Review Article

Recent Progress on Nanostructures for Drug Delivery Applications

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With the rapid development of nanotechnology, the convergence of nanostructures and drug delivery has become a research hotspot in recent years. Due to their unique and superior properties, various nanostructures, especially those fabricated from self-assembly, are able to significantly increase the solubility of poorly soluble drugs, reduce cytotoxicity toward normal tissues, and improve therapeutic efficacy. Nanostructures have been successfully applied in the delivery of diverse drugs, such as small molecules, peptides, proteins, and nucleic acids. In this paper, the driving forces for the self-assembly of nanostructures are introduced. The strategies of drug delivery by nanostructures are briefly discussed. Furthermore, the emphasis is put on a variety of nanostructures fabricated from various building materials, mainly liposomes, polymers, ceramics, metal, peptides, nucleic acids, and even drugs themselves.

1. Introduction

In the past few decades, nanostructures have attracted intensive research interest due to their unique and superior properties as compared with conventional bulk materials. They have been applied in a wide range of fields, such as materials, electronics, sensing, catalysis, environment, and drug delivery. In drug delivery systems, some of the challenges which need to be faced include bioavailability, *in vivo* stability, solubility, absorption, sustained and targeted delivery to site of action, therapeutic efficacy, side effects, and fluctuation of drug concentration in plasma [1]. To surmount these challenges, large quantities of studies have been carried out to explore the fabrication and application of various nanostructures in drug delivery.

Generally, nanostructures used in drug delivery are constructed via "bottom-up" approach, which is achieved by growing or assembling of building blocks [2]. It is noteworthy that a considerable proportion of nanostructures are obtained via the self-assembly of building blocks. Based on the properties and structures of building blocks, various kinds of noncovalent interactions play significant roles in the self-assembly processes and contribute to the stability of resultant nanostructures.

In the delivery process, passive delivery of drugs as "cargoes" by nanocarriers is the most common strategy. The association between drugs and nanocarriers is achieved by either physical encapsulation or chemical conjugation. Meanwhile, self-delivery is another alternative which builds nanostructures with drug molecules themselves instead of drug molecules only being "cargoes" needed to be delivered.

The fabrication of well-defined nanostructures with distinct properties, especially through self-assembly process, has been an extremely active field in drug delivery. A large variety of nanostructures, including liposomes, polymeric, ceramic, metallic, peptides-based, nucleic acid-based, and drug-based nanostructures, have already emerged and found

their applications in the delivery of various drugs, including small molecules, peptides, proteins, and nucleic acids.

2. Driving Forces for Self-Assembly of Nanostructures

In drug delivery system, many nanostructures are formed by self-assembly, which is a force balance process in which well-defined structures or patterns are spontaneously formed from building blocks without human intervention [3]. The most important driving forces in self-assembly process are noncovalent interactions, including van der Waals interactions, hydrophobic effect, electrostatic interactions, hydrogen bonding, π-π staking interactions, steric and depletion forces, coordination bonding, and solvation and hydration forces [3]. Compared with covalent bonds, noncovalent interactions are much weaker, which involve more dispersed variations of electromagnetic interactions between molecules or within a molecule [4]. However, noncovalent interactions possess the ability to significantly influence the detailed structures of self-assembled nanostructures, separately or synergistically.

2.1. Hydrophobic Effect. Among various noncovalent interactions in self-assembly process, hydrophobic effect is the most important. A wide range of building blocks for self-assembly are amphiphilic molecules, including many synthetic building blocks and biomolecules such as proteins and lipids. Due to the coexistence of polar and nonpolar regions, the self-assembly of amphiphilic molecules can be readily accomplished through microphase separation driven by thermodynamics. In aqueous solutions, the nonpolar regions of the building blocks will collapse and cluster together to expose the smallest possible hydrophobic area to water while the polar regions attempt to maximize their interaction with water [3]. Taking amphiphilic diblock copolymers as an example, when the concentration is higher than the critical micelle concentration (CMC), the hydrophobic block will assemble into a core, and the hydrophilic block stretches itself in water and thus forms a shell surrounding the hydrophobic core.

2.2. Electrostatic Interactions. Electrostatic interactions, which involve both attractive and repulsive forces between charged atoms, ions, or molecules, also have a strong effect on many self-assembly processes. Cationic polymers can interact with anionic proteins or genes through electrostatic interactions, forming stable nanoparticles in aqueous solutions [5]. For example, according to Xia et al. [6], water-soluble cationic conjugated polymer can bind to DNA by both electrostatic interactions and hydrophobic effect in the delivery of DNA. Upon reducing the strength of the hydrophobic effect, electrostatic attractions became the important interaction that regulated the binding between the water-soluble conjugated polymer and DNA.

2.3. Hydrogen Bond. Hydrogen bond is the electrostatic attraction between H atom and a highly electronegative atom nearby, such as N, O, or F. Hydrogen bond attractions can occur both between molecules (intermolecular) and within different parts of a single molecule (intramolecular). It is very common both in inorganic molecules (e.g., water) and in organic molecules (e.g., DNA and proteins). For instance, hydrogen bond exists between the amides and carbonyls in the backbone of β-sheets formed by the self-assembly of peptides and enhances the stability of the self-assembled nanostructures [7].

