based drug system, bioactivity is an important factor for its potential application. Bioactivity studies demonstrated that mesoporous silicas, MCM-48, MCM-41, and SBA-15, are bioactive materials for the drug delivery system. However, the biocompatibility is not so strong. Modification of silica with phosphorous material or active components such as hydroxyapatite will

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significantly improve its biocompatibility (Yousefpour and Taheran, 2013; Huang et al., 2012; Vallet-Regi et al., 2005).

3. Polymers in drug delivery systems

Engineering polymeric nanostructures such as hyperbranched polymers, dendrimers and polymeric micelles (Xu et al., 2012; Gong et al., 2012a,b) are a growing area of contemporary biomaterials science, due to their unique properties and large potential in drug delivery (Kim et al., 2012; Lim and Simanek, 2012; Bielawski et al., 2011). For using polymers in drug delivery, a polymer must be biocompatible. Biocompatibility was defined by (Williams (1999)) as the ability of a material to act with an appropriate host response in a specific application. Moreover, biocompatible polymers used in drug delivery are often biodegradable with the formation of non-harmful byproducts, such as non-toxic alcohols, acids and other easily eliminated low molecular weight products. They can indeed contribute to the drug release as a result of their erosion/degradation, in addition to drug diffusion through the polymeric material. Biodegradable polymer (Table 1), in the development of drug delivery systems, must meet very specific requirements such as:

a. Biocompatibility backbone of the polymer and its degradation products.
b. Mechanical strength sufficient to meet the needs of specific applications.
c. Degradability with degradation kinetics matching a biological process such as wound healing.
d. Processibility using available equipment.
e. Solubility in various solvents.
f. Chemical, structural and application versatility.
g. Economically acceptable shelf life.
h. European Medicine Evaluation Agency (EMEA) or Food and Drug Administration (FDA), USA. (Coulembiera et al., 2006).

Stimulus-responsive polymers, as 'intelligent', 'smart' or 'environmentally sensitive' polymers, are systems that exhibit large, sharp changes in response to physical stimuli (such as temperature, solvents, or light) or to chemical stimuli (such as reactants, pH, ions in solution, or chemical recognition). Responses differ depending on the stimulus applied and may include changes in shape, volume, mechanical properties, or permeation rates, among other things. These systems possess a variety of interesting applications for encapsulation, controlled delivery, or as intelligent switches—to mention just a few (York et al., 2008). In this section of review, we discuss about the type of polymeric nanostructures and stimulus-responsive systems.

3.1. Polymeric Micelles

Polymeric micelles are nanoscopic (>100 nm) amphiphilic block copolymers with a core–shell structure (Fig. 1A). Polymeric nanoparticles designate cores of biodegradable hydrophobic polymers protected by an amphiphilic block copolymer that stabilizes their dispersion in aqueous media (Fig. 1B). Liposomes are vesicles consisting of one or more phospholipidic bilayer(s), with an aqueous core (Fig. 1C) (Butsele et al., 2007).

In addition, polymeric micelles display larger cores than surfactant micelles, leading to higher solubilization capacity than the regular micelles (He et al., 2011). Among the polymers displaying micelle-formation ability, micelles with blocks made of poly(ethylene oxide) are sterically stabilized and undergo less opsonization and uptake by the macrophages of the reticuloendothelial system (RES), allowing the micelles to circulate longer in blood (He et al., 2011, Barratt, 2003).

polymeric micelles and nanoparticles have been investigated extensively for drug delivery. Polymeric micelles can be regarded as unique systems where aggregated amphiphilic copolymers are in dynamic equilibrium with free unimers. While polymeric nanoparticles share a core–shell structure with micelles, they are matrix-type, solid-colloidal particles and, therefore exhibit generally greater stability than micelles. They are typically larger (100–500 nm) than polymeric micelles (10–100 nm) and may display somewhat more polydisperse size distributions. Both polymeric micelles and nanoparticles are stabilized by surface-bound hydrophilic polymers. Polysaccharides, such as chitosan, dextran and heparin (Lemarchand et al., 2004; Wang et al., 2011), as well as poly(amino acids) (Gao et al., 2011), have been used as corona-forming materials, in some cases for the delivery of taxanes (Kim et al., 2006).

Recently, the use of micelles prepared from amphiphilic copolymers (fig 2) for solubilization of poorly soluble drugs has attracted much attention (Li et al., 2011, Luo and Jang, 2012, Xiong et al., 2011). Amphiphilic block copolymers with having a large solubility difference between hydrophilic and hydrophobic segments, have a tendency to self-assemble into micelles in a selective solvent. In an aqueous solution, micelles with core– shell structures are formed through the segregation of insoluble hydrophobic blocks into the core, which is surrounded by a shell composed of hydrophilic blocks. This core–shell structure facilitates their utilization, where depending upon the polarity the drug molecule can be entrapped in the (i) core (non polar molecule), (ii) shell (polar molecule) and (iii) in-between the core and shell (intermediate polarity) (Kataoka et al., 2001, Guo et al., 2011; Kaditi et al., 2011).

The unique characteristics of polymeric micelles, such as size in the nanometer range, relatively high stability due to

Table 1 Classification of biodegradable polymers used in drug delivery systems (Coulembiera et al., 2006).

Synthetic biodegradable polymers		Natural biodegradable polymers	
Polyesters	Polyoxalates	Starch	Albumin
Polyorthoesters	Polyiminocarbonates	Hyaluronic acid	Dextran
Polyanhydrides	Polyurethanes	Heparin	Chitosan
Polydioxanones	Polyphosphazenes	Gelatin	–
Poly(a-cyanoacrylates)	–		

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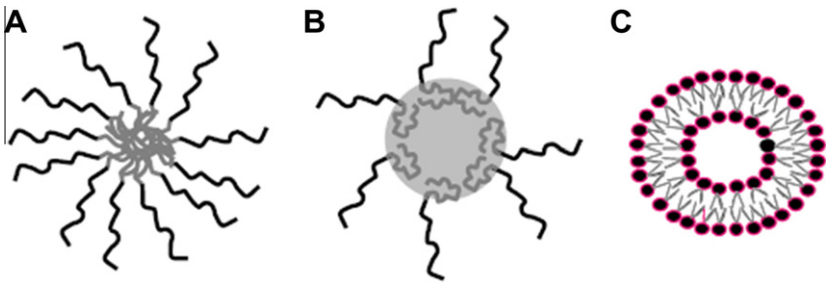

Figure 1 Schematized polymeric nanocarriers: (A) micelle, (B) polymeric nanoparticle and (C) liposome (Butsele et al., 2007).

