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Study on the Preparation Method and Application Prospect of Drug-Carrying Microspheres of Polylactic Acid and its Copolymers

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Abstract: This paper reviews the principles, advantages and disadvantages, and scope of application of different processes for the preparation of drug-carrying microspheres of polylactic acid (PLA) and its copolymers, and explores the potential of PLA drug-carrying microspheres for drug delivery, tissue engineering and fluorescent labeling, etc. It also summarizes the limitations of the current technology, and proposes to optimize the drug-carrying system through the design of bilayer structured, responsive and multifunctional integrated microspheres, with a view to providing theoretical basis and technical support to the research of the related fields. We also summarize the limitations of the current technology and propose to optimize the drug-carrying system by designing bilayer structure, responsive and multifunctional integrated microspheres, in order to provide theoretical basis and technical support for the related fields.

Keywords: Poly (Lactic Acid) and its Copolymers; Drug-carrying Microspheres; Preparation Process; Sudden Drug Release; Multifunctional Integration.

1. Introduction

Polylactic acid (PLA), which is usually generated by the polymerization of lactic acid and eventually metabolized to water and carbon dioxide in the human body, is a biodegradable material approved by the U.S. Food and Drug Administration (FDA) for use in the human body. Scholars have carried out a lot of research on it and synthesized various types of copolymers based on PLA, such as: right-handed polylactic acid and poly-l-lactide. They have excellent biocompatibility. They have excellent biocompatibility[1] , suitable mechanical strength[2] , and controllable biodegradability[3] , and have gradually become a hot material in the research of drug delivery system. At present, researchers have developed a variety of methods to prepare drug-carrying microspheres using PLA and its copolymers as carriers, such as emulsification solvent evaporation method, spray drying method and microfluidic technology, etc. These methods have their own advantages and disadvantages in controlling the microsphere particle size, the encapsulation rate of the drug and the release behavior. The aim of this paper is to systematically summarize these preparation methods, explore their advantages and disadvantages and their latest application progress, and discuss and propose improvements to the current preparation techniques, such as drug sudden release and single function of microspheres, so as to provide references for the research in the medical fields of biological tissue engineering, drug delivery and so on.

2. Preparation of Drug-carrying Microspheres

2.1. Emulsification-solvent Evaporation Method

The emulsification-solvent evaporation method is a technique for the preparation of drug-loaded microspheres based on interfacial stabilization and solvent diffusion kinetics. According to the difference of emulsification system, it can be divided into two categories: single emulsion method and complex emulsion method.

The single emulsion method builds a dispersion system through a single emulsification step, and is divided into oil-in-water and oil-in-water methods. Oil-in-water (O/W) type, the hydrophobic drug and PLA dissolved in the organic phase such as methylene chloride, dispersed into the water phase containing surfactant to form emulsion, the solvent volatilization of the PLA interface curing, for fat-soluble drugs; water-in-oil (W/O) type, the water-soluble drug dissolved in the inner aqueous phase and then dispersed in the oil phase, the interphase diffusion leads to a low rate of encapsulation, need to be heated to promote the removal of solvents. Single-emulsion method is easy to operate, low cost, and suitable for industrialized production. The double emulsion method realizes the simultaneous encapsulation of complex drug systems through double emulsification. The inner aqueous phase and the organic phase of PLA form a W/O colostrum, which is then dispersed into the outer aqueous phase to build a W/O/W complex emulsion, and the solvent is evaporated to form core-shell microspheres by cross-linking PLA. The complex emulsion method can extend the drug applicability while regulating the particle size, but the process is complicated and the solvent residue is high, and the emulsification parameters need to be optimized to balance the performance.

This method is widely used due to the low cost of equipment and simple process, and the particle size can be regulated by adjusting the parameters such as polymer type, mixing rate, and water-oil ratio, but there are shortcomings such as easy aggregation of microspheres, high organic solvent residue, and limitations on the sudden release of the drug and the efficiency of encapsulation, which need to be combined with the surface modification or process improvement to enhance the performance of[4] .