2.4. π-π Staking. In addition, π-π staking can also play a role in maintaining the nanostructures from self-assembly. In the multiscale self-assembly of diphenylalanine (FF), the backbone hydrogen bonds and π-π interactions from the aromatic peptide side-chains hold the self-assembled FF structures together [8]. In alkaline solution, folic acid can self-assemble via the formation of Hoogsteen-bonded nanoscale tetrameric discs, which then stack through π-π interactions and interdisc hydrogen bonding to form chiral columns [9, 10]. However, due to the lack of hydrogen bond, methotrexate was unable to form any well-defined nanostructures with similar treatment [11].

In summary, noncovalent interactions play important roles in the formation of nanostructures, separately or synergistically. Good control of physical properties of nanostructures is highly important for their successful utilization in drug delivery. When designing nanostructures for drug delivery, noncovalent interactions should be taken into consideration and be rationally applied in the strategies.

3. Strategies of Drug Delivery by Nanostructures

3.1. Passive Delivery. In drug delivery by nanostructures, drugs are frequently associated with nanocarriers by either physical encapsulation or chemical conjugation [12] and thus passively delivered as "cargoes" by nanocarriers.

In the former method, drugs are physically incorporated into the internal cavity and stabilized by noncovalent interactions between drugs and nanocarriers, especially hydrophobic effect [13, 14]. Many nanostructures such as nanomicelles, nanocapsules, and porous nanoparticles have a net hydrophobicity to stabilize the entrapped drug molecules [15]. When the nanostructures are disassembled at target sites of action, drugs will be released as a consequence. However, physical encapsulation into hydrophobic compartments often results in very low drug loading contents (DLC), typically on the order of 2–5% by weight [16]. It is one of the crucial challenges posed by nanostructures on drug delivery.

The second method is to attach cargo drugs to the nanocarriers by direct chemical conjugation. In order to have a good control over the triggered release of drugs, the conjugation between nanocarriers and drugs should be cleavable at target sites. If drugs cannot be cleaved from their nanocarriers in time, their bioactivity and efficacy will be reduced. On the other hand, if drugs tend to be dissociated from their nanocarriers too quickly, they will fail to reach the target sites of action in a significant dose. This is so-called "burst release," which will lead to rapid clearance of the drugs from the body
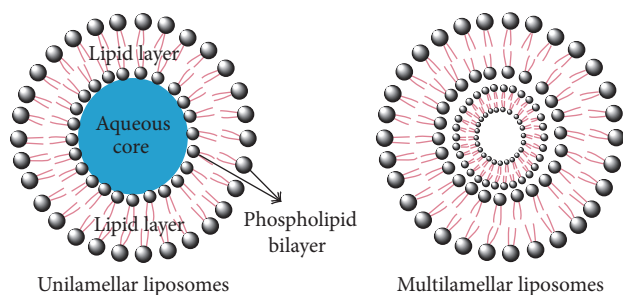
FIGURE 1: Schematic representation of basic structures and different types of liposomes [19]. Copyright © 2011, Mishra et al.

[13]. Therefore, rational design of the chemical conjugation between a drug and its nanocarrier is of great importance.

3.2. Self-Delivery. Apparently, the common strategies mentioned above merely consider drugs as active pharmaceutical compounds which need to be delivered. However, their properties, such as self-assembly ability and solubility, are ignored. In recent years, there is a growing trend to build well-defined nanostructures with drug molecules as building units. Through this strategy, the distribution and content of drugs in the nanostructures can be accurately controlled. Via rational analysis, design, and fabrication, lots of self-delivering nanostructures with high and fixed drug contents have been created. Detailed illustration and examples will be given in Section 4.8.

4. Various Nanostructures for Drug Delivery

In the past few decades, nanostructures with various shapes and sizes have been fabricated and applied for many drugs. In this section, various nanostructures fabricated by different materials and their applications in drug delivery are illustrated and discussed in detail.

4.1. Liposomes Nanostructures. Liposomes have been under extensive investigation and have become a common nanocarrier for drug delivery since 1965. Nanostructures fabricated with liposome are the first drug delivery system on the nanoscale to make the transition from concept to clinical application and have become a well-established technology platform with considerable clinical acceptance [17].

Liposomes are small artificial vesicles developed from phospholipids such as phosphatidylglycerol, phosphatidylserine, and phosphatidylcholine [18]. On the basis of lipid bilayers, liposomes can be classified into unilamellar vesicles (UVs) and multilamellar vesicles (MLVs), as shown in Figure 1. UVs consist of an aqueous core surrounded by a lipid bilayer, separating the inner aqueous core from the outside. As metastable energy configurations, MLVs are composed of various layers of lipid bilayers [19].

Due to the structures described above, liposomes have the ability to compartmentalize and solubilize both hydrophilic and hydrophobic materials by nature. This unique feature, along with biocompatibility and biodegradability, makes liposomes attractive as drug delivery vehicles. Particularly, hydrophobic drugs can place themselves inside the bilayer of liposomes and hydrophilic drugs are entrapped within the aqueous core or at the bilayer interface [20].