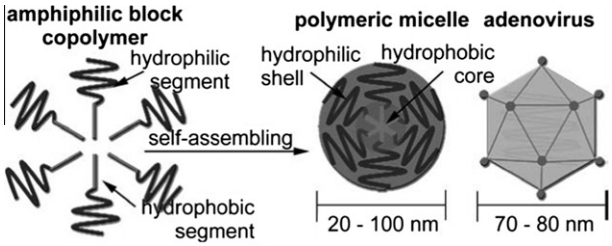

Figure 2 Amphiphilic block copolymers and polymeric micelles.

low critical association concentrations (CMC), and core–shell arrangement, make them attractive for use in drug delivery systems in clinical applications, especially for hydrophobic drugs with very low solubility in water (Butun et al., 2011; Chen and Liu, 2012).

In this review, the polymeric micelles are categorized into two groups depending on drug-loading methods including 'physical drug entrapment type micelles' and 'covalent drug conjugation type micelle'. For the physical drug entrapment type micelles, they incorporate drug payloads through the hydrophobic interaction in the micelle core (Gong et al., 2012). Drugs can be entrapped also in gel-like amorphous core. In either case, the equilibrium rates determine the physicochemical stability and drug release patterns of the polymeric micelles, which are controlled time-dependently. In contrast, covalent drug conjugation type micelles have drug-binding linkers that stably tether drugs in the micelle core until the polymeric micelles accumulate in the site of action and are exposed to the in vivo stimuli such as ions, endogenous signal peptides, enzymes, and pH that trigger drug release (Nishiyama et al., 2005). Covalent drug conjugation type micelles appear to be more stable than physical drug entrapment type micelles as long as the linkage remains intact. Since their drug release patterns can be modified according to the chemical stability of drug-binding linkers, covalent drug conjugation type micelles provide environment-responsive controlled drug release systems, intelligent drug delivery systems (Vigderman and Zubarev, 2012).

Several factors are effective in the loading of drugs in polymeric micelles, including the physicochemical characteristics of the drug and core-forming polymer, the loading method and the parameters. Hydrophobic block length as well as other parameters, such as the nature of the solvent used in the loading method. Other factors, such as chemical composition of the core-forming polymer, polymer–drug compatibility as well as physical state of the micelle core, can substantially alter drug loading and release kinetics (Jie et al., 2005, He et al., 2007).

3.1.1. Stimuli-Responsive Micelles

Stimuli-responsive micelles received wide studies attributed to their unique intelligent property, as potential drug delivery systems, Stimuli-responsive block copolymers contain a permanently hydrophilic segment and a stimuli-responsive block which can undergo a conformational change, promoting the self-assembly of the block copolymers into micelle-like structures with a hydrophobic core and a hydrophilic corona (Fig. 3). These amphiphilic structures can sequester hydrophobic segments that can be released in response to changes in the surrounding environment. For example, temperature sensitive micelles can be formed as a result of the assembly of block copolymers composed of a temperature sensitive block and a hydrophobic block. The temperature-sensitive property is possessed by the outer shell of the polymeric micelles and the drug molecules are incorporated into the hydrophobic inner core (Ganta et al., 2008).

Polymeric micelles are unable to sense a signal and respond by changing their structures. To develop stimuli-responsive micelles sensitive to environmental changes, the polymers were synthesized with a stimulus-responsive moiety into the polymeric structure (Rijcken et al., 2007; Schmaljohann, 2006). To date, numerous distinctive intelligent nano-scaled micelles, such as temperature (Wei et al., 2005), pH (Zhao et al., 2012) and magnetic field (Park et al., 2008) responsive micelles have been reported in drug delivery systems.

3.1.1.1. Response to Temperature. Temperature sensitivity is one of the most interesting properties in stimuli-responsive polymers. These intelligent polymeric systems are able to stimulate chemical, physical or mechanical changes, due to small temperature differentials, as they cross the relevant transition temperature. In other words, the drug release could be controlled by local heating or cooling during a particular time period. The most extensively investigated temperature sensitive polymer is Poly(N-isopropylacrylamide) (PNIPAAm) (Hoffman, 1987; Cohn et al., 2006), poly(ethylene oxide)–poly(propylene oxide)– poly(ethylene oxide) triblocks (PEO–PPO–PEO) (Niu et al., 2011) and multiblocks (Cohn et al., 2003), and poly(ethylene glycol) poly(lactic acid)–poly (ethylene glycol) triblocks (PEG–PLA–PEG) (Ruan and Feng, 2003).

3.1.1.2. Response to pH. Polymeric drug carrier with pH sensitive (pH-cleavable) bonds that are used to produce stimuli-responsive drug delivery systems that are stable in the circulation or in normal tissues, however, acquire the ability to degrade and release the entrapped drugs in body areas or cell compartments with lowered pH, such as infarcts, tumors,

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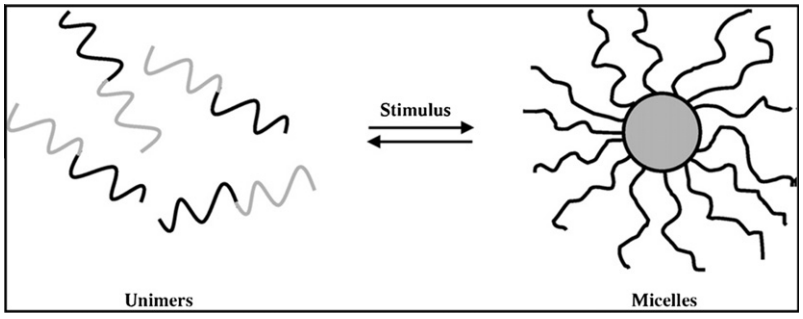

Figure 3 Reversible micellization in response to an external stimulus.

inflammation zones or cell cytoplasm or endosomes (Liu et al., 2011; Islam and Yasin, 2012).

