

Application of carrier free nanomaterials in healthcare

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Abstract. Nanodrugs offer a means of delivering drugs that can enhance their bioavailability. However, the practical application of nanomedicines is hindered by the use of carrier materials in their construction, which can make them potentially toxic. Carrier-free nanomaterials are currently receiving significant attention due to their simple composition, high drug loading capacity, and low toxicity, making them widely used in medical applications. This paper outlines the self-assembly mechanism of carrierless nanomaterials, details their applications in antitumour, antibacterial, anti-inflammatory and antioxidant applications, and finally briefly discusses the development of carrierless nanomaterials.

Keywords: carrier-free nanomaterials, self-assembly mechanism, anti-tumour, anti-bacterial, anti-inflammatory.

1. Introduction

Nanomedicine has garnered significant attention as a potential treatment for diseases with the advancement of nanotechnology. Nanomedicine refers to the use of nanotechnology to make drugs and the like into particles with a nanoscale, or to form particles with a nanoscale by combining the drug with an appropriate carrier material. Nanomedicine has a variety of unique advantages, can improve the oral absorption of insoluble drugs, to achieve targeted and localised release of drugs, can reduce the dose of drugs to reduce side effects.

The rapid development of nanomedicines has led to the study of a variety of nanocarriers for drug delivery and diagnostics. This solves the problems of poor solubility and adverse side effects of chemical drugs. The materials currently used as drug carriers include polymers, dendrimers, liposomes, inorganic nanoparticles and cellular components [1]. The use of diverse nanocarrier materials is of great significance for the development of nanodrugs. However, nanocarrier drugs often contain carriers that lack drug activity, resulting in the disadvantages of potential toxicity, low drug-carrying capacity, and poor biosafety, which seriously affect their medical applications. Additionally, the complex preparation process of nanocarriers currently limits their large-scale production and real-life application.

Carrier-free nanomaterials are a type of highly researched nanomaterials with excellent potential in the medical field. Nanomedicine constructed using carrier-free nanomaterials does not require any carrier, such as organic or inorganic. Its main components are substances such as drugs, biologically active molecules, and functional ingredients. Carrier-free nanomedicine avoids the undesirable side effects of carriers and can achieve high drug loading rates and low toxicity [2]. Carrier-free nanomaterials are currently widely used in healthcare. This paper reviews the self-assembly mechanism of carrier-free nanomaterials and describes their medical applications, including antitumour, antibacterial, anti-inflammatory and antioxidant properties. Finally, the paper looks forward to the future development of carrier-free nanomaterials.

2. Self-assembly mechanism of carrier-free nanodrugs

Carrier-free nanodrugs are assembled from multiple components, and non-covalent Kin is important for the construction of carrierless nanodrugs. The carrierless nanodrugs are mainly driven by intermolecular forces such as hydrogen bonding interaction, π - π stacking interaction, hydrophobic interaction, and electrostatic interaction.

2.1. Hydrogen Bonding Interactions

When hydrogen atoms are covalently bonded to atoms with high electronegativity, they can form a special inter- or intramolecular interaction force with nearby atoms of high electronegativity, known as a hydrogen bond. This force is relatively weak, with a bonding energy in the range of 25-40 kJ/mol. Although hydrogen bonding is a weaker force, it is a very important force driving the self-assembly of carrierless nanomaterials. Many current drugs contain amino, hydroxyl, amide, or carboxyl groups that provide sites for the formation of hydrogen bonds. This allows the drug to self-assemble into a carrier-free nanodrug.

For instance, honokiol (HK) is an anticancer drug with a hydroxyl and benzene ring structure. However, its hydrophobicity, low bioavailability, and rapid metabolism greatly limit its application. To address this issue, Ji et al. formed carrier-free nanoparticles (SA) through the self-assembly of HK, which involved hydrogen bonding and hydrophobic interactions [3]. SA exhibited good solubility and stability, excellent tumour targeting, and anti-tumour immunity, thereby enhancing the targeted therapy of HK.

2.2. π - π Stacking Interactions

π - π stacking is a weak intermolecular force that often occurs between aromatic rings. This interaction is typically between two molecules, one electron-rich and the other electron-deficient. The carrier-free nanomaterials formed using π - π stacking interactions do not change the structure of the drug and have the advantages of reversibility and convenience, which enhance the drug-carrying capacity of the nanomaterials.

