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Application of self-assembly technology in the field of medicine

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Abstract. In recent years, the preparation of polymer micelles and self-assembled nanomaterials by amphiphilic block copolymers has attracted great interest and has now become a research hotspot in the field of polymer science. Based on the self-assembly technology of block compounds, this paper introduces how self-assembly technology can play a role in the clinical environment, especially for the treatment of tumors and cancer, and controlled drug release. Finally, the related challenges and opportunities for self-assembled nanoparticles are described and prospected. Currently, although block copolymers have great performance in many fields, it is difficult to summarize one or a series of regular methods for the preparation of block copolymers and we also did not find a preparation method suitable for industrial production and wide application.

Keywords: block copolymer, self-assembly, controlled drug release, polymeric micelle, nanomedicines.

1. Introduction

In recent years, the preparation of polymer micelles and self-assembled nanomaterials by amphiphilic block copolymers has attracted great interest. Polymer micelles are self-assembled structures formed by amphiphilic block copolymers in selective solvents. According to different solvents, they can form various structures and shapes such as spherical, vesicle, rod, ring and spiral. It can solubilize hydrophobic drugs into micelles, prolong the circulation time and biological half-life of drugs in the body, and have controlled release and specific targeted distribution. Also, in recent years, the incidence of tumor is increasing day by day, which seriously threatens human life and health, and has become one of the major lethal diseases in the world[1-2]. Previous researches always focus on those main methods of clinical treatment of tumors as surgery, radiotherapy and chemotherapy[3]. Now the research on self-assembled nanomaterials can help to solve this problem effectively. Self-assembly technology has shown great advantages in the preparation of clinical drugs: 1) Due to the non-covalent nature of the driving force, the synthesis of nanoparticles prepared by self-assembly is usually convenient, fast and environmentally friendly, which is conducive to large-scale synthesis and preparation; 2) Non-covalent synthesis The weak interaction force of the valence bond makes the multifunctional nanomedicine easy to depolymerize in the unique human microenvironment, showing the characteristics of intelligent responsiveness and targeting; 3) The basic unit components used to construct nanoparticles generally include natural products, endogenous biomolecules or metal elements, and some Through the US Food

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and Drug Administration-approved drugs, these compositions have good biocompatibility and high safety for the human body, which is conducive to the transformation of laboratory results into clinical and industrial mass production. Consequently, based on the self-assembly technology of block compounds, this paper introduces how self-assembly technology can play a role in the clinical environment, especially for the treatment of tumors and cancer, and controlled drug release. Finally, the related challenges and opportunities for self-assembled nanoparticles are described and prospected. It is hoped that the research of the paper can provide ideas for the in-depth application of nanomaterial self-assembly in medical modernization research.

2. Block copolymers&self-assembly

2.1. Block copolymers

Amphiphilic block copolymers are a class of polymers that contain both hydrophilic and hydrophobic parts. It can self-assemble in a selective solvent to form polymer nanomicelles with a core-shell structure, and has a wide range of applications in various fields such as emulsification and dispersion technology, nanomaterials, carrier catalysts, biomedical materials, and controlled drug release[4].

2.2. Microphase separation of block copolymers

The tendency of block copolymers to self-assemble into ordered phase morphology depends on the strength of the mutual repulsion between the blocks, denoted by χN, where χ is the Flory-Huggins interaction parameter between blocks AB, N is the total polymerization degree of the block copolymer. Microphase separation occurs when this value exceeds the critical value for order-disorder transition. As shown in Figure 1, the important parameter to control the microphase separation of block copolymers is χN. When $\chi N \leqq 10$, weak phase separation occurs; when $\chi N \geqq 10$, strong phase separation occurs. The AB type diblock copolymer solution forms different ordered structures in turn according to the volume fraction of the A monomer. When it is small, the A block forms a microdomain, and the B block forms the matrix. When it is large, the B block forms a microdomain, and A block forms the matrix[5].

