MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
KYIV NATIONAL UNIVERSITY OF TECHNOLOGIES AND DESIGN

Faculty of Chemical and Biopharmaceutical Technologies
Department of Industrial Pharmacy

Master's thesis

on the topic

STUDY ON PREPARATION AND PROPERTIES OF SIMVASTATIN LOADED BIODEGRADABLE MICROSPHERES

Completed: student of the group MPhch-20

of the speciality 226 Pharmacy, industrial pharmacy
(code and title of the specialty)

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Kyiv 2021

KYIV NATIONAL UNIVERSITY OF TECHNOLOGIES AND DESIGN

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"14" December 2021

ASSIGNMENTS
FOR THE MASTER'S THESIS

Ruiqi Kong
(Full Name)

1. Thesis topic Study on preparation and properties of simvastatin loaded biodegradable microspheres
2. Scientific supervisor Olha Nikitina, Associate Professor, PhD
(first name, last name, patronymic, academic degree, academic title)
approved by the order of the higher educational institution on 4th October 2021, N 286

3. Deadline for student submission of work 14th December 2021

4. Initial data for work: scientific and information sources, methodological and technological literature, scientific periodicals, international and domestic regulations and standards for the development and production of medicines

5. Content of the thesis (list of questions to be developed) *a review of the literature on biodegradable materials as the basis for the formation of microspheres, the development of stages of obtaining microspheres SIM-PLGA, the study on manufacturing and Quality Control of drugs with System of sustained and controlled release*

6. Consultants of the master's thesis sections

Section	Surname, initials and positionof the consultant	Signature	
		the task wasissued	the task accepted
Section 1	Olha Nikitina, Associate Professor, PhD		
Section 2	Xu Jinku, Associate Professor, PhD		
Section 3	Olha Nikitina, Associate Professor, PhD		

7. Date of issue of the assignment September 20, 2021

Execution schedule

No	The name of the stages of the master's thesis	Terms of performance of stages	Note on performance
1	Introduction	20.09 –27.09.2021	
2	Section 1 *Characterization of biodegradable materials as the basis for the formation of microspheres*	28.09. – 11.10.2021	
3	Section 2 *Experimental preparation of microspheres loaded with simvastatin and determination of their properties*	12.10 – 25.10.2021	
4	Section 3 *Manufacturing and Quality Control of drugs with system of sustained and controlled release*	26.10 - 08.11.2021	
5	Conclusions	09.11.-15.11.2021	
6	Draw up a master's thesis (*final version*)	16.11.-04.12.2021	
7	Submission of master's thesis to the departmentfor review (*14 days before the defence*)	06.12.-14.12.2021	
8	Checking the master's thesis for signs of plagiarism (*10 days before the defence*)	14.12-18.12.2021	
9	Submission of master's thesis to the master's department to check the implementation of theappendix to the individual curriculum (*10 daysbefore the defence*)	16.12-18.12.2021	
10	Submission of master's thesis for approval by the head of the department (*from 7 days before the defence*)	18.12-21.12.2021	

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SUMMARY

Ruiqi Kong. Study on preparation and properties of simvastatin loaded biodegradable microspheres

Master's thesis on the specialty 226 Pharmacy, industrial pharmacy. - Kyiv National University of Technology and Design, Kyiv, 2021.

Simvastatin was loaded into microspheres to detect the drug release rate. Through passive distribution, active targeted binding or magnetic attraction, improve the local effective concentration of drugs in the body, and reduce the drug concentration in other parts, so as to reduce the systemic toxicity and adverse reactions of drugs.

The physicochemical properties of simvastatin were analyzed. After the preparation of polyvinyl alcohol in the aqueous and oil phases, microspheres were prepared, filled with the preparation by the method of solvent evaporation. The surface morphology, microstructure and particle size of the obtained microspheres are characterized. A drug release experiment was conducted. The drug encapsulation efficiencies and drug loading of the microspheres were calculated according to the cumulative drug release.

Microspheres filled with simvastatin were prepared by mechanical evaporation of the solvent and simvastatin. The process of obtaining and the morphology of microspheres filled with a drug was investigated, a method for the quantitative analysis of drugs was established, and the conditions for dissolution of microspheres were determined. The surface is smooth, and the particle size is about 100 microns. Microspheres have a uniform particle size and sustained release. The material used for the manufacture of microspheres with a drug has good biological compatibility and is biodegradable, and the decomposition products are harmless to human health.