In particular, pH-sensitive bonds cleavable under mildly acidic conditions and stable under neutral pH are studied [4,14] because the pH value of the interstitial space of solid tumours as well as the interior of endosomes is usually more acidic (pH close to 5) than blood plasma (pH 7.4) (Qiu and Park, 2001).Hruby et al. (2005) synthesized and characterized a new polymeric micellar pH-sensitive system for the drug delivery of doxorubicin. Polymeric structures were prepared by self assembly of amphiphilic copolymers in aqueous solutions (Fig. 4). The copolymers consist of a hydrophilic poly(ethylene oxide) (PEO) block and a hydrophobic block containing covalently bound anthracycline antibiotic DOX. The block copolymers poly(ethylene oxide)-block-poly(allyl glycidyl ether) (PEO-PAGE) with a very narrow molecular weight distribution were prepared and the copolymers were covalently modified via reactive double bonds by the addition of methyl sulfanyl acetate. The resulting ester subsequently reacted with hydrazine hydrate yielding polymer hydrazide. The hydrazide was coupled with DOX yielding pH-sensitive hydrazone bonds between the drug and carrier. After incubation in buffers at 37 8C DOX was released faster at pH 5.0 (close to pH in endosomes) than at pH 7.4 (pH of blood plasma).

Moreover, several examples of versatile systems with multi-stimuli responsive aptitude have been described in the literature (Hernández et al., 2005). For instance, Armes et al. described 'schizophrenic' diblock copolymers that form direct and inverse micelles in the same solvent. They prepared different systems exhibiting such behavior. One was based on a diblock copolymer weak polybase: poly[2-(N-morpholino) ethylmethacrylate-b-2-(diethylamino)ethylmethacrylate] (MEMA-b-DEA EMA). DEAEMA cores were formed by adjusting the pH of the solution (Bütün et al., 1998).

Szczubialka and Nowakowska (2003), synthesized a series of amphiphilic terpolymers based on sodium 2-acrylamido-2-methyl-1-propane sulfonate (AMPS), N-isopropylacrylamide (NIPAM), and cinnamoyloxyethyl methacrylate (CEMA). The terpolymers were soluble in water, prone to self-assemble into micelles, and sensitive to three stimuli: (a) temperature, due to the NIPAM block that imposed a lower critical solution temperature, (b) UV irradiation, due to the presence of the cinnamoyl block, and finally (c) ionic strength, that at an elevated concentration provoked loss of the temperature-sensitivity.

3.1.1.3. responsive to reductive environment. Considering the difference of redox potential (~100–1000 fold) existing between the extracellular space and the intracellular space, it has been well-established that intracellular space is reductive while the extracellular is oxidative, which is strongly related to the intra- and extracellular glutathione concentration (Schafer and Buettner, 2001). Based on these principles redox-sensitive systems are a promising approach for intracellular delivery especially for gene delivery. The glutathione pathway which controls the intracellular redox potential (Meister et al., 1983) is significantly involved in such stimuli-sensitive mechanism. On the other hand, a drug or gene fragment can be encapsulated or conjugated to redox-sensitive nanocarriers carrying disulfide bonds. Once the disulfide bonds are reduced in the presence of an excess of glutathione inside the cell, the drug or gene present in the nanocarrier is released.

He et al. (2012) modified the natural anionic polysaccharide hyaluronic acid (HA) by introducing reduction-sensitive disulfide bonds between the carboxyl groups and the backbone of HA (HA-SS-COOH). Reducible shielding (HA-SS-COOH) and stable hyaluronic acid shielding were introduced in the formation of DNA/ PEI complexes via electrostatic interaction. The disulfide bonds of the crosslinked polymer/DNA complexes proved to be susceptible to intracellular redox conditions. The presence of HA-SSCOOH and HA coating showed lower cytotoxicity, higher gene transfection efficiency and greatly enhanced cellular uptake by HA receptor over-expressed carcinoma cells. Moreover, HA-SSCOOH shielding was superior to HA due to the extra reduction responsive deshielding function.

3.2. Polymeric nanoparticles

Polymeric nanoparticles (NPs) are < 1000 nm in size and are composed of biodegradable or biostable polymers and copolymers. The drug molecules can be (i) entrapped or encapsulated within the particle, (ii) physically adsorbed on the surface, or (iii) chemically linked to the surface of the particle (Kuo and Chen, 2006; Parveen et al., 2012; Zensi et al., 2009).

Polymeric nanoparticles possess a core–shell structure which can be varied by changing the composition of hydrophobic and hydrophilic blocks on the polymer chains. The core consists of a dense polymer matrix in which a hydrophobic drug can be encapsulated. The corona is made of a hydrophilic polymer, such as PEG, PVP, or polysaccharides, which serves to confer steric stability and stealth properties to the particles upon intravenous IV administration. Some of these structures are good candidates for drug delivery applications (Discher and Eisenberg, 2002, Costantino et al., 2012).

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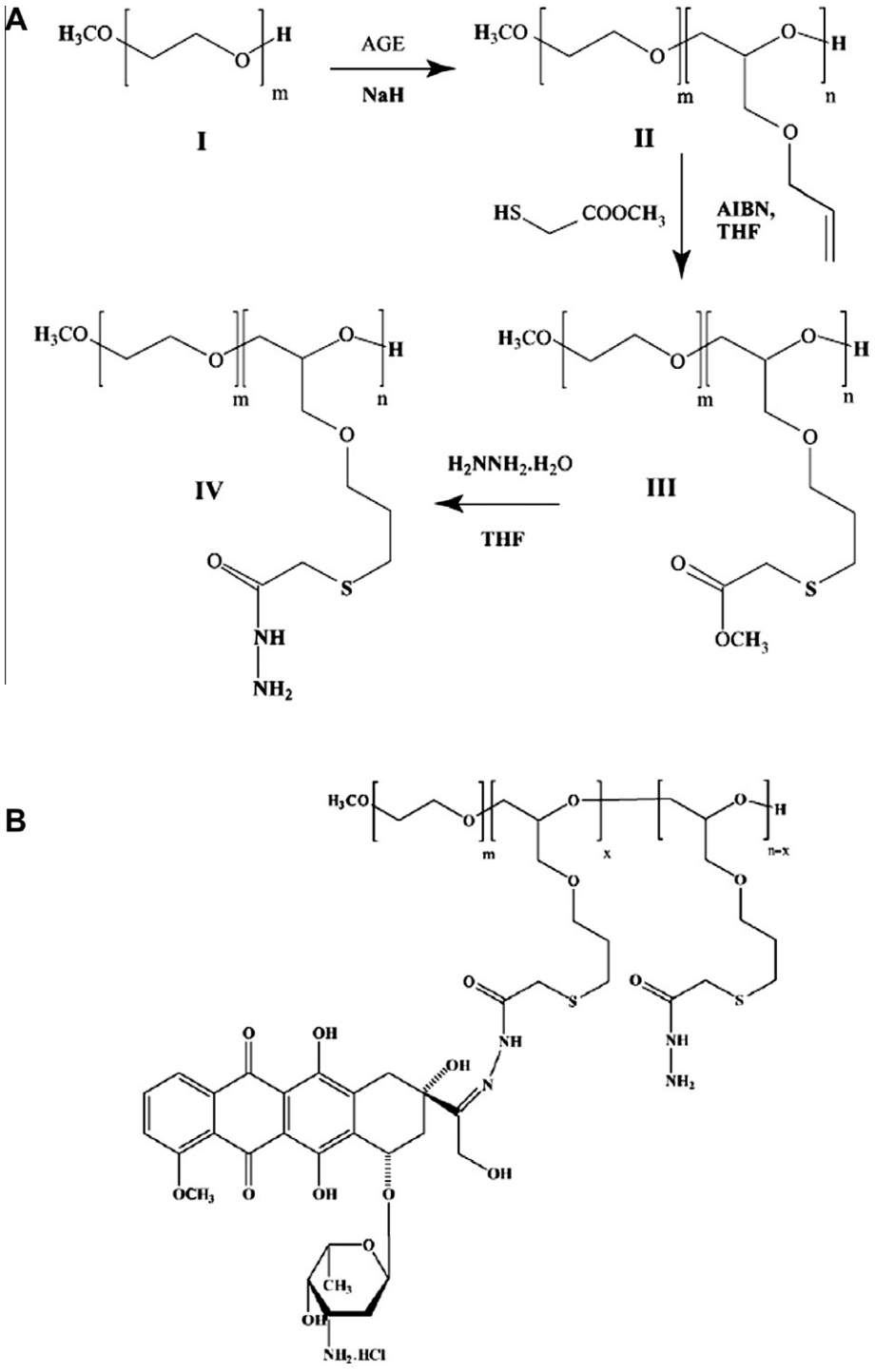