Besides, liposomes have the functions to prevent drug degradation, reduce side effects, and target drugs to site of action [18, 21]. Hydrophobic drugs such as cyclosporin and paclitaxel are usually formulated in surfactants and organic cosolvents to increase their solubility in water. However, these solubilizers may cause toxicity at the doses needed to deliver the drug. In contrast, liposomes, which are nontoxic, biocompatible, and biodegradable, can deliver water-insoluble drugs with much less side effects. For example, they have been successfully applied in transdermal drug delivery to enhance skin permeation of drugs with high molecular weight and poor water solubility [22]. Besides, liposomes can accumulate at sites of increased vasculature permeability, when their average diameter is in the ultrafilterable range (<200 nm) [17].

However, the membrane of liposomes is generally thin, fragile, and thus inherently not stable [23]. Liposomes are also limited by their low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components, and poor storage stability [21, 24].

In the past five decades, many important technical breakthroughs, such as remote drug loading, extrusion for homogeneous size, long-circulating (PEGylated) liposomes (stealth liposomes), triggered release liposomes, liposomes containing nucleic acid polymers, ligand-targeted liposomes, and liposomes containing combinations of drugs, have led to numerous clinical trials in the delivery of diverse drugs, such as anticancer, antifungal, and antibiotic drugs, gene medicines, anesthetics, and anti-inflammatory drugs [17].

4.2. Polymeric Nanostructures. In the field of drug delivery, various polymeric nanostructures have been a hot topic of research for a long time. Generally speaking, polymer-based drug nanocarriers can significantly increase the solubility of hydrophobic drugs, reduce their cytotoxicity toward normal tissues, prolong the circulation time of drugs in blood, facilitate the entry of nanoparticles, and improve the utilization efficiency [25].

It is widely acknowledged that polymers used for drug delivery should be nontoxic and biocompatible. Natural polymers, such as chitosan [26], dextran [27], heparin [28], and hyaluronan [29], have been well investigated for drug delivery in the past few decades. However, research on using synthetic polymers to build various nanostructures is more prevalent in the field of drug delivery. Polyesters, polycarbonates, polyamides, polyphosphazenes, and polypeptides are among the most commonly used synthetic polymers [5].

4.2.1. Polymeric Nanomicelles and Nanovesicles. Owing to a great diversity of polymers, nanostructures of different sizes and morphologies have been obtained. As mentioned above, amphiphilic molecules are prone to self-assemble into various nanostructures driven by hydrophobic effect. Therefore, amphiphilic polymers containing both hydrophilic and hydrophobic blocks have been extensively studied for use in drug delivery. By controlling the hydrophilic/hydrophobic
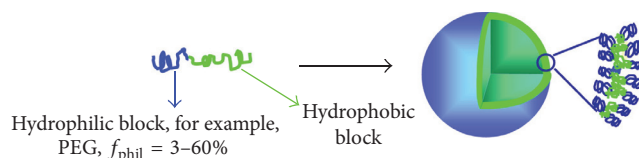
FIGURE 2: Polymeric vesicles derived from asymmetric block copolymers [23]. Copyright © 2009, American Chemical Society.
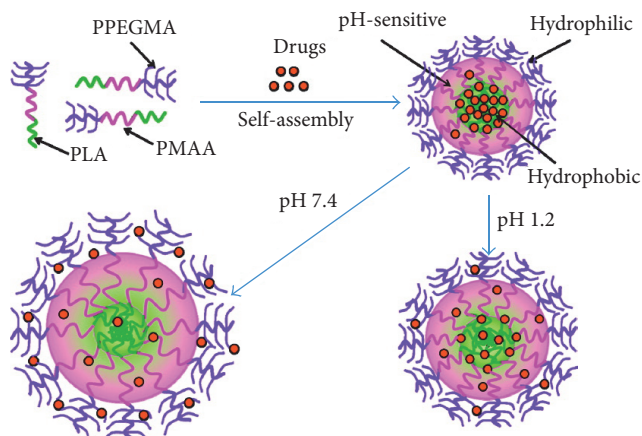

FIGURE 3: Schematic illustration of drug loading and pH-dependent release from PPEGMA-b-PMAA-b-PLA micelles [51]. Copyright © 2012, American Chemical Society.

balance, various nanostructures, such as spherical micelles, cylindrical micelles, and vesicles, can be formed from amphiphilic polymers. According to Won et al. [30], the weight fraction of the hydrophilic block (f_{phil}) can play a vital role in controlling the shapes of nanostructures from amphiphilic polymers in a pure water medium. At f_{phil} = 55–70%, spherical micelles are predominant; at f_{phil} = 45–55%, spherical vesicles tend to form; at f_{phil} = 20–40%, vesicles are favoured. Both polymeric micelles and vesicles are the most common and stable morphological structures of amphiphiles in water [23]. Polymeric micelles are nanostructures with a hydrophilic core and a hydrophilic shell (see Figure 2). Generally, hydrophilic drug molecules are encapsulated in the core of nanomicelles. Meanwhile, polymeric nanovesicles possess bilayer structures with an aqueous interior core, isolating the core from the external medium [31]. Polymeric vesicles can encapsulate hydrophilic molecules within the aqueous interior and also integrate hydrophobic molecules within the membrane. Therefore, polymeric vesicles have the capability to deliver hydrophilic as well as hydrophobic drugs such as anticancer drugs, genes, and proteins.