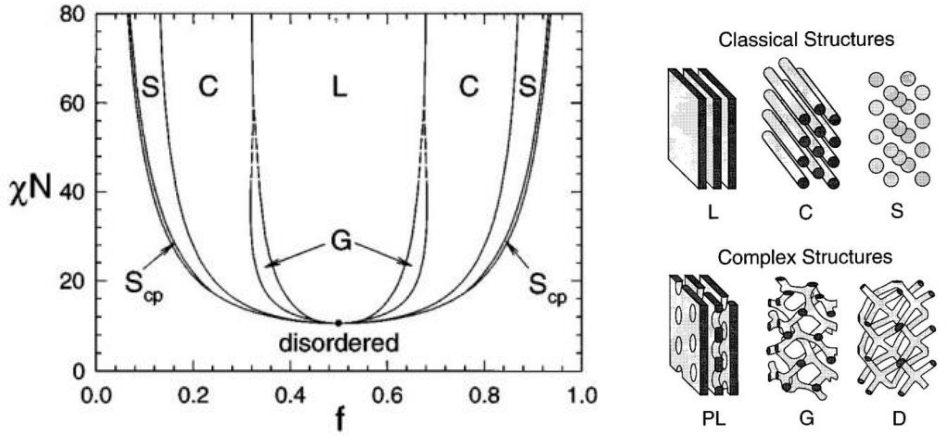

Figure 1. The relationship between f and χN and simple structures of diblock copolymers[5].

The typical microstructures are flat lamellae(L), hexagonally-packed cylinders(C), and spheres arranged on the body-centered cubic lattice(S). Recently several complex structures have been observed. A perforated lamellar(PL) structure occurs when the thin minority layers of the L phase each develop a hexagonal array of passages through which the majority layers are connected. Also a bicontinuous structure with Ia3d space-group symmetry is reported, denoted the gyroid(G) phase, where the minority component domain forms two interweaving three-fold coordinated lattices[6].

2.3. Self-assembly

In a selective solvent, the hydrophilic and hydrophobic segments of the block copolymer have

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differences in interaction and solubility, and the block copolymer will spontaneously arrange in order under specific conditions. This process is called the self-assembly of block copolymers. For example, as shown in Figure 2, block copolymers form spherical micelle-like polymers with hydrophobic segments forming a core within the micelles. The hydrophilic segment forms a shell around the core in a solvated form, thereby ensuring the overall stability of the micelle.

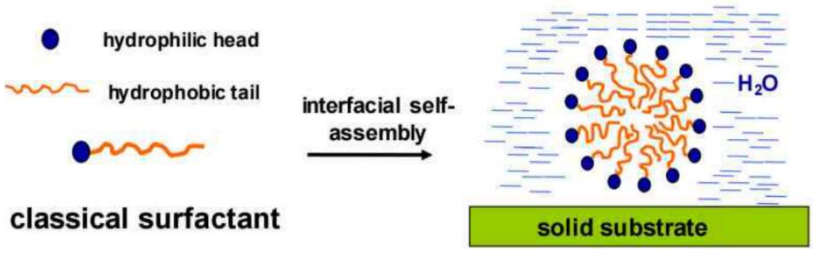

Figure 2. How block copolymers form spherical micelle-like polymers[7].

Flat lamellae(L), cylinders packed hexagonally(C), and spheres grouped on a body-centered cubic lattice are the usual microstructures(S). Numerous intricate structures have been spotted recently. When the thin minority layers of the L phase grow a hexagonal array of channels that connect the majority layers, the result is a perforated lamellar(PL) structure. Additionally, a bicontinuous structure with Ia3d space-group symmetry, known as the gyroid(G) phase, is reported. In this structure, the minority component domain forms two intertwining three-fold coordinated lattices[6].

3. Types of self-assembled nanodrugs

3.1. One-component self-assembled nanoparticles

Some block copolymers have both hydrophobic and hydrophilic ends. Such amphiphilic drugs tend to bury the hydrophobic end in water because of their supramolecular interactions such as hydrophilic and hydrophobic interactions. When the hydrophilicity and hydrophobicity are balanced, they formedordered and stable nanoparticles[8]. In addition, a small number of non-amphiphilic drugs can form water-soluble nano-aggregates by themselves through π π stacking, hydrophobic interaction, etc. due to their unique structures, such as large conjugated planes. Since most of the diagnostic reagents are hydrophobic, the hydrophobic drugs are changed into amphiphilic drugs by covalently modifying the hydrophilic functional end. Therefore, single-component self-assembled nanoparticles can be divided into self-assembly of drugs with therapeutic properties themselves. Nanoparticles and nanoparticles need to be self-assembled by the covalent modification to convert drugs into amphiphilic molecules. Due to the hydrophobicity of most drugs, the drugs to be covalently modified are subdivided into drug & drug and drug & non-drug single-component self-assembled nanoparticles.