Key words: *Biodegradable materials, microspheres, simvastatin, polylactic acid glycolic acid copolymer*

АНОТАЦІЯ

Руїці Конг. Вивчення приготування та властивостей біорозкладних мікросфер з симвастатином.

Магістерська робота за спеціальністю 226 Фармація, промислова фармація – Київський національний університет технологій та дизайну, Київ, 2020.

Симвастатин завантажували до мікросфер і визначали швидкість вивільнення. Завдяки пасивному розподілу, активному цілеспрямованому зв'язуванню та магнітному притяганню, покращується місцева ефективна концентрація ліків в організмі та зменшується концентрація ліків в інших частинах, що зменшує системну токсичність та побічні реакції.

Проаналізовано фізико-хімічні властивості симвастатину. Після приготування розчину полівінілового спирту у водній та масляній фазі готували мікросфери, наповнені препаратом методом випарюванням розчинника. Охарактеризовано морфологію поверхні, мікроструктуру та розмір частинок отриманих мікросфер. Був проведений експеримент із вивільненням лікарського засобу. Ефективність інкапсуляції лікарського засобу та завантаження лікарським засобом мікросфер, були розраховані відповідно до кумулятивного вивільнення лікарського засобу.

Мікросфери, наповнені симвастатином, готували методом механічного випаровування розчинника та симвастатину. Досліджено процес одержання та морфологію мікросфер, наповнених лікарським засобом, встановлено метод кількісного аналізу лікарських засобів та визначено умови розчинення мікросфер. Поверхня гладка, а розмір частинок близько 100 мкм. Мікросфери мають однорідний розміром частинок і тривале вивільнення. Матеріал, який використовується для виготовлення мікросфер із лікарським засобом, має хорошу біологічну сумісність і біологічно розкладається, а продукти розпаду нешкідливі для здоров'я людини.

Ключевые слова*: биоразлагаемые материалы, микросферы, симвастатин, сополимер полимолочной кислоты и гликолевой кислоты.*

ABBREVIATION LIST

CH - cholesterol
TG - triglyceride
LDL-C - low density lipoprotein cholesterol
HDL-C - high density lipoprotein cholesterol
ASCVD - atherosclerotic cardiovascular diseases
SIM - simvastatin
PLGA - polylactic acid glycolic acid copolymer
LA - lactic acid
FDA - Food and Drug Administration
PHA - polyhydroxyfatty acid ester
PBS − polybutylene succinate
PVA - polyethylene glycol
SA - sodium alginate

CONTENT

Introduction

The development of dosage forms with controlled release of biologically active compounds attracts the attention of a large number of researchers around the world. Such drugs are relevant if it is necessary to prolong the effect of the drug and not exceed the permissible concentration in the circulating blood. One of these conditions is hyperlipidemia. Hyperlipidemia is one of the common chronic cardiovascular diseases. Usually, the patients have higher incidence rate of cardiovascular and cerebrovascular diseases. Hyperlipidemia can also be called hyperlipidemia or dyslipidemia. It refers to the increase of CH, TG and LDL-C in serum and the decrease of HDL-C [1]. Unhealthy lifestyle, diabetes and genetic factors may lead to hyperlipidemia. Hyperlipidemia can lead to ASCVD such as coronary heart disease. In addition, hyperlipidemia also increases the risk of tumor [2]. Selecting appropriate and scientific drug treatment in clinical application can improve the prognosis of patients and control the level of blood lipid.

SIM mainly used for hyperlipidemia and coronary heart disease, to avoid elevated blood lipids [3]. PLGA is a degradable functional polymer organic compound, which has good biocompatibility, non toxicity, good encapsulation and film-forming properties. It is widely used in pharmaceutical, medical engineering materials [4] and modern industrial fields. PLGA is used as a carrier. The microspheres prepared with PLGA have uniform size and porous structure inside, which can promote the release of drugs, not only achieve and maintain the effective concentration of drugs, but also reduce the damage of drugs to human body [5-6]. At the same time, polymer materials can be modified to control drug release.

As drug carriers, polymers can dissolve and concentrate drugs, improve drug stability and bioavailability, and prolong drug or gene effects through continuous administration.

Biodegradable polymer materials, polymer solid particles, due to their high dissolution rate, improve the bioavailability of drugs [7-8]. In addition, the use of biodegradable and compatible polymer materials can reduce the risk of harmful

toxicity and adverse effects of drugs or other substances. These systems have been shown to be delivery platforms for a variety of compounds, from small molecules to macromolecules such as proteins and oligonucleotides [9]. Microsphere is a spherical or quasi spherical particle dispersion system composed of polymers. It refers to the very small spherical body formed by dispersing or adsorbing specific drugs in the matrix of polymer materials. Microspheres are usually better than nanospheres because the release of drugs in microspheres can last longer with the decrease of specific surface area. The drug loaded microspheres can be prepared by solvent evaporation [10], spray drying [11], via small hole injection polymer solution [12-13], porous glass membrane emulsification technology and condensation method.