4.2.2. Polymeric Nanogels. However, polymeric nanomicelles and nanovesicles can only be maintained above the critical micelle concentration (CMC). Below CMC, they will dissociate into single polymer chains and thus lose the function as drug carriers. In order to avoid the dissociation of the self-assembled nanostructures, linking the polymers to obtain nanogels which are more stable in different conditions has become a common and effective approach. In recent years, nanogels have drawn increasing attention because of their high loading capacity and good stability [5].

4.2.3. Polymeric Nanocapsules. Hollow polymeric nanocapsules have also been developed by miniemulsion polymerization in the past few decades. Drugs are confined in the cavities of nanocapsules and surrounded by external polymer membranes [32]. Nanocapsules are able to improve the oral bioavailability of proteins and peptides, including insulin, elcatonin, and salmon calcitonin [32, 33]. Nanocapsules can protect the degradation of drugs, reduce systemic toxicity, provide controlled release, and mask unpleasant taste [34]. Nevertheless, due to high stability and low permeability of nanocapsules, drugs carried by nanocapsules have trouble both in encapsulation into the capsules after formulation and in the release at target site [18].

4.2.4. Polymeric Dendrimers. Apart from these nanostructures, dendrimers with three-dimensional, hyperbranched globular nanopolymeric architectures have been the research focus of many scientists these years. Due to their attractive features like nanoscale size, narrow polydispersity index, excellent control over molecular structures, and availability of multiple functional groups at the periphery and cavities in the interior [35], dendrimers have been explored to be used in the delivery of different bioactive agents such as drugs [36], oligonucleotides [37], enzymes [38], vaccines [39], and genes [40]. Drugs can be either incorporated into the interior or attached on the surface. Due to their versatility, both hydrophilic and hydrophobic drugs can be associated with dendrimers [18].

4.2.5. Polymeric Stimulus-Sensitive Nanostructures. Particularly, recent research has focused on stimulus-sensitive (smart) nanostructures for drug delivery because it is a superior approach for delivering and releasing drugs to specific site at the desired time. Many kinds of stimuli, including chemical (e.g., redox, pH), physical (e.g., temperature, light), and biological (e.g., enzymes) ones, have been exploited in the design of smart drug delivery systems [5]. Figure 3 represents a drug delivery system based on pH-sensitive PPEGMA-b-PMAA-b-PLA micelles.

4.3. Ceramic Nanostructures. Ceramic nanostructures refer to the porous structures of nanoparticles, which are fabricated from biocompatible inorganic compounds, such as silica, calcium phosphate, alumina, and titania. In the biomedical field, ceramic nanostructures are considered to be excellent carriers for drugs, genes, and proteins.

4.3.1. Mesoporous Silica Nanostructures. Mesoporous silica nanoparticles (MSN) have been the most extensively studied ceramic nanoparticles for drug delivery in the last twenty years. MSN possesses a lot of favourable properties, including monodispersity, high specific surface area, tunable pore size and diameter, and versatile functionalization [41, 42]. A large variety of drugs have been successfully loaded in MSN or

covalently grafted at MSN, such as camptothecin [42], paclitaxel [43], doxorubicin [44], cysteine [45], telmisartan [46], and chlorambucil [47]. Generally speaking, MSN are often functionalized to achieve a better delivery of drugs. For example, mannose or galactose functionalized MSN have been reported to induce a higher cytotoxicity of cancer cells than unfunctionalized ones and target to cancer cells more efficiently [48, 49]. Folate, a targeting ligand, has been covalently attached to amino-functionalized silica nanoparticles loaded with a hydrophobic small molecule anticancer drug. Folate-functionalized nanoparticles turned out to be significantly cytotoxic to tumor cells, whereas normal cells were much less affected by the presence of these structures [50].

4.3.2. Calcium Phosphate Nanostructures. Calcium phosphate systems, including hydroxyapatite and tricalcium phosphates, are soluble under acidic conditions (pH ≤ 5) during bone remodelling. After cellular uptake, calcium phosphate systems are soluble under the conditions of lysosomal degradation [52]. The variable stoichiometry, functionality, and dissolution properties make these ceramic nanoparticles suitable for drug delivery. Their chemical similarity to bone and thus biocompatibility as well as variable surface charge density contribute to their controlled release properties [53].

4.3.3. Alumina and Titania Ceramic Nanostructures. In addition, much progress has also been made in the development of alumina and titania ceramic nanoparticles for drug delivery. Water dispersible, highly stable, and fluorescent alumina nanoparticles have been capped with natural proteins [54]. Diverse spherical titania nanostructures, including mesoporous spheres, spherical flaky assemblies, and dendritic particles of variable diameter and monodispersity in size, have been demonstrated in recent years [55].

However, there are concerns on the application of nonbiodegradable ceramic nanoparticles, such as hydroxyapatite, alumina, and titania, because they will accumulate in the body and cause harmful effects [56].

4.4. Metallic Nanostructures. Metallic nanostructures generally mean the spherical metallic nanoparticles, such as gold, silver, gadolinium, and iron oxide, which have also been studied for targeted drug delivery.