Figure 4 (A) Reaction scheme of the preparation of the polymeric drug carrier IV (B) Structure of the conjugate V (Hruby et al., 2005).

The polymeric nanoparticles can be stimulus responsive by introducing stimulus responsive building blocks into the polymeric structure, and these drug carriers made from nanoparticles have drawn tremendous attention over the past decades (Wel et al., 2006). It would be of great benefit to introduce stimuli-responsive polymers to magnetite to construct a novel drug delivery. Magnetite nanoparticles were conventionally used as ferrofluids and only lately much attention has been directed to their biomedical applications, especially as targeted drug delivery devices (Li et al., 2012; Gupta et al., 2005; Sahu et al., 2012). The reduced size of magnetite nanoparticles enable them to be directed in biological systems by an external magnetic field.

Kim et al. (2008) demonstrated the preparation of temperature-responsive magnetomicelles (Fig. 5) that consist of a functionalized magnetic core, Fe_3O_4-undecylenic acid (Fe_3O_4-UA), and an amphiphilic layer of temperature-responsive polymer. The functionalized magnetic Fe_3O_4-UA core was

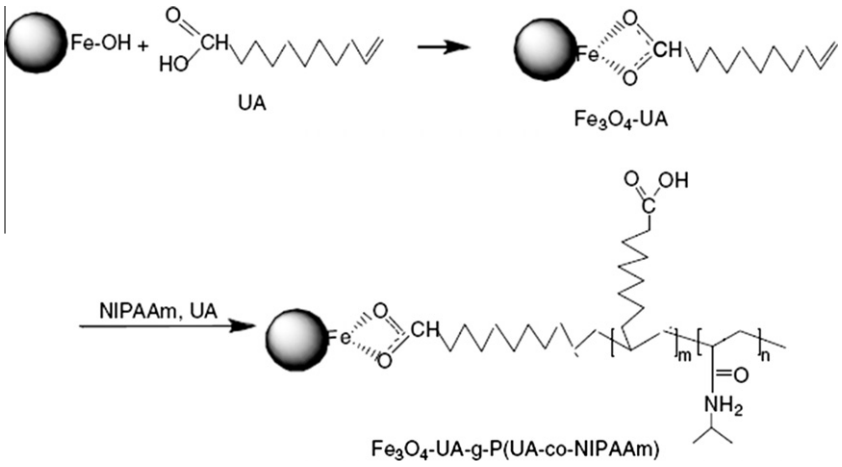

Figure 5 The synthesis route of the Fe_3O_4-UA-g-P(UA-co-NIPAAm) nanoparticles(Kim et al., 2008).

prepared by a suspension-oxidation reaction in an aqueous solution, during which the formation of Fe_3O_4 and the coordination of UA to Fe_3O_4 occurred simultaneously. Amphiphilic poly(undecylenic acid-co-Nisopropyl acrylamide) (P(UA-co-NIPAAm)) was grafted to the Fe_3O_4-UA core as a temperature- responsive micellar surface layer to prepare well dispersed Fe_3O_4-UA-g- P(UA-co-NIPAAm) magnetomicelles with the size of around 8 nm in water. The application of resulted nanosized Fe_3O_4-UA-g-P(UA-co-NIPAAm) magnetomicelles in intelligent drug delivery was further investigated and it was found that resulting magnetomicelles exhibited good potential for temperature triggered controlled drug release (Fig. 6).

3.3. Dendrimers

The term dendrimer, first proposed by Tomalia in 1985, was chosen due to its structural shape, with highly branched, three-dimensional features that resemble the architecture of a tree (Tomalia et al., 1990). A typical dendrimer (Fig. 7) consists of three main structural components: a) a focal core, (b) building blocks with several interior layers composed of repeating units, and (c) multiple peripheral functional groups. The branched units are organized in layers called ''generations'', and represent the repeating monomer unit of these macromolecules (Bronstein and Shifrina, 2012).

Two major synthetic strategies are used for the synthesis of dendrimers, namely, the divergent approach and convergent approach. Both synthetic strategies possess relative advantages and disadvantages and the appropriate route depends mainly on the kind of monomer employed and the target polymer structure (Ihre et al., 1998; Labbe et al., 1996; Kawaguchi et al., 1995). These macromolecules have a multi-branched, three dimensional architecture with very low polydispersity and high functionality. For that reason, dendrimers have fascinated escalating attention for various applications in many fields (Bhadra et al., 2003).