SIM is one of the drugs for the treatment of hyperlipidemia. But after oral simvastatin, It is still a difficult problem in clinical application to release its efficacy in human body and its drug action efficiency. Improve the local effective concentration of the drug in the body and reduce the drug concentration in other parts, so as to reduce the systemic toxicity and adverse reactions of the drug [14].

The **purpose of the study** is: prepare microspheres from a biodegradable polymer capable of retaining and controlled release of the drug substance simvastatin.

The **research objectives of the study:**

- to study the main types of biodegradable materials and the factors affecting their technological characteristics and the possibility of controlled release of medicinal substances;

- to designate the field of application of microspheres in medical and pharmaceutical practice;

- to elect a biodegradable polymer as a basis for microcapsules loaded with simvastatin and determine the method of microspheres boiling;

- experimentally obtain microspheres loaded with simvastatin based on PGLA and study their biopharmaceutical characteristics.;

- to characterize the production and quality control of drugs with a system of prolonged and controlled release.

The **object of MTh** is are PLGA material was selected to prepare a biodegradable microspheres. Simvastatin was loaded into PLGA microspheres to detect the drug release rate and the related properties of PLGA microspheres.

The **subject of MTh** to development of a technology for the preparation of a carrier of simvastatin agent, combining biocompatibility, degradability and controlled release, to enable its practical application in the field of pharmaceuticals.

Research methods: PLGA microspheres loaded with SIM drugs were prepared by mechanical emulsification solvent evaporation method with PLGA and DCM solution of simvastatin as oil phase and PVA aqueous solution as aqueous phase. The preparation process and morphology of drug loaded microspheres were studied, the quantitative analysis method of drugs was established, and the drug dissolution properties of drug loaded microspheres were measured.

Practical value it is hoped that through the research of this subject, it is expected to establish a preparation technology of drug carrier integrating biocompatibility, degradability and controlled release, so as to make its practical application in the field of pharmaceutical preparations possible.

Elements of scientific novelty. The process of obtaining and the morphology of microspheres based on PGLA filled with simvastatin was investigated, a method for quantitative analysis of simvastatin was established, and the conditions for dissolution of microspheres were determined.

Section1. Characterization of biodegradable materials as the basis for the formation of microspheres

1.1. Main types of biodegradable materials

Degradable materials are materials that can be degraded in the sense of thermodynamics and kinetics in a period of time. According to the external factors of degradation, it can be divided into photodegradable materials, biodegradable materials, etc. [16]. The influencing factors mainly include temperature, molecular weight, material structure, etc.

According to the external factors of degradation, it can be divided into:

1. Photodegradable materials: degraded due to the action of sunlight;

2. Biodegradable materials: degraded due to the respiration or chemical energy synthesis of natural microorganisms such as fungi and bacteria, and finally decomposed into carbon dioxide and water [17];

3. Environmental degradation materials: degraded under natural environmental conditions such as light, heat, water, polluting compounds, microorganisms, insects and mechanical forces.

In the pharmaceutical process, we often use biodegradable materials. Main types of biodegradable materials is a PLA is a LA derivative produced from renewable resources such as wheat, straw, corn and sorghum. PLA has the characteristics of non-toxic, non irritating, good biocompatibility, high strength, good processability and biodegradability [18]. The sheets, fibers and films made of PLA are widely used in packaging [19], textile and medical [20] and other fields after secondary processing such as thermoforming and spinning. Their wastes can be decomposed into water and carbon dioxide by microorganisms.

PLA is completely biodegradable and can be decomposed into water and carbon dioxide by microorganisms. Because PLA is highly safe for human body, can be absorbed by tissues (can reduce rejection after entering human body), and

has satisfactory physical and mechanical properties [21], PLA is widely used in the field of medicine. In the human body, PLA can be decomposed into La and then metabolized by the human body. It is non-toxic and harmless. Its degradation can be used for drug release. Polylactic acid as a carrier, the microspheres prepared with polylactic acid have uniform size and porous structure, which can promote the release of drugs. It can not only achieve and maintain the effective concentration of drugs, but also reduce the damage of drugs to human body. At the same time, polymer materials can be modified to control drug release [22].