Icariin (ICA) can be used to treat osteoarthritis due to its anti-inflammatory effects and ability to prevent chondrocyte apoptosis. However, its poor bioavailability limits its efficacy. Curcumin (Cur) is a molecule with anti-inflammatory properties that can increase chondrocyte viability and reduce pro-inflammatory factors. Both drugs contain aromatic rings. Dai et al. constructed carrier-free nanopharmaceuticals (Cur/ICA NPs) for the treatment of osteoarthritis based on their structural peculiarities [4]. The Cur/ICA NPs have pH-responsive properties, releasing the drug according to the therapeutic environment, and slow-release effects that can be used for fluorescence imaging. The efficacy of osteoarthritis treatment was improved with Cur/ICA NPs compared to the two drugs used alone.

2.3. Hydrophobic Interactions

Hydrophobic interaction is the main driving force for the self-assembly of hydrophobic drugs to form nanoparticles. Since hydrophobic molecules cannot fully interact with water molecules, they tend to aggregate in aqueous solution in a form that minimises the surface area, thus reducing the total energy and improving the stability of nanostructures. In recent years, many researchers and scholars have self-assembled drugs into carrier-free nanomedicines through hydrophobic interactions.

As an illustration, Zhou et al. developed a carrier-free nanomedicine (GosCe) based on Gos and the photosensitiser chlorine e6 (Ce6) for tumour therapy [5]. The photosensitiser Ce6 exerts photodynamic therapy (PDT), converting oxygen (O_2) to reactive oxygen species (ROS), oxidising unsaturated proteins, lipids and DNA, which in turn leads to apoptosis, autophagy and necrosis. However, upregulation of b-cell lymphoma (Bcl-2) in tumour cells inhibits PDT-induced apoptosis. In addition, overexpression of Bcl-2 promotes glutathione (GSH) production to deplete ROS, leading to attenuated oxidative damage by PDT. Gossypol (Gos), a natural polyphenol constituent extracted from cottonseed, is a potent inhibitor of Bcl-2 but its application is restricted by limited solubility. Based on this, Zhou et al. combined Ce6 and Gos to simultaneously reverse the antioxidant and anti-apoptotic pathways through a strategy of PDT and Bcl-2 inhibition, thereby increasing the sensitivity of PDT. In this case, Ce6 and Gos binding was carried out through the hydrophobic interaction between the two. In vitro and in vivo studies have shown that GosCe has a high drug loading rate, which improves the efficacy of PDT and provides a new strategy for cancer therapy.

2.4. Electrostatic Interactions

Electrostatic interactions are due to electric charge, repulsion occurs for the same charge and attraction occurs for opposite charges. Electrostatic interactions are the essence of ionic bond formation, therefore interactions between components with different electronegativity can lead to the formation of self-assembled nanomaterials. Self-assembled carrier-free nanodrugs based on electrostatic interactions have been studied for a long time.

In this regard, Zhao et al. developed a carrier-free photodynamic immunostimulant called BVC [6]. BVC is based on the structures of Ce6, an ASCT2 inhibitor (V9302), and a PD1/PDL1 blocker (BMS-1). Ce6 has a carboxyl group and a pyrrole structure, while V9302 has an amino, carboxyl, and benzene ring structure, and BMS-1 has a carboxyl group and a benzene ring structure. The self-assembly of the BVC is primarily facilitated by electrostatic and hydrophobic interactions. Specifically, the amino group of V9302 and the pyrrole of Ce6 interact with the carboxyl group of Ce6 and BMS through electrostatic interactions. Additionally, hydrophobic interactions between the aromatic and porphyrin groups drive the self-assembly of the drug. Experimental verification has shown that BVC has a higher delivery efficiency in terms of cellular uptake and tumour penetration, as well as a potent PDT effect. Additionally, BVC offers a strategy for reprogramming glutamine metabolism, which can improve immune recognition and reduce immune escape of tumour cells, making it an effective treatment for malignant tumours.

3. Applications of carrier-free nanomaterials

The advantages of carrier-free nanomaterials allow them to be used in medical applications, and they are now widely used in anti-tumour, anti-bacterial and anti-inflammatory applications.

3.1. Application in anti-tumour

A tumour is a biological organism formed by the proliferation of local tissue cells under the action of various carcinogenic factors. Tumours are divided into benign and malignant tumours. Malignant tumours can cause serious harm to the human body as they grow rapidly, damage normal tissues, and metastasize to other parts of the body, causing serious damage to organ function. This can lead to the formation of cancer, which is a serious threat to human health. According to the World Health Organisation (WHO) statistics for 2020, there will be approximately 20 million new cases of cancer and 9.96 million cancer-related deaths worldwide.