In the last two decades of the scientific research, the development of dendrimers as potential drug vehicles is one of the most active areas of biomedical and pharmaceutical sciences. Dendrimers offer several featured advantages as drug carrier candidates. These advantages include: (1) high density and reactivity of functional groups on the periphery of dendrimers

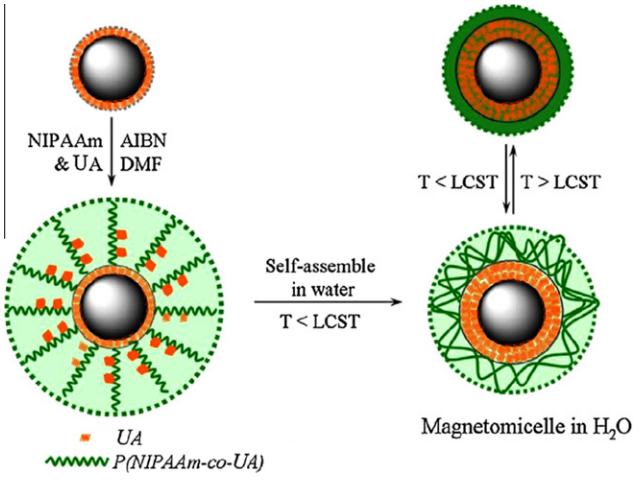

Figure 6 Schematic illustration of the nanosized thermosensitive Fe_3O_4-UA-g-P(UA-co-NIPAAm) magnetic micelle for drug delivery (Kim et al., 2008).

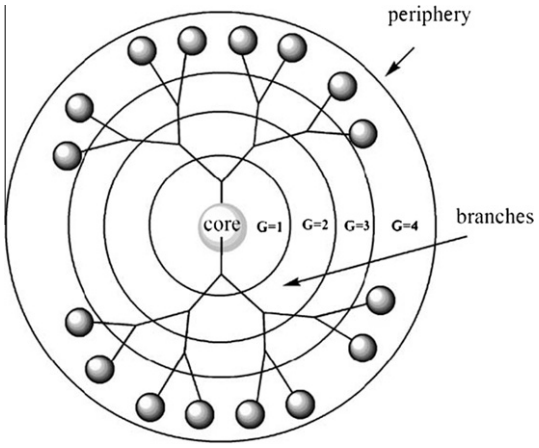

Figure 7 Typical architecture of a fourth generation dendrimer (Flomenboma et al., 2005).

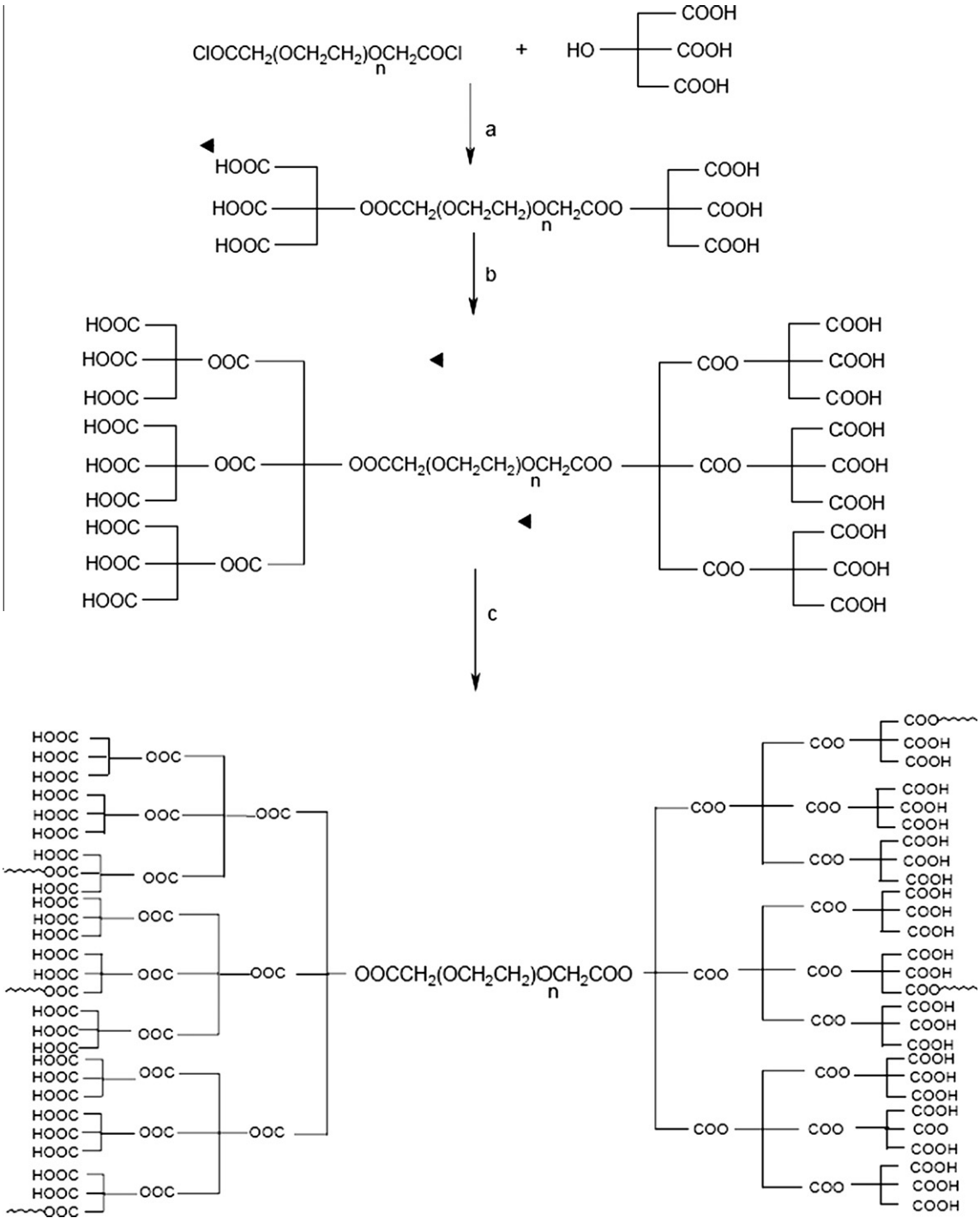

Figure 8 The preparation routes of G_1, G_2, G_3 and the structures of the guest molecules; (a) r.t, Et_3 (b) citric acid. DCC or citric acid, thionyl chloride and (c) citric acid, DCC (Namazi and Adeli, 2005).