Polylactic acid has the following advantages: first, raw materials are easily available and renewable, which is suitable for large-scale intensive production; Second, the air permeability, transparency, gloss, hardness, tensile and flexural modulus can be comparable to those of traditional plastic resins; Third, better biocompatibility. Its monomer raw material L-lactic acid is an endogenous active substance in human body. Therefore, polylactic acid products are non-toxic and non exclusive to human body, and can be absorbed by human body. It can be made into medical tissue skeleton materials and medical carriers, which can be safely used in human body, and has obtained FDA certification; Fourth, complete degradability. It can be degraded into carbon dioxide and water after being buried in soil for 6 ~ 12 months.[23]

World carbon dioxide emissions according to news reports, the global temperature will rise to 60 ℃ in 2030. The treatment method of ordinary plastics is still incineration and cremation, resulting in a large number of greenhouse gases discharged into the air, while polylactic acid is buried in the soil for degradation. The generated carbon dioxide will directly enter the soil organic matter or be absorbed by plants, and will not be discharged into the air, resulting in no greenhouse effect.

Polyhydroxyfatty acid ester, a biopolymer material developed rapidly in recent 20 years, is an intracellular polyester synthesized by many microorganisms. It is a natural polymer biomaterial. Because PHA has good biocompatibility, biodegradability and thermal processing properties of plastics, it can be used as

biomedical materials and biodegradable packaging materials, which has become the most active research hotspot in the field of biomaterials in recent years. PHA also has many high value-added properties such as nonlinear optics, piezoelectricity, gas separation and so on.

PHA plays a more and more important role in drug sustained-release system because of its good biodegradability and biocompatibility. The earliest research on PHA as drug release encapsulated microspheres was the research on PHB in 1983. After that, with the development of PHBV, the drug encapsulation research of PHA has made great progress. The research shows that the controlled rate release of drugs can be realized by adjusting the monomer composition, molecular weight, drug encapsulation amount and encapsulated particle size of PHA. In addition, many scholars have also used other polymers such as PCL and PHA to mix and package drugs, and have made some achievements.

Because of its biocompatibility and biodegradability, PHA can be used as implant materials in vivo, including tissue engineering materials and drug controlled release carriers. This characteristic can also be used as a carrier for wrapping fertilizers or pesticides in agriculture to slowly release the wrapped substances in the process of slow degradation of PHA, so as to maintain long-term fertilizer effect or efficacy, reduce the dosage, prolong the action time and protect the long-term plantability of cultivated land. The monomers constituting PHA have chirality. They are intermediates in the chemical synthesis of many drugs and have high value-added applications. Many different chiral monomers can be obtained by synthesizing PHA in vivo and degrading PHA in vivo [24].

PHA is not only an environment-friendly bioplastics with excellent performance, but also has many adjustable material properties. With the further reduction of cost and the development of high value-added applications, PHA will become a biomaterial with multi application fields whose cost can be accepted by the market [25]. Because it is a wide family, its properties from hard to high elasticity make it suitable for different applications. The structural diversity and performance variability of PHA make it an important member of biomaterials.

Compared with PLA, PHA has a short development history, greater development potential and greater application space.

Polybutylene succinate is synthesized by condensation polymerization of succinic acid and butanediol. The resin is milky white, odorless and tasteless. It is easy to be decomposed and metabolized by a variety of microorganisms in nature or enzymes in animals and plants, and finally decomposed into carbon dioxide and water. It is a typical fully biodegradable polymer material. It has good biocompatibility and bioabsorbability; The density is 1.26g/cm, the melting point is 114 ℃, and the crystallinity is between 30 ~ 45% according to the molecular weight and molecular weight distribution.

It entered the field of material research in the 1990s, and quickly became one of the hot research materials of general biodegradable plastics that can be widely popularized and applied. The source of synthetic raw materials can be either petroleum resources or biological resources fermentation [26]. Because PBS has excellent comprehensive performance, reasonable cost performance and wide application. In practical application, polybutylene succinate (PBS) can be used as garbage bags, packaging bags, cosmetic bottles, various plastic cards, baby diapers, agricultural materials and drug sustained-release carrier matrix [27]; There are other plastic products related to environmental protection, such as civil greening net, film, etc. It can be used in packaging, tableware, cosmetic bottles and drug bottles, disposable medical supplies, agricultural films, pesticide and fertilizer slow-release materials, biomedical polymer materials [28].

1.2. Factors affecting the characteristics of degradable materials

The degradability of polymer degradable materials is the most important part in application. There are also many factors that affect the degradation performance of degradable materials.

