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Construction of drug-controlled release system - mesoporous silica nanoparticles

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Abstract

This paper reviews the research progress of Mesoporous Silica Nanoparticles (MSNs) in the construction of drug carrying system in past studies. Through the design of its structure and chemical properties, drug carrying system with various functions can be prepared, which is suitable for drug sustained release system and targeted treatment of various pathological tissues, thus representing a revolutionary biological nano technology.

Introduction

High blood pressure, heart disease, various kinds of cancer and other diseases have become serious hazards to people's health. From the perspective of treatment, these diseases require long-term drug treatment, so drugs should have the characteristics of long-term stability, etc. Moreover, the use of nanomaterials as carriers to load anticancer drugs and build an intelligent responsive controlled release system can effectively solve the shortcomings of traditional drug therapy and reduce the side effects of treatment [1-3].

Controlled drug release system combines drugs with materials having good biological compatibility in a physical or chemical way. The system can control the drug release rate and cycle, and released continuously in human's body by diffusion or penetration. Therefore, the preparation of drugs that can continuously release ingredients is essential for the treatment process. One of the most critical factors is the preparation of carrier materials. Currently, there are many kinds of drug carrier materials. From the clinical perspective, organic drug carriers are relatively mature, such as microemulsion, lipid nanoparticles, biodegradable polymer nanoparticles, and molecular gels, et al [4]. However, the instability and low loading rate of onboard drug systems limit the application in preclinical and later clinical applications. Compared with organic drug carrier, inorganic drug carrier shows high thermal or chemical stability, corrosion resistance, biological compatibility, low biodegradation rate,

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and can be given special structure. So, it has shown the specific function and nature, such as porosity, magnetic, fluorescence, et al. [5]. Magnetic nanoparticles [6,7], semiconductor quantum dots [8,9], carbon-based nanomaterials [10,11], metal nanoparticles [12,13], layered hydroxides [14], et al. At present, drug-controlled release system has shown excellent performance and has been widely used in nano medicine.

According to the regulations of the international union of pure and applied chemistry (IUPAC), mesoporous materials refer to a class of porous materials with pore diameter between 2-50nm. Mesoporous materials have high specific surface area, regular and ordered pore structure, narrow pore size distribution and continuous adjustable pore size, which make them play a role in adsorption and separation for catalytic reactions. Its small and quantum size effect are expected to be widely used in electrode materials, photoelectric devices, microelectronics, chemical sensors, nonlinear optical materials and other fields. Since its birth, mesoporous materials have attracted extensive interest in the multidisciplinary research fields of physics, chemistry, biology, materials and information, etc. At present, mesoporous materials have become one of the hot interdisciplinary frontiers in the world [15].

The synthesis of mesoporous materials began in 1990. Yanagisawa et al mixed layered silicate material Kanemite with long chain Alkyl Trimethylamine (ATMA) under alkaline conditions to conduct ion exchange and obtain three-dimensional mesoporous silica materials with narrow pore size distribution [16]. It was the first mesoporous silica material discovered, but it did not attract the attention of scientists because its structure was not ideal. It was not until 1992 when Kresge and Beck reported that cationic surfactants were successfully used to synthesize a new type of ordered mesoporous material M41S silica (aluminum) based mesoporous material with an adjustable aperture of 1.5-l0nm for the template agent, that the research on ordered mesoporous materials blew a trumpet [17].

The successful synthesis of ordered mesoporous films was first reported by Brinker in 1997. High quality silica mesoporous films can be synthesized by using acidic alcohol solution as reaction medium and volatile induced self-assembly process, which opens up a broad prospect for the application of mesoporous materials in membrane separation and catalysis, microelectronics, sensors and photoelectric functional devices [18]. In 2003, Zhao proposed the concept of “acid-base pair” and synthesized a series of non-silicon mesoporous materials by using acid-base paired inorganic precursors to control the acidity through “self-regulation” in a non-water system. This method solves the problem of how to find the precursor of metallic sol to some extent, and it is a universal method to synthesize multicomponent oxide mesoporous materials [19-22].

MSNs drug carrier

Compared with the organic drug systems, the inorganic ones exhibit high thermal and chemical stability, corrosion resistance to physiological environment, biocompatibility and low biodegradation rate. Inorganic drug systems can be easily endowed with special structural and physical/chemical properties to display specific functions and properties, such as porosity, magnetism, fluorescence, etc. Different inorganic drug systems have shown excellent performance and are widely used in nano-medicine.