4.4.1. Gold and Silver Nanostructures. Gold nanoparticles have been frequently used in drug delivery due to their favourable optical and chemical properties, including tunable sizes in the range of 0.8 to 200 nm, easy surface modification with different functional groups, good biocompatibility, and visible light extinction behaviour [57]. They can be conjugated with polyethylenimine (PEI) to deliver genes [58] and be modified and conjugated with suitable proteins/peptides to target the cell nucleus [59]. Folate-functionalized Au or Ag nanoparticles have been demonstrated to be able to lower the unwanted toxicity of diminazene aceturate and improve its selectivity and therapeutic efficacy [60]. In many cases, gold nanoparticles are covalently bounded to polymers, greatly enhancing the stability of polymeric nanoparticles for drug delivery [61]. The cytotoxicity of gold nanoparticles is quite low [62], and they have served as scaffolds for drug delivery. In contrast, silver nanoparticles are relatively not favoured for drug delivery due to their toxicity to eukaryotic cells.

4.4.2. Gadolinium Nanostructures. Due to the large neutron capture cross-section area and emission of photons with long flight ranges, gadolinium is a potential agent for neutron capture therapy of tumors [57]. Gadolinium has been studied for enhanced tumor targeted delivery by modification of the nanoparticles with folate. The recognition, internalization, and retention of gadolinium nanoparticles in tumor cells were enhanced, indicating a high potential of gadolinium nanoparticles in tumor-targeted delivery [63].

4.4.3. Superparamagnetic Oxide Nanostructures. Superparamagnetic oxide nanoparticles, such as magnetite (Fe_3O_4) and maghemite (Fe_2O_3), have been also proposed for target delivery by using magnetic force. Drug molecules are conjugated onto the surface modified magnetic nanoparticles, and then the organic/inorganic superparamagnetic nanohybrids are concentrated at a specific target site within the body by an external, high-gradient magnetic field [57, 64]. Efficient delivery of genes has been realized by the modification of the magnetic nanoparticles. They can be positively charged by polymers and thus bound to the negatively charged DNA by electrostatic attractions and also protect the DNA [65].

4.4.4. Two-Dimensional Transition Metal Dichalcogenides. Two-dimensional transition metal dichalcogenides (2D TMDCs) are planar crystals consisting of one or a limited number of TMDC unit cells. Single-layered TMDCs can be described by the formula MX_2, where M is the transition metal from groups 4–10 of the periodic table and X is a chalcogen (S, Se, or Te) [66]. Various combinations of transition metals and chalcogens as well as their different arrangements in the 2D crystals can lead to a wide variety of favourable properties [67, 68], making these materials suitable for applications in drug delivery. For example, the drug loading capability of 2D MoS_2 systems has turned out to be even better than that of graphene oxide due to their surface adsorption effect caused by hydrophobic interactions [69, 70]. Their properties of photothermal and photosynthesis can also be combined with drug carrying property to deliver specific drugs [70, 71].

4.5. Peptides-Based Nanostructures. One of the most promising areas of research in drug delivery is the utilization of peptides as biodegradable, physiologically sensitive, inherently "tunable" and remarkably facile design platform for highly sophisticated drug delivery systems [13].

Peptides have many unique advantages for use in drug delivery: (1) biocompatibility and biodegradability make peptide-based nanostructures suitable for drug delivery [72]; (2) naturally occurring self-assembly motifs present in proteins such as α-helices, β-sheets, and coiled-coils can be used to drive the self-assembly process [73]; (3) peptides can form well-defined nanostructures of any size and shape [72];
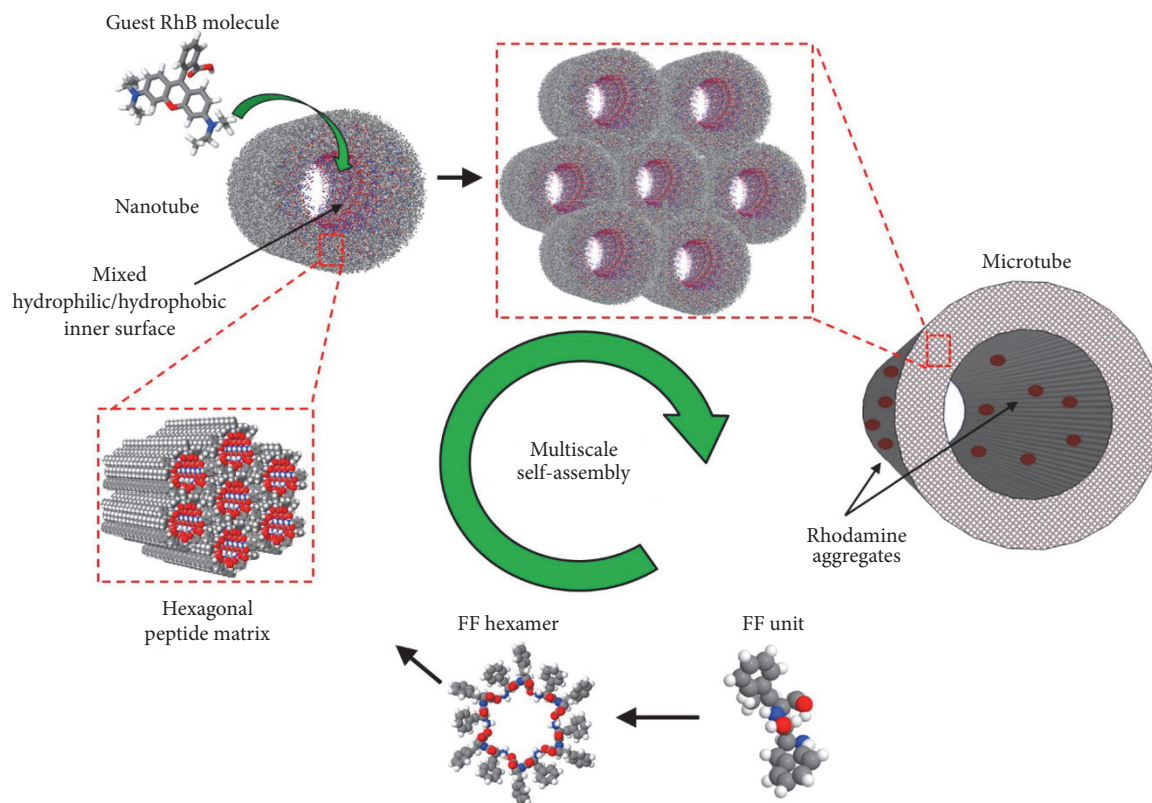
FIGURE 4: Schematic representation of the multiscale self-assembly of the FF-microtubes and their conjugation to rhodamine. Stacked FF hexamers form honeycomb-like arrays, which give rise to nanotubes. Subsequently, these nanotubes cluster into larger microtubes. The inner surfaces of the nanotubes exhibit both hydrophobic and hydrophilic groups, with the latter being able to trap polar species [8]. Copyright © 2013, American Chemical Society.