Effect of pH value on degradation of polymer materials. Some studies believe that the change of pH value has a great impact on the hydrolysis rate of copolymer chain, but the degradation rate is not very different in different parts of the organism.

The degradation of copolymer can form an acidic microenvironment, which promotes the self catalysis of copolymer, resulting in its degradation [29].

Effect of temperature on degradation of polymer materials. In the experiment, it is rare to see the relationship between the degradation of materials and temperature. This is because in vitro experiments are often carried out by simulating body temperature, and the human body temperature does not change much. However, in the process of in vitro experiment, sometimes for the needs of experiment, it can be heated appropriately to shorten the experimental cycle. However, in the process of accelerated degradation, the temperature should not be too high or too low, because the polymer will have side reactions when the temperature is too high; When the temperature is too low, the purpose of accelerating degradation can not be achieved[30]. Therefore, in order to avoid the influence of temperature and air flow on degradable materials, degradable materials are stored in a low-temperature sealed environment.

Effect of molecular weight on degradation of polymer materials. The hydrolysis rate of the material is significantly affected by the molecular weight and distribution of the copolymer. This is mainly because each ester bond may be hydrolyzed, and the ester bond hydrolysis on the molecular chain is irregular. When the polymer molecular chain is longer, the more parts it can hydrolyze, the faster and faster the degradation.

Effect of material structure on degradation of polymer materials. Anhydrides and orthoesters are easily hydrolyzed[31]. Because the mass and molecular weight of comb copolymer decrease rapidly, the polarity of skeleton is conducive to the fracture of ester bond. Therefore, the degradation rate of comb molecular copolymers is greater than that of linear molecules.

Effect of monomer composition on degradation of polymer materials. The degradation behavior of materials is related to the physical and chemical properties of materials. The polarity, molecular weight and distribution of polymers all affect the degradation performance of materials [32]. It is considered that the degradation of the copolymer is closely related to the molecular weight and crystallinity of the

copolymer. For example, the crystallinity of glycolide and lactide copolymers is lower than that of their homopolymers.

Glycolic acid is more hydrophilic than lactic acid. Therefore, PLGA copolymer with more glycolide has better hydrophilicity than PLGA copolymer with more lactide, so it can degrade faster. The hydrophilic polymer has large water absorption, the internal molecules of the material can fully contact with water molecules, and the degradation rate is fast. On the contrary, hydrophobic polymer materials have less contact with water molecules and slow degradation rate.

Effect of enzymatic hydrolysis on degradation of polymer materials. There are many reactions in organisms that can lead to the degradation of polymers, including oxidation in body fluids, chemical hydrolysis and enzymatic reactions[33]. In the early glassy state, it is difficult for enzymes to participate in the degradation, but enzymatic hydrolysis is the main factor affecting the copolymers in rubber colloidal state.

Effect of polymer hydrophilicity / hydrophobicity on degradation of polymer materials. Hydrophilic polymers can absorb a large amount of water and accelerate the degradation rate; Hydrophobic polymers have less water absorption and slow degradation rate. In particular, polymers containing hydroxyl and carboxyl groups are easy to degrade.

1.3. Application of degradable microspheres

Microsphere is a spherical or quasi spherical particle dispersion system composed of polymers. It refers to the very small spherical body formed by dispersing or adsorbing specific drugs in the matrix of polymer materials. The particle diameter of microspheres is usually 1-250μM. But in fact, there is no precise limit on its diameter. Generally speaking, microspheres can be divided into nano spheres and micro spheres. Small ones can have several nanometers, and large ones can reach hundreds of nanometers. Nanoscale microspheres are often called nanospheres. Nanoscale microspheres are often called nanospheres. Because of the

unique morphology and characteristics of microspheres, they are widely used in various fields.

Medical accessories with the aging of the population, the number of skin wounds such as diseased skin ulcers is increasing, and the demand for qualified and ideal wound dressings is also increasing. In order to meet people's demand for "quality" and "quantity" of medical dressings, synthetic materials need to be introduced into modern medical dressings.[34]

Although the application of biomedical hydrogel in drug delivery system is very effective [35], but the single hydrogel structure has been unable to meet the current clinical needs. In recent years, biomedical hydrogels are often combined with microspheres to form multiple carriers. Their structures have better drug release properties due to the addition of microspheres, the targeted delivery of drugs is more precise, and the clinical therapeutic effect is also better than [36]. Microspheres are actually a drug release system that can adjust the characteristics of drug absorption and release. Like drug loaded hydrogels, it can extend drug release time, reduce toxic and side effects, and deliver drugs slowly and effectively. However, unlike the ordinary hydrogel, microspheres are spherical particles with a diameter of 20-200 pum, which have larger surface area and can load more controlled release drugs. The microspheres have good dispersion and can flow freely. They can be used as injection scaffolds to repair damaged tissues.

