The application and research progress of ZIF-8 nanomaterials in biomedicine

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Abstract: As a subclass of metal organic frameworks (MOFs), Zeolitic Imidazolate Framework 8 (ZIF-8) can be formed by self-assembly of zinc ions and 2-methylimidazole under simple conditions. Taking advantage of its acid sensitivity, high loading capacity and easy functionalization, ZIF-8 has a wide range of applications in biomedical fields. ZIF-8 is an ideal carrier for controlled drug transport and release, as it can efficiently transport not only small molecules for antibacterial and antitumor applications, but also It can act as a protective layer for peptides and other biological macromolecules, as well as modify the surface of implants and be used to assist in vivo bioimaging. Based on this, this paper reviews the applications and progress of ZIF-8 in the biomedical field and provides an outlook.

Keywords: ZIF-8, Acid sensitivity, Biomedical

Introduction

Metal-organic framework (MOF) is a kind of hybrid material, which is formed by self-assembling inorganic metal and organic ligand through covalent or ion-covalent bonding, and is a nanomaterial with periodic mesh structure. Metal ions or clusters of metal ions are the nodes, and organic ligands with multiple coordination points are the connection points, which self-assemble to form a highly regular mesh skeleton structure by coordination[1; 2]. Such inorganic-organic hybrid materials combine the excellent properties of both inorganic and organic materials, not only have high specific surface area, tunable size and porosity, but also have high drug loading rate and can be surface modified, so they are widely used in such applications as drug delivery[3], material storage[4], catalysis[5], and bioimaging [6], energy storage[7], etc.

The crystallization process is a long-standing challenge in chemistry and materials, and there are a large number of theories, hypotheses, and models applicable to the formation of various crystals. Chen[8]et al. Introduced imidazole in the synthesis process and successfully prepared a stable porous MOF material. Among them, the synthesis process of zeolite imidazole ester skeleton material (ZIF-8) includes two parts: nucleation and crystal growth. In the reaction solution, an excess of 2-methylimidazole deprotonated with zinc ions coordinated to form nuclei, then the nuclei grew rapidly to form ZIF-8 nanocrystalline particles, and finally the reaction was terminated by the binding of neutral 2-methylimidazole with positively charged ZIF-8. The cage-like coordination compound formed in the reaction has a regular rhombic dodecahedral structure and is a typical zinc-based MOF. it is an ideal responsive carrier for drug transport and slow release due to its superior properties such as high porosity, good biocompatibility, high binding capacity, and high specific surface area, and thus is receiving increasing attention and developed for a variety of applications[9]. Based on the excellent properties of ZIF-8 and its composites, the application of ZIF-8 and its composites in bioimaging, drug mitigation, protection of biomolecules, and modification of implant surfaces is gaining more and more attention.

1. Synthesis of ZIF-8 nanoparticles

The components of ZIF-8 nanoparticles are zinc ions and 2-methylimidazole, which form porous crystalline materials by the self-assembled coordination of both. This process includes two steps of nucleation and crystal growth: i) deprotonation of excess 2-methylimidazole in the reaction system with zinc ions to form nuclei; ii) rapid growth of nuclei to form ZIF-8 nanocrystalline particles, and finally the reaction is terminated by the binding of

neutral 2-methylimidazole to positively charged ZIF-8[10]. The synthesis methods include solvothermal synthesis, microfluidic method and microwave-assisted method.

In 2006, Yaghi[11]et al. synthesized the ZIF-n series using the solvothermal method, which involves dissolving zinc ions and 2-methylimidazole in water or organic solvents and synthesizing ZIF-8 directly by heating a solution of metal ions and ligands.This method is convenient in operation, but has the disadvantages of long reaction time, high energy consumption, and easy solvent waste.