An excellent drug-controlled release carrier material, it should have the following characteristics:

1. The carrier material does not have the biological toxicity.
2. High surface area and large pore volume. The total surface area and pore volume allows high loadings of drug molecules.
3. Unique structure allows the selectively functionalization to achieve the desired “zero premature release” of drug, and locate specific cells.
4. Drug molecules are released at controlled release rates.

Among many inorganic drug systems, silica is one of the most biocompatible materials. It is an endogenous material where mainly distributed in bones. It has been used in commercial applications as oral tablets. In addition, the US Food and Drug Administration (FDA) calls silica “recognized as safe” [23-25].

MSNs is an excellent drug carrier because it is characterized by continuously adjustable pore channels, large specific surface and pore volume, easily modified surface and good biocompatibility. Since 2000, the research of mesoporous silica in the field of nano-biotechnology and nano-medicine has entered an era of rapid development.

Morphology control

As early as 1992, Kresge et al prepared mesoporous silica materials by surfactant template method [26], and carried out a series of studies on them. Researchers use these materials in catalysis [27], separation, sensor [28], and control release of materials. Although some results were achieved, there were no reports of these applications at that time. It wasn’t until the 2000s, people discovered that this could be due to a lack of control over the shape of the material. Due to the imperfect preparation methods at that time, silica particles of different shapes and sizes were produced. Particle shape, size, porosity and specific surface area of materials will have a direct impact on intelligent drug delivery system. Therefore, how to effectively regulate the morphology of mesoporous silica is a great significance of the preparation for drug-controlled release system.

Ordinary mesoporous silica

Ordinary mesoporous silica with small pore size is often used as a basic research material for biological behavior due to its characteristics of strong reproducibility and high quality of its synthesis. The preparation methods of mesoporous silica include template method, sol-gel method and hydrothermal synthesis method. The most commonly is the template method, it used organic molecules as template agent, interface reaction with inorganic or organic silicon source, form the orderly assembly containing silica body, by calcining or solvent extraction after removal of the template agent, keep silica inorganic skeleton, mesoporous silica materials is obtained (Figure 1) [29].

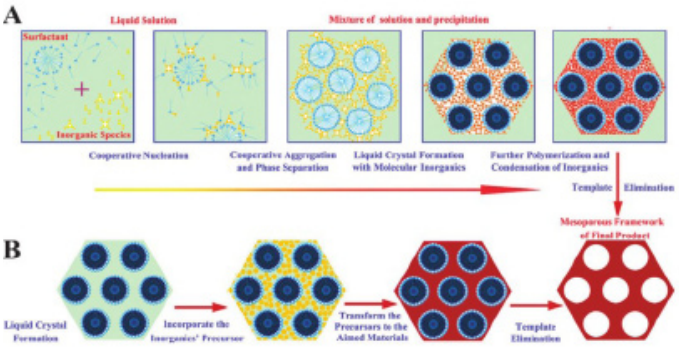

Figure 1: Two synthetic strategies of mesoporous materials: (A) cooperative self-assembly; (B) "true" liquid-crystal templating process.

Recent studies have shown that large-pore mesoporous silica nanoparticles (LP-MSNs, <200 nm) is a promising carrier for large molecular cell carrier. The ideal nanocarrier should be able to optimize the master-guest interaction according to its surface characteristics. Hsin-Yi Chiu et al. added different organic groups to the silica skeleton and synthesized various functional LP-MSNs by means of co-condensation. In addition, a delayed co-condensation strategy is used to create spatially separated core-shell LP-MSNs. Different particle morphologies were obtained by adding different organic silane into the solution of silicon precursor. As shown in the figure 2 [30].