(4) additional peptide functionalization can easily be performed by introducing various compounds to the peptide structure [72]; (5) oligopeptides can be easily produced in large scale via standard solid-phase synthesis at a relatively low cost [13].

In recent years, a wide range of self-assembled peptides have been put forward for drug delivery, such as diphenylalanine (FF), various peptide amphiphiles (PA), and collagen mimetic self-assembled peptides [74]. For instance, on the basis of FF, a variety of functional nanostructures have been fabricated, such as nanotubes, spherical vesicles, nanofibrils, nanowires, ordered molecular chains, and hybrid nanoparticles [75]. As Figure 4 shows, FF peptide nanotubes have been utilized to load rhodamine (RhB) and have been found to have the ability to conjugate both hydrophobic and hydrophilic compounds due to their highly hydrophobic aromatic rings and hydrophilic peptide matrix [8]. Peptide amphiphiles are prone to self-assemble to form nanofibers, micelles and vesicles, nanotapes, nanotubes, and ribbons. The sizes, shapes, and morphologies of nanostructures can be altered simply by changing the structural elements of the peptide amphiphiles [76].

Since most chemotherapeutic drugs are hydrophobic, they suffer from poor water solubility. Besides, they are toxic to organisms to some extent [77, 78]. Conjugation of these drugs to hydrophilic peptides would create an amphiphilic

system necessary for self-assembly, reduce their side effects, and improve their efficiency via their incorporation into a drug delivering nanocarrier [13]. Peptide-based drug delivery systems are currently of wide scientific interest. Rational design of the peptide-based nanostructures can improve their drug loading capacities (DLC). For example, due to the high internal packing of hydrophobic segments, previous utilization of peptide amphiphiles as drug carriers was generally limited by low DLC (about 2–5%) [78]. However, by incorporating multiple short hydrophobic tails, the nanostructure's inner domain has been obviously enlarged and thus the loading efficiency has remarkably increased to 7% [79].

More and more novel nanostructures with various peptide motifs, stimuli-responsive function, and triggered drug delivery at disease sites are constantly emerging. The well-defined nanostructures produced by the self-assembly of peptides are highly promising for drug delivery.

4.6. Nucleic Acid-Based Nanostructures. As we all know, nucleic acid can be divided into two categories: DNA and RNA. In recent years, nucleic acid nanotechnology has progressed rapidly, especially DNA nanotechnology. A great variety of nucleic acid-based nanostructures with various dimensions, sizes, geometries, and shapes have been well investigated for drug delivery.
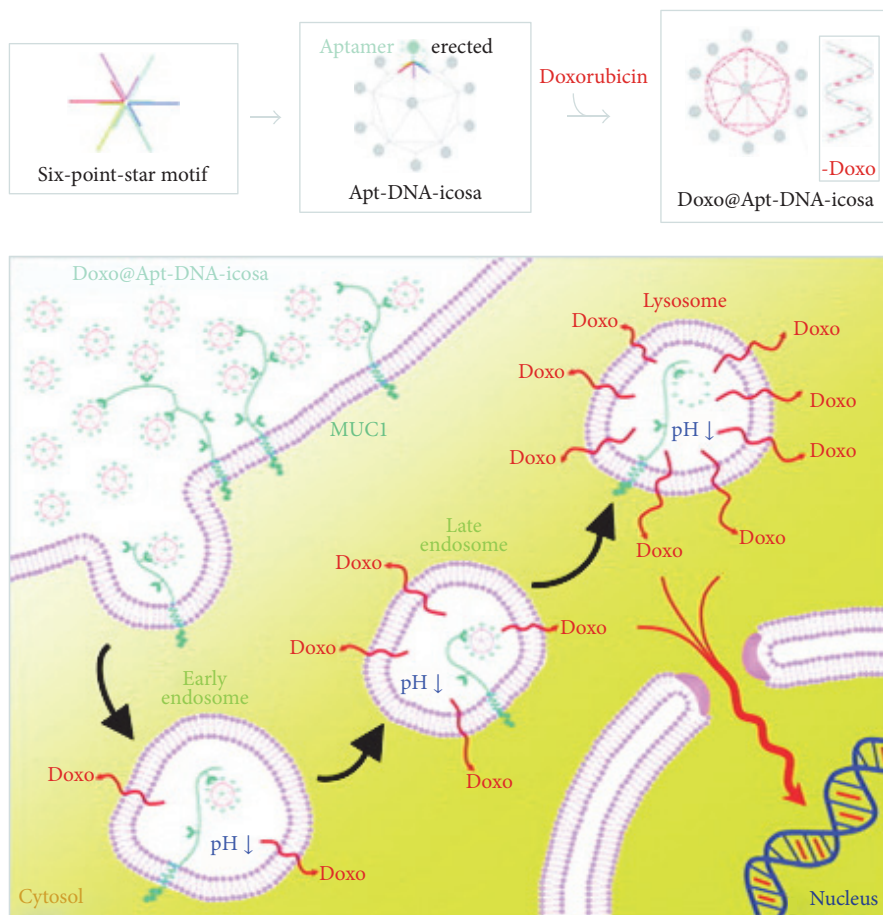
FIGURE 5: Schematic representation of aptamer-conjugated DNA icosahedral nanoparticles as a carrier of doxorubicin (DOX) [81]. Copyright © 2011, American Chemical Society.