Microfluidic technology applied to chemical synthesis has advantages in heat and mass transfer, and is a widespread and effective method for preparing nanoparticles. This technology can precisely control the flow rate, feeding ratio, temperature and other parameters during the reaction process by precisely controlling the micro-scale fluid through an electronic chip, which makes the heat and mass transfer during the reaction process easy to control. By controlling the nucleation and crystallization process of ZIF-8 using microfluidics, ZIF-8 with uniform size and regular morphology can be synthesized and the particle size can be adjusted in a wide range [12].

In microwave-assisted synthesis, the energy provided by microwave radiation interacts directly with the reactants, and this method is based on the interaction of electromagnetic waves with charge-rich materials, such as polar molecules in solvents or conducting ions in solids, and the thermal energy is transferred directly from the heat source to the binding sites of the crystals, so that the reaction rate of this method is much faster than that of the solvothermal method, and smaller particle sizes can be obtained[13; 14].

2. Use of ZIF-8 in antibacterial

Antibiotics have long been the most effective means of treating bacterial infections, but the development of new antibiotics has lagged behind the rapid growth of bacterial resistance, leading to increased difficulty in treating infectious diseases and rising mortality rates. In the face of these challenges, it is of great importance to develop new targeted antibacterial agents with both efficient targeting and slow-release effects. With the advancement of nanotechnology, researchers are applying it to various fields. In the biomedical field, it can be used as a vehicle for drug delivery, which is expected to achieve targeted and slow release of antimicrobial agents at the infection site.

ZIF-8 is a cage-like material with good biocompatibility constructed from 2-methylimidazole and zinc ions, which is structurally stable in neutral aqueous solutions but can be degraded in acidic environments with low pH. Recent studies on ZIF-8 as an antimicrobial drug carrier have also demonstrated many advantages: high porosity, adjustable cage structure, large pore volume, high hydrothermal and chemical stability, and pH responsiveness. It is well known that because bacterial metabolites are acidic, bacterial infectious inflammatory responses tend to present an acidic environment. Therefore, the acidic conditions inside the biofilm just provide a suitable environment for the disintegration of the ZIF-8 framework, thus achieving a slow release of the antimicrobial agent. These properties make ZIF-8 a promising carrier for high drug loading and pH responsive antimicrobial agents.

Currently, ZIF-8 loaded antimicrobial drugs are mainly encapsulated by a facile one-pot synthesis method, which can be completed by in situ self-assembly around drugs larger than the pore size of ZIF-8, and appropriate addition of organic solvents in the reaction system can improve the drug loading rate. Currently, ZIF-8 can undergo disassembly based on inflammatory acidic conditions (pH=5.4) within the biofilm and has been widely used to encapsulate antibiotics for antibacterial studies. Vancomycin has excellent antibacterial ability against methicillin-resistant Staphylococcus aureus, Xiao [15]et al. used ZIF-8 for encapsulating vancomycin and modified polydopamine (PDA) on the surface of the composite Van@ZIF-8 to improve the biocompatibility of the material, which can also synergize with the photothermal properties of PDA for antibacterial purposes. The results showed that the composite Van@ZIF-8@PDA showed outstanding photothermal conversion ability, significant antibacterial and dissipative ability against planktonic methicillin-resistant Staphylococcus aureus as well as to mature biofilms.ZIF-8 was also applied to encapsulate antibacterial drugs such as ciprofloxacin[16], gentamicin[17], and rifampicin [18], enabling tightly controlled drug delivery and providing a promising potential strategy to circumvent antibiotic-resistant bacterial infections in clinical applications.