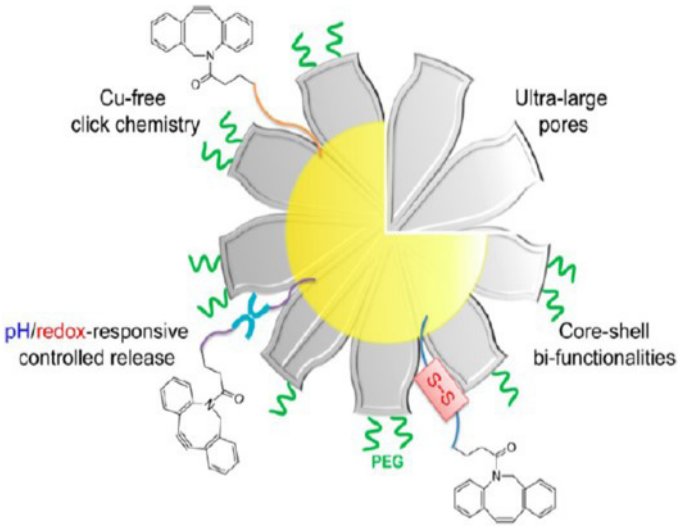

Figure 2: Schematic Illustration of the Multifunctional Large-Pore MSNs Established in This Study for Different Applications

Surface functionalization

MSN has two functional surfaces, the internal and the external surface, allowing us can selectively function materials. There are three common methods of co-condensation (one-pot synthesis), invention (post synthesis modification), and imprint coating method [31,32]

1. Co-condensation has been widely used in the preparation of inorganic - organic systems. The method has many advantages, such as suitable for a variety of organic alkoxy silanes, and various reaction conditions; This method has high load on functional groups and little effect for pore structure. During the reaction process, it is necessary to avoid the phase separation of precursor and the break Si-C bond during the removal of surfactant. The electrostatic matching effect of various anion by the organic functionalization degree of MSNs has been studied in the early stage [33]. When both acidic and alkaline basic functional groups are introduced, MSNs will produce interesting chemical properties and have new application prospects (Figure 3).

2. The grafting method is usually carried out by silylation on free (Si-OH) and geminal silanol (Si $(OH)_2$) groups. During the experiment, the surfactant is usually removed by calcination, which results in the loss of surface functional groups. In order to minimize the loss of surface functional groups, an extraction process is required. The most prominent feature of the grafting method is the ability to selectively functionalize the external or internal surfaces of MSNs. For example, 1,5, 6-epoxyhex-yltriethoxysilane (EHTES) can be successfully grafted onto the outer surface of MSNs before the surfactant is removed, and the external groups can react further [34] (Figure 4).

3. Imprint coating is a novel method. A stepwise surface functionalization methodology has been developed to synthesize mesoporous sol-gel sorbents containing the ethylenediamine functionality. The N-[3-(trimethoxysilyl)-proryl] ethylenediamine (TMSen) ligand is first coated on MCM-41, followed by sorption of Cu (II). A second exposure to TMSen results in the formation of a 2:1 TMSen:Cu(II) complex on the surface of the mesopores. Acid washing protonates the amino groups which release the copper ions. This results in the formation of binding sites that are uniquely designed with the coordination environment Cu (II) prefers. This material has large surface areas and good mass transfer [32].

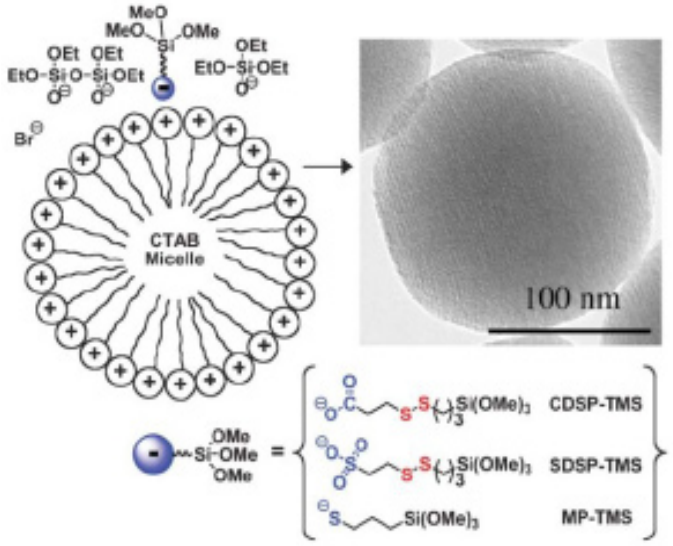

Figure 3: Schematic representation of the utilization of anionic organoalk- oxysilane for controlling the functionalization of the MSN materials. The MCM-41 type mesoporous channels are illustrated by the parallel stripes shown in the TEM micrograph of the MSN-SH material.

