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Self-assembled nanostructures for anticancer applications: Advances and limitations

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ABSTRACT

Self-assembled nanostructures can be created as the spontaneous organization of individual nanomaterials via entropy maximization (under suitable conditions) into ordered nanostructures by non-covalent interactions such as van der Waals and hydrophobic interactions. Nucleic acids, amino acids, and lipids are the main building blocks to producing natural self-aasembled nanostructures. For self-assembled nanocarriers as reversible organization, several advantages have been found including biocompatibility, biochemical diversity, and high loading efficiency for both hydrophilic and hydrophobic therapeutic agents, and ability to passive and active targeting. In the case of cancers, these benefits can improve formulations due to inactivation or eradication of various cancer cells. However, there are some limitations such as low stability in the physiological conditions for these formulations, which we have tried to address these issues.

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1. Introduction

Severe side effects and multidrug resistance (MDR), mainly caused by overexpression of drug efflux, are two main disadvantages of chemotherapy by conventional drugs [1]. In recent years, nanoformulations of anticancer agents have obtained enormous progress owing to their unique physicochemical properties compared to bulk ones [2-5]. Molecular units can form self-assembled micro and nanostructures under specific conditions by nan-covalent interactions (hydrogen and electrostatic bonds) [6-8]. Generally, van der Waals interactions, electrostatic interactions and electric double layer, hydrophobic interactions, hydrogen bonding, and aromatic π-π stacking are the main forces for micro and nanoformulations of micelles, fibrillar networks or hydrogels, and vesicles [9]. In the case of the self-assembled nanostructures, entropy has a key role during the process of self-assembly via minimization of the free energy owing to an augment in the entropy, entropy maximization [10]. In bottom-up approaches, colloidal particles are assembled individually or "digitally" [11]. Using template agents can promote multicomponent self-assembly by both nan-covalent and covalent bonds [12]. There is a direct relationship between disorder and entropy value in a medium which can be controlled by physical, chemical, and biological templates. Silica membranes, metal/metal oxide nanoparticles, and nucleic acids can be used as physical, chemical, and biological templates, respectively [13]. In addition, the self-assembly process can be induced by exotic energies caused by light, laser, Brownian/hydrodynamic forces, and magnetic/electric fields [14]. Drug delivery systems prepared from synthetic/natural polymers, lipids, DNA, and small peptides have opened up new avenues for treating various diseases, specifically cancers (Table 1)[15, 16]. Low stability is the significant limitation of self-assembled nanocarriers in physiologicsl conditions, which may be improved using various organic or inorganic stabilizers such as polyethylene glycol succinate, polyvinyl alcohol,

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polyvinyl pyrrolidone, carboxymethylcellulose sodium, and sodium lauryl sulfate [17].

Table 1. Physicochemical properties and anticancer activity of drug delivery systems composed of synthetic/natural polymers, lipids, DNA, and small peptides.