Not only applied to the controlled delivery of antibiotics, ZIF-8 can act as a carrier for other hydrophobic antimicrobial materials, which is helpful to solve the problems of low dissolution rate, difficult preservation and rapid degradation of hydrophobic materials in the application process. Duan[19] et al. wrapped the photosensitizer

CCM in ZIF-8. Polymeric hyaluronic acidand chitosan with good biocompatibility were modified onto the surface of ZIF-8 composite nanoparticles by layer-wise self-assembly technique to obtain CCM@ZIF-8@HA@CS nanoparticles with positive surface charge. The electrostatic interactions are used to effectively bind them to bacteria with negative surface charges to achieve targeted and precise antibacterial activity against E. coli and S. aureus.Duong[20]et al. used zeolite imidazole skeleton-8 (ZIF-8) to encapsulate iodine. ZIF-8 loaded with iodine (I @ZIF-8) efficiently killed E. coli and S. aureus at pH < 7 and for a short period of time, however, no significant antibacterial activity was detected at pH > 7. The loading of iodine was achieved using ZIF-8, which degrades the released iodine at acidic pH, and the high local concentration of iodine exerts a rapid bactericidal effect.

ZIF-8 not only acts as an antibacterial drug delivery carrier, but also its antibacterial properties. Since ZIF-8 crystals release Zn^{2+} by disintegration in an acidic environment, Zn^{2+} is attracted by electrostatic interactions with bacterial cell walls and is readily internalized into bacterial cell walls, thus exerting antibacterial properties[21; 22].Based on the acidic environment of the oral cavity, ZIF-8 has also been widely used in the study of oral infectious diseases such as antiperiodontitis-causing bacteria and caries-causing bacteria[23]. Li[24] et al. modified ZIF-8 by adding different ratios of Ce in the synthesis of ZIF-8 to give it some antioxidant capacity. It was used for the treatment of periodontitis disease, using ZIF-8 to release Zn2 + against periodontopathogenic bacteria and anti-biofilm in an acidic environment, while Ce exerted antioxidant effects.

3. Use of ZIF-8 in the protection of biomolecules

Biomolecules have become indispensable for the treatment of diseases, such as antimicrobial peptides, which are natural antimicrobial proteins present in the human body, and a class of therapeutic biomolecules widely used in scientific research and clinical practice[25]. However, often these biopharmaceuticals suffer from poor stability, aggregation or degradation, and are susceptible to temperature changes, external shocks, chemical reagent corrosion, and other microenvironments, leading to the reduction or even loss of the activity of therapeutic drugs. However, storing and transporting biopharmaceuticals greatly increases the cost of their application and poses additional biosafety risks. Therefore, there is a need to develop simple and effective strategies to stabilize biomolecules, which will enhance their application in therapeutic, chemical processing and biological storage.

In aqueous solutions at room temperature, the biomimetic mineralization of ZIF-8 can be completed in a few minutes without the assistance of heating, organic solvents [26]. In solutions containing protein molecules, ZIF-8 can undergo a biomineralization-like behavior. Self-assembly can occur around proteins and encapsulate macromolecules in a rigid crystal structure.ZIF-8 has been used as a protective backbone for a variety of biomaterials.Wang[27]et al. demonstrated that ZIF-8 not only efficiently encapsulates insulin, but also greatly preserves the chemical stability and structural integrity of insulin under non-refrigerated conditions.Lin[28] et al. used ZIF-8 as a coating using a sandwich ELISA assay for neutrophil gelatinase-associated lipid transport protein as a model system, ZIF-8 was able to uniformly cover the surface-bound anti-NGAL IgG. the material had a dynamic range of stable assays and detection sensitivity even when stored at high temperatures for more than 4 weeks. This approach facilitates the extension of the shelf life of the antibody assay as well as greatly improves the stability of the antibody.

Carraro[29] et al. prepared AAT@ZIF-8 nanomaterials by encapsulating the clinical therapeutic agent α1-antitrypsin in ZIF-8. After releasing the biotherapeutic agent from the composite in clinical application, the trypsin of AAT its biological activity and inhibitor function were preserved. Meanwhile, ZIF-8 composites have good dispersion and flow synthesis properties in solution, as well as controllable particle size of nanocomposites, which facilitates the realization of intravenous delivery of drugs.

4. Use of ZIF-8 in anti-tumor

ZIF-8 metal skeleton has various advantages, such as high porosity, large specific surface area and high drug loading rate. It is an ideal carrier for drug loading and sustained drug release because it can maintain stability under physiological conditions and achieve drug release in the weak acidic microenvironment of tumors.