3.1.1. The drug itself self-assembles nanoparticles. Due to their large conjugated structures, some drugs can generate ordered self-assembled structures such as H-aggregates or J-aggregates under specific conditions like camptothecin(CPT), indocyanine green(ICG), IR825, etc[9-10].

3.1.2. Drug-non-drug covalently linked self-assembled nanoparticles. Non-drugs refer to ingredients that do not have therapeutic and pharmacological properties. Such ingredients are often hydrophilic and biocompatible oligomers, polymers, biomolecules, or hydrophilic functional groups. They are easily degraded in the human body and do not cause a violent immune response and produce toxic side effects. Common non-drug materials mainly include triethylene glycol, polyethylene glycol and its derivatives, polyacrylic acid and its derivatives, various polysaccharides, and glycosides[11-13]. In addition, there are also studies on linking biomolecules such as polypeptides, nucleic acids, and proteins as hydrophilic segments to hydrophobic drugs, which have resulted in studies on various biomolecule-based multifunctional self-assembled nanoparticles[14-16].

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3.1.3. Drug-drug covalently linked self-assembled nanoparticles. The hydrophilic drug was introduced into the hydrophobic drug as the hydrophilic end to obtain the amphiphilic drug, which showed the synergistic effect of the drug[17]. The newly obtained multifunctional molecules have unique properties, and the bonds connecting the two drugs are usually bonds that are easy to break into two drugs in the tumor microenvironment, such as ester bonds, disulfide bonds, etc[18]. At present, the common self-assembly method is to connect hydrophobic drugs and hydrophilic antitumor drugs through ester bonds or disulfide bonds, etc., to obtain new amphiphilic prodrug molecules that can self-assemble in aqueous solution. Commonly used drugs at the hydrophobic end in the study of self-assembled nanoparticles include CPT, chlorambucil(Cb), bendamustine(BdM), and paclitaxel (PTX). Commonly used drugs at the hydrophilic end include gemcitabine(Gem), irinotecan(Ir), floxuridine(FUDR), methotrexate (MTX), cytarabine(Ara-C), etc.[19]

3.2. Bicomponent and multicomponent self-assembled nanoparticles.

Bicomponent and multicomponent self-assembled nanoparticles are nanocomposites, that is, multifunctional nanoparticles formed by two or more different molecules or ions through hydrogen bonding, ππ stacking, hydrophobic interaction, and other supramolecular forces according to a specific geometric structure. These self-assembled nanoparticles are composed of rich and diverse components. In theory, such self-assembled nanoparticles have infinite combinations, which can flexibly design nanostructures.

3.2.1. Self-assembled *nanoparticles of conjugated system complexes.* The remarkable feature of the self-assembled nanoparticles in this system is that the components have aromatic rings and large conjugated structures, and the nanoparticles are self-assembled mainly by supramolecular forces such as hydrogen bonding, π π stacking, hydrophobic interaction and electrostatic interaction. At present, organic drug molecules commonly used in clinical often contain hydrophilic groups, such as carboxyl, amino, hydroxyl, amino and(hetero) aromatic ring conjugated systems, and different drugs can form nanocomplexes through weak supramolecular interactions, and The drugs are not connected by covalent bonds and do not affect the physiological activity of the drugs in the body.

3.2.2. Organometallic composite self-assembled nanoparticles. Because N, O, S and other elements widely exist in drug molecules or amino acids, and they have excellent coordination ability with most metal cations, many organometallic complex drugs have been approved by the FDA for clinical treatment of tumors, such as cisplatin. Platinum, oxaliplatin, etc.[20]

3.2.3. Macrocyclic host-guest complex self-assembled nanoparticles. Host-guest complexes refer to supramolecular complexes in which host and guest are combined by supramolecular forces that satisfy the lock-and-key principle. The study of host-guest complexes is of great significance in the field of life sciences. With the rapid development of hydrophilic macrocyclic compounds such as crown ethers, cucurbit rings, and cyclodextrins, there have been a lot of studies on macrocyclic host-guest self-assembled complexes[21].

3.2.4. Self-assembled nanoparticles of biomolecular-related complexes. Biomolecules(such as proteins, nucleic acids, etc.) are a special class of natural materials that exist in the body and can be used to construct nanoparticles. As building blocks, they generally have excellent biocompatibility and low immunoreactivity. Supramolecular self-assembly can also be seen everywhere in organisms, and biomolecules can easily self-assemble to form complexes through hydrogen bonding or other supramolecular forces[22].