Self-assembled nanostructures	Anticancer activity	Ref.
Complex of self-assembled polyethylenimine-graft-poly(ε-caprolactone) micelles and a reporter gene (pCMV-Luc) loading doxorubicin (DOX) prepared via coupling poly(ε-caprolactone) to branched polyethylenimine by an amide group.	Less toxicity to HepG2 cells compared to blank micelles and improved gene transfection efficiency by combined gene and drug therapy synergistic effects.	[18]
Spherical self-assembled nanoparticles composed of oleoyl-chitosan with a mean diameter of 255.3 nm loading DOX	An encapsulation efficiency of 52.6%, sustained release at pH 7.4, and rapid release at pH 3.8, The inhibitory rates of nanoformulation against several human cancer cells, including SGC-7901, Bel-7402, A549, and HeLa, significantly better than DOX solution.	[19]
Self-assembled glycol chitosan bearing fluorescein isothiocyanate and doxorubicin	Lower toxicity with antitumor activity compared to free doxorubicin; after intravenous injection, the concentration of self-assembled nanostructure was higher than 8% even at three days.	[20]
Self-assembled mesoporous and spherical submicron-sized capsules (dandelions) of ZnO nanoparticles and nanorods loading DOX, the fluorescent molecules (Rhodamine 6G), DOX), and DNA	Sustained drug and gene delivery were observed for these nanoformulations, ~88% of DOX molecules and ~78% of Rhodamine 6G over a period of 12 h.	[21]
L-DNA (a mirror form of natural d-DNA)	Similar thermodynamic properties compared to d-DNA, while having enhanced serum stability, augmented cellular and tissue penetration in rumor and higher anticancer activity than to PEGylated liposomes.	[22]
Doxorubicin (Dox)-binding multifunctional DNA nanoflowers (NFs) with a mean diameter of ~200 nm	Drug-loading capacity of 71.4%, wt/wt, stable at physiological pH, drug release under acidic or basic conditions, decreasing side effects, inhibition of drug efflux, and increasing drug retention in MDR cells in the breast cancer cell and leukemia models.	[1]
Floxuridine-integrated DNA polyhedral as DNA Trojan Horses	Reduction in tumor volume related to HeLa cells and side effects of floxuridine	[23]
Incorporation of aptamers, fluorophoresm, and doxorubicin into the multifunctional DNA dendrimer prepared by functional Y-shaped building blocks (Figure 1a)	Greater drug loading capacity, suitable biostability, biocompatibility, significant selectivity, binding affinity, and appropriate cell internalization efficiency.	[24]
Self-assembled DNA nanotube bearing multiple DNA sequences (hairpin, single-stranded,	Prominent reduction in both miRNA levels followed by inhibition of cancer	[25]

and duplex forms) complementary to a target oncogenic miRNA (miR-21 in MCF-7 breast cancer cells and miR-155 in NSCLC (non-small-cell lung cancer) cells (Figure 1b)	cell growth.	
Mitomycin C-phospholipid complex-loaded DSPE (1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine)-(Polyethylene glycol) PEG-folate nanoparticles	Augmented tumor accumulation of mitomycin C in HeLa tumor-bearing nude mice, cellular uptake followed by its distribution into nuclei.	[26]
Four-armed amphiphilic copolymer, Pt-PAZMB-b-POEGMA, containing a metallacycle, fluorescent probe, and anticancer drugs of the 3,6-bis[trans-Pt(PEt3)2]phenanthrene and DOX	Significant antitumor efficiency with low systemic toxicity resulted from controlled drug release, enhanced permeability, and retention effect.	[27]