Several studies have demonstrated that under simulated physiological conditions (pH=7.4), ZIF-8 can maintain the stability of the overall structural framework, while structural collapse can occur in a weakly acidic environment (pH=5.4-6) [30; 31]. This is mainly due to the protonation of N in 2-methylimidazole under acidic conditions which

leads to the inability to maintain a stable coordination between Zn 2+ and N. The acidification of the tumor microenvironment due to the production of acid by glycolysis in the tumor provides the conditions for the disassembly of ZIF-8, which is able to load antitumor drugs with a high loading rate, remain relatively stable under physiological conditions, safely transport the drugs to the tumor cells and release them inside the tumor to exert their corresponding effects.

Li[32]et al. took advantage of the structural advantages of ZIF-8 material for efficient loading of bee venom peptides. The unique pore structure of the material protects the drug from being destroyed in the body. The MLT@ZIF-8 nanocomposite material can reach the tumor site and enter the tumor cells precisely after delivery, and then use the pH-sensitive characteristics of ZIF-8 material to realize the precise and controlled release of bee venom peptides.
The tumor interior is not only in a slightly acidic environment but also rich in glucose reserves. Liu[33]et al. encapsulated both glucose oxidase and peroxidase into ZIF-8 to catalyze the production of reactive oxygen species inside the tumor for antitumor via the enzymatic cascade reaction of both. The designed ZIF@GOx/GQDs disintegrated under acidic tumor conditions to release peroxidase nanoparticles (GQDs), a highly efficient artificial enzyme. Meanwhile, glucose oxidase consumes glucose to produce acid further exacerbates the collapse of ZIF-8 structure and promotes the penetration and dispersion of the nanase inside the tumor. Further, hydrogen peroxide produced within the tumor can be catalyzed into toxic hydroxyl radicals by the infiltrating peroxidase nanoenzymes. Conventional ROS-based nano-agents are prone to deactivation in extremely hypoxic tumorcenters, however, ZIF@GOx/GQDs not only facilitate their permeability within the tumor, but also induce exogenous ROS production directly within the tumor without additional oxygen supply as well as external energy input.

5. Use of ZIF-8 in implants

Recent studies have shown that MOF can be used for surface modification of different materials by self-assembling at functional interfaces to form interfacial coating materials. Implants are widely used in the biomedical field, especially in dentistry, and artificial dental implants have become one of the main restorative methods for missing teeth. Titanium (Ti) metal has high mechanical strength, good biocompatibility and corrosion resistance, and has a wide clinical application in the treatment of dental defects and loss[34]. However, untreated titanium metal differs significantly in structure and properties from bone tissue and does not easily form a good chemical bond, and does not have antibacterial properties, which makes it easy for bacteria to adhere and accumulate, causing peri-implantitis and implant denture failure. Surface modification of implants to improve their osseointegration and give them antibacterial and antimicrobial properties is an effective way to promote their long-term and stable retention in vivo and to increase the success rate of implants. Therefore, surface modification of implants has become a hot and difficult area of research in this field.

Currently available methods for implant surface modification include chemical, physical, and biochemical modifications [35]. Chemical modification methods (e.g., anodic oxidation, acid-base treatment, etc.) are simple to operate and provide a uniform surface after treatment. Physical modification methods (e.g., grinding, polishing, sandblasting, hydroxyapatite spraying method, etc.) increase the surface roughness of the implant to enhance mechanical embedding. Biochemical modification methods (such as layer self-assembly, etc.) mainly rely on the action of bioactive molecules, which are more direct and effective than physical and chemical modification methods, simple and easy to implement, and mild preparation conditions, and are gradually gaining attention in the research of dental materials.