2.2. Spray Drying Method

Spray drying method is a microsphere preparation technology based on rapid solvent evaporation and interfacial curing mechanism, and its core process includes three successive stages of dispersion, evaporation and curing. After dissolving the drug and PLA or its copolymer in a volatile organic solvent to form a homogeneous solution, the solution is dispersed into micron-sized droplets through a high-speed atomization device, and the solvent is instantaneously evaporated in a high-temperature airflow, which leads to cross-linking and curing of the polymer on the surface of droplets and the formation of drug-carrying microspheres with a core-shell structure. The key parameters of this technology include atomization pressure, air inlet temperature and solution viscosity, which can be adjusted to control the particle size and surface morphology of the microspheres.

The technology achieves precise control through quantifiable modeling of process parameters, combined with a rapid phase change process to significantly shorten the drying cycle, excellent product homogeneity and low raw material loss, and a significant increase in drug encapsulation efficiency. Its potential for large-scale production and compatibility with multiple types of drug carriers further strengthens the advantages of industrial-scale applications. However, the process has problems such as high dispersibility index of microsphere particle size and high adhesion rate on the inner wall of the equipment, and is limited by the thermodynamic sensitivity and narrow temperature window, which results in limited applicability for heat-sensitive drugs. The temperature deviation from the threshold value may cause microsphere deformation or solvent residue exceeding the standard, and the temperature gradient needs to be precisely controlled to adapt to different drug-carrier systems[5] .

2.3. Supercritical Fluid Dispersion Method

The supercritical fluid dispersion method is based on the unique physical and chemical properties of supercritical fluids (such as low viscosity, high diffusivity and zero surface tension), and utilizes the rapid mixing of supercritical CO_2 and organic solvents to promote the supersaturation and precipitation of solutes, so as to realize the precise preparation of drug-carrying microspheres. The core process is divided into three stages: firstly, PLA is dissolved in organic solvents such as dichloromethane to form a homogeneous solution; subsequently, the solution is rapidly mixed with supercritical CO_2 in a high-pressure granulation kettle, which instantly reduces the solvent solubility and triggers the rapid supersaturated precipitation of solute through the highly efficient mass transfer of supercritical fluids; and ultimately, microspheres with uniform particle size are obtained through the adjustment of the phase state of the fluids[6] . The key parameters of this technique include solvent system polarity, pressure gradient and temperature field, and the directional regulation of microsphere particle size can be realized by regulating these parameters.

This technology is based on the green solvent property of supercritical CO_2, which is both environmentally friendly and safe, avoiding organic solvent residue, and optimizing interfacial tension through solvent polarity adjustment, precisely regulating microsphere particle size and dispersion uniformity, thus guaranteeing the construction of high crystallinity drug-carrying system. However, the demand for high-pressure reaction system and precision temperature control equipment significantly increases the production cost, and the small fluctuation of process parameters (such as temperature and concentration) can easily lead to the widening of particle size distribution or particle fusion agglomeration, thus restricting the consistency of the product and causing production bottlenecks.

2.4. Microfluidics

Microfluidic technology is based on the principle of precise manipulation of fluids in micrometer-sized channels to realize the controlled synthesis of drug-carrying microspheres through multiphase hydrodynamics. The core mechanism is that the immiscible dispersed phase and the continuous phase are synergized by shear force and interfacial tension at the intersection of microchannels to form monodisperse droplets. The droplet size is regulated by the channel geometry, the two-phase flow rate ratio and the interfacial tension, and by adjusting the above parameters, microspheres with highly uniform particle size can be realized[7] . After the droplets are generated, they are solidified by solvent evaporation, cross-linking or phase separation to form microspheres with a core-shell or porous structure, whose internal morphology can be precisely regulated by multistage channel design.