that make multifarious bioactive molecules to be easily modified onto the surface (Ciolkowski et al., 2012; Gurdag et al., 2006) (2) well-defined globular structure, predictable molecule weight and monodispersity of dendrimers ensure reproductive pharmacokinetics (Grassi et al., 2012), (3) controllable size (generation-dependent) of dendrimers satisfies various biomedical applications (Siewiera and Watala, 2012), (4) high penetration abilities of dendritic structures through the cell membrane cause increased cellular uptake level of the drugs complexed or conjugated to them (Yang et al., 2009), (5) the lack of immunogenicity of dendrimers makes them much safer choices than synthesized peptide carriers and natural protein carriers (Yang et al., 2009), (6) enhanced penetration and retention (EPR) effect of dendrimers offers preferential uptake of the materials by cancer tissues (Imae and Hamaguchi, 2012), (7) well-established methodologies proposed to construct nanodevices with various functional moieties based on dendrimers provide miscellaneous biomedical applications of

these promising materials, such as cancer targeting therapy, magnetic response imaging, photodynamic therapy, and neutron capture therapy (Konda et al., 2002); (8) Perfectly programed release of drugs molecules or other bioactive agents from dendrimers leads to reduced toxicity, increased bioavailability and a simplified dosing schedule (Konda et al., 2002; Kojima et al., 2000) Prolonged residence time of the drug in the blood and protection of the bioactives from their environment with increased stability are other potential advantages of dendrimeric architecture (Gajbhiye et al., 2009).

Different types of dendrimers, include polyamidoamine (PAMAM), polypropylene imine (PPI), polylysine dendrimers have been used as host for both hydrophilic and hydrophobic drugs. An ideal dendritic drug-carrier must be non-toxic, non-immunogenic, preferably biodegradable; present an adequate biodistribution and allow tissue targeting (Pan et al., 2011).

3.3.1. Dendrimers for drug delivery

Two strategies are used for the application of dendrimers to drug delivery: drug encapsulation by dendritic structure and drug conjugation to dendrimers. Firstly, the drug molecules can be physically entrapped inside the dendrimers; secondly, the drug molecules can be covalently attached onto the surface or other functionalities to afford dendrimer–drug conjugates (Liu et al., 1999).

Dendritic macromolecules have non-polar cavities in their interior, which ensures them capable of encapsulating hydrophobic drug molecules (Gupta et al., 2006). Moreover, there are large numbers of positively or negatively charged functional groups on the surface of dendrimers, which make it easy for drug molecules with opposite charges to attach (Cheng and Xu, 2005). These non-covalent inclusions or complexes offer a variety of promising advantages such as enhanced water solubility, drug stability, programed release of drugs from the matrixes, and improved pharmacodynamic (PD) and pharmacokinetic (PK) behaviors (Gupta et al., 2006).

Fréchet and co-workers examined hydrophobic interactions between a poly(benzyl ether) dendrimer having a carboxylic acid surface and a hydrophobic chromophore (Fréchet., 1993). The dendrimer was able to dissolve hydrophobic molecules such as pyrene in water with π–π interactions between benzyl ether and aromatic guest molecules, which is a very promising strategy from a therapeutic point of view, because many drugs have hydrophobic characteristics. Acid–base interactions and hydrogen bonding have been utilized for the formation of host–guest systems.

Although drug-encapsulating dendrimers are thought to be useful because the drug molecules remain intact inside the dendrimers (Oliveira et al., 2010), the dendritic nanostructures released their contents quickly under physiological conditions. Therefore, their encapsulation ability is still to be improved for drug delivery systems. To elevate the ability of dendrimers to retain small guest molecules in the non-polar interior, introduction of shell structures to the dendrimer surface might be an effective strategy (Fréchet., 1993). Citric acid–polyethylene glycol–citric acid (CPEGC) triblock dendrimers as biocompatible compounds containing G_1, G_2 and G_3 [fig. 8] were applied as the drug-delivery systems by Namazi and Adeli (2005). The guest molecules, which are hydrophobic when trapped into the suitable sites of dendrimers, are becoming soluble in aqueous solution. The quantity of trapped molecules and drugs such as 5-amino salicylic acid (5-ASA), pyridine, mefenamic acid, and diclofenac was measured. The controlled release of the above-mentioned molecules and drugs in vitro conditions was also studied.

Conjugation of drugs to the dendrimer is an attractive approach for intelligent drug delivery because a single dendrimer molecule can stably carry many drug molecules using many functional groups on the outer shell and reach the target cancer site through EPR effects. Stability and cleavability of the linkage, which combines a polymer and a drug molecule, are important keys for the effectiveness of the polymer drug conjugates to release drug molecules at the target.

Large numbers of functional groups on the outer shell of dendritic polymer are responsible for high reactivity and expected to conjugate with a type of bioactive molecules such as therapeutic agents, targeting moieties, imaging chemicals, and biocompatible molecules (Cheng et al., 2007). Drugs covalently conjugated to the periphery of dendrimers can lead to a much slower release rate from the polymer matrixes and are much more influenced by the PD and PK behaviors and by the properties of the dendrimers, compared to those encapsulated in the non-polar cavities by electrostatic interactions and loaded on the surface of dendrimers by electrostatic interactions (Cheng et al., 2007; Najlah et al., 2006).

One of the first groups to experiment on the use of dendritic – drug conjugates was Fréchet and coworkers in 1999 (Liu et al., 1999a,b). In this research, a poly(arylether) dendrimer was designed with two different surface functionalities that were able to covalently bind model drugs and solubilise groups. PEG was chosen as the solubilising group as a result of its high water-solubility and biocompatibility. Different

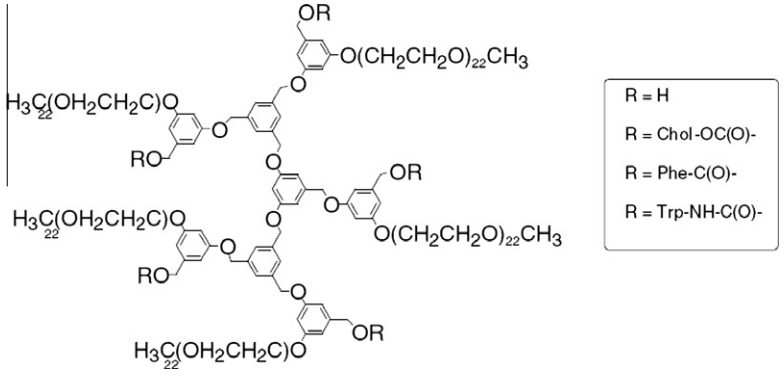

Figure 9 Poly(arylether) dendrimer–drug conjugate (Liu et al, 1999a,b).

kinds of hydrolytically labile linkages were investigated for drug conjugation including carbonate, carbamate and ester linkages, while the drugs used were cholesterol and two amino acids, phenylalanine and tryptophan (Fig. 9).

