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Gallium-based Liquid Metal Nanoparticles for Drug Delivery Applications

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Abstract: Drug delivery systems have been widely investigated over the past decades for their ability to enhance drug efficacy and reduce side effects. However, in order to be applicable to a wide range of diseases and drugs, research on diverse and effective controlled delivery systems is imminent. The specificities of gallium-based liquid metal nanoparticles (Ga-based LMPs), such as low toxicity, core-shell structure, mobility, and photothermal effect, make them full of potential for development in drug delivery. Functional gallium-based LMPs can be driven by physical or chemical stimuli for targeted drug transport to the lesion. This review introduces the recent research progress of Ga-based LMPs by summarizing its unique advantages in the field of drug delivery. At the same time, this paper introduces some Ga-based LMPs drug delivery opportunities in conjunction with its advantages and challenges. This review will provide some directions for the future development of Ga-based LMPs in the field of drug delivery.

Keywords: drug delivery, gallium-based liquid metal, nanoparticle.

1. Introduction

Drug delivery system (DDS) is a technology that delivers drugs precisely to specific sites in the body. By creating a variety of DDS, it is possible to increase the efficacy of drugs and reduce their side effects on the body. Drug delivery technology has evolved phenomenally since the advent of the Spansule® extended-release capsule in 1952 [1]. Conventional drug delivery systems use systemic delivery. This makes the side effects of drugs more visible and varied, while the effectiveness of the drug may be significantly reduced as a result. Therefore, the development of controlled drug delivery systems is one of the hot topics of interest in this field.

Ga-LMPs are both liquid and metallic at room temperature. Their fluidity makes them less difficult to prepare and they can be nanosized in a simple top-down manner. After nanosizing, liquid metal nanoparticles have the potential to implement the theory of enhanced permeability and retention (EPR effect), thereby producing products with fewer side effects and higher efficacy. The core-shell structure of gallium-based liquid metal nanoparticles gives them the potential to be surface-modified, transport drugs, and release them through environmental stimuli [2]. Gallium metal has low toxicity, good biocompatibility, and photothermal and vortex effects of a metal [3]. These features make it possible to develop controlled drug delivery systems based on Ga-LMPs. Currently, the research of Ga-LMPs in the field of drug delivery mainly focuses on the application of its photothermal effect

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and electromagnetic effect [4-7]. Researchers are also exploring the surface modification and structural adjustment of Ga-LMPs for drug delivery systems [8, 9].

This review summarizes the basic mechanisms of controlled drug delivery systems as well as the properties and common preparation methods of Ga-LMPs that are advantageous in the therapeutic field. They are followed by a summary of research applications in drug delivery systems such as photo stimulation, magnetic field stimulation, and acoustic stimulation. This paper will provide some insights into the research of Ga-LMPs in the field of drug delivery.

2. Fundamentals of drug delivery

Conventional drug delivery systems are based on mechanisms such as dissolution, diffusion, osmotic pressure, and ion exchange. in addition, another passive targeted delivery system has been developed to take advantage of natural distribution characteristics in the body (e.g., the "funnel effect" of tumors). These delivery methods have disadvantages in terms of poor precision and unwanted side effects. To solve the problems of conventional drug delivery systems, controlled drug delivery mechanisms such as active targeted delivery, environmentally responsive delivery, and biologically responsive delivery have been proposed. These mechanisms will be briefly introduced in this section.

2.1. Active targeted delivery

By combining specific biomarkers (e.g. antibodies or ligands), targeted and precise delivery of drugs to specific cells or tissues can be achieved. Saha et al. coupled anti-CD47 and anti-programmed death ligand 1 on the surface of nanoparticles to enable targeted delivery of drugs, which can aggressive lung cancer cells to show better anti-tumor effects [10]. Chen et al. embellish trastuzumab on zeolite imidazolium framework nanoparticles coated with carboxymethyl sodium salt for the drug's HER2 targeting function [11]. Elechalawar et al. synthesized a gold nano-formulation containing a cetuximab targeting agent as well as a chemotherapeutic agent, which enabled targeted delivery to both pancreatic cancer cells and pancreatic stellate cells, resulting in effective inhibition of pancreatic cancer growth [12].

2.2. Environmentally responsive delivery

In environmentally responsive delivery mechanisms, the release of a drug is regulated by the external environment such as temperature, pH, light, or magnetic fields to achieve more precise drug release. Environmentally responsive delivery systems also provide protection against premature degradation of the drug and reduce the side effects of the drug on non-targeted tissues. Pal et al. reported a lower critical solution temperatures nanoparticle synthesized based on specific ratios of N-vinyl-2-pyrrolidone (NVP) and sub-NVP to achieve its stable drug self-assembly at normal human tissue temperatures and drug release at mildly elevated temperatures in tumor regions [13]. Yan et al. coated poly(ethylene glycol)- modified polydopamine on tetrahedral framework nucleic acid nanogel for drug release under near-infrared irradiation using the excellent photothermal conversion effect of the coating layer [14]. Adlsadabad et al. The synthesized core-shell structure of the azobenzene molecule undergoes cis-trans isomerization in the presence of light to achieve shell separation and shrinkage of the hydrophobic core to release the drug it carries [15]. Demirbüken et al. synthesized a micro-motor consisting of gold and iron-nickel coupled, with Adriamycin loaded with antibodies in the gold part and iron-nickel as the driving part guided to the lesion by an external magnetic field [16].

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2.3. Biologically responsive delivery

Biologically dependent delivery systems control drug release using their response to biological signals such as enzymes, antibodies, and ion concentrations within specific cells that are unique to the body's inflammatory or tumor tissues. Carrillo-Carrión et al. synthesized a nanoscale Zr-based metal-organic framework drug delivery system that can be triggered by enzyme alkaline phosphatase (ALP) to achieve controlled drug release in higher ALP gene-expressing cellular regions to achieve controlled drug release [17]. Xie et al. exploited the overexpression of quinone oxidoreductase 1 (NQO1) reductase in certain cancer cells to synthesize a reduction-sensitive polyurethane micelle to achieve an NQO1-reducing environment to stimulate drug release [18]. Cheng et al. reported drug-loaded micelles based on amphiphilic triblock poly(ethylene glycol)-modified polyurethanes synthesized with selenium dioxide cross-linking agent, whose shells that can be dislodged under acidic and certain hydrogen peroxide concentrations, thereby achieving the release of indomethacin at specific sites [19].

3. Gallium-based liquid metal nanoparticles

3.1. Overview of Ga-LMPs

Liquid metals (LM) refer to a class of metals and their alloys that have melting points close to or below room temperature, which possess both the low viscosity and fluidity of liquids as well as the electrical and thermal conductivity of metals. The well-used liquid metals include mercury and its alloys, which are difficult to use in biomedical applications due to their high toxicity and possible environmental pollution. On the other hand, gallium and its alloy materials have good biocompatibility, especially eutectic gallium-indium (EGaIn) and gallium-indium-tin (Galinstan) nanoparticles have been widely explored in the field of medical materials due to their excellent properties. In this section, the advantageous properties of Ga-LMPs for therapeutic applications and the common preparation methods will be introduced.

In the preparation of gallium-based liquid metal nanoparticles, an oxide layer of predominantly gallium oxide composition is formed on the surface of the particles. The thickness of the oxide layer is influenced by oxygen, water, and surface-modifying substances and grows to a final passivation thickness (typically 0.7-3 nm) within a few days [2]. This core-shell structure gives Ga-LMPs interesting properties. For example, generating an oxide layer of other metals on the particle surface by adding other metals, or modifying the surface functionality of the nanoparticles by attaching certain molecules to the surface of the metal or oxide (this can be done by attaching an initiator to the surface of the particle so that a polymerization reaction takes place on its surface), thereby. Using this modifiable core-shell structure, a variety of drug delivery systems can be designed.

3.2. Advantages of Ga-LMPs in therapeutic applications

3.2.1. Electromagnetic properties

Gallium-based liquid metals have higher conductivity than most electrolyte solutions or conductive polymers. According to Faraday's Law of Electromagnetic Induction, eddy currents are formed in the presence of an alternating magnetic field within the metal cores in gallium-based liquid metal nanoparticles, which releases heat and raises the temperature. The efficiency of vortex effect warming is related to the thickness of the nanoparticle oxide layer [20]. With this property, Ga-LMPs will achieve targeted drug release or hyperthermia by controlling magnetic field changes.

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3.2.2. Photothermal conversion properties

Near-infrared light (NIR)--triggered therapy has been widely studied for its good penetration ability in biological tissues. The surface plasmon resonance effect of gallium-based liquid metal nanoparticles give them a light-absorbing behavior. This photoexcitation resonance effect may lead to its near-infrared light-induced exothermic phenomenon. It has been demonstrated that near-infrared light can trigger an increase in the temperature of a suspension of Ga-LMPs. In the therapeutic field, this photothermal conversion capability of gallium-based liquid metals can be utilized to achieve targeted drug release or localized hyperthermia.

3.2.3. Electrochemical properties

Gallium-based electrodes can be applied to the sensing of heavy metal ions. Because of the ability of surface regeneration, alloy with other metals, and absorption and release of heavy metal ions, Ga-LMPs can be used to make sensitive electrochemical sensors for lead, cadmium, and other heavy metal ions [3].

3.2.4. Redox reaction

Gallium ions can replace iron ions in cancer cells or bacteria because of their chemical properties like those of iron ions, with the effect of disrupting the normal mechanism of cellular activity. Ga-LMPs can be taken up by cells in varying amounts due to their excellent biocompatibility (especially after being polyethylene glycolised). In cells, nanoparticles can release Ga^{3+} and generate reactive oxygen species (ROS) via redox reactions [21]. Most studies have focused on the tumor cell-killing effect of reactive oxygen species during this process, the therapeutic effect of gallium ions should also be looked at and considered for a more complete understanding of the drug.

3.3. Ga-LMPs preparation strategy

In general, metal nanoparticles can be prepared using bottom-up methods including chemical reactions, physical deposition, and thermal decomposition. However, for gallium-based liquid metals, gallium is not suitable for nanoparticle preparation using metal salt reduction due to its high reducibility. At the same time, the liquid metal's fluidity makes it easier to be prepared by top-down methods.

Among the top-down preparation methods, extrusion by hand syringe/pipette is one of the simplest preparation methods, but it produces large droplet diameters, which affects the properties of the nanoparticles to some extent [22]. Nanoparticles can be prepared in bulk by the molding method, i.e., by pressing liquid metal into a template with grooves [23]. The manufacturing efficiency of this method is low compared to other laboratory methods. Therefore, the two most used laboratory preparation methods are ultrasonic treatment and shear treatment. Ultrasonication generates very high local temperatures and pressures by triggering the formation and bursting of gas bubbles in the liquid, allowing the liquid metal to be broken up and dispersed into nanoparticles, stabilized by some surfactants or hydrophilic polymers [24]. The shearing process breaks down the liquid metal directly with a stirring device [25]. The size of the shear-prepared particles can be further controlled by varying the shear rate and the shear liquid.

4. Ga-LMP for drug delivery applications

The aforementioned properties of Ga-LMPs have led to their extensive study in the field of drug delivery. Some representative examples of application studies are presented in this section.

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4.1. Light-responsive drug delivery

The mechanisms of gallium-based liquid metals involved in light-responsive drug delivery can be classified into self-photothermal and surface modifier photothermal effects. Ga-LMPs possess excellent photothermal conversion ability and can release localized heat and ROS under near-infrared light irradiation. Wang et al. achieved controlled drug release by disrupting the hydrogel structure of calcium alginate through the photothermal effect of gallium-based liquid metals by loading gallium-indium eutectic alloy nanoparticles dispersed with iron nanoparticles onto Fe@EGaIn/CA microspheres prepared on calcium alginate [4]. In another study, Lu et al. designed an EGaIn nanoparticle covered with graphene quantum dots on the surface to achieve nanoparticle morphology changes due to near-infrared light irradiation to release the drug [5]. The principle may be that the heat released from graphene quantum dots under the photothermal effect with ROS drives the conversion from Ga to GaOOH, which converts the structure of the nanoparticle into a hollow mandrel that can lead to the rupture of the endosomal membrane, which in turn releases drug molecules within the particle [5].In addition, the near-infrared absorption properties of Ga-based LMPs allow them to be used for photothermal cancer therapy applications.

4.2. Electromagnetic field responsive drug delivery

The eddy current effect of metals allows them to raise their local temperatures under alternating magnetic fields, and gallium-based liquid metals are no exception. Yu et al. mixed liquid metals with agarose to make hydrogel composites, which were remotely suspended in an alternating magnetic field and heated up to melt the hydrogel to release the drug [6]. In the experiment, the study used rhodamine B as a drug model encapsulated in a hydrogel and achieved 100% drug release by switching an external alternating magnetic field (AMF) on and off five consecutive times (150 seconds on, 150 seconds off) [6].This drug delivery system can also move and not release rhodamine B driven by low power AMF, while releasing the drug at high power AMF [6]. This achieves its spatiotemporally targeted drug release. Wang et al. Modification of eutectic gallium-indium alloys with PEG to reduce their surface tension and maintain their magneto-thermal properties [7]. After loading the drug, experiments showed that different AFMs can affect the release of the drug within the nanoparticles [7].

4.3. Ultrasound field responsive to drug delivery

Ultrasound field stimulation can control the direction and speed of movement of nanoparticles of a specific structure, but other means such as photothermal effects or magnetic field changes are often required to assist drug release. Wang et al. synthesized a gallium-based nano-swimmer with a needle-like structure and avoided contamination during transport and enhanced cancer cell recognition by covering its surface with a leukocyte membrane coating [8]. The structure ensures that the direction and speed of movement can be controlled by an ultrasound field with adjustable frequency and voltage and that the drug is released at a specific location in conjunction with a photothermal conversion effect [8]. The high acoustic impedance and mobility of liquid metals give them the potential for acoustic field stimulation of drug release, but they have not yet been studied in depth.

4.4. Targeted drug deliver

Gallium oxides on the surface of the core-shell structure of the base liquid metal nanoparticles make them pH sensitive. Tumor cells exhibit a strong acidity within the cells due to their hypoxic environment. Lu et al. facile assemble the thiolate ligands on the surface of eutectic gallium-indium

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alloy nanoparticles for drug loading and active targeting [9]. This agent is enriched in the tumor fraction and fuses and releases the drug in the weakly acidic microenvironment of the endosome [9].

5. Conclusion

This paper summarizes the applications of Ga-based LMPs in the field of drug delivery. The unique physical/chemical properties of Ga-based LMPs such as photothermal effect, electromagnetic response, and mobility are analyzed in detail. These properties give it a unique advantage in precision drug release and controlled drug delivery systems. The current state of research shows that Ga-based LMPs have a wide range of potential applications in light-responsive, magnetic-field-responsive, acoustic stimulation, and targeted delivery, but they still face some challenges.

Currently, the medical properties of gallium metal have not been fully and completely analyzed. Although it does have better biocompatibility and lower toxicity, it is not yet entirely certain whether it is safe for humans and can actually be used for drug delivery. Meanwhile, the stability of Ga-based LMPs is affected by alloy composition, ambient temperature, and humidity, even though suitable protection strategies need to be developed. Furthermore, the targeting of Ga-based LMPs still needs to be improved, enhancing the ability of particles to target delivery to specific cells or tissues and developing precise release mechanisms will be an ongoing focus in this field.

With a better understanding of Ga-based LMPs, we can more safely utilize their unique advantages to solve more nanotherapeutic challenges.

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