Current cancer treatments rely on surgery, chemotherapy, and radiation. Surgical resection remains the primary option for early-stage solid tumours. However, it is less effective and more traumatic for advanced and metastatic lung cancer. Radiation therapy is suitable for early-stage lung cancer and does not harm tissues and organs beyond the radiation exposure. Nevertheless, the treatment scope is limited, and the side effects are significant. Chemotherapy is a systemic treatment that uses chemical drugs to inhibit cell division. It takes advantage of the fact that cancer cells grow faster than normal cells. Chemotherapy can kill metastatic cancer cells, but unfortunately, most chemotherapeutic drugs do not have specificity. While killing cancer cells, they also harm normal cells. Currently, cancer is too complex to be treated by a single traditional method. Therefore, the development of a novel nanomaterial for tumour therapy is imminent.

Various carrier-free nanomedicines have been developed for cancer therapy due to their high drug loading capacity. These drug delivery systems are effective in treating cancer. Ursolic acid is a natural product with potent anticancer activity. To address its poor water solubility, Fan et al. synthesized self-assembled nanopharmaceuticals (UA NPs) through electrostatic and hydrophobic interactions between ursolic acid molecules [7]. The UA NPs exhibit excellent antitumor effects, enhancing the immunostimulatory activities of TNF- α , IL-6, and IFN- β , while reducing the activity of STAT-3 that affects tumour cell transcription. Compared to free UA, UA NPs significantly increased the number of CD4⁺ T cells in the peripheral blood of the treated animals and improved the infiltration of

CD4⁺/CD8⁺ T cells, demonstrating immunotherapeutic potential. UA NPs is a promising carrier-free nanomedicine that can further enhance its anticancer efficacy and immune function.

In addition to drug self-assembled carrier-free nanomaterials that can be used for anti-tumour applications, metal and drug self-assembled nanomaterials can also be used for anti-tumour applications. Geng et al. formed a carrier-free nanoparticle for the treatment of malignant bone tumours based on the coordination of metal ions and drugs [8]. The nanoparticles were first formed by the self-assembly of Fe (III) with zoledronate (ZOL) and then modified with hyaluronic acid to obtain metal-drug nanoparticles (HA@FeZOL). The built-in ZOL and the modification of hyaluronic acid can make the nanoparticles not absorbed by the bone, and after accumulating increase in the tumour, the ZOL released from HA@FeZOL attenuates the osteoclast activity around the tumour to inhibit bone destruction. It also generates hydroxyl radicals through a Fenton-like reaction mediated by iron-containing nanoparticles, which behave as radiosensitisers and kill cells. In a synergistic manner of radiosensitisation and osteolysis inhibition, HA@FeZOL nanoparticles effectively inhibited in situ osteosarcoma with minimal cytotoxicity, demonstrating great promise for the clinical translation of metal-liganded carrier-free nanomedicines.

3.2. Applications in Antimicrobial

Bacterial infections are acute systemic infections caused by pathogenic or conditionally pathogenic bacteria that invade the blood circulation, grow and multiply, and produce toxins and other metabolites. Bacterial infections can lead to a wide range of diseases, seriously endangering human health, and the ever-grave problem of bacterial infections urgently needs to be solved. Antibiotics are the main drugs used to treat bacterial infections, solving part of the problem of bacterial infections and effectively controlling bacterial-related infectious diseases. However, the overuse of antibiotics has led to the gradual development of bacterial resistance to antibiotics, and the problem of bacterial infections is facing greater challenges. Nanomaterials can effectively treat bacterial resistance and reduce the use of antibiotics, so the strategy of synthesising nanomaterials for the treatment of bacterial infections has been proposed.

Multidrug-resistant *Staphylococcus aureus* (MRSA) is a bacterium that has mutated to become resistant to multiple antibiotics. It poses a significant threat to human health, making the treatment of MRSA infections challenging. Liu et al. synthesized natural small-molecule carrier-free nanoparticles self-assembled from berberine (BBR) and gallic acid (GA) [9]. BBR is a clinically used natural benzylisoquinoline alkaloid with strong antimicrobial properties and bacterial biofilm scavenging ability. GA and BBR are natural phenolic acids with antioxidant and anti-inflammatory properties. They also promote bacterial wound healing and bacterial biofilm removal, respectively. The unique structures of GA and BBR allow them to self-assemble into nanoparticles (GA-BBR) through electrostatic interactions, π - π stacking, and hydrophobic interactions. In an in vivo MRSA-infected wound model, GA-BBR was shown to have antimicrobial effects and accelerate wound healing. This provides a new idea for designing carrier-free nanomedicines to combat multidrug-resistant bacterial infections.