4.6.1. DNA-Based Nanostructures. DNA-based nanostructures are quite appealing in drug delivery applications for many reasons: (1) they can be decorated with a multitude of functionalities and become multifunctional carriers; (2) they can be easily fabricated by self-assembly; (3) they are of low immunogenicity; (4) they have large flexibility of how drugs can be loaded into the DNA carrier; (5) they allow superb control over release [80].

Oligonucleotides have been successfully applied in the creation of many types of structures such as nanotubes, dendrimer-like DNA nanostructures, polypods, tetrahedra, icosahedra, and many other polyhedral structures [81]. For instance, Figure 5 gives a schematic representation of aptamer-conjugated DNA icosahedral nanoparticles as a carrier of doxorubicin (DOX) for cancer therapy.

In the last decade, an approach for constructing various DNA structures, named as DNA origami, has emerged [83]. It folds a long stranded bacteriophage through the use of more than 200 complementary staple strands to fold the backbone [84]. Various nanostructures, both 2D and 3D, such as smiley faces, tetrahedrons, DNA nanotubes, DNA barrels, and DNA "dolphins," have been fabricated through DNA origami [83, 85–89]. As Figure 6 shows, DNA tube and DNA triangle
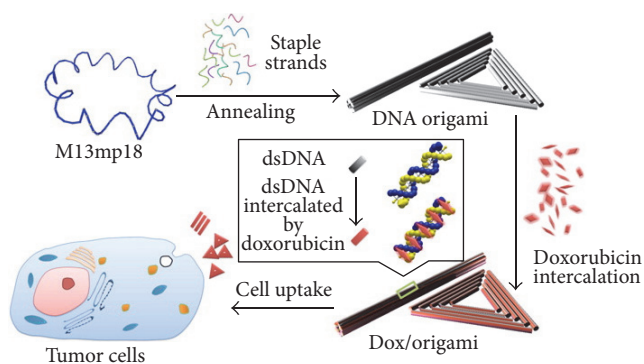
FIGURE 6: Schematic representation of DNA origami systems, DNA tube and DNA triangle, for doxorubicin (DOX) delivery [82]. Copyright © 2012, American Chemical Society.

obtained from DNA origami can be used for DOX delivery. DNA origami structures allow for either controlled or triggered release of drugs through either the intercalation of positively charged molecules or the linking of certain peptides or proteins onto the surface of the DNA origami [84].

Besides, DNA nanotubes, nanoballs, nanobelts, and nanoclews have also been produced by another innovative approach—rolling circle amplification, which creates long stranded structures with repeating DNA sequences through the use of a circular template and DNA polymerase [84]. They can be used as precise delivery vehicles for drugs and genes.

In addition, many other unique DNA nanostructures have also been put forward for drug delivery, such as DNA nanofilms [90] and hydrogels [91]. A DNA block copolymer system consisting of polypropylene oxide (PPO) and DNA has been utilized for the delivery of hydrophobic drugs [92]. The obtained hybrid particles were about 10 nm, with a hydrophobic PPO core to incorporate DOX and a DNA shell functionalized by folate to target cells.

However, there are some obstacles to be tackled in the applications of DNA-based nanostructures for drug delivery. For example, the expense of the starting materials is high and the *in vivo* pharmacokinetic bioavailability of the DNA-based structures needs to be improved [93].

4.6.2. RNA-Based Nanostructures. Due to the impression that RNA seems unstable, the potential of RNA in drug delivery has been overlooked for many years. However, with the development of RNA nanotechnology, RNA-based nanostructures, especially those based on phi29 pRNA, have been utilized in drug delivery in recent years.

According to Heoprich et al. [94], targeted hammerhead ribozymes delivery has been achieved by using ligand conjugated RNA nanoparticles based on phi29 pRNA. Besides, RNA nanoparticles can also deliver CpG DNA to macrophages specifically [95]. What is more, RNA origami nanostructures have also been reported [96]. With excellent thermodynamic stability and plasma stability after chemical modifications, RNA origami is expected to be more favourable than its counterpart DNA origami as a drug carrier for achieving controlled drug release [97].