4. Preparation of a specific nanodrug — block copolymer micelles

4.1. Potential advantages of polymeric micelles

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The first application of polymer micelles in tumor therapy was by Gros et al.[23]. A common polymer micelle is a self-assembly with a hydrophobic inner core and a hydrophilic outer shell formed spontaneously by amphiphilic block copolymers after dissolving in water and driven by intermolecular forces such as hydrophobic, hydrogen bonding, and electrostatic forces. structure, and the particle size is 10 to 100 nm[24]. The molecular aggregates formed by the weak molecular interaction between the monomer structures are called supramolecular polymers or supramolecular polymeric micelles. As the main binding force of supramolecular interactions, non-covalent bonds are far less strong than covalent bonds, but have a high degree of responsiveness to changes in external conditions such as temperature and solvent, making materials reversible. It plays an important role in molecular device, sustained drug release, cell recognition, and membrane delivery, which provides the possibility for the versatility of polymer micelles[25].

Improving the solubility and bioavailability of antitumor drugs is an urgent problem facing medicine. For example, paclitaxel mainly acts on the β subunit of tubulin, inhibits cell mitosis and proliferation, and induces tumor cell apoptosis. However, its solubility in water is only 1.5 μg/ml, and its high lipophilicity makes it easy to penetrate the cell membrane when injected intravenously, resulting in the rapid accumulation of drugs to form capillary embolism. If poorly soluble drugs are encapsulated in the inner core of polymeric micelles, the apparent solubility of the drugs will be significantly increased. Studies have shown that the concentration of paclitaxel encapsulated in micelles in water can be increased by 3 orders of magnitude, up to 2 mg/ml[26]. Due to poor solubility or high toxicity, many drugs have unsatisfactory effects in the process of tumor treatment, and their applications are greatly limited. The use of polymer micelles as drug carriers will greatly improve this situation. In addition, the drug encapsulated by polymer micelles can avoid enzymatic degradation and inactivation, making it more stable.

In the process of drug absorption in the body, the hydrophilic shell of the polymer micelle and the nano-sized particle size also play an important role, which can effectively reduce the interaction with immunoglobulins, prevent the aggregation of particles, and protect the micelles from being Identified and cleared by the reticuloendothelial system(RES). At the same time, due to the low critical micelle concentration(CMC) of polymer micelles (generally 10^{-7}-10^{-6} mol/L), the formed micelles have better stability in vivo, thus prolonging the retention of drugs in the blood circulation, which is beneficial to improve the bioavailability of the drug[27]. Due to the enhanced permeability of tumor blood vessels to macromolecular substances, the retention and accumulation of macromolecular substances in tumor tissue will increase(ie, the EPR effect). It is generally believed that the distribution of drug-loaded particles in tumor tissue depends on the particle size of the particles and the residence time in the blood circulation. Therefore, the nano-sized particle size and long-cycle effect of polymer micelles help it to utilize the EPR effect to increase the accumulation in tumor tissue to achieve the effect of passive targeting.

4.2. Direct dissolution method for pH adjustment

Lu et al. have reported the preparation of PtBA60-b-P4VP80-micelles[28]. Since P4VP is hydrophilic in acidic aqueous solution and hydrophobic in alkaline aqueous solution, PtBA60-b-P4VP80 can form a micelle with the P4VP as the shell and the PtBA segment as the core in acidic aqueous solution. When an aqueous hydrochloric acid solution with pH=2.5 was added dropwise to the DMF solution where the two block copolymers, PtBA45-b-PEG114 and Pt-BA60-b-P4VP80 were dissolved simultaneously, the PtBA chains in the two block copolymers gradually become insoluble, and they gather and self-assemble with each other to form micelles with PtBA as the core and PEG and P4VP segments as mixed shells[29].

4.3. Utilize the interaction between ions

Under certain conditions, the action of polyelectrolytes with oppositely charged surfactants can generate polyelectrolyte-surfactant complexes. Ishzu et al. firstly reported that the micelles formed by polyacrylic acid-g-poly-methylstyrene/poly4-vinylpyridine-g-poly-methylstyrene blend system in mixed organic[30]. The polyelectrolyte complex formed by poly-4-vinylpyridine constitutes the core of the

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micelle, and the polymethylstyrene molecular chain forms the shell of the micelle. Besides it is also reported a micellar structure formed by polyethylene oxide-b-polyacrylate sodium salt block copolymer and N-alkylpyridinium salt surfactant, and the aggregates formed had a narrow distribution and spherical structure[31]. Polyelectrolyte complexes can be produced when mixed with oppositely charged polyelectrolytes. When a block polyelectrolyte(i.e., a block copolymer containing polyelectrolyte chains) is mixed with another polyelectrolyte homopolymer that is oppositely charged, the water-soluble micelles with a polyelectrolyte complex as the core and a dissolved uncharged block as the shell will be formed.