3.3. Application in anti-inflammatory

Inflammation is the body's defence response to stimuli, but excessive or persistent inflammation can be damaging to the body. Inflammation is also associated with a variety of diseases such as arthritis, dry eye and diabetes. Often chronic inflammation can lead to systemic disease, and acute inflammation can develop into a serious illness or even become life-threatening. However, adverse effects of therapeutic anti-inflammatory drugs make the treatment less effective than expected, so there is a need to develop novel strategies for anti-inflammatory applications.

Curcumin is a natural polyphenol with anti-inflammatory activity, but its application is limited by insolubility and low bioavailability. Several studies have been conducted to construct carrier-free nanomaterials containing curcumin for the treatment of inflammation. Zhang et al. constructed nanomaterials (NCAs) for anti-inflammatory applications by combining curcumin (Cur), resveratrol

(Res), and quercetin (Qur) with poly (ethylene glycol) dimethyl ether [10]. NCAs are self-assembled from polyphenols, which solves the low drug loading and cytotoxicity problems and do not affect the anti-inflammatory and antioxidant capacity of the drug. The performance of NCAs in an acute sepsis model and a mouse model of ulcerative colitis demonstrated that the nanomaterials can effectively inhibit the expression of inflammatory factors and have a therapeutic effect superior to that of free curcumin. The construction of curcumin-based carrier-free nanomaterials broadens the application of anti-inflammatory drugs. Curcumin can also be used to construct carrier-free nanomaterials with other substances. Chen et al. self-assembled curcumin and 2-deoxy-D-glucose (2-DG) into a nanomedicine (2-DGNP) for rheumatoid arthritis treatment [11]. Glycolysis is increased in the inflamed joints of rheumatoid arthritis (RA) and modulation of glycolysis levels can alleviate inflammation. 2-Deoxy-D-glucose (2-DG) is a well-characterised inhibitor of glycolysis, but rapid clearance in vivo and its indiscriminate partitioning limits application. DCNP is composed of curcumin and 2-DG, and experiments have revealed the presence of hydrophobic interactions and hydrogen bonding in the formation process. The prepared 2-DCNP can regulate the abnormal glucose metabolism at the site of inflammation and thus inhibit the proliferation of inflammation-associated cells, providing a new strategy for the treatment of RA.

3.4. Application in antioxidant

Reactive oxygen species (ROS) are chemically reactive substances produced during aerobic cellular metabolism, mainly including superoxide anion, hydrogen peroxide, hydroxyl radical, singlet oxygen, ozone and nitric oxide. Reactive oxygen species are important for the regulation of physiological functions, but excessive amounts of reactive oxygen species can have deleterious effects on biomolecules, such as DNA damage, protein oxidation and lipid peroxidation, leading to cellular damage and disease. The development of diseases such as cancer, cardiovascular disease and Alzheimer's disease is related to reactive oxygen species. Therefore, maintaining a stable level of reactive oxygen species is important for maintaining normal physiological functions and reducing the occurrence of diseases. Current antioxidants used to remove excess ROS from organisms have the disadvantages of low stability, non-specificity and short lifetime. Therefore, it is important to develop novel carrier-free nanomedicines to effectively eliminate overexpressed ROS in cells and prevent cellular oxidative stress damage.

Wang et al. then developed a carrier-free nanomaterial (MP₂-TK@RU NPs) for the treatment of damage secondary to spinal cord injury [12]. Spinal cord injuries lead to severe motor, sensory, and autonomic dysfunction, resulting in permanent disability and affecting daily life. Among other things, spinal cord injuries are associated with oxidative stress and inflammation, so the development of drugs that modulate micro-oxidative stress and inflammation is an effective approach to treat spinal cord injuries. Methylprednisolone (MP), an anti-inflammatory steroid, is currently the most commonly prescribed drug for the treatment of acute spinal cord injury. Rutin (RU) is a natural flavonoid with bracketed anti-inflammatory and antioxidant properties. However, the side effects and non-targeted delivery of these two drugs limit their clinical applications. Wang et al. first prepared a ROS-cleavable thioketone (TK) molecule, and then synthesized ROS-cleavable MP dimer (MP₂-TK) using TK, and then co-assembled hydrophobic MP₂-TK and amphiphilic rutin to prepare MP₂-TK@RU NPs. The nanomedicines were capable of accumulation at the site of spinal cord injury, releasing MP and rutin through reactive oxygen species cleavage, which can eliminate reactive oxygen species to inhibit the secretion of inflammatory factors and reduce the secondary damage of spinal cord injury.