The technology is based on the hydrodynamic regulation of micrometer-scale channels, forming monodisperse droplets through the synergistic action of shear force and interfacial tension, which can precisely regulate the microsphere size and morphology. Its process simplifies the construction of complex drug-carrying systems with high batch-to-batch consistency, and the release rate can be programmed and designed. However, it is difficult to meet the demand of industrialized batch due to its low single-channel yield and high time cost.

2.5. Interfacial Deposition Method

The interfacial deposition method is based on the mechanism of polymer phase separation in solvent-nonsolvent system, and the directed assembly of drug-carrying microspheres is realized by interfacial energy modulation. The core of the process is that the drug particles or emulsion are dispersed in the organic solution of PLA to form a homogeneous suspension system, and then the non-solvent phase is introduced to induce the layer-by-layer deposition of PLA molecules on the surface of drug carrier cores by decreasing the solubility of the polymer. In this process, the diffusion rate of the non-solvent and the stirring intensity together affect the surface morphology and particle size distribution of the microspheres.

This method can be used to prepare nanospheres with uniform particle size. The drug acts as the nucleation center and is completely encapsulated by the PLA layer, allowing for high encapsulation rates. The technique can be operated at room temperature without complex equipment and is suitable for the retention of activity of thermosensitive drugs. However, it requires a large amount of flocculant, which is costly, the precise control of reaction conditions is difficult, the available precipitants are limited, and the impurity residue rate in the finished products is generally high.

2.6. High-pressure Electric Injection Method

The high-voltage electric jet method drives the drug-containing PLA solution to form monodisperse microspheres through a high-voltage electrostatic field. The core of the process is: the PLA-drug co-solution system is injected at

high speed through a precision nozzle, and under the action of electric field force to overcome the solution viscous resistance and surface tension constraints, so that the jet is broken into homogeneous liquid droplets. The droplets fly to the collection device under gravity or electric field traction, and are cured by solvent volatilization or non-solvent induced phase separation. The coaxial electrospray technology can be used to construct core-shell structure microspheres, and the particle size and morphology can be precisely controlled by adjusting the voltage gradient, solution conductivity and nozzle diameter.

The microspheres prepared by this method have high uniformity in particle size and can optimize the structure of the drug-carrying system to improve the drug loading efficiency and encapsulation efficiency significantly. However, the high cost of equipment, process complexity, low production efficiency, and strict requirements on material conductivity and viscosity, there are safety hazards, thus limiting the application of the method.

3. Role of Drug-carrying Microspheres

3.1. Modifiable Drug Slow Release

Polylactic acid and its copolymers, as biodegradable carrier materials, achieve controlled drug release through the ester bond hydrolysis of molecular chains. By matching the half-life of the drug with the degradation rate of the material, the drug-carrying microspheres can significantly prolong the maintenance time of effective blood concentration and reduce the frequency of drug administration, and their release kinetics are synergistically regulated by the physicochemical properties of the material and the structure of the microspheres. High molecular weight PLA can achieve long-lasting and slow release due to its tightly wound molecular chain and slow degradation rate, while low molecular weight PLA can shorten the release period by accelerated hydrolysis due to its enhanced hydrophilicity. The core-shell structure can inhibit the sudden release of the drug and delay the diffusion of the drug through the dense polymer barrier of the outer layer, while the homogeneous dispersion system can realize the zero-grade release through the ontogenetic degradation. The degradation products of microsphere carriers are both therapeutically safe and environmentally friendly, providing an ideal solution for chronic disease management and development of long-lasting formulations. For example, conventional erythromycin[8] and exenatide[9] require frequent administration to maintain effective blood concentration due to their short half-life, but their preparation into PLA-carrying microspheres significantly extends the stabilization time of the blood concentration and reduces the local irritation and patient discomfort caused by frequent administration.