Biodegradable microspheres are widely used in clinic. It can be orally or externally applied. It can also be used as raw materials for drug suppositories [36], porous scaffolds, injections [37], etc. and take effect through direct contact with cells. The clinical application of non biodegradable microspheres is limited to oral treatment.

The preparation materials of biomedical hydrogels can be classified into natural polymers and synthetic polymers. Common natural medical hydrogels are collagen, chitosan and dextran, etc. the synthetic synthetic medical hydrogel materials have polyethylene glycol. Alibolandi, et al. Biodegradable loaded

curcumin nanosutran dextran hydrogel was prepared for the treatment of full-thickness wound healing. Chitosan, collagen sodium alginate composite dressing was prepared by XieH, and its promoting effect on wound healing was studied. Summa M and so on prepared biocompatible sodium alginate / povidone iodine. Membrane enhanced wound healing: Karmoun E.A. et al. Summarized polymer hydrogel membranes for wound dressing applications: PVA/PVP based hydrogel based on PVA hydrogel dressing, Kanca and so on. The effect of PVA/PVP Blend Hydrogel on the tribological properties of articular cartilage was studied. PVA/PVP hybrid hydrogel as cartilage substitute has been extensively studied. The chain between PVA hydroxyl group and PVP carbonyl group is also studied. Hydrogen bonding enhances the stability of polymer networks, which increases the crystallinity and reduces the degradation of PVA hydrogels [24].

Common microsphere preparation materials. SA, glycan anhydride acid extracted from brown algae. Its structure is a linear molecular chain, which is formed by the irregular arrangement of Gulo anhydride units and mannan acid. It is a polymer polyelectrolyte [38]. Low cost, non-toxic and harmless, good biocompatibility and strong hydrophilicity. It is widely used in the field of tissue engineering, pharmaceutical field and drug release system. For example, SA nonwovens prepared by wet spinning method in the field of medical dressings in recent years [39]. SA can absorb the leachate continuously until it is saturated and expanded into gel form. It can also create a humid environment for wound, and has good degradability, easy removal and no residue. The disadvantage is that the viscosity is low, and a secondary dressing is needed to help fix it.

Chitosan as a natural, positively charged polysaccharide, chitosan has good biocompatibility and biodegradability, and is very suitable for the application of biomedical dressings [40-41]. Chitosan is non-toxic and harmless, low irritation, no sensitization, good hemostasis, and even has very excellent antibacterial properties. It can inhibit the growth of fungi, bacteria and other microorganisms, especially harmful to human body Bacteria, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida albicans*, have obvious inhibitory effect.

At present, there is no final conclusion on the mechanism of its bacteriostatic effect. One hypothesis is that the positive charge in chitosan molecule reacts with the negative charge carried by the cell membrane of bacteria and fungi, resulting in the loss of structural components of bacteria and fungi to achieve the bacteriostatic effect. Another hypothesis is that chitosan molecule can form a film on the cell surface of bacteria and fungi to prevent cells from absorbing nutrients so as to achieve the sterilization effect.

Organization engineering. Biomaterials play a very important role in tissue engineering. At the same time, tissue engineering also puts forward problems and points out the development direction for biomaterials. Because the traditional artificial organs (such as artificial kidney and liver) do not have biological functions (metabolism and synthesis), it can only be used as an adjuvant treatment device. The research on tissue-engineered artificial organs with biological functions has attracted extensive attention all over the world. The construction of tissue-engineered artificial organs requires three elements, namely "seed" cells, scaffold materials and cell growth factors. Recently, stem cells have been used as "seeds" because of their strong differentiation ability issue engineering has made some breakthroughs in artificial skin, artificial cartilage [42], artificial nerve, artificial liver and so on.

Degradable drug loaded microspheres. In recent years, the related products of microsphere preparation have great added value. The rich morphology of microsphere is the main reason for their great progress in the medical field. Compared with the traditional single microsphere, special-shaped microsphere can better meet the needs of the contemporary medical industry [42-44]. Because microsphere preparation has good long-term sustained-release effect or targeting effect, it can greatly improve the Patient Health Convenience of using drugs.