4. Conclusion

In conclusion, this paper focuses on outlining the self-assembly mechanism of carrierless nanomaterials and their applications in antitumor, antibacterial, anti-inflammatory and antioxidant applications. Carrier-free nanomaterials, which are prepared with simple components and synthesized in a simple process, have the advantages of high drug-carrying capacity and no carrier toxicity, and

are a new type of nanomedicine with unique potential for medical applications. Although a variety of strategies have been developed for the use of carrierless materials in medical treatment, in-depth studies of carrierless nanomaterials are still needed to further advance their application in the clinic.

This paper only briefly introduces the self-assembly mechanism for constructing carrierless nanomaterials, which is not studied in depth enough, and further research is needed on how to utilize the structure of drug molecules for precise combinations. With the progress of molecular simulation technology, it is now possible to simulate the formation of intermolecular self-assembly by accurate molecular simulation models, and use the results obtained by simulation to guide further experimental design. Therefore, constructing a database of self-assembled drugs is of great significance for the design and synthesis of carrierless nanomaterials. The stability of carrierless nanomaterials also limits their applications. Since it is mainly weak interaction forces that drive the formation of carrierless nanomaterials, the stability of nanostructures is susceptible to environmental influences, so new modification methods need to be investigated to improve the stability. In addition, the size of nanoparticles affects their biodistribution, cellular internalization, plasma and in vivo excretion, which has a great impact on therapeutic efficacy. Therefore, development of new synthesis methods to prepare carrier-free nanomaterials with uniform particle size can achieve better therapeutic efficacy.

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References

- [1] Huang, L., Hu S., Fu Y.-N., et al. Multicomponent carrier-free nanodrugs for cancer treatment [J]. *Journal of Materials Chemistry B*, 2022.
- [2] Li-Han, L., Xian-Zheng Z. Carrier-free nanomedicines for cancer treatment [J]. *Progress in Materials Science*, 2022.
- [3] Ji, H., Wang W., Li X., et al. Natural Small Molecules Enabled Efficient Immunotherapy through Supramolecular Self-Assembly in P53-Mutated Colorectal Cancer [J]. *ACS Applied Materials & Interfaces*, 2022.
- [4] Dai, W., Jin P., Li X., et al. A carrier-free nano-drug assembled via π - π stacking interaction for the treatment of osteoarthritis [J]. *Biomedicine & Pharmacotherapy*, 2023.
- [5] Zhou, X., Li Y., Li X., et al. Carrier free nanomedicine to reverse anti-apoptosis and elevate endoplasmic reticulum stress for enhanced photodynamic therapy [J]. *Acta Biomaterialia*, 2022.
- [6] Linping, Z., Xiaona R., Rongrong Z., et al. Targeting glutamine metabolism with photodynamic immunotherapy for metastatic tumor eradication [J]. *Journal of Controlled Release*, 2023.
- [7] Fan, L., Zhang B., Xu A., et al. Carrier-Free, Pure Nanodrug Formed by the Self-Assembly of an Anticancer Drug for Cancer Immune Therapy [J]. *Molecular Pharmaceutics*, 2018.
- [8] Geng, H., Zhou M., Li B., et al. Metal-drug nanoparticles-mediated osteolytic microenvironment regulation for enhanced radiotherapy of orthotopic osteosarcoma [J]. *Chemical Engineering Journal*, 2020.
- [9] Gao, S., Zheng H., Xu S., et al. Novel Natural Carrier-Free Self-Assembled Nanoparticles for Treatment of Ulcerative Colitis by Balancing Immune Microenvironment and Intestinal Barrier [J]. *Advanced Healthcare Materials*, 2023.
- [10] Zhang, L., Xia H., Du S., et al. Carrier-free curcumin nanoassemblies for enhancing therapy effects in inflammation related disease [J]. *Materials & Design*, 2022, 222: 111087.
- [11] Chen, T., Lin X., Li D., et al. Carrier-free nanodrug targeting glucose metabolism for enhanced rheumatoid arthritis treatment [J]. *Colloids and Surfaces B: Biointerfaces*, 2024, 233: 113668.
- [12] Wang, H., Lin F., Wu Y., et al. Carrier-Free Nanodrug Based on Co-Assembly of Methylprednisolone Dimer and Rutin for Combined Treatment of Spinal Cord Injury [J]. *ACS Nano*, 2023.