3.2. Targeted Delivery of Drugs

Through functionalized modification of drug-carrying microspheres, such as the introduction of specific antibodies, ligands or magnetic materials, the active targeting ability of microspheres can be realized in order to accurately treat the area and improve the therapeutic effect. For example, using antigen-antibody specific binding, microspheres can accurately recognize and enrich in the lesion area; magnetically modified microspheres can realize magnetic guided targeting under the effect of applied magnetic field. At the same time, the microspheres can also deliver drugs to target organs or tissues through embolic targeting. Studies have shown that surface modification of PLA microspheres, such as using chitosan quaternary ammonium plating, can significantly improve the adsorption capacity of the microspheres with tumor cells and enhance the cellular uptake efficiency of the drug[10] . These properties enable the drug-carrying microspheres to achieve drug concentration and maintain a certain release rate in the target organ, thus improving the therapeutic effect.

3.3. Reduction of Toxic Side Effects

As a non-toxic, non-irritating and biodegradable drug carrier material, PLA and its copolymers have good biocompatibility, which can effectively avoid drug-carrying microspheres from triggering inflammation or immune response in vivo, and the design of material properties and functionalization can synergistically reduce the toxicity of the drugs to ensure the safety of drug administration. The microspheres can reduce the peaks and valleys of blood drug concentration through continuous drug release, lower the toxic load of the heart and other organs, and also reduce the frequency of drug administration to improve the drug tolerance of patients. Wang et al.[11] prepared rotigotine PLGA microspheres to avoid the first-pass effect of the drug in animal experiments, and experiments have shown that it can significantly reduce the toxicity of the drug when used in conjunction with levodopa.

4. Application of Drug-Carrying Microspheres

4.1. Drug Delivery Systems

Drug-loaded microspheres play an important role in drug delivery systems due to their tiny size structure and large surface area to volume ratio, which can effectively enhance the bioavailability of the encapsulated drug, and at the same time, make their surface modification highly flexible and functional[12]. Zhang et al.[13] A novel urea derivative was loaded in PLGA, and a slow-release formulation of PLGA-loaded microspheres with low cytotoxicity and effective anticaries was prepared. PLGA-loaded microspheres were used to prepare a slow-release formulation with low cytotoxicity and effective anti-caries properties. Sebelemetja et al. [14] loaded flavonoids into PLGA microspheres in order to enhance the stability and bioavailability of the flavonoids. The experiments showed that the drug-loaded microspheres not only retained the inhibitory effect of the flavonoids against Streptococcus pyogenes, but also achieved a slow-release of the flavonoids at the cariogenic pH, which indicates that the drug loaded in PLGA microspheres has good drug delivery stability.

In addition, PLA microspheres, as an efficient drug delivery vehicle, can effectively penetrate the biofilm barrier and realize the targeted and efficient drug delivery. Cheng Guohua et al. investigated the targeted delivery effect of tetrandrine. Mice were given PLA microspheres of tetrandrine and conventional injections, respectively. The data showed that the drug accumulation in the lungs was significantly higher in the PLA microsphere group compared to other tissues, which demonstrated the good lung-targeting properties of the formulation[14] , a finding that strongly validates the advantages of microsphere drug delivery systems for targeted drug delivery.

4.2. Tissue Engineering Applications

Drug-loaded microspheres play an important role in bone tissue repair, catheter artery embolization therapy, and novel tissue skin construction. PLA microspheres loaded with bioactive molecules, such as bone morphogenetic protein (BMP), can release active factors in a controlled manner to promote cellular osteogenic differentiation and new bone formation, which is promising in the field of bone tissue regeneration. Boda et al[15] loaded BMP-2 into PLGA nanofiber fragments to develop a novel material that was applied to the repair of periodontal bone defects in rats. The results showed that the bone density and bone volume of the experimental group increased nearly three times compared with the control group, which fully demonstrated its high efficiency in bone regeneration. It has been shown that angiogenesis is an indispensable part of bone formation and plays a key regulatory role in bone morphogenesis. Wang et al. In order to further enhance the effect of bone regeneration[16], designed and developed a multifunctional microsphere based on poly(DL-lactic acid)- glycolic acid copolymer (PDLLA-PLGA) material loaded with both vascular endothelial growth factor (VEGF) and BMP-2 multifunctional microspheres of both active factors. This two-factor loading system successfully realized the synergistic effect of osteogenesis and angiogenesis, and provided a new idea for the design of bone regeneration scaffolds and bone tissue repair therapy.