Due to some advantages of microparticles in biomedical applications, there are more and more studies on microparticles as drug sustained-release carriers [45]. For example, microspheres can be manufactured to have a uniform size and shape, which can enable microspheres to be delivered to a specific target location. In

addition, the particles have a larger surface area, which can provide sufficient therapeutic coating and increase the degradation rate [46-47]. In the future, drug loaded microspheres will become the focus of drug research and development and have a broad market space. Microsphere is a very small spherical body formed by dispersing or adsorbing model drugs in polymer matrix.

Targeting: through passive distribution, active targeted combination or magnetic attraction, it can improve the local effective concentration of drugs in the body and reduce the drug concentration in other parts, so as to reduce the systemic toxicity and adverse reactions of drugs.

Sustained release and long-term effect: it can reduce the frequency of administration times and reduce the peak valley fluctuation of blood drug concentration. Biodegradable microspheres also have long-term effect.

Embolic: the particles are directly guided through the arterial tube and blocked in the tumor blood vessels. The microspheres can block the tumor feeding and the drugs released by the drug loaded microspheres can inhibit and kill tumor cells and play a dual anti-tumor role.

Others: cover up the bad smell and taste of drugs to reduce local irritation; improve the stability of drugs and reduce gastric irritation; it is conducive to the solid state of liquid drugs and is convenient for storage and transportation. Disadvantages: limited drug loading, complex production process and quality standards, etc.

1.4. Method of preparation of microspheres

There are many methods for preparing microspheres, among which the most commonly used methods are emulsification, coagulation, etc. people will choose different preparation methods according to the actual application needs of preparing microspheres. Now there are many novel methods, as follows: microfluidic method. Microfluidic method is one of the most reliable methods for manufacturing microspheres. So far, only a few technologies have been found that it is essentially

suitable for manufacturing monodisperse microspheres with controlled size. Microfluidic technology has attracted extensive attention because of its ability to prepare high roundness microspheres in batch [48]. Lee et al. Used microfluidic technology to produce biodegradable microspheres with uniform size and achieve hydrophilic activity Continuous release of sexual substances [49].

Microfluidics is a technology that uses this channel to control fluid in micron scale. It uses microchannels in microfluidic devices to operate, process and control micro liquids or samples. This method can be used to prepare drug loaded microspheres, which are usually divided into two steps: (1) emulsion formation (monomer or polymerized liquid emulsification, droplet formation in microfluidic channels); second, emulsion droplet solidification or polymerization.(emulsion droplets are solidified in situ to form microspheres). The curing methods mainly include polymerization, freezing and solvent evaporation [50-51].

Coaxial electrospray method. Electrospray technology is also one of the mature methods for preparing microspheres. Electrospray coating, also known as electrostatic spraying, is used to prepare polymer microspheres and composite microspheres by electrostatic force on polymer solution under high pressure. In the field of electrical spraying, electrical spraying is the most commonly used coaxial method.

Coaxial device 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. In the process of preparing microspheres, charged droplets deform in the electric field and finally form a cone. This is called Taylor cone. The shape of Taylor cone is related to the surface charge density of fluid and the shape of nozzle Shape and stability directly determine the morphology and efficiency of particle formation. Therefore, the study of Taylor cone has always been one of the focuses of coaxial electrospray method.

Coaxial electric spray is mainly used for the preparation of core shell microspheres [52]. Especially when preparing microspheres loaded with drugs,

coaxial electrospray technology can effectively protect the biological activity of drugs because the drugs are wrapped in the nuclear layer. In addition, because of the high encapsulation efficiency of drugs, they can effectively reduce the sudden release of drugs, so they are especially suitable for various drugs, proteins and substances. Bioactive packaging.

The emulsion method is the most commonly used method for preparing natural polymer microspheres. After many years of development, the emulsion method has been very mature. The principle of emulsion method is that in the presence of emulsifiers, two kinds of non solvent solvents are used to form a uniform emulsion. Solid phase can be separated from emulsion by some physical methods. In the process of aggregation, they are wrapped in a small spherical droplet. Therefore, they will form spherical particles and avoid the aggregation of each particle [53].

According to different internal curing methods, emulsion method can be divided into emulsion solvent evaporation method, emulsion condensation method and emulsion crosslinking method. Solvent evaporation method, also known as liquid drying method, means that the carrier material can be solidified into balls by simply removing solvent by evaporation method. For gelatin, agarose and other materials, they can only be dissolved in hot water, but not soluble in cold water, so they can pass milk. The solidified microspheres were obtained by melting and cooling.