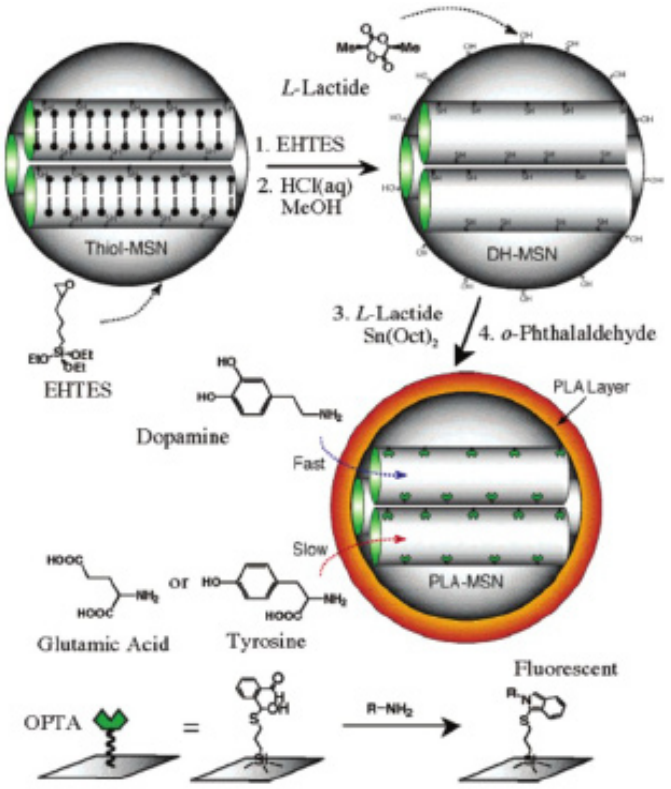

Figure 4: Schematic representation of the synthesis of PLA-coated MSN-based fluorescence sensor system for detection of amine-containing neurotransmitters, i.e., dopamine, glutamic acid, and tyrosine (R-NH 2).

The gatekeeping concepts

In order to release the drug to the target at an appropriate concentration within a specified time, the drug delivery system needs to meet certain conditions. C. Y. Lai's team developed an intellectual response system based on MSNs, which proposes the concept of gatekeeping [35]. The advantage of this system is that various materials (such as nanoparticles, organic molecules, or supramolecular assembly) can be used as gatekeeper to regulate the release of drug molecules (Figure 5). It can be triggered by different conditions, such as photochemical [36], pH responsive [37], and redox [38]. This precise control of drug release location and time will be a breakthrough in the application of controlled release drug delivery system.

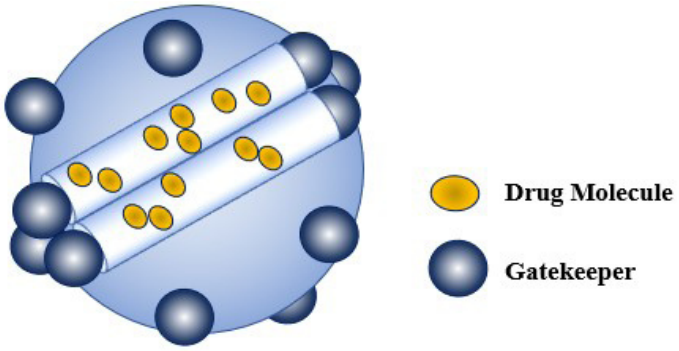

Figure 5: An MSN loaded with drug molecules and end-capped with a gatekeeper.

Application of drug-controlled release system

Sustained-release drug

Compared with common drugs, the frequency of sustained-release drugs is reduced, blood concentration is more stable than common drugs, and patient compliance can be significantly increased [39]. Common drugs need to be given several times a day that is inconvenient to use, and blood drug concentration fluctuation range. At peak blood concentration, side effects and even toxicity will be occurred. Oral administration of drugs is the most common way of drug administration. Despite obvious deficiencies, which are mainly reflected in the following aspects: low permeability of drugs to mucous membrane; osmosis is limited to the gastrointestinal tract, and low-solubility drugs have a low dissolution rate in viscous fluids. It makes most drugs have been excreted before being absorbed. Proteins, peptides, genes, oligonucleotides and other drugs have poor stability in the gastrointestinal environment [4]. In order to obtain good therapeutic effects, oral administration is often replaced by injection and other ways. However, drugs can be uniformly distributed in the systemic circulation. Before reaching the lesion, only a small number of drugs can reach the lesion after the steps of protein binding, excretion, metabolism and decomposition. This problem is well solved by the controlled release system. Sustained-release drugs can improve the utilization rate, reduce the drugs frequency, reduce the blood drug concentration, improve the efficacy and patient compliance [40-42].