Therefore, the complexation of drugs to dendrimers via hydrophobic encapsulations or electrostatic interactions usually preserves the chemical integrity and pharmacological properties of drugs, while covalent attachment of drugs to the surface groups of dendrimers through chemical bonds is more suitable for a better control over drug release than can be achieved by simple encapsulation/electrostatic complexation of drugs into/with the dendrimers (Li et al., 2012a,b; Cheng et al., 2008).

4. Carbon nanotubes in drug delivery

Since the discovery of carbon nanotubes (CNTs) in 1991 (Iijima, 1991), CNTs have raised considerable attention due to their excellent mechanical, electrical and surface properties that have made them ideal candidates for a wide range of applications such as structural materials (Guldi et al., 2006; Goldberger et al., 2006). Recently, its potential application in biotechnology has attracted much interest, as CNTs have been reported to exhibit great advantages in biosensors (Qureshi, et al., 2012; Zhang et al., 2007a), biomedical devices (Li et al., 2011) and drug delivery systems (Karchemski et al., 2012; Zhang and Olin, 2012) etc.

Pristine, CNTs tend to bundle up and are insoluble in most types of solvents (Tasis et al., 2003) making it difficult to use them in biological systems. Moreover, some CNTs without any functionalization have been shown to be cytotoxic (Colvin, 2003; Warheit et al., 2004). Therefore, to integrate CNTs into biological systems, CNTs need to be functionalized. Functionalization can make CNTs soluble and improve their biocompatibility properties. Moreover, through functionalization, bioactive agents can be conjugated to CNTs which can serve as a carrier for drugs, antigens and gene delivery (Tran et al., 2009).

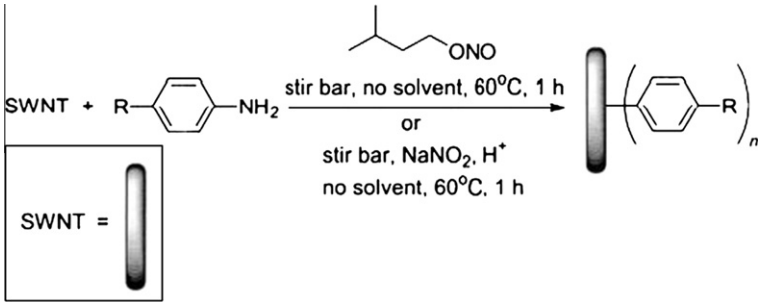

Figure 10 Schematic representation of SWCNT functionalization by addition reactions (Dyke and Tour, 2004).

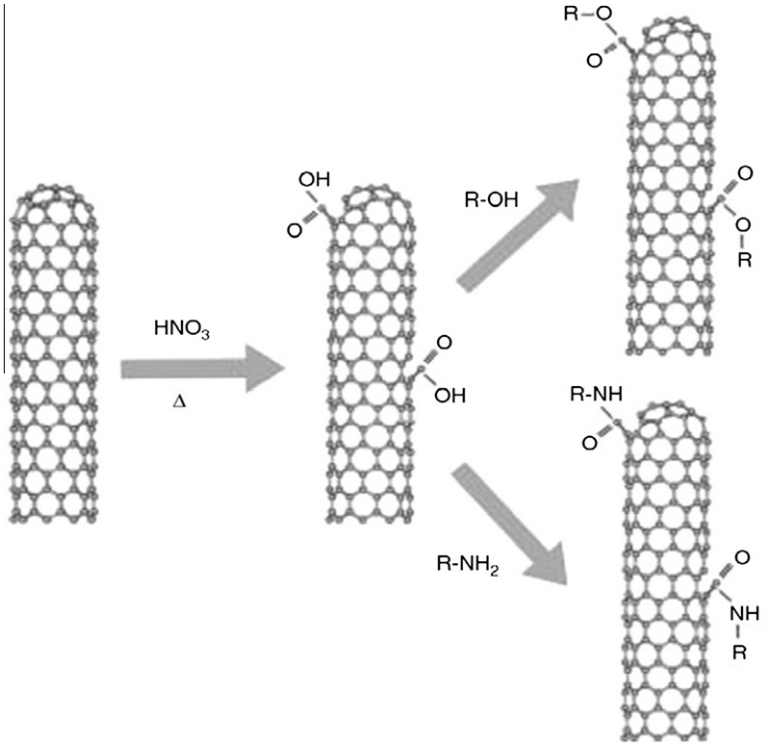

Figure 11 Functionalization of CNTs through oxidation (Balasubramanian, 2005).

Functionalization strategies can be divided into two main approaches: (i) additional reactions to the sidewalls and tips of CNTs and (ii) oxidation followed by carboxyl based couplings. In the first strategy, additional reactions are employed to attach some organic groups to the sidewalls and/or tips of the CNTs. The process is schematically shown in Fig. 10. The advantages of this functionalization strategy include its simplicity, its ability to produce highly soluble materials and its ease to implement in the industrial scale (Dyke and Tour, 2004). However, this simple functionalization method has the disadvantage of not allowing for many desirable further modifications of the tubes.

The second functionalization process is through oxidation and carboxyl-based couplings. In this method, the tube cap openings are created and holes in the side walls are formed by an oxidation process in which strong acids are used (Adeli et al., 2008a). The carboxylic groups also allow for covalent couplings with other molecules through amide and ester bonds (Fig. 11). Through this process, CNTs can be conjugated with various bioactive agents such as peptides (Pantarotto et al., 2004), proteins (Shi Kam et al., 2004), nucleic acids (Lacerda et al., 2008) and therapeutic agents for example anti-cancer drugs (Liu et al., 2008). Importantly, by bonding with suitable groups, CNTs can become soluble in aqueous (Fernando et al., 2004) or organic solvents.

Functionalized CNTs have been shown in many studies to be able to cross cell membranes (Pantarotto et al., 2004; Shi Kam et al., 2004; Kam et al., 2005). The ability of CNTs to cross cell membranes has allowed them to become of particular high interest for drug delivery strategies. In targeting the delivery of drugs to cells, drugs are first attached to the carrier by either covalent or noncovalent bonding.

There are several factors that are using CNTs as a vehicle to transport drugs into cells. First, surface properties of CNTs can greatly influence their interaction with cells and therefore their internalization into the cells. For example, there are hydrophobic and hydrophilic regions on cell membranes and the hydrophobic and/or hydrophilic interaction of the cells with CNTs will be influenced by the hydrophilicity of the tubes. Second, size and shapes of CNTs can also be important in their abilities to go into cells. CNTs which are well dispersed and have shorter lengths will be more likely to be internalized by the cells than bundled CNTs or CNTs that have longer lengths (Tran et al., 2009).