The advantage of the emulsion method is that it is simple and low cost. But there are some shortcomings that cannot be overlooked. First of all, the oil phase is unavoidable in the process of preparing microspheres, therefore, it will destroy the biocompatibility of microspheres. In the subsequent use of microspheres, it may cause harm to the environment. In addition, the difficulty of adjusting the morphology of microspheres caused by the heteromorphism of emulsion polymerization and Complexity, which will also become the focus of future research.

The factors affecting the particle size of microspheres include drug concentration, surfactant, dispersion medium, preparation method, stirring speed, emulsification time, temperature and so on.

Quality evaluation. Inspection of appearance and morphology: good microsphere properties should be round spherical entity, full shape, uniform particle size, and no adhesion between microsphere. Various devices can be used to monitor its appearance and morphology.

Determination of particle size and particle size distribution: this evaluation is the key factor affecting the release behavior of microspheres. The distribution of particle size can be expressed by particle size distribution diagram, polydispersity index (PDI) and span.

Determination of in vitro release degree and sudden release rate: sudden release effect (in the initial stage of drug release, the drug adsorbed on the particle surface of drug loaded microspheres can be rapidly released through diffusion in a short time) may cause the concentration of drug in human body to rise rapidly in a short time, and shorten the time for drug to exert its efficacy. Therefore, this factor is the key problem limiting the wide application of microspheres. Therefore, in the process of quality control, we should focus on the data of sudden release rate.

Determination of drug loading and entrapment efficiency: these two data are important indicators of drug content in microsphere preparation, and the inter batch stability of drug loading is also an important sign of process maturity.

Entrapment efficiency (%)= (Drug content in microspheres/The total amount of medicine added) *100%

Drug loading (%)=(Drug content in microspheres/The total weight of the microsphere) *100%

Other evaluations: inspection of relevant substances and magazines, determination of potential, detection of carrier excipients, detection of volatile components, bacterial endotoxin and sterility, etc.

Simvastatin is a white non hygroscopic crystalline powder, very slightly soluble in water and easily soluble in chloroform, methanol and ethanol solutions. It needs to be sealed, protected from light and stored below 30 ° C. It is mainly used for hyperlipidemia and coronary heart disease.

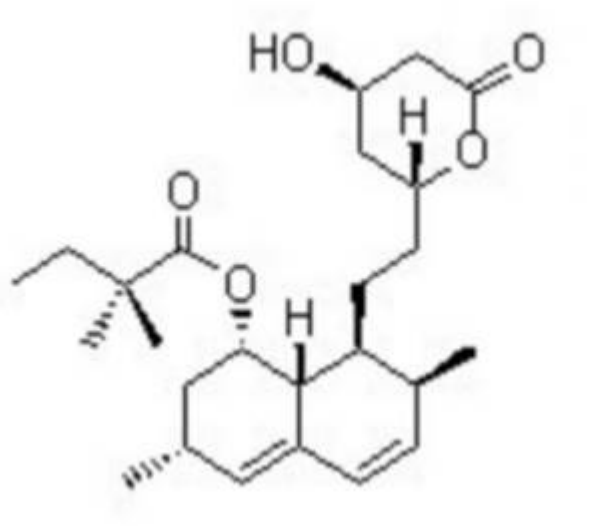

Figure 1.1 - Structure of Simvastatin

Polylactic acid glycolic acid copolymer is a degradable functional polymer organic compound, which is randomly polymerized by two monomers - lactic acid and glycolic acid. It has good biocompatibility, non toxicity, good encapsulation and film-forming properties [54]. It is widely used in the fields of pharmacy, medical engineering materials and modern industry. In the United States, PLGA has passed FDA certification and is officially included in the USP as a pharmaceutical excipient.

Different types of PLGA can be prepared with different monomer ratios. For example, PLGA 75:25 indicates that the polymer is composed of 75% lactic acid and 25% glycolic acid. All PLGA are amorphous and their glass transition temperature is between 40-60 ° C. Pure lactic acid or glycolic acid polymers are difficult to dissolve. The difference is that PLGA shows a wider solubility. It can be dissolved in more and more common solvents, such as chlorinated solvents, tetrahydrofuran, acetone or ethyl acetate.

The destruction of ester bond will lead to the degradation of PLGA. The degree of degradation varies with the monomer ratio. The greater the proportion of

glycolide, the easier it is to degrade. There are also special cases. When the ratio of two monomers is 50:50, the degradation speed will be faster, which takes almost two months.

The degradation products of PLGA are lactic acid and glycolic acid, which are also by-products of human