Targeted therapy

With the continuous progress of MSNs research, a lot of work in recent years began to focus on selective targeted therapy. Normally, how to efficiently kills tumor cells is the focus of tumor therapy. So, the most important thing for drug delivery system is that can distinguish between cancer cells and healthy cells. Currently, a widely studied method is developed to modify the outer surface of MSNs with that can interact with in tumor cells [43.44]. Another is to modify MSNs with targeted ligands that have affinity for blood and destroy the nutrition and oxygen supply of the tumor by washing the tumor [45]. By utilizing the designability of MSNs, the drugs can reach the lesion site more smoothly and be released by different stimuli, including internal stimuli, such as PH, redox potential and enzymes. And external stimuli, such as magnetic fields, ultrasound and light.

Internal Stimuli-Responsive

As the response of different pathologies to endogenous MSNs is different, further understanding of biochemical and human metabolic processes is needed [46-48]. At present, there have been many reports on the design of intelligent MSNs through internal stimulus response, such as pH change [49-51], REDOX potential [52-54], and overexpression of certain enzymes [55-57]. In general, these intelligent drug delivery systems contain one or two elements, namely sensitive connectors and gatekeepers. Reactive ligands can be broken or degraded by specific stimuli. This gatekeeper, such as inorganic nanoparticles, polymers, or large molecules, blocks the entrance of the mesopore, preventing the early release of the drugs.

External stimuli-responsive

Magnetic response MSNs. Superparamagnetic iron oxide (SPIONs) is the most widely used magnetic nanoparticles for the drugs delivery. These nanoparticles convert magnetic energy into heat through Brownian or Nell waves [58]. Generally, SPIONs of 5-10nm are encapsulated in MSNs and realized through aerosol technology or sol-gel process. Because a magnetic field causes temperature to rise, MSNs can bind to temperature-reactive molecules to act as gatekeepers, triggering pore openings and drug releases [59]. Zheng Wang prepared a magnetic

mesoporous silica nanoparticle (M-MSNs) with controllable shape, and studied its performance under Magnetic Resonance Imaging (MRI) guidance, magnetic targeting and high temperature enhanced gene therapy for liver cancer suicide. Compared with spherical MSNs, rod MSNs has higher load capacity, stronger magnetic enhancement gene delivery and better magnetothermal characteristics. Using the improved magnetic properties of M-MSNs, effective dual-magnetic enhanced suicide gene therapy can be demonstrated in vivo, reducing systemic toxicity, and it can be monitored treatment results by MRI [60].