Continuation of Table 1

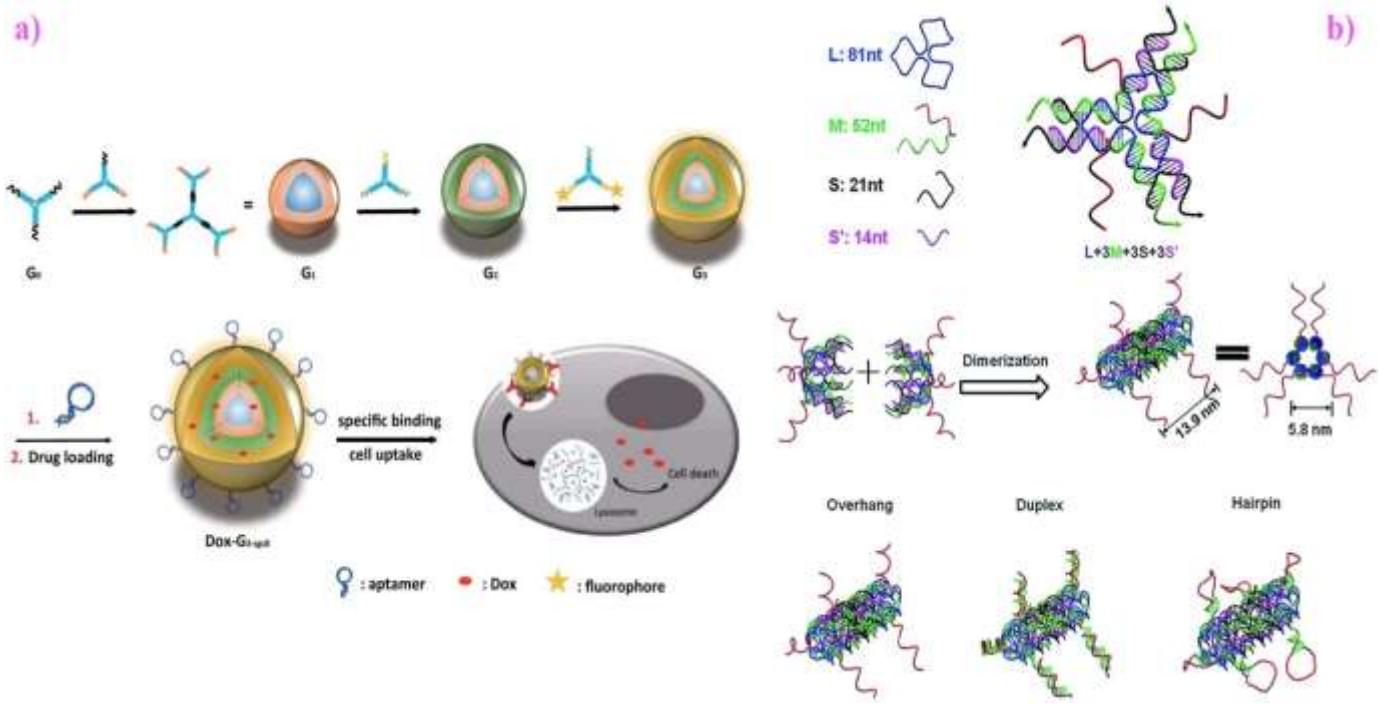

Fig. 1. a) Incorporating aptamers, fluorophoresm, and doxorubicin into the multifunctional DNA dendrimer prepared by functional Y-shaped building blocks and b) Self-assembled DNA nanotube bearing multiple DNA sequences [24, 25].

2. Conclusions

Biocompatibility and targeting of anticancer drugs with low side effects are two main objectives for new promising formulations. In this case, nanotechnology has presented new nanoformulations composed of synthetic/natural polymers, lipids, DNA, and small peptides based on self-assembly feature. Self-assembled nanostructures can be generated as the spontaneous organization of individual nanomaterials via entropy maximization into ordered nanostructures. There are several advantages for self-assembled nanocarriers involving biocompatibility, biochemical diversity, ability to passive and active targeting, and high loading efficiency for both hydrophilic and hydrophobic therapeutic agents. However, low stability is still the major limitation of these formulations in physiological conditions, which can be modified by organic or inorganic stabilizers specifically polymers such as polyvinyl alcohol, polyethylene glycol succinate, polyvinyl pyrrolidone, and carboxymethylcellulose sodium.

Study Highlights

- Targeting of anticancer drugs with low side effects is the critical factor for new effective formulations.

- Self-assembled nanostructures can be obtained as the spontaneous organization of individual nanomaterials via entropy maximization into ordered nanostructures.
- There are several benefits for self-assembled nanocarriers involving biocompatibility, biochemical diversity, ability to passive and active targeting, and high loading efficiency for both hydrophilic and hydrophobic therapeutic agents.
- Low stability is the major limitation of these formulations in physiological conditions, which can be modified by organic or inorganic stabilizers specifically polymers such as polyvinyl alcohol, polyethylene glycol succinate, polyvinyl pyrrolidone, and carboxymethylcellulose sodium.

Abbreviations

MDR: Multidrug resistance
DOX: Doxorubicin
DSPE:1,2-Distearoyl-sn-glycero-3-phosphoethanolamine
PEG: Polyethylene glycol
NSCLC: Non-small-cell lung cancer

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution

Both authors: conceptualization, preparing the first drafting, and revising the manuscript.

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