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Preparation of Single, Heteromorphic Microspheres, and Their Progress for Medical Applications

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Microspheres applied in medical applications experience explosive development in recent years, such as drug release, cell culture, and bone tissue engineering, etc. However, there are still some bottlenecks both in economy and technology lay that cannot be ignored. For instance, microsphere technology has not been used in cell culture widely because of its uneconomical cost; as the core of drug-loaded microsphere, targeted microsphere technology is still not mature enough. Besides, the common microsphere fabrication methods: microfluidic or emulsion technology is difficult to guarantee high biocompatibility of microsphere due to utilization of photoinitiator, crosslinking agent, surfactant, and other substances. Therefore, gas-shearing technology has been proposed to solve these above shortcomings successfully. This paper focuses more on heteromorphic microspheres rather than on single microspheres which begins with a minute introduction of microsphere preparation methods: microfluidic, coaxial electrospray, emulsion, and gas-shearing technology. Then its medical applications: drug release, cell culture, bone tissue engineering, and hemostasis are discussed in detail. The disadvantages of fabrication methods and bottlenecks for medical applications at present are also stated. At the end, perspectives of microsphere development are put forward.

1. Introduction

Microsphere has attracted wide attention due to its applications in medical territory.[1] In recent years, the research progress of microspheres is emerging. Explosive progress has been made in such fields as diagnosis and drug anticounterfeiting, etc. (**Figure 1**)[2,3] based on microspheres. The rich morphology of microspheres is the main reason why they can make great progress in the medical field. Compared with the traditional single microsphere, the heteromorphic microsphere (porous microsphere, core–shell microsphere, multicompartmental microsphere, etc.) can better meet the needs of the contemporary medical industry (**Figure 2**).[4–7]

Microsphere is a kind of particle dispersion system made of polymer and polymerization whose shape is spherical or quasispherical.[4] There are many materials for the preparation of microspheres, which are mainly divided into natural polymer microspheres (e.g., starch microspheres, albumin microspheres, gelatin microspheres, chitosan, etc.) and synthetic polymer microspheres (e.g., polyactic acid microspheres).[8] In the study of microspheres, compatibility is a very important aspect. Compatibility mainly includes biocompatibility and geometric compatibility. For biocompatibility, this is often determined by the materials used to make microspheres. As for geometric compatibility, this is often related to roundness. Basically, the closer the roundness is to 1, the better the geometric compatibility is.[9,10]

There is also no precise limit on the diameter of the microsphere. In general, microsphere can be divided into nanomicrosphere and micro-microsphere. The small one can be several nanometers and the large one can reach several hundred micrometers. Nanoscale microspheres are also commonly referred to as nanospheres.[11–13]

Microspheres have been widely used in the medical field, among these applications, drug release is the most important. The great potential of microspheres in drug release is closely related to their specific surface area.[14] The surface area of a gram of microspheres is equivalent to a football field. If there are some special groups on the surface of microspheres, they can selectively adsorb the effective ingredients of drugs.[15–17]

In recent years, drug-loaded microspheres as a new embolic material can embolize tumor blood supply artery to make tumor ischemic and necrotic. At the same time, it is also a carrier of chemotherapy drugs. It can load chemotherapy drugs and release them slowly and continuously in tumor area, maintain high blood concentration in tumor area

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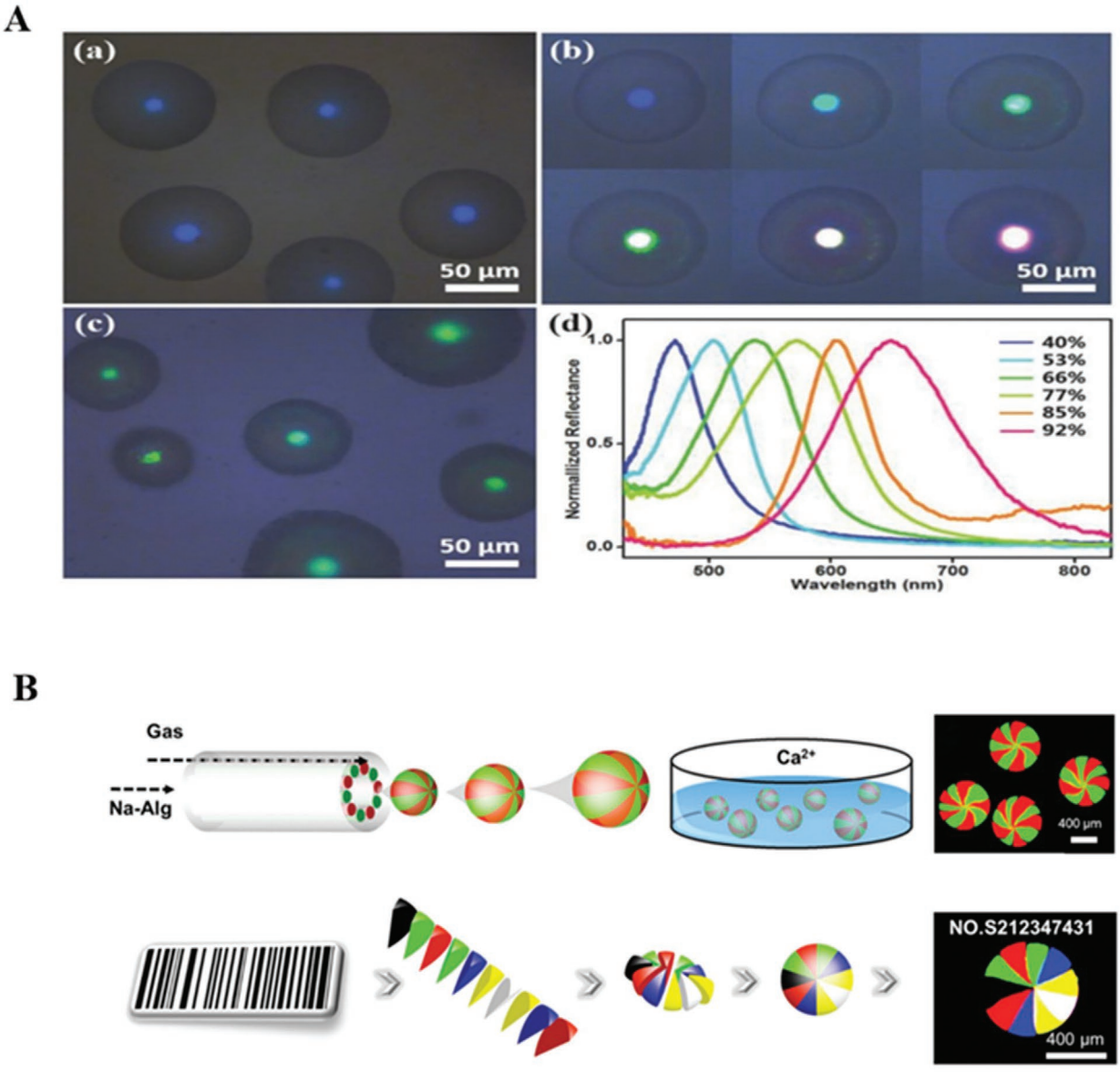

Figure 1. Examples of microsphere progress in medical fields. A) Responsive block copolymer photonic core-shell microspheres and their potential application in the fields of displays, sensing, and diagnostics. Reproduced with permission.[2] Copyright 2018, Wiley-VCH GmbH. B) Biocompatible multicompartmental memo-microspheres fabricated by gas-shearing method used for digitally color-tunable bar coding. Reproduced with permission.[3] Copyright 2020, Wiley-VCH GmbH.

and then kill tumor cells.[18,19] Animal experiments showed that after loading 40 mg doxorubicin into 1 mL drug-loaded microspheres, the drug concentration in peripheral blood was lower than that in traditional transcatheter arterial chemoembolization.[20] Besides, the drug concentration in liver tissue reached 245.70 from 40.27 μg mL^{-1} one week after perfusion. Therefore, drug-loaded microspheres have the characteristics of high local drug concentration and relatively low peripheral blood circulation concentration.[21,22]

As a recognized method for the treatment of refractory and unresectable liver cancer, radiation embolization has been widely used in recent years. Radiation embolization is based on the injection of 90^{Y} microspheres into the hepatic artery. 90^{Y} microsphere is a kind of targeted radioactive microsphere.[23] Its successful preparation is of great significance for radioactive embolization. At present, many researchers focus on this. Dziel et al. prepared yttrium oxide spherical microspheres by sol–gel method. The final product 90^{Y} microsphere has a specific activity suitable for hepatic malignant tumor transarterial embolization.[24] Besides, scientists invented theranostic barcoded nanoscale microparticles for personalized cancer medicine, which may be a boon for cancer patients. Yaari et al. used 100 nm liposomes loaded with a variety of anticancer drugs and corresponding synthetic DNA barcodes. Based on the matched barcodes, they found an association between cell activity and the drug exposed. Therefore, they demonstrated the effectiveness

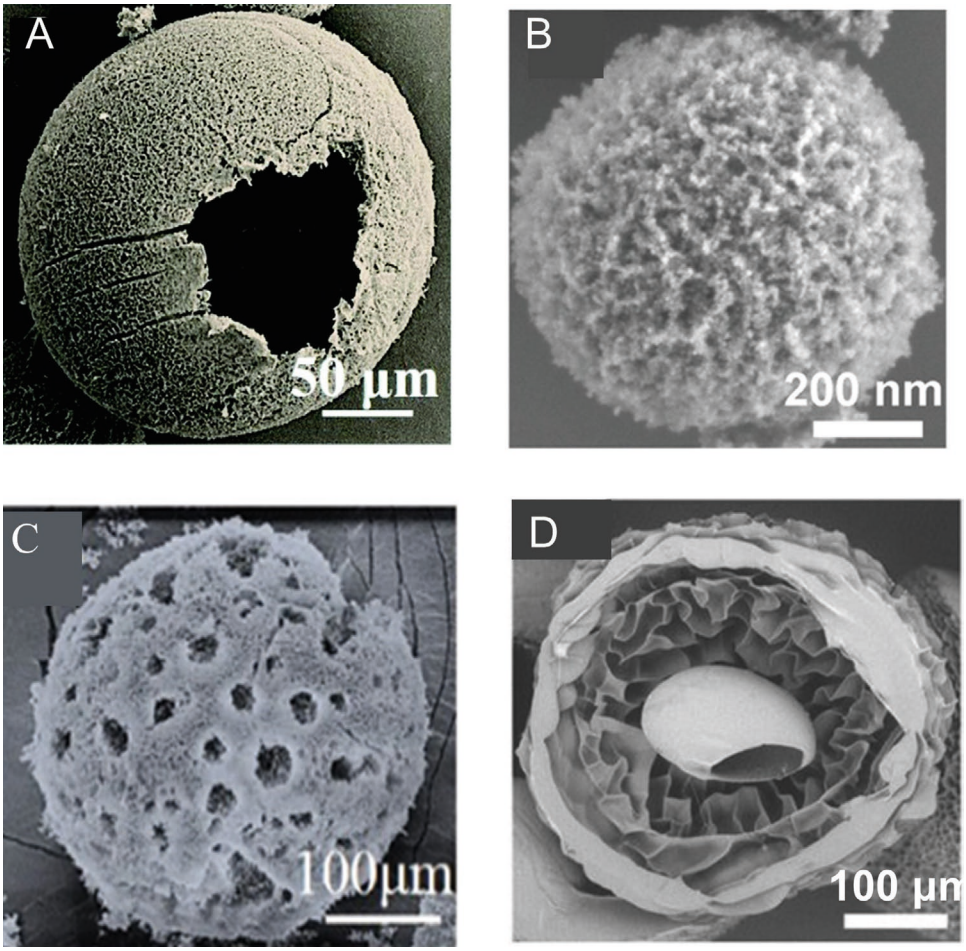

Figure 2. Various morphologies of heteromorphic microspheres. A) Hollow microsphere. Reproduced with permission.[4] Copyright 2019, The Royal Society of Chemistry B) Microspheres with villous appearance. Reproduced with permission.[5] Copyright 2020, Wiley-VCH GmbH. C) Microspheres with perforated surfaces. Reproduced with permission.[4] Copyright 2019, The Royal Society of Chemistry D) Core–shell microsphere. Reproduced with permission.[7] Copyright 2018, Wiley-VCH GmbH.

of nanoscale microparticles for screening individualized treatment regimens for different patients.[25]

Microspheres also have great application values in other medical fields, such as cell culture, hemostatic materials, tissue engineering, etc. Microsphere used in cell-culture changes the situation of traditional 2D cell culture and makes 3D cell culture and coculture technology possible.[26] The porous structure of microsphere enables it to absorb water, concentrate red blood cells, and platelets quickly. This forms a colloidal barrier on the wound and prevent blood loss. Compared with other biological scaffolds, microspheres with uniform size and shape make ions, drugs and extracellular molecules better adsorbed or diffused in the regeneration process.[27]

In addition to these above applications, the unique potential of microspheres in degrading antibiotics needs to be singled out here. In contemporary's society, the abuse of antibiotics is more and more serious, which brings serious threat to the ecological environment and human health.[28] In view of this problem, Wang et al. prepared mesoporous manganese oxide (MnOx) microspheres by the method of soft template P123. Fluoroquinolone antibiotics can be removed by using peroxomone sulfate as an oxidant under ultraviolet or simulated sunlight.[29]

Because of the wide applications in the medical field and the existing preparation methods are not perfect, finding a method can efficiently prepare microspheres with high biocompatibility at a low cost is particularly important. As one of the most proven technologies, microfluidic technology has been widely concerned due to its accurate ability to control the size and shape of droplets. However, oil and some surfactants are inevitably used in the preparation process, as a result, microspheres often lack good biocompatibility.[30,31] Emulsion method faces the similar problem. This has become the main factor restricting the further development of microfluidic and emulsion technology. The appearance of gas-shearing technology can solve this problem successfully.

For the coaxial electrospray method, the mass production of multilayer microsphere is hindered due to the lack of effective particle collection method and the design device of nozzle. Besides, the complex physical process and tedious industrial design, material and process parameters also bring challenges

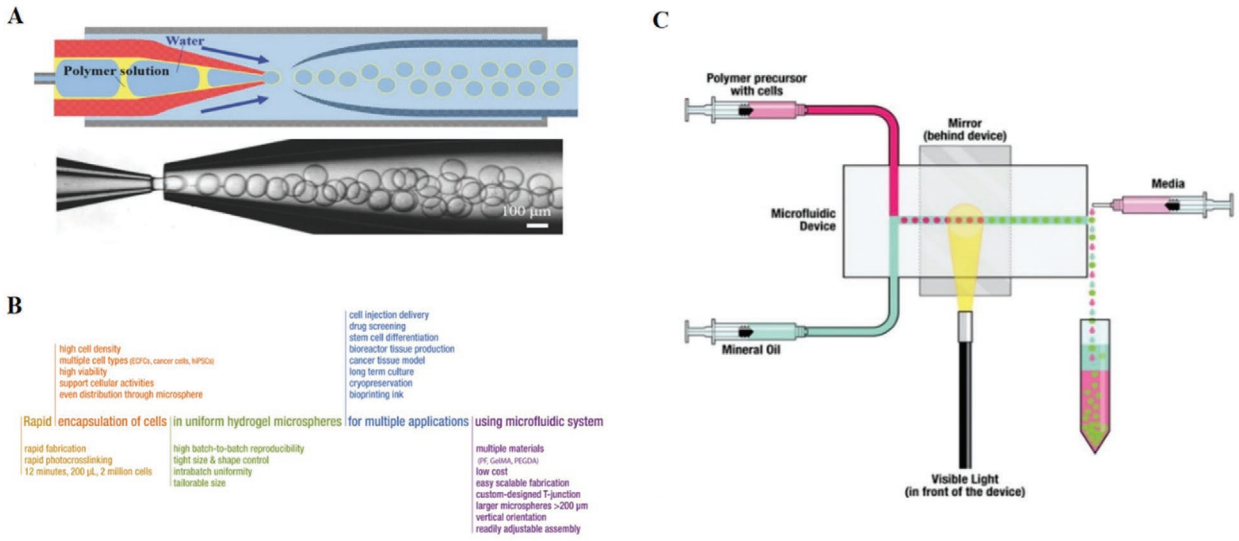

Figure 3. Schematic diagram of microfluidic device. A) Schematic illustration and optical microscope (OM) image of a capillary microfluidic device showing the generation of double emulsion drops with an ultrathin shell. Reproduced with permission.[35] Copyright 2017, Wiley-VCH GmbH. B) Summary of the advantages of the microfluidic encapsulation platform. Reproduced with permission.[45] Copyright 2019, Wiley-VCH GmbH. C) Schematic of the microfluidic encapsulation platform with an innovative chip used to fabricate cell-laden hydrogel microsphere. Reproduced with permission.[45] Copyright 2019, Wiley-VCH GmbH.

to further development.[32] Therefore, developing a preparation method that can not only efficiently prepare microspheres at a low cost but also ensure the good biocompatibility of microspheres should be the focus of the following scholars.

2. Preparation of Microsphere

2.1. Microfluidic

Microfluidic method is one of the most proven ones to fabricate microspheres. To date, only a few technologies have been found to be inherently suitable for manufacturing monodisperse microspheres of controlled size. Microfluidic technology has received considerable attention for its ability to prepare microspheres with high roundness in batches.[33,34] Lee et al. used microfluidic technology to produce homogeneous biodegradable microspheres with uniform sizes which achieve continuous release of hydrophilic active substances (**Figure 3**A).[35]

Microfluidic method is a technology using the channel to control fluid under micrometer scale, which uses microchannels in microfluidic devices to manipulate, treat, and control trace liquids or samples on a microscopic scale.[36] The preparation of microspheres by microfluidic technology is generally divided into two steps: 1) emulsion formation, that is, monomer or polymeric fluid emulsifies and forms droplets in microfluidic channels; 2) emulsion droplets are cured or polymerized. Emulsion droplets are then cured in situ to form microspheres. The curing methods mainly include polymerization, freezing and solvent evaporation.[37,38]

There are many factors affecting the preparation of microspheres by microfluidic devices, including the material properties of microchannels, the geometric size and shape of microchannels, the properties of fluids and the flow rate ratio. Microchannel materials can be divided into hydrophilic and hydrophobic materials, which have a great impact on the shape of microspheres. The geometric size and fluid properties of microchannels have great influence on the formation of milk droplets. By adjusting the channel diameter, liquid flow and other factors, the diameter uniformity and roundness of microspheres can be well controlled.[39]

In addition to ensuring uniformity and high roundness of the microspheres, microfluidic platform can also prepare microspheres with high elastic modulus and mechanical strength. Because of this, cells can be well protected, as a result, they can maintain a high survival rate and cell activity in long-term encapsulated culture.[40,41] Besides, the cells can still maintain normal activities after being encapsulated, including the ability to proliferate and reconstruct in microspheres.[42] Zheng et al. realized the multifunctional regulation of 3D cell-laden microsphere culture on a microfluidic device, the oxidative stress injury and mitochondrial accumulation in cells were reduced. The cells showed excellent ability to proliferate and reconstruct.[43]

Microfluidic technology has made great progress, compared with other preparation methods, microfluidics method also has many advantages (Figure 3B).[44,45] However, there are still many bottlenecks that cannot be ignored. First of all, traditional microfluidic technology has only one microchannel in the microreactor, which greatly limits the rate of the ball. Making multiple microchannels in a single microreactor may solve this problem well. In addition, there are few models for predicting droplet diameter. In view of this problem, it may be a good solution to establish a droplet characteristic model by studying the formation mechanism of droplets.

The core of microfluidic technology device is microfluidic chip, and most of the research on microfluidic technology

should be carried out on microfluidic chip. Existing microfluidic platforms have high technical requirements for traditional precision machining equipment. At the same time, iterative design changes are time-consuming and expensive. This problem can be solved by fabricating microfluidic chips which are easy to adjust. The traditional microfluidic chip mostly adopts standard customization. The complex lithography technology brings difficulties to the adjustment of channel size of microfluidic chip. To solve this problem, Seeto et al. established an innovative microfluidic platform. The core technology is to develop a new microfluidic chip forming technology. This new technology overcomes the inherent challenge of using standard customized microfluidic chips and shows great flexibility (Figure 3C).[45]

However, although some groups have developed a series of new microfluidic chip forming technology, this technology is still in the theoretical stage. Once it is used for mass production, whether there is a corresponding microfluidic chip for different microsphere preparation requirements is not known. Therefore, the next generation of microfluidic application emphasizes in various environments flexibility and practicality.[46] A relatively new application is microfluidics for particle synthesis. Microfluidic particle synthesis technology is considered as one of the latest methods for the preparation of microsphere with simple to complex structural characteristics. Because of its flexibility and potential, it can create particles with unique chemical properties and controllable morphology.

Besides, another crucial problem in microfluidic technology also cannot be neglected here. Due to inevitable use of oil and some surfactants in the preparation process, microspheres usually lack good biocompatibility. Therefore, how to avoid the use of oil and surfactants in the preparation of microspheres should also be the focus of future research.

2.2. Coaxial Electrospray

Electrospray is also one of the mature methods to prepare microspheres. Electrospray method, also known as electrostatic spray technology, It uses electrostatic force on polymer solution under high voltage to prepare polymer microspheres and composite microspheres. In the territory of electrospray method, coaxial electrospray is the most commonly used. It is mainly discussed here.

Coaxial electrospray developed on the basis of traditional single axis electrospray technology. The process is to produce multilayer particles and nanoparticles by introducing a coaxial charged jet. Coaxial electrospray method has the advantages of short preparation cycle, low equipment cost, high encapsulation efficiency, and uniform particle size distribution.[47]

The device of coaxial electrospray is mainly composed of high-voltage power supply, coaxial nozzle device, core–shell solution storage device, core–shell solution propulsion device and particle collection device.[48] In the process of preparing microspheres, charged droplets deform in the electric field and end up with a cone. This is called Taylor cone (**Figure 4**).[49] The shape of Taylor cone is related to the surface charge density of fluid and the shape of nozzle. The shape and stability of Taylor cone directly determine the morphology and

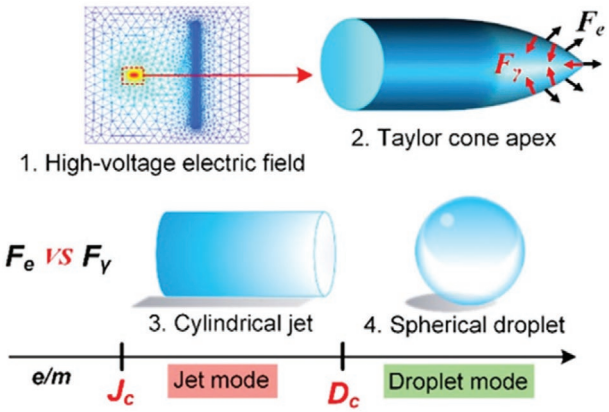

Figure 4. Schematics showing the formation of Taylor cone apex: Two ejection modes at the Taylor cone apex based on the competition between Coulomb repulsion (Fe) and hydrostatic pressure (Fγ). 1, high-voltage electric field; 2, Taylor cone apex; 3, Cylindrical jet; 4, Spherical droplet. Reproduced with permission.[49] Copyright 2019, American Chemical Society.

preparation efficiency of the microparticles. Therefore, the study of Taylor cone is always one of the focuses of the coaxial electrospray method.

Coaxial electrospray is mainly used for the preparation of core–shell microspheres.[50] Especially, when preparing drug-loaded microspheres, the coaxial electrospray process can effectively protect the biological activity of drugs because the drugs are encapsulated in the nuclear layer. In addition, because the drugs have relatively high encapsulation efficiency and can reduce the sudden release of drugs effectively, it is particularly suitable for various drugs, proteins and biological activities encapsulation of substances. Xue et al. prepared core–shell microspheres containing nerve growth factor (NGF) by coaxial electrospray. Under the light and heat of near-infrared laser, NGF was slowly released. It has good biological activity and can effectively promote the growth of nerve process (**Figure 5**A).[51]

There are many factors that affect the feasibility of coaxial electrospray, such as the concentration and properties of the solution, the structure of the coaxial nozzle device, the flow rate ratio of the core layer to the shell layer and the voltage. The concentration of the solution is a very important factor to determine the feasibility of the electrospray method. Changing the concentration will affect the viscosity and conductivity of the solution and then affect the formation of microspheres. At the same time, the concentration of the solution will also affect the particle size, the thickness of the shell and the core-shell thickness ratio of the microsphere.[52]

In recent years, the development of coaxial electrospray technology has enabled people to control the size and shape of microspheres more accurately. For instance, John et al. fabricated ideal engineering biomimetic nanofiber microspheres (NMs) with tailored size, predesigned structure and desired composition via gas bubble mediated coaxial electrospray. This new type of microsphere has great potential in many biomedical applications, such as tissue filling, cell and drug delivery, and minimally invasive tissue regeneration.[53]

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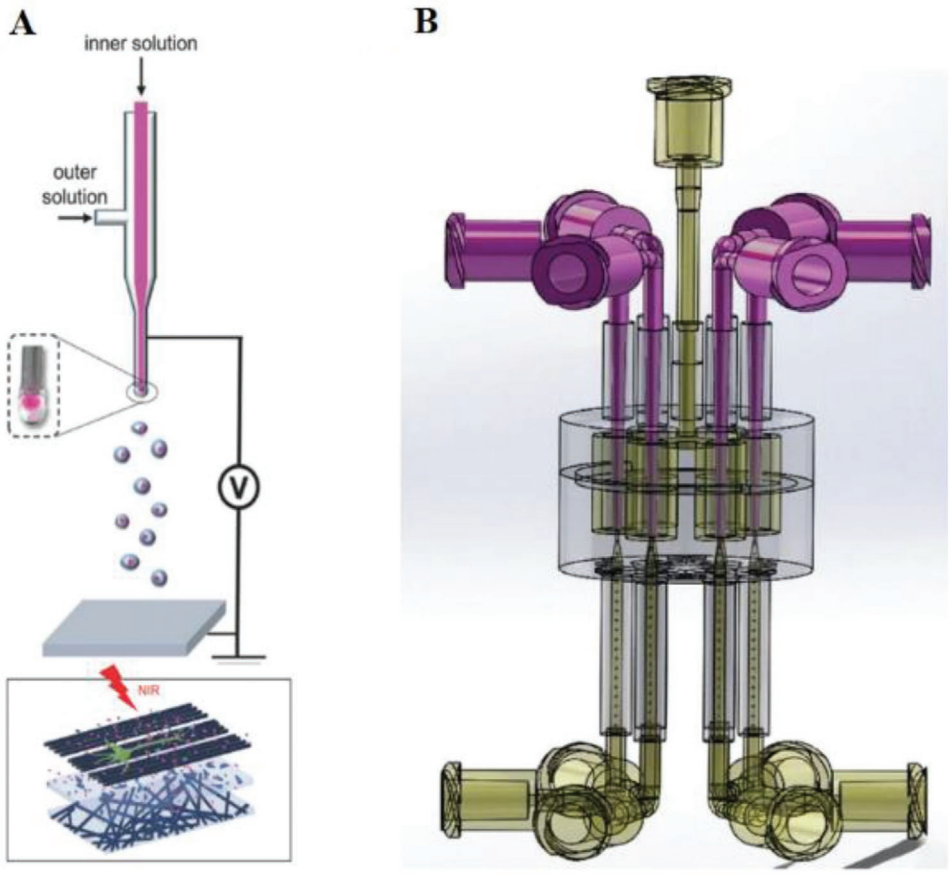

Figure 5. Schematic diagram of coaxial electrospray device. A) Schematic illustration of the coaxial electrospray setup used for the fabrication of microparticles containing a payload in the core region and the neurite outgrowth from spheroids of cells. Reproduced with permission.[51] Copyright 2018, Wiley-VCH GmbH. B) Schematic of six-coaxial micronozzles set, which can quickly prepare microspheres. Reproduced with permission.[55] Copyright 2019, Springer Nature.

Coaxial electrospray technology has many advantages for fabricating microspheres, but its complex physical process, tedious industrial design, materials, and process parameters bring challenges to further development. For example, the mass production of multilayer microsphere is hindered due to the lack of effective microsphere collection method and prolific nozzle design devices. For mass microsphere collection, the general one-step program collection method may cause microsphere adhesion and aggregation, so a more effective microsphere collection method needs to be found.[54]

For the nozzle design, the existing single nozzle system has greatly hindered the progress of mass production of microsphere. This requires the design of a micromachined coaxial nozzle set. In view of this problem, Jaligama and Kameoka developed a 3D coaxial multi nozzle flow focusing device through a simple 3D printing method. The air inlet and nozzle can be made by 3D printer respectively and the uncured light curing resin is used as glue to bond them together. The device has six coaxial micro nozzles, each of which can produce microspheres efficiently. Therefore, it is one of the future research trends to push coaxial electrospray set technology from theoretical stage to market and then form industrialization (Figure 5B).[55]

2.3. Other

2.3.1. Emulsion Method

Emulsion is the most commonly used method to prepare natural polymer microspheres. After many years of development, emulsion method has been very mature. Li et al. prepared porous chitosan microspheres (CSMS) by emulsion method which has great application potential in the field of hemostasis in vivo and in vitro (**Figure 6**A).[56]

The principle of emulsion method is to use two incompatible solvents in the presence of surfactant to form a uniform emulsion.[57] The solid phase can be separated from the emulsion, which can make nucleation, growth, coalescence and agglomeration process confined to a tiny spherical droplet. As a result, they can form spherical particles and avoid further agglomeration among particles.[58]

According to different internal phase curing methods, emulsion method can be divided into emulsion-solvent volatilization method, emulsion-condensation method, and emulsion-crosslinking method. Solvent evaporation method, also known as liquid drying method, refers to simply remove the solvent

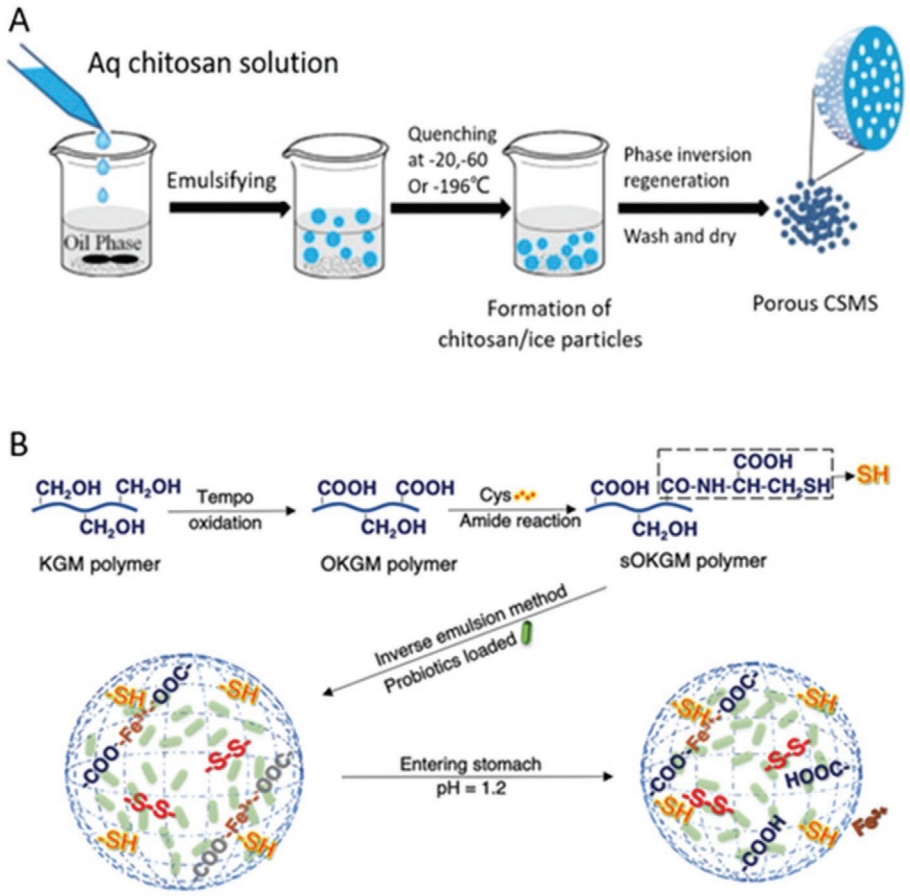

Figure 6. Schematic diagram of emulsion. A) Fabrication procedure for CSMS through W/O emulsion, Aq means aqueous. Reproduced with permission.[56] Copyright 2017, Elsevier Ltd. B) Konjac glucomannan (KGM) was selectively oxidized to introduce carboxyl groups through oxidation, and cysteines were conjugated to carboxyl groups on oxidized konjac glucomannan (OKGM) polymers by amide reaction to form sOKGM. sOKGM microspheres were prepared through inverse emulsion method. Reproduced with permission.[60] Copyright 2020,Wiley-VCH GmbH.

(water) by evaporation method to solidify the carrier material into a ball. For gelatin, agarose and other materials, since they are soluble only in hot water but not in cold water, solidified microspheres can be obtained by emulsifying and cooling. Natural macromolecules with amino, carboxyl reactive groups, such as gelatin, chitosan, hyaluronic acid, etc. can be added with cross-linking agent of double functional groups to make the polymer cross-linked and cured.[59]

In recent years, inverse emulsion method has gradually come into people's vision. Liu et al. prepared thiolated oxidized konjac glucomannan microspheres (sOKGM)with pH response and adhesive properties by inverse emulsion method. The experimental results showed that sOKGM could increase the abundance of bifidobacteria, balance intestinal flora, relieve constipation in mice and enhance gastric acid resistance and intestinal adhesion colonization (Figure 6B).[60]

The advantage of emulsion method is that it is simple and the cost is low. But there are also drawbacks that cannot be ignored. First, it is inevitable to use oil-phase in the preparation of microspheres, as a result, this will damage the biocompatibility of microspheres. In the subsequent use of microspheres, it may cause harm to the environment.[61] Besides, due to the difficult visibility and the complexity of microsphere morphology regulation caused by heteromorphic of emulsion polymerization, it will also be the focus of future research.

2.3.2. Gas-Shearing Technology

Microfluidic and emulsion methods are mature relatively. They can produce microspheres with uniform diameters on a large scale. However, due to the inevitable use of oil, photoinitiator, cross-linking agent, surfactant and other substances in the preparation process, microspheres themselves often lack good biocompatibility. For this reason, it is urgent to develop a new fabrication strategy which can avoid the use of hazardous reagents.[62–64]

In recent years, a new technology with gas shearing as the power and no need to use oil, photoinitiator and other substances in the preparation process has appeared. It is called gas-shearing technology. Prior to our research group, other research groups have prepared microspheres or microcapsules by gas-shearing technology.[65] Lu et al. used gas-shearing technology to produce

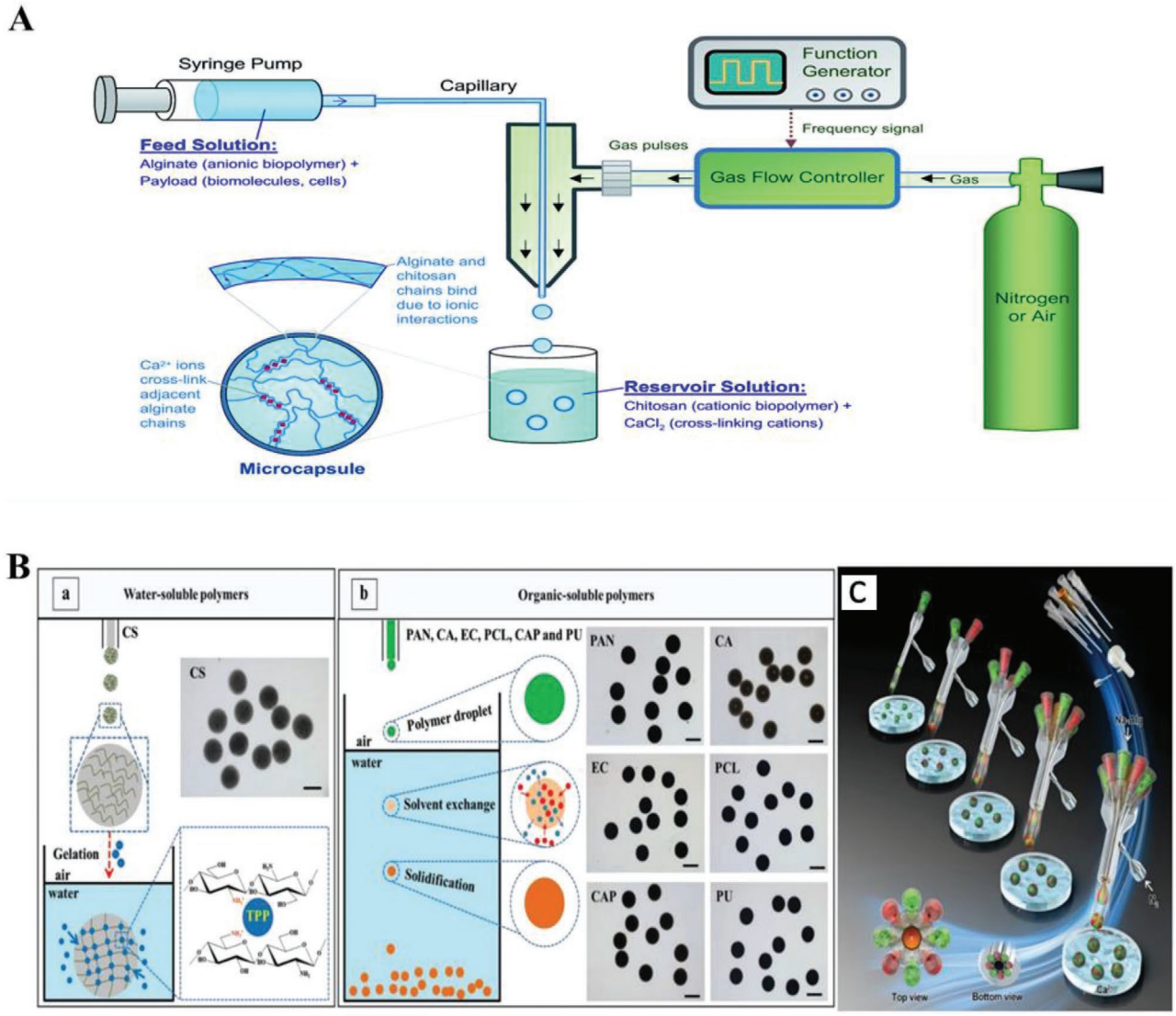

Figure 7. Schematic diagram of gas-shearing. A) Synthesis of microcapsules by traditional gas-shearing technology. Reproduced with permission.[66] Copyright 2017, The Royal Society of Chemistry. B) Schematic illustration of improved gas-shearing technology. a) Schematic illustration of the ionic crosslinking (using thiamine pyrophosphate) of chitosan aqueous droplets into chitosan microspheres. b) Schematic illustration of the solvent exchange process resulting in polyacrylonitrile (PAN), cellulose acetate (CA), ethylcellulose (EC), polycaprolactone (PCL), cellulose acetate phthalate (CAP), and polyurethane (PU) microparticles. c) Schematic illustration of the formation of the multifaced microspheres with different SEDs and the assembly of the needle system in the SED-8 configuration. Reproduced with permission.[67] Copyright 2019, Wiley-VCH GmbH.

highly compatible biopolymer microcapsules that had a discrete structure, which looks like eukaryotic cells (**Figure 7**A).[66]

Although gas-shearing technology has made great progress, there are still some problems. First, the inlet pipe is mainly manually propelled, as a result, the unstable propulsion speed causes the instability of the microsphere. Besides, the application of multicompartmental microspheres is more and more extensive in recent years. But the preparation of multicompartmental microspheres by traditional gas-shearing method is still premature.

In this case, the traditional gas-shearing device needs to be improved. Our group adopted the push pump to push the inlet pipe and made a self-made coaxial needle system called spray ejector device (SED) for the preparation of 1-10 compartmental microspheres. Great breakthroughs have been made in the preparation of microspheres, especially in the field of multicompartmental microspheres (Figure 7B).[3,67]

Compared with other preparation methods, gas-shearing method has two major advantages. First, microspheres have good biocompatibility since oil, photoinitiators, cross-linking agents, and surfactants are not used in the preparation process. In addition, the gas-shearing device is simple and the fabrication cost is low.[68]

In addition to these above preparation methods, centrifugal method, spray drying method and 3D printing developed in recent years are also often used to prepare microspheres, which will not be described here.

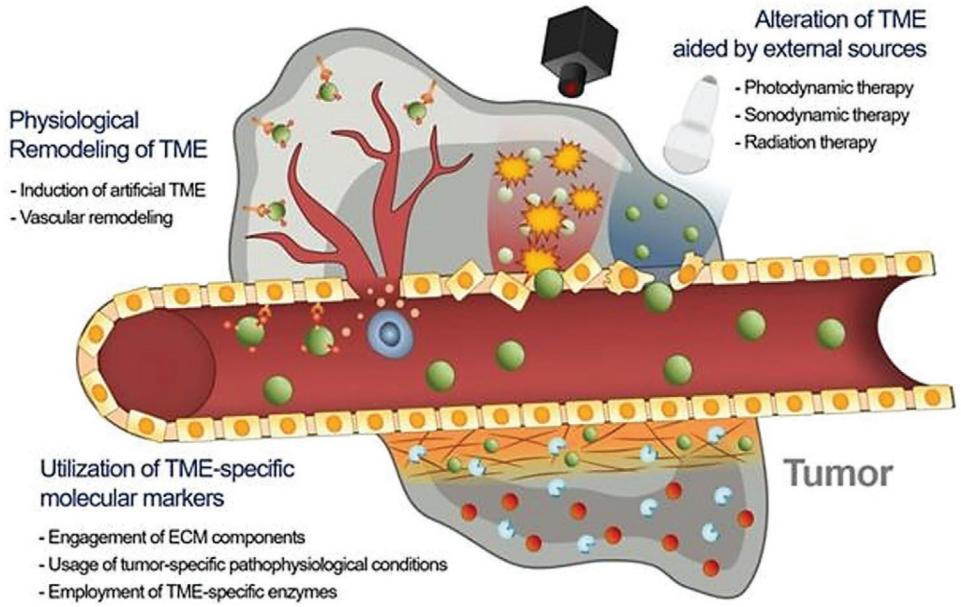

Figure 8. Schematics showing the EPR effect: the high-permeability and retention effect of solid tumors, refers to the property that molecules or particles of certain size tend to aggregate in tumor tissues more than normal tissues. Reproduced with permission.[72] Copyright 2019, Ivyspring International Publisher.

3. Medical Applications

3.1. Drug Release

Drug release is one of the most important applications of microsphere. Microsphere has long-term, sustained-release and targeting effects, which can greatly improve the convenience and compliance of patients' medication.[69–71] In the field of drug release, anticancer is an important aspect. The advantage of microsphere used in anticancer field mainly comes from enhanced permeability and retention (EPR) effect. It refers to the phenomenon that some macromolecules or particles of specific sizes are more likely to penetrate tumor tissues and stay in them for a long time than normal tissues (**Figure 8**).[72] When the drug-loaded microspheres with nanoscales reach the tumor tissues, they can easily penetrate the tumor tissues due to EPR effect, thus achieving the therapeutic purpose.[73,74]

Compared with other drug release modes, microsphere as a carrier plays an irreplaceable role, the drugs are released in the required parts of the body through passive distribution, active target combination, or magnetic attraction. This can improve the effective concentration of drugs and reduce the concentration of drugs in other parts, thus reducing the systemic toxicity and adverse reactions of drugs.[75–77]

Microsphere drug loading is very flexible, for different symptoms, only loading the corresponding drugs can achieve the purpose of treatment.[78] Zhang et al. developed an injectable hydrogel microsphere encapsulating bupivacaine (BUP) and dexmedetomidine (DEX) with 3D porous network structure. The release test shows that BUP and DEX could release slowly for several days in vitro, showing a good sustained analgesic effect (**Figure 9**A).[79] To achieve synergistic therapeutic effect, the microspheres need to be loaded with multiple drugs.[80]

In recent years, polymer microspheres, especially poly (lactic-*co*-glycolic acid) (PLGA) microspheres, have been widely used as carriers of small molecules, proteins and genetic materials due to their good biocompatibility and biodegradability.[81] For instance, Mayol et al. prepared PLGA-based biodegradable microsphere with good biocompatibility. It can release the corresponding therapeutic proteins into the vitreous, showing good therapeutic effect.[82]

Intravenous injection is one of the most common forms of drug delivery. Compared with the traditional way of injection, microsphere has the advantages of poor invasiveness and good repeatability.[83] The treatment of diabetes often uses subcutaneous injection of insulin, as a result, frequent injection causes serious damage to the skin and blood vessels of patients.[84] For this question, Lin et al. used SC-CO_2 technology to prepare insulin-loaded poly (L-lactide) porous microspheres (INS-PLLA-PMS). The microsphere was used as inhalation drug delivery system for diabetes treatment, thus successfully avoiding frequent subcutaneous injection (Figure 9B).[85]

In the field of drug release, single microsphere is more and more difficult to meet daily medical needs. Under this circumstance, the development of heteromorphic microsphere (e.g., multicompartmental microsphere and core–shell microsphere) is particularly important.[86,87] Different compartments of multicompartmental microspheres can encapsulate different drugs. This ensures that drugs can be individually encapsulated without cross infection, which has great application value for the collaborative release of drugs.[88] The core–shell microsphere can effectively encapsulate drugs in the core of the particle and the shell can alleviate the release of the drug through diffusion to a certain extent. As a result, microsphere can reduce the sudden release behavior of the drug to a certain extent, thus reflecting a better slow release effect. For

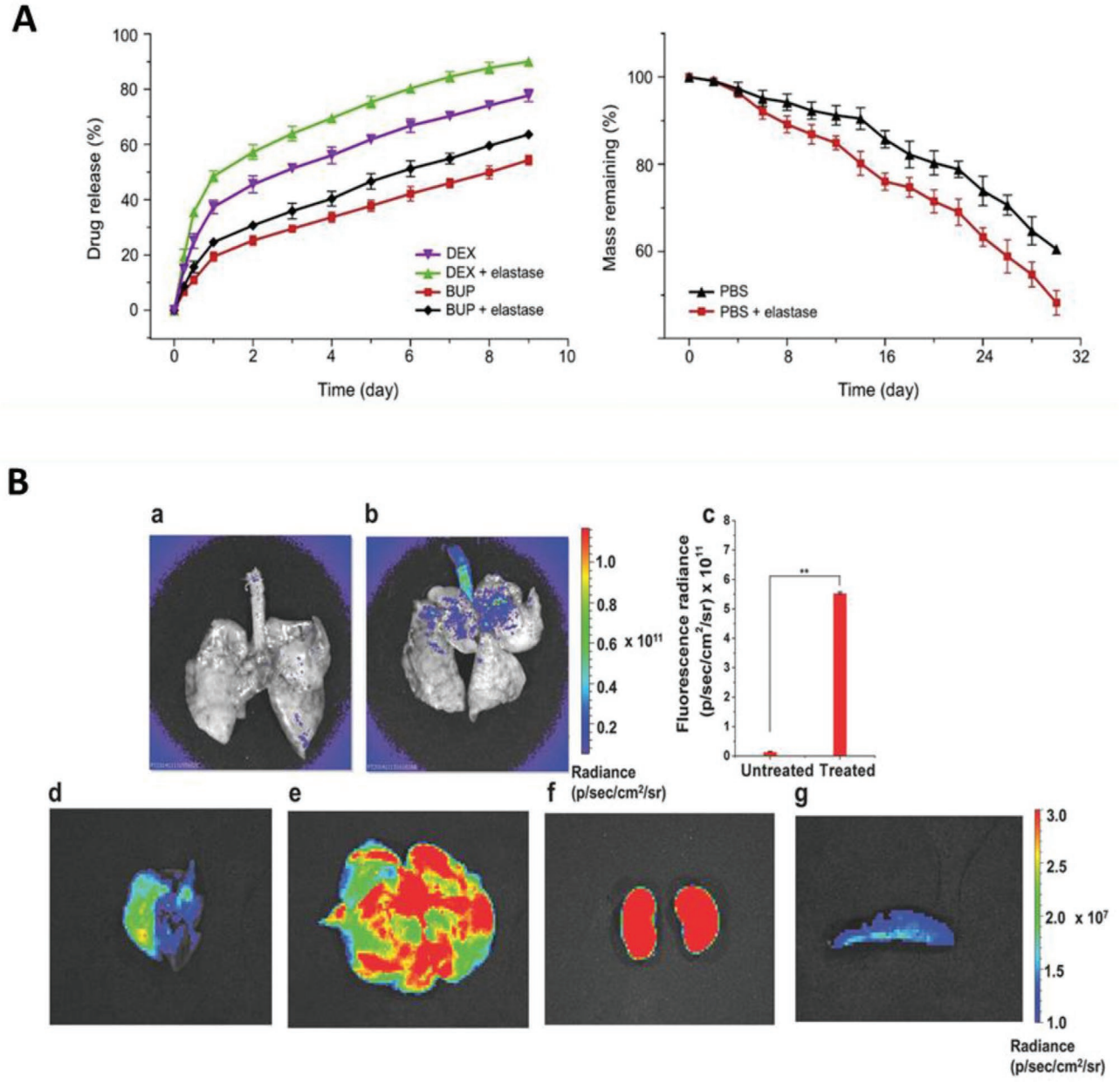

Figure 9. Microsphere used in drug release. A) In vitro BUP, DEX release and mass-remaining profiles incubated in PBS without or with elastase. Reproduced with permission.[79] Copyright 2018, Elsevier Ltd. B) Comparison of fluorescence intensities after 30 min of inhalation between a) untreated lung tissue and b) FITC-PLLA PMs administered lung tissue. c) Quantification of fluorescence intensities in different treatment groups. Fluorescent images of dissected organs: d) lung, e) liver, f) kidney, and g) spleen of Sprague–Dawley (SD) rats after 4 h inhalation of FITC-PLLA PMs. Reproduced with permission.[85] Copyright 2019, Wiley-VCH GmbH.

example, Qi et al. prepared goserelin-loaded PLGA microsphere with core-shell structure. It has high encapsulation efficiency (94.16%) and low burst release (less than 2%).[89]

In the field of drug release, sustained-release and targeting effects are two focuses of research. The sustained-release microsphere technology is proven and has been put into production. It has similar advantages with sustained-release preparations, such as reducing the number of drug administration and the fluctuation of blood concentration.[90] As for targeting-effect, although some progress has been made, overall, the research progress is not perfect.[91] However, for microspheres drug release technology, targeting is still the top priority. Only by solving the problem of targeting can the researchers fundamentally avoid the fatal side effects of anticancer drugs. The research of targeted microspheres needs more efforts of researchers.[92]

3.2. Cell Culture

Cell culture is another important application of microsphere. Whether the cells can maintain a high survival rate and rapid

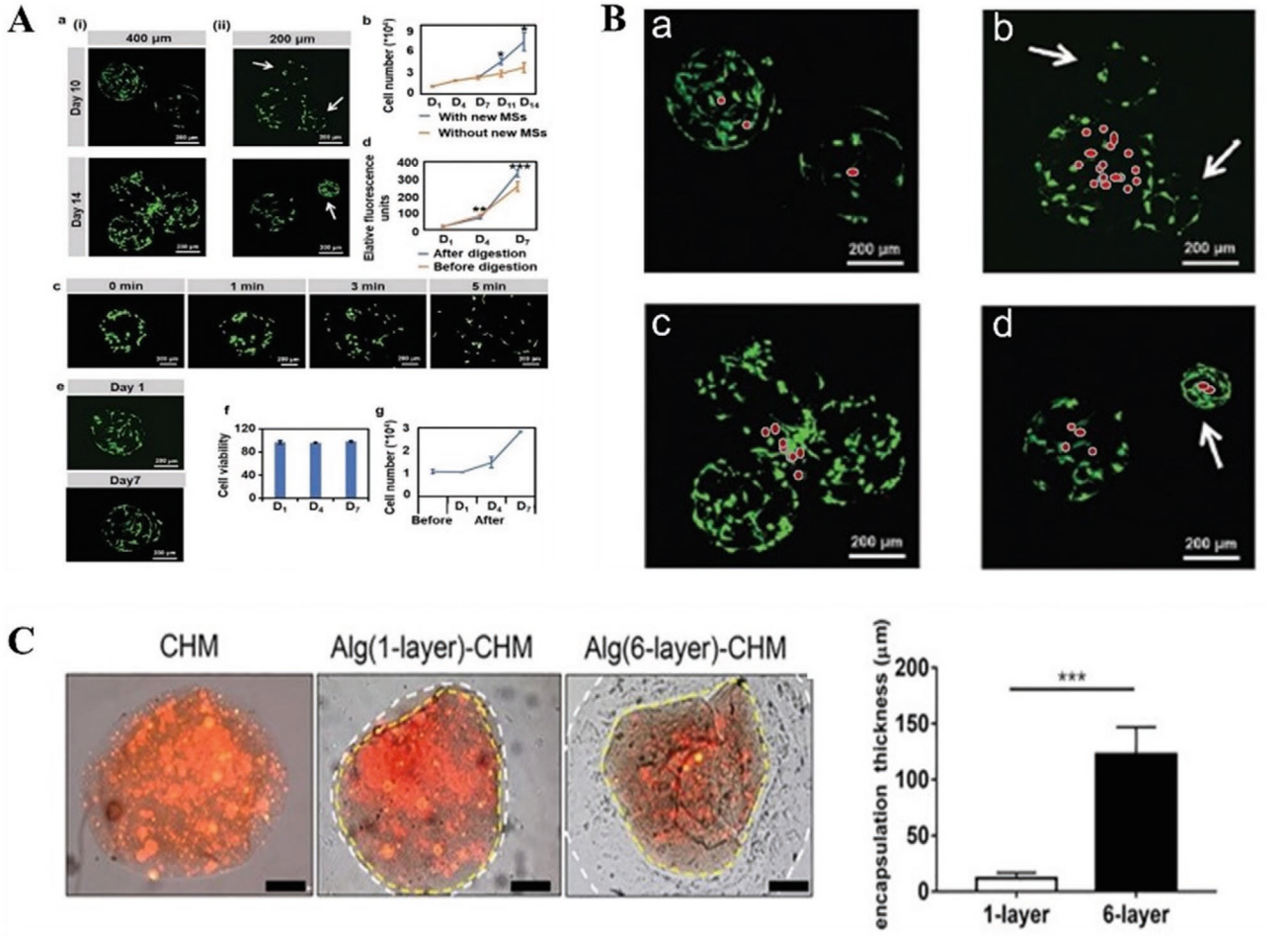

Figure 10. Examples of microsphere for cell culture: A) Printed GelMA MSs for cell passage, cell harvest, and cell cryopreservation. a, b) Confocal fluorescence images of live/dead staining and cell number of cells after adding fresh microspheres. c) Fluorescence images of live/dead staining of cells during MS digestion. d) Prestoblue testing of cells before and after digestion. e–g) Confocal fluorescence images of live/dead staining, cell viability, and cell number of cells after freezing and thawing process. Reproduced with permission.[100] Copyright 2020, Wiley-VCH GmbH. B) Confocal laser scanning microscopy (CLSM) images of stained cells showing living (green) and dead (red) cells on different particle sizes of microspheres on day 3 and 10. Reproduced with permission.[103] Copyright 2020, Wiley-VCH GmbH. C) Collagen hydrogel microspheres (CHM) with fluorescent red latex bead without coating, with one-layer, and six-layer coating. Scale bar: 100 μm. Reproduced with permission.[109] Copyright 2019, Elsevier.

proliferation depends largely on whether the growth environment can guarantee a large number of cytoplasmic matrixes. The cytoplasmic matrix is the main site for the metabolism of living cells, which can provide the necessary materials for the process of metabolism, besides, it can also provide stable microenvironment for cells and influence the shapes of cells.[93]

Traditional culture dishes such as 2D culture cannot provide enough cytoplasmic matrix for cell proliferation. Due to the lack of exchange of metabolites and substrates, there is a risk of abnormal cell growth, apoptosis and even cell shedding. Therefore, 2D cell culture technology has been proved to be insufficient to meet the expected commercial needs of cell therapy products.[94]

Under this circumstance, the development of 3D cell culture is extremely important. At present, 3D cell culture models mainly include hydrogel, fiber, and microsphere. Compared to hydrogel and fiber, the surface of microsphere is not flat but curved, which can better increase the particle size and simulate the extracellular matrix.[95]

In addition, the rich and diverse morphology of microspheres also provides many possibilities for cell culture.[96–99] As a result, microsphere can simulate cell growth in the microenvironment in vivo, so as to support large-scale cell manufacture. He et al. prepared gel microspheres with rough surface structure through 3D digital light treatment technology. Cells cultured in microspheres show high viability, attachment, proliferation, activity and differentiation potential (**Figure 10**A).[100]

Microsphere used for cell culture mainly includes single microsphere and heteromorphic microsphere (e.g., multicompartmental microsphere, porous microsphere, etc.). Compared to single microsphere, heteromorphic microspheres are more widely used. The different compartments of the multicompartmental microsphere make it possible to culture different types of cells without interacting with each other. Porous microspheres have more potential, it is noted here. Porous

microsphere has unique potential in cell culture because of its special physical structure. The interconnected porous structure not only expands cell surface and internal area, but also promotes the entry and exit of nutrients and metabolites.[101] As a result, it can promote the cell proliferation and differentiation. Besides, porous microsphere can support the growth of a variety of mammalian cells, such as monkey fibroblasts, human liver cells and even human stem cell microspheres.[102] Zhang et al. prepared two kinds of cross-linked polyvinyl alcohol (PVA)/cellulose nanofiber (CNF) mixed aerogel microspheres with different particle sizes by water-in-oil (W/O) emulsification and freeze-drying method. The SEM photos shows that porous nanofiber structure can successfully promote cell attachment, differentiation and proliferation (Figure 10B).[103]

For porous microsphere, the size, density, and pore size all affect the cell survival rate and material transfer. In general, the particle size distribution of porous microspheres should be as narrow as possible to provide a more uniform culture environment for cells. The density of the porous microspheres should be slightly higher than that of the medium.[104] Therefore, the microspheres can be suspended in the medium after light agitation and precipitate rapidly after stop of agitation. In terms of pore size, different cell types need microspheres with different pore sizes, so there is no unified conclusion.[105–107]

In recent years, the application of coculture model in tissue engineering is more and more extensive, which puts forward higher requirements for cell culture model. Direct contact coculture model can provide a better exchange of bioactive molecules and promote the interaction between cells, but it is difficult to isolate and easy to cross infection. The noncontact mode makes cells easy to separate, however, the long distance between cells limits the interaction between cells.[108] Liu and co-workers solved this problem successfully by fabricating a mobile superparamagnetic alginate coated collagen core hydrogel microsphere. The microsphere has a mobile superparamagnetic sodium alginate coating. It ensures the minimum distance between cells and promotes the interaction between cells, making it easy to separate (Figure 10C).[109]

Microsphere technology used for cell culture has made great progress, however, it still faces some challenges in the development process. First, how to reduce the cost of microsphere culture technology is an urgent task. Compared with traditional culture medium technology, microsphere technology has high cost. Besides, at the technical level, the sampling and separation of microspheres are also a problem that has not been completely solved.[110] Therefore, problems on economic and technical levels urge the researchers to put in more efforts.

3.3. Other

3.3.1. Bone Tissue Engineering

Bone tissue damage is very common in life. Slight bone injury can be repaired by self-repair, but serious bone tissue injury needs bone transplantation. Bone tissue engineering based on composite microspheres is expected to benefit these patients.[111] Liu et al. fabricated a porous polycaprolactone/hydroxyapatite (PCL/HA) scaffold modified with vascular endothelial growth factor (VEGF) through 3D biomimetic selective laser sintering (SLS). Animal experiments showed that PCL/HA/VEGF scaffolds could significantly promote the formation of new blood vessels in rat skull defect models (**Figure 11**).[112]

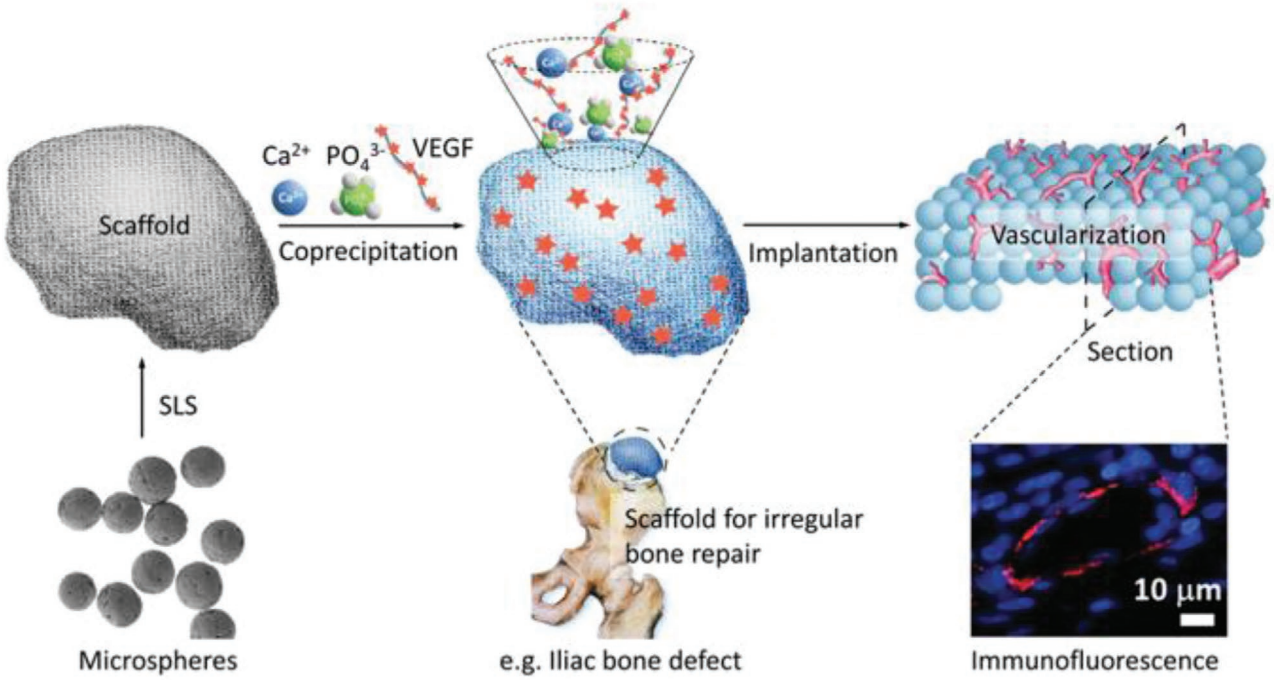

Figure 11. Schematic illustration for the principles of VEGF loading and its application in bone regeneration in bone defect. Reproduced with permission.[112] Copyright 2020, Wiley-VCH GmbH.

Composite microsphere can not only promote the formation of new blood vessels, but also promote the proliferation of fibroblasts. As a result, it can induce the migration of host cells in the whole defect and microspheres, so as to promote the formation of new bone.[113,114] Jiang et al. fabricated microsphere by recombining collagen (COL) and bacterial cellulose (BC). Its 3D porous structure and components could effectively promote the adhesion proliferation and osteogenic differentiation of mouse MC3T3-E1 cells.[115]

Compared with other biomaterials, microspheres have uniform size and shape, which make ions, drugs and extracellular molecules better adsorbed or diffused in the regeneration process.[116] In addition, microspheres have great advantages in cell proliferation, drug absorption and release kinetic due to their appropriate specific surface area and porosity. In recent years, the scaffold which can release growth factors has been widely concerned in the field of bone repair and regeneration. The drug delivery system coordinates with the natural process of bone formation and release of growth factors through bone regeneration.[117]

As the most widely used carrier in drug delivery system, microspheres have advantages in controlled-release injection and digestion. The microspheres can be loaded into the composite scaffold and evenly distributed in the scaffold.[118] Dou et al. prepared hydroxyapatite collagen (HC) column composite scaffolds with microspheres. HC composite scaffolds with good growth factors can promote the formation of blood vessels and collagen.[119]

3.3.2. Hemostasis

Bleeding is one of the inevitable phenomena in life and operation. If bleeding is not controlled in time, it will cause shock or even death.[120] Bleeding can be divided into external bleeding and internal bleeding. The traditional external hemostasis method is gauze compression. But this method has great disadvantages, such as secondary injury to the wound. Besides, improper compression also increases the amount of bleeding.[121]

Therefore, modern medical needs put forward new requirements for hemostasis methods. In view of this problem, Xi et al. prepared a kind of "lotus seedpod surface-like" polysaccharide hemostatic microsphere (PHMS), showing good hemostasis performance.[122]

Compared with compression method, microsphere method has better adaptability to the wound with complex shape. It can form a colloidal barrier on the wound and prevent blood loss by quickly absorbing water, concentrate red blood cells and platelets.[122] Tong et al. prepared poly (γ-glutamic acid)/alginate/Ag nanoparticle (AgNPs) composite microspheres by in-situ ultraviolet reduction and emulsion gel method. The microsphere with porous and hollow network structure shows good antibacterial and hemostatic properties (**Figure 12**A).[123] Especially, some studies indicate that microspheres with porous and hollow network structure can swell when pH changes. Therefore, microsphere is a superb material with great potential in the field of hemostasis in vitro.[124,125]

For internal bleeding, open surgery is a common treatment. But it will cause secondary injury or even death to the injured, so it is urgent to find a new hemostasis method.[126] So far, transcatheter arterial embolization (TAE) has become the standard method for the treatment of intracavitary hemorrhage, which can replace the surgical treatment. Biodegradable materials have good biocompatibility and no residue in vivo, so they are the first choice for TAE.[127] A new biodegradable polymer, calcium alginate thrombin microsphere was prepared by Rong and co-workers. It has a strong drug carrying capacity and can well encapsulate thrombin. This new microsphere is expected to be an ideal embolization material for blunt trauma and solid abdominal organ bleeding (Figure 12B).[128]

Besides, Li et al. prepared injectable negative charge gelatin microsphere gel as a hemostatic agent for surgical operation and deep wound bleeding. This type of gelatin microsphere has smooth surface and good sphericity, which can self-expand to the whole cavity and deep wound. For this reason, it can interact with the bleeding site to prevent bleeding.[129] In general, microspheres technology has great potential in the field of hemostasis.

In addition to the above applications, microspheres also have great application potential in the field of drug anticounterfeiting, antibiotic removal and medical diagnostic detection, etc. Here is not a tautology.

4. Conclusion and Perspective

In this feature article, we summarize the common fabrications and applications of microspheres in the medical field. Microspheres have made tremendous progress in the medical field, the preparation method has also been greatly improved. However, some existing problems both in manufacturing and application cannot be ignored.

Preparation: for microfluidics and emulsion techniques, it is difficult to ensure the biocompatibility of microspheres due to the use of oils and other surfactants, which is an important reason to limit their development. For coaxial electrospray method, it is mainly limited by the lack of effective particle acquisition method and nozzle design device. Therefore, developing a method that can not only achieve mass production, but also ensure good biocompatibility and controlled cost of microsphere is an urgent task. The appearance of gas-shearing technology can solve this problem well. It may be a wise thought to make gas-shearing device industrialization.

Application: drug release is the most important medical application of microsphere and targeting is still the top priority of drug release technology. However, targeted microsphere technology is still in the research stage. Besides, microsphere technology has not been widely used in cell culture because of its uneconomical-cost. It is worth noting that there are already reports about nanoscale-microspheres being used for personalize cancer treatment, and personalized medicine could revolutionize cancer treatment by matching each patient to the most effective treatment. This may be a whole new area of research with great promise. All of this puts a higher demand on researchers.

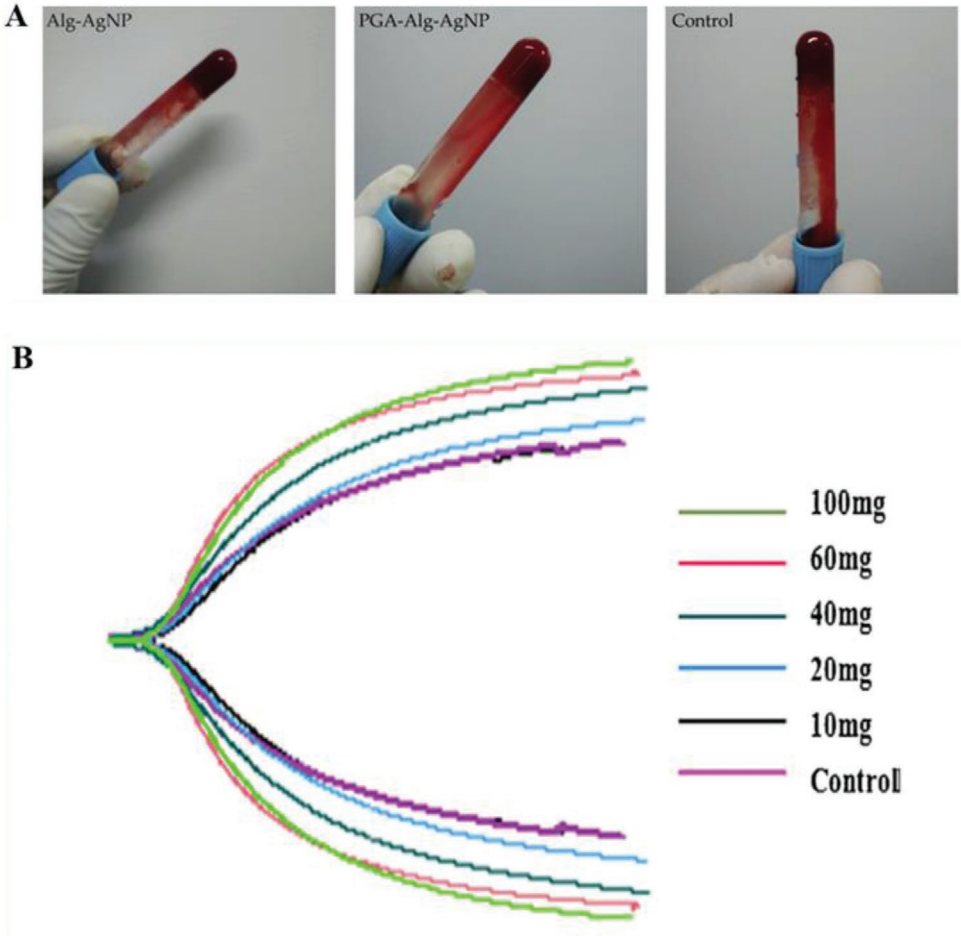

Figure 12. Examples of microspheres for hemostasis. A) Coagulation images of alginate/ AgNPs, polyglycolic acid /alginate/AgNPs composite microspheres and RPMI 1640 medium with 10% bovine serum (control group). Reproduced with permission.[123] Copyright 2015, Elsevier. B) The thrombograms of a health beagle's blood after being mixed with different doses of thrombin-loaded alginate-calcium microspheres (TACMs). The citrated blood sample mixed with 10 U thrombin was used as control. Reproduced with permission.[128] Copyright 2019, Elsevier.

In addition, compared with single microspheres, heteromorphic microspheres (e.g., multicompartmental microsphere, core-shell microsphere, porous microsphere, etc.) have unique application potential in medical field due to their special physical structure. Therefore, the exploration of heteromorphic microsphere should be the focus of future study.

In general, advances in microspheres have given a huge boost to the medical field and greatly improved people's lives. However, existing problems both in preparation and application require researchers to make greater efforts.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

cell cultures, drug release, heteromorphic, microspheres, preparation

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