Zhang [36]et al. modified the implant surface with ZIF-8 coating and investigated the effect of the modified implants on the surrounding osteogenesis. The results demonstrated that the implant material ZIF-8@AHT with optimized ZIF-8 ratios could upregulate the expression of osteogenic genes in the surrounding bone tissue to a certain extent, and also promoted the secretion of osteogenic-related proteins alkaline phosphatase and osteoprotegerin in mouse embryonic osteoblast precursor cells MC3T3-E1, which provided a favorable theoretical basis for clinical improvement of osseointegration of titanium implants. Although titanium-based implants have good biocompatibility and stability, they lack antibacterial ability.Wang [37]et al. modified the surface of titanium dioxide nanotubes (a medical titanium-based implant) with ZIF-8 loaded with naringin (Nar) by a facile hydrothermal treatment and demonstrated that the nanotubes coated with the addition of TNT-ZIF-8@Nar had some bactericidal ability and could effectively kill Escherichia coli and Staphylococcus aureus on their surface. The results also showed that the surface coating facilitated the proliferation and osteogenic differentiation of osteoblasts in

bone tissue. The coating not only gives the implant antibacterial ability and inhibits related infections, but also facilitates good osseointegration of the implant.

6. Use of ZIF-8 in biological imaging

Nanomaterials are widely used as a new imaging probe in the field of biomedical imaging. Metal organic backbone MOFs can be used as carriers for imaging agents and fluorescent materials for developers, thus assisting in the development and imaging of organisms. Compared with conventional nanocarriers, nano MOFs have many special properties, including tunable composition and structure, high loading force, and good biodegradability.MOFs can be used as contrast agents for confocal microscopy or magnetic resonance imaging (MRI) for biomedical imaging and diagnosis [38].

Imaging systems such as MRI, optical imaging or X-ray tomography (CT) are all important methods for tumor visualization, but single imaging modalities have many shortcomings, such as poor penetration and low sensitivity.MRI is a form of visualization based on nuclear spin orientation in a magnetic field, and some contrast agents are usually used to further improve the quality of visualization, which is important for improving the imaging resolution in the diagnosis of early cases [39]. However, small molecules of contrast agents are easily eliminated from the body, therefore, the sensitivity of contrast agents can be improved and their toxicity reduced by loading them with nanomaterials such as ZIF-8[40].

The encapsulation of contrast agents and anti-cancer drugs enables them to reach the tumor site precisely and the concentrated release at the tumor site, which greatly improves the relative concentration of contrast agents and anti-cancer drugs in the tumor tissue. It not only improves the drug utilization rate, but also enhances the image contrast between the tumor and the surrounding normal tissue, which is important for improving the imaging resolution for early case diagnosis.Shu[41]et al. encapsulated the antitumor drug DOX into ZIF-8, while modified the surface with polydopamine (PDA) and imparted activity to the surface, which was modified on the surface through the coordination of Fe 3+ with PDA to The assembled DOX@ZIF-HA not only targets prostate cancer cell line PC-3 cells, but also has in vitro MR imaging capability. The constructed multifunctional nanocarriers have both therapeutic and diagnostic functions.

7. Conclusion

In summary, ZIF-8, as a new organic-inorganic hybrid crystalline porous material with large specific surface area, high porosity and diverse structure, can achieve efficient drug loading compared with traditional nano-drug carriers, and can remain stable in the physiological state and disintegrate under acidic conditions, thus achieving controlled release of drugs in acidic environments. ZIF-8 not only delivers antibacterial drugs to the infection site, but also acts as an antibacterial agent to release Zn2+ for antibacterial activity. Furthermore, ZIF-8 can realize the storage and rapid release of biomolecules at room temperature, which is of great significance for the wide application of biomolecules in clinical practice. At the same time, the application of ZIF-8 materials also has some urgent problems to be solved, such as the clinical translational application of drug delivery and the potential mechanisms affecting tumor development, which still need to be further explored. Through the cross-collaboration and continuous in-depth research of different disciplines such as chemistry, material science and biomedicine, it is expected that more applications of ZIF-8 materials in biomedical field will be further developed and extended.

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