4.1. Polymeric carbon nanotubes

Many studies have reported on the toxicity of CNTs that is important in biological systems. The most important factor related to the toxicity of these materials is their high hydrophobicity or poor water solubility in biological mediums which increases their interactions with cells membranes and causes the formation of aggregated particles and therefore causes heterogeneous interactions with cell components (Ding et al., 2005).

Chemical modification of the surface of CNT reduce their aggregations and size polydispersity and raise their solubility, leading to an increase in their biocompatibility (Tsubokawa, 2005; Zhang et al., 2007b; Zeineldin et al., 2009). Varieties of organic compounds such as polymers and dendrimers are conjugated onto the surface of CNTs (Feng et al., 2007; Campidelli et al., 2006; Yingkui et al., 2007; You et al., 2007).

Modification of the CNTs by polymers are based on either physical interactions or chemical bonding and are called "noncovalent" or "covalent" approaches respectively. Noncovalent approach is based on poor vanderWaals interactions between CNTs and polymers and includes dispersion with the low molar mass polymers, polymer wrapping and polymer adsorption (Adeli et al., 2008a). In the covalent approach, organic molecules or macromolecules are grafted onto the convex and tip of CNTs through chemical linkages. This method is very effective because grafted macromolecules raise the solubility of CNTs even with a low degree of functionalization (Star et al., 2001; Chen et al., 2002; Narizzano and Nicolini, 2005).

Two methods are used for Covalent attachment of polymers to the surface of CNTs including "grafting to" or "grafting from" methods. In the "grafting to" method, polymers are connected to the functionalized CNTs through a chemical reaction between their functional groups. The "grafting to" method, in which a polymer containing a reactive functional group can be attached to a functionalized CNT by the usual chemical reactions (Díez-Pascual et al., 2012). The "grafting from" method in which polymerization of a suitable monomer is initiated from the reactive sites of CNTs. This method leads to the higher grafting density and control over the polymer growth with the possibility of designable structure (Adeli et al., 2008b; Qin et al., 2004).

Recently, among polymeric materials, dendrimers and hyperbranched polymers have attracted more interest due to their unique molecular features and properties (Namazi and Adeli, 2005, Namazi et al., 2007; Adeli et al., 2007, 2008b).

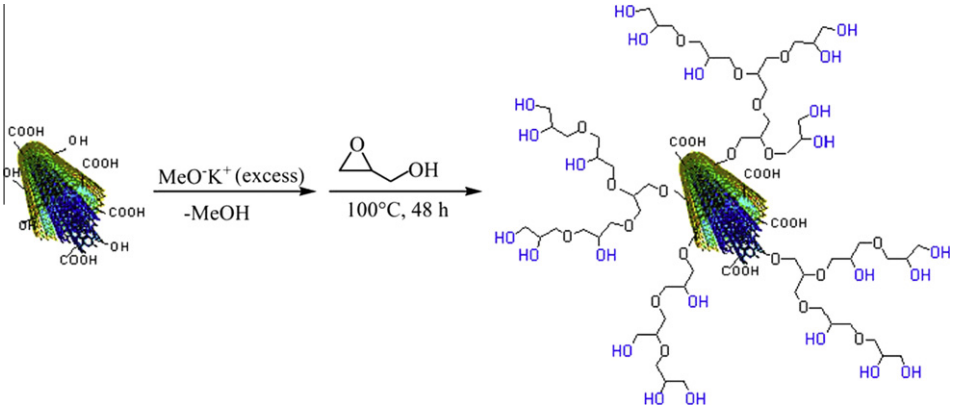

Figure 12 Synthetic process for the MWCNT-g-PG hybrid materials (Adeli et al., 2009).

Additionally some hybrid materials containing carbon nanotubes and grafted hyperbranched polymers are synthesized through "grafting from" approach (Adeli et al., 2009). Adeli et al. (2009) synthesized carbon nanotubes-graft-polyglycerol (Fig. 12) and some short-term in vitro cytotoxicity and hemocompatibility tests were conducted on HT1080 cell line (human Fibrosarcoma). They reported that the functionalization of the carbon nanotube by polyglycerol is to decrease in vitro cytotoxicity of the carbon nanotube.

Also, these research groups reported (Adeli et al., 2011) an anticancer drug delivery system based on carbon nanotube–dendrimer hybrid nanomaterials. In this work, γ-Fe_2O_3 nanoparticles, were deposited onto the surface of multi-walled carbon nanotubes and CNT/g-Fe_2O_3 hybrid nanomaterials were obtained. Then block copolymers poly(citric acid)- polyethylene glycol- poly(citric acid) (PCA–PEG–PCA), were synthesized and cisplatin was conjugated with their carboxyl functional groups and anticancer prodrugs were prepared. There are several key features of these hybrid drug delivery systems: (i) their ability to cross cell membranes and also high surface area per unit weight for high drug loading assigned to CNTs, (ii) high functionality, water solubility and biocompatibility assigned to PCA–PEG–PCA linear-dendritic copolymers and (iii) targeting tumors using a magnetic field assigned to γ-Fe_2O_3 nanoparticles. The efficacy of drug delivery systems for killing the cancer cells and targeting the drugs toward tumors was investigated.

5. Conclusions and Future Perspectives

Nanotechnology will assume an essential place in drug delivery and human therapeutics. Although the development of drug delivery systems, is just emerging, it shows a promising future. Nanotechnology, which is still in its infancy, provides opportunities for physicists, chemists and biochemists, etc. to develop systems that may eventually match in sophistication and precision of biological structures elaborated by nature.

Nanotechnology is an emerging field that is potentially changing the way we treat diseases through drug delivery. However, significant challenges remain in pushing this field into clinically viable therapies. The design and testing of novel methods of controlling the interaction of nanomaterials with the body are some of the current barriers to translating these technologies to therapies. Methods of targeting nanomaterials to specific sites of the body while avoiding capture by organs, such as the liver and spleen, are major challenges that need to be addressed.

Nanoscale structures such as surface topography and patterning could be used to direct cell behavior. The incorporation of these strategies within tissue engineering scaffolds could further enhance their function. As Feynman had predicted, there has been plenty of room at the bottom to modify and enhance existing technologies by controlling material properties at the nanoscale. Therefore, with sufficient time and research, the promise of nanotechnology based medicine may become a reality.

Acknowledgment

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