4.7. Carbon Nanostructures. With the rapid development of carbon nanostructures, many attempts have been made to investigate their applications in drug delivery in the past twenty years. A variety of carbon nanostructures, including carbon nanotubes, graphene, and fullerenes, have been utilized. Graphene can be wrapped into spherical structures (zero-dimensional fullerenes), rolled into one-dimensional (1D) structures (carbon nanotubes, CNTs), or stacked into three-dimensional (3D) layered structures (graphite) [98]. Therefore, CNTs, graphene, and fullerenes are analogous but vary in wall number, diameter, length, and surface chemistry. Although they are all insoluble by nature, they can be modified into water-soluble species and realize drug delivery in organisms.

4.7.1. Graphene. Graphene is an atomic-scale honeycomb lattice made of carbon atoms. Due to the favourable properties, such as good biocompatibility, low cytotoxicity, and unique physicochemical properties in chemistry, electrics, optics, and mechanics, graphene has been explored as one of the most promising carbon nanostructures for drug delivery.

Compared with CNTs, graphene exhibits some important qualities such as low cost, facile fabrication and modification, and a higher drug loading ratio with two external surfaces [99]. Thus, graphene and its derivatives (e.g., graphene oxide) have been widely explored in the past decade for drug delivery applications.

4.7.2. Carbon Nanotubes. Carbon nanotubes (CNTs) have shown promise for the targeted delivery of drugs, proteins, and genes because of their favourable properties similar to graphene. More importantly, CNTs offer some interesting advantages over spherical nanoparticle. For instance, their large inner volume allows the loading of small drug molecules while their outer surface can be chemically modified to load proteins and genes for effective drug delivery. In recent years, both single-walled CNTs and multiwalled CNTs have been modified and turned out to be effective in the delivery of drugs, proteins, peptides, and nuclear acids [100–102].

4.7.3. Fullerenes. As nanomolecular carbon cages, fullerenes can also serve as drug vectors or drug delivery scaffolds with noncovalent linkages or with covalent linkages between the fullerene and a bioactive moiety [103]. After proper functionalization, such as attaching hydrophilic moieties, fullerenes have turned out to be able to work as drug carriers [57, 103].

4.8. Drug-Based Nanostructures. As mentioned above, drug molecules can also be used as building units to deliver themselves. Through rational design of the number and type of the drugs incorporated, the obtained nanostructures can exhibit various morphologies, such as nanospheres, rods, nanofibers, or nanotubes, to facilitate their delivery to particular sites [104].

4.8.1. Small Molecule Drugs. Some small molecule drugs have shown reversible self-assembly behaviour, which can be used to form supramolecular nanostructures of well-defined size and shape [104]. For example, nanofibers or lozenge-like platelets have been obtained by the self-assembly of folic acid in methanol/water mixtures [11]. As a result of the self-assembly of quinoline alkaloid camptothecin (CPT), 100–400 nm wide helical nanoribbon structures have been fabricated from the injection of an organic solution of CPT into water [105].

4.8.2. Hydrophobic Drugs. Hydrophobic drug molecules can be conjugated to hydrophilic polymers to form amphiphilic prodrugs which can spontaneously self-assemble into stable nanostructures. For example, cisplatin and PEG-P(Glu) can form coordination bonds by the coordination between Pt and P(Glu) carboxylate side-chains and then self-assemble into micelles (about 28 nm in diameter). In this way, a self-delivery system can be obtained and it can provide a sustained drug release [106]. With the evolution of self-delivering drugs, various supramolecular nanostructures have been formed from the self-assembly of amphiphilic prodrugs, such as one-dimensional filamentous structures, nanofilaments, nanospheres, and hydrogels [107].

5. Conclusions and Future Perspectives

Due to their unique and valuable properties, nanostructures have been more and more widely used in drug delivery these years. They have the advantages of increasing solubility of poorly soluble drugs, reducing side effects, improving efficacy of the existing drugs, and so on. What is more, owing to the great diversity of nanostructures, the range of choices of nanostructures for drug delivery system has been significantly broadened.

However, nanostructures for drug delivery are also faced with many challenges, such as scaling up, cost issue, and safety concerns. The fabrication method and process of many nanostructures are rather complicated compared with traditional drug delivery vehicles. Although nanostructures consume much less materials than bulk delivery materials, the whole expense of production is often uneconomic, which is another great obstacle. More importantly, only limited information about the influence of nanostructural properties on organisms is available at present. The utilization of nanostructures in drug delivery has aroused concerns all over the world.

To surmount all these problems and challenges, active research on nanostructures in drug delivery is underway. It is a common belief that future development will overcome current problems of nanostructures in the applications of drug delivery. Despite the fact that people are always reluctant to accept new technologies, numerous benefits brought about by nanotechnology will contribute to change the mind of the general public.

Competing Interests

The authors declare that they have no competing interests.
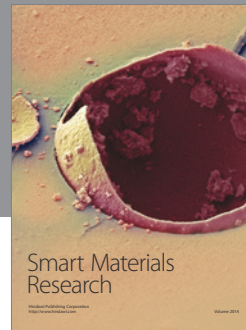
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