4.4. Induction of micellization by the presence of intermolecular secondary bonds

The core-shell is connected by covalent bonds during most of the micellization process. In recent years, based on the long-term study of hydrogen bonding complexation, a new micellization process in which there is no covalent bond between the core and shell but only hydrogen bonding has been proposed. For example, if polystyrene(MCPS) with a terminal carboxylic acid group is mixed with poly-4-vinylpyridine(PVPy) in chloroform, there is a hydrogen bond interaction between the carboxyl group and the pyridyl group, and a copolymer with PVPy as the main chain and PS as the branched chain can be formed between MCPS and PVPy. Then, toluene was added to it. PVPy aggregated because it was insoluble in toluene, but did not precipitate due to the interaction with MCPS. Therefore, a micelle structure with PVPy as the core and PS as the shell was formed in the solution[32].

4.5. Micellarization with heat-sensitive polymers

Some water-soluble polymers are heat-sensitive in aqueous solution, such as: PNIPAM, when the temperature exceeds 30.9 °C, phase separation occurs. If other water-soluble monomers are copolymerized to it, such as: acrylamide and acrylic acid, the phase separation temperature can be adjusted. Tenhu and Qiu et al. studied the micellization of poly-N-methacrylamide-g-polyethylene oxide(PN/PAM-g-PEO) in aqueous solution by changing the temperature[33-34]. There are also reports that PN/PAM-g-PEO could form core-shell micelles in water by changing the temperature and controlling the heating rate[34].

4.6. Micellarization of Radical Copolymerization of Amphiphilic Random Copolymers

Liu et al. reported that Using azobisisobutyronitrile(AIBN) as initiator, obtaining amphiphilic graft copolymer(MAF) by free radical copolymerization with macromonomers Caprolactone-modified acrylate (FA), methyl methacrylate(MMA) and hydrophilic monomer acrylic acid(AA) in the N, N-dimethylformamide (DMF), self-assembling MAF with biodegradable homopolymer caprolactone (PCL) in aqueous solution, and finally form composite micelle with a core-shell structure with the PFA segment and PCL as the core and the PAA segment as the shell in MAF[35]. Yan et al. used CUCL/bpy as the catalyst and Ethyl 2-bromopropionate as the initiator to first synthesize a polystyrene macroinitiator with a halogen atom at one end, and then this macroinitiator initiates the block polymerization of methyl methacrylate, and finally, the amphiphilic block copolymer was obtained by hydrolysis under acidic conditions[36].

5. Discussion

After analyzing this topic, the paper found it difficult to summarize one or a series of regular methods for the preparation of block copolymers and also did not find a preparation method suitable for industrial production and wide application. The author thinks this is a problem that we need to do research to solve at the moment. Looking to the future, supramolecular self-assembly, especially two-component or multi-component self-assembly, exhibits the advantages of flexibility and convenience. The preparation of nanoparticles by self-assembly technology provides a new strategy for the treatment of diseases. Also, the polymer micelles formed by the self-assembly of amphiphilic block copolymers have unique properties and have broad application prospects in various fields such as biology, medicine, catalysis, and molecular optoelectronic devices, and have become a research hotspot in the field of self-assembly.

It is believed that with the deepening of research work, amphiphilic polymer micelles will be more widely used in nano-drug carriers. It is expected to become the most potential drug delivery system.

6. Conclusion

In this paper, based on the microstructure of block copolymers and their self-assembly principles, the types of self-assembled nanomaterial drugs and their great contributions to clinical medicine are reviewed from the principal of self-assembly of block copolymers to how to different types of medical drugs formed by block copolymers. Meanwhile, taking the amphiphilic block copolymer micelle as an example, various preparation methods of a self-assembled nanomaterial drug were reviewed. This paper summarizes the profound potential of block copolymers in the field of re-medicine through a review, hoping to provide further inspiration for subsequent research. However, there are still many deficiencies in this paper. For example, the lack of literature references makes it impossible to compare the amphiphilic block copolymer micelles with other nanomaterial drugs, so it is impossible to determine whether the micelles have obvious advantages over other materials in terms of preparation or performance.

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