4.3. Bioimaging and Fluorescent Labeling

Nanospheres play an important role in the field of bioimaging and fluorescent labeling. Their small size and high specific surface area enable them to be loaded with a large number of fluorescent dyes or imaging probes, significantly improving imaging resolution and sensitivity. Through surface modification of targeting molecules, nanospheres are able to precisely localize target cells or tissues, enhancing the specificity of imaging. In addition, the nanospheres can protect the fluorescent dyes from degradation in the biological environment, enabling dynamic tracking over long periods of time. Their versatility also supports multimodal imaging and diagnostic integration, providing a powerful tool for disease research and clinical diagnosis. For example, Li[17] et al. prepared multifunctional chemoembolization PLGA microspheres with fluorescence imaging properties using nanoparticles (Re NPs) with good fluorescence imaging properties in NIR-II, which are expected to enable NIR-II fluorescence imaging and surgical navigation in future liver cancer surgeries, as analyzed in imaging systems as well as in cytological experimental tests. PLGA microspheres, due to their excellent PLGA microspheres have significant advantages in in vivo bioimaging and fluorescent labeling due to their excellent biocompatible properties, providing important technical support for disease diagnosis, treatment evaluation and surgical navigation.

5. Discussion

5.1. Sudden Release of Drugs

In the application of PLA and its copolymers drug-carrying microspheres, the sudden release of drug is the key issue. When the drug-carrying microspheres enter the body, the drug is easy to be released in large quantities within a short time. Sudden release in excess of the range can lead to unstable blood concentration, exceeding the toxicity threshold and increasing the risk of toxic side effects[18] . The reasons for sudden release include the drug or embedded in the surface layer of microspheres, which rapidly dissolves and diffuses on contact with body fluids. At the same time, pore defects present on the microsphere surface can accelerate drug release. Currently, it is mainly solved by optimizing the preparation process, adjusting the microsphere structure and developing responsive microspheres.

5.1.1. Optimization of the Preparation Process

There are various factors in the preparation process of microspheres that can affect the rate of abrupt release[19] , so precise control of the process parameters is crucial to address drug abrupt release. An et al.[20] pointed out that the lower the relative molecular mass of PLGA, the higher the burst release of microspheres with more pores. And when the relative molecular mass of PLGA shows a trend to be larger, the microsphere structure is denser, the porosity is lower, and the abrupt release is smaller[21] . Wang et al[22] In the preparation of risperidone PLGA microspheres, it was found that when the ratio of LA/GA increased, the overall hydrophobicity of PLGA was enhanced due to the stronger hydrophobicity of LA than that of GA, and the amount of the sudden release was significantly reduced. And when the ratio of GA increased[23] , the hydrophilicity of PLGA was enhanced, the microsphere degradation speed was accelerated, and the burst release effect was significant. In addition, the increase in temperature will allow peptides to diffuse to the surface of the microspheres, increasing the surface area of drug release and enhancing the sudden release effect. It can also have an effect on the sudden release of drugs[24] . Related studies have shown that[25] PLGA microspheres can enhance the sudden release effect by increasing the concentration difference between the inside and outside of the microspheres when the amount of drug loaded is increased. Rational adjustment of process parameters such as relative molecular mass of PLGA, LA/GA monomer composition ratio, temperature and loading capacity can effectively improve the structure of the microspheres and precisely control the release rate of the microspheres.

5.1.2. Adjustment of Microsphere Structure

Optimization of microsphere structure the commonly used emulsification solvent evaporation method for the preparation of PLGA drug-carrying microspheres is simple and can be mass-produced, but it has the problems of organic solvent residue, low encapsulation rate, and sudden drug release. Although new methods such as spray drying, microfluidic method and supercritical fluid method have been improved, the problem of sudden drug release has not been solved. At present, some new slow-release microsphere formulations are expected to overcome the shortcomings of the traditional formulations, and have the advantages of simple operation, good biocompatibility and low cost.

Bilayer structure drug-carrying microspheres, a structure in which a drug is formed with a biodegradable polymer to form the inner core and another biodegradable polymer as the outer shell. The outer polymer layer encapsulates the inner core, which can effectively reduce the drug's sudden release effect[26] and increase the encapsulation rate[27] of the drug. Xu et al.[28]By preparing bilayer-structured drug-carrying microspheres with a PLLA shell, a PLGA core, and investigating the drug release behavior, it was found that at the initial stage, the PLLA can effectively inhibit the drug from being released suddenly. At the later stage, the drug can

be released normally and slow release is achieved. Devrim et al.[29] prepared ovalbumin-containing bilayer microspheres. The rate of sudden release was only 10.36% and the encapsulation rate was 93.98%. It was much better than single polymer microspheres (44.11% burst release rate and 64.11% encapsulation rate), which fully demonstrated the advantages of bilayer drug-carrying microspheres in reducing the burst release rate and increasing the encapsulation rate.

Self-healing porous microspheres, a common method used in the preparation of PLGA microspheres for peptide drugs. The principle is mainly related to the ability of PLGA to transform under the influence of temperature[30][31][32]. Some studies have reported[33] that the method is the preparation of porous microspheres after lyophilization immersed in a high concentration of peptide drug solution, and finally adjust the temperature so as to realize the drug loading, which can effectively avoid the denaturation and inactivation of protein drugs, and also have an improvement on the phenomenon of sudden release of the drug. Desai et al.[34] loaded the vaccine antigens into the porous microspheres and accomplished the self-healing under the control of the temperature and experimental results showed that the microspheres played a long-lasting role in the healing process of the vaccine antigens and the self-healing was accomplished under the control of the temperature. Xi et al.[35] used this method to load soft serum proteins into PLA microspheres, and the pore-healed microspheres achieved a slow release of soft serum proteins within 3 weeks and triggered a sustained immune response at the aggregation site of the microspheres.

5.1.3. Development of responsive microspheres

The development of responsive microspheres is an innovative strategy to address the problem of sudden drug release. By intelligently designing microspheres to precisely release drugs under specific environments (e.g., enzyme, ATP, temperature, and pH), abrupt release can be reduced[36] ,[37] ,[38]. Zheng[40] prepared enzyme reactive microspheres by attaching peptides to the molecular chain of PLA, which can achieve enzyme reactive controlled release of anti-tumor drugs in a matrix metalloproteinase environment. Yu[40] ATP-responsive PLGA porous microspheres developed by utilizing the difference in ATP concentration between normal and diseased sites were able to rapidly release Doxorubicin (Dox) in an ATP environment, and to achieve slow release of the drug in a non-ATP environment. Lu[41] pH-responsive PLA microspheres were prepared using hyperbranched polyacetal molecules with good pH sensitivity. The pH-responsive controlled drug release was achieved by hydrolysis of hyperbranched polyacetal molecules in acidic environment. The pH-responsive microspheres are capable of precise drug release according to the environmental changes, and show a broad application prospect in many fields.

5.2. Microspheres with a Single Function

With the deepening of research on disease treatment mechanisms and the continuous improvement of clinical needs, it is difficult for single-function drug-carrying microspheres to meet the demand. Most of the current PLA and its copolymer drug-carrying microspheres are focused on drug delivery, with less integration of other functions. In this context, it is of great practical significance to find effective solutions to promote the development of drug-carrying microsphere technology and to meet the increasing clinical demands.

5.2.1. Achieving Multifunctional Integration

Due to the mono-functionality of PLA and its copolymer drug-loaded microspheres, it is difficult for them to excel in some special or emerging applications. Loading multiple drugs into the same microsphere allows the drug-carrying microspheres to exert synergistic effects on each other and improve their multifunctional therapeutic effects, thus providing better solutions for complex clinical diseases. Wang et al.[42] prepared biodegradable drug-carrying microspheres with PLGA as a carrier and loaded with curcumin and Dox, two anticancer drugs with different solubility properties, to construct a biodegradable microsphere in which hydrophilic and hydrophobic drugs coexist. This study provides a reference for the future preparation of dual antitumor drug-carrying microspheres that exert synergistic effects. Xu et al.[43] co-loaded Dox with chitosan-DNA nanoparticles (chi-p53) into microspheres. The results showed that the drug-loaded microspheres co-coated with Dox and chi-p53 presented stronger cytotoxicity and more pronounced antiproliferative effects than the cells treated with free drug, compared to the drug-loaded microspheres loaded with Dox and chi-p53 individually, respectively.

Combine the diagnostic function with drug delivery function to prepare diagnostic and therapeutic integrated microspheres. Imaging contrast agents, such as magnetic nanoparticles and quantum dots, are introduced into the microspheres, and magnetic resonance imaging, fluorescence imaging and other technologies are used to monitor the distribution of the microspheres in vivo, drug release and therapeutic effects in real time, so that the drug-carrying microspheres have a therapeutic monitoring function, which can help personalized medicine. Tang[44] combined quantum dots with polymer PLA-MA to prepare fluorescent microspheres with good stability and constructed a liquid-phase biological suspension microchip using microspheres as a carrier, which is characterized by high sensitivity, high efficiency and good detection performance, and has a broad application scenario in the field of biomolecular analysis.

5.2.2. Composite other Functional Materials

The introduction of materials with special functions such as iron oxide nanoparticles, indocyanine green and carbon nanotubes into drug-loaded microspheres of polylactic acid and its copolymers can give new properties to the microspheres. Fang[45] Magneto-responsive PLGA drug-loaded microspheres for combined tumor thermotherapy and chemotherapy were produced by loading γ-Fe_2O_3@DMSA nanoparticles on the microsphere surface. Yang et al.[46] prepared DOX-loaded photothermal-responsive microspheres from indocyanine green and PLGA by microfluidic technique, and the realized structures showed good photothermal responsiveness and slow release, which is expected to open up a new avenue for tumor photothermal/chemotherapeutic combination therapy.

6. Summary

Poly (lactic acid) and its copolymer drug-carrying microspheres have become a research hotspot in the fields of drug delivery, tissue engineering and bioimaging due to their excellent biocompatibility, controlled degradation and flexible process tunability. With the advantages and disadvantages of emulsification solvent evaporation, spray

drying and microfluidic technology, researchers are able to precisely regulate the particle size, drug encapsulation rate and release behavior of the microspheres, but they are still facing technical bottlenecks such as sudden release of drugs and single function. Existing studies have shown that by optimizing process parameters, designing bilayer structure and responsive microspheres, the sudden release effect can be significantly suppressed and the release performance can be improved; meanwhile, the integration of diagnostic and therapeutic functions (e.g., fluorescent labeling, magneto-thermal response) and multi-drug synergistic delivery strategy provides a new idea for the treatment of complex diseases. Future research should further explore intelligent and multifunctional microsphere systems, combining new materials (e.g., quantum dots, magnetic nanoparticles) and advanced technologies (e.g., microfluidic chips, supercritical fluids), to promote the clinical application of drug-carrying microspheres in precision medicine, tissue regeneration, and multimodal diagnostics, which not only break through the limitations of existing technologies, but also bring more efficient, safe, and personalized therapeutic solutions in the field of biomedicine.

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