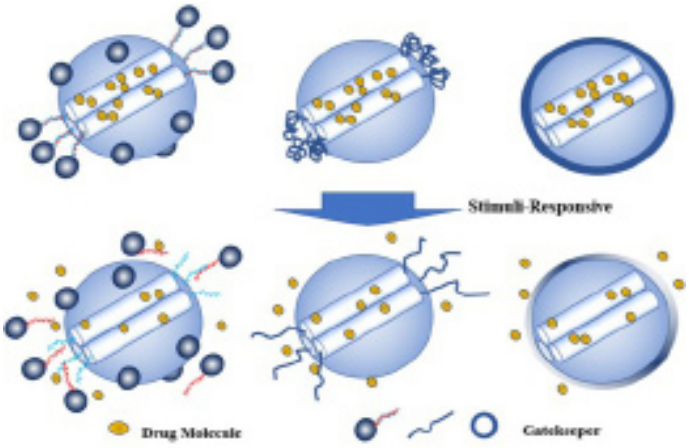

Figure 6: Schematic depiction of three representative Gatekeepers

Ultrasound (US) - triggered MSNs. The advantage of US is that it has non-invasive, non-ionizing radiation and can control the penetration depth of tissues by adjusting parameters [61,62], so that to prevent damage for healthy tissues, and it is an effective method to achieve targeted delivery of drugs. US can trigger MSNs to release drugs through thermal effects. In current job, ultrasound-induced inertial cavitation was evaluated as a mechanism to promote their extravasation in a flow-through tissue-mimicking agarose phantom. Two different ultrasound frequencies, 0.5 or 1.6 MHz, with pressures in the range 0.5–4 MPa were used to drive cavitation activity which was detected in real time. Experiments show that the combination of MSNs with submicron nuclei may be helpful to enhance the exosmosis of nanocarriers, thus making continuous release of drugs possible [63].

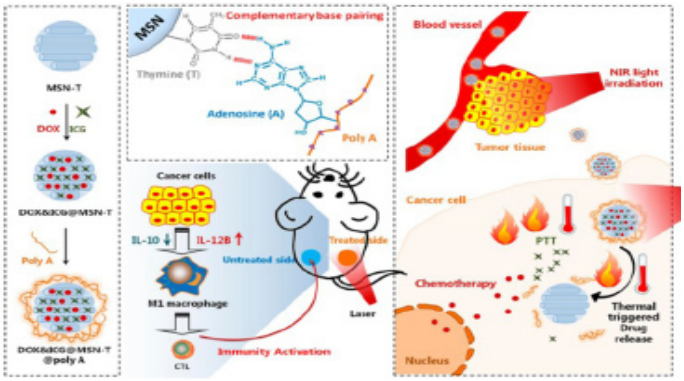

Figure 7: Schematic Presentation of DOX & ICG @ MSN-T @ poly A Design, Preparation, Triggered Drug Release, Anticancer Process, and Immunity Activation Mechanism

Light-triggered MSNs. Because there are different properties for different wavelengths of Light, we can release drugs as needed by this feature [64]. The advantage of light is ease of use, low toxicity and precise focus where needed. However, the tissue penetration capacity of light is low, which is usually solved by using auxiliary medical equipment. Ultraviolet stimulation is a common method to trigger MSNs drug release [65], because ultraviolet light can easily break the bond by the highest power. However, the harm of ultraviolet light to organs and the low penetration hinder its application in biomedicine [66,67]. Compared with ultraviolet light, visible and infrared light have lower harm and higher penetration rate, which has received more and more attention in recent years. Figure 7 shows an example of a drug delivery system based on infrared light triggering MSNs [68]. MSNs was modified by poly adenine (Poly A), and the thymine (T) to the end of RNA was used as a gatekeeper. Both established an A-T base pairing system. A near-infrared laser is used to trigger the release of the drug on the tumor tissue. Experiments have shown that nanoscale drugs can effectively inhibit tumor growth and activate antitumor immunity.

Advantages and challenges

When a drug is used alone, either orally or intravenously, the serum concentration of the drug peak. Then that concentration would be reduced until the next drug administration, which would produce again a concentration peak. Sometimes, the maximum may exceed the human body's tolerance level, and the minimum may be below the optimal treatment level. Using MSNs as a drug control delivery system can maintain optimal drug concentrations for a long time, improve treatment efficiency, avoid any type of potential toxicity and subsequent side effects. MSNs can transport two or more drugs into the same nanoparticles, making it possible to treat multidrug-resistant tumors. MSNs for drug delivery can also protect drugs as they travel through the body, and it can be precisely controlled drug release, whether is internal and characteristic of the treated pathology, or externally applied by the clinician. In this sense, the control provided by the stimuli-responsive MSNs system prevents the premature release of therapeutic drugs, and is crucial for the protection of other healthy organs from drug damage.

However, before entering the market, all drugs must complete the transition of industrialization. MSNs is usually developed in the laboratory, and materials are obtained in the order of milligram or gram. It is difficult to guarantee good material performance in large-scale production. Repeatability is a complex problem for all nanoscale drugs and that takes a long time to resolve. On the other hand, how to design the clinical trial of MSNs. There is no clinical trial to evaluate MSNs. In oncology, the results have been largely stopped animal studies, and with only 2% of people entering clinical trials. But there are differences between human body and animals, which is one of the important factors restricting the industrialization of the drug-controlled release system.

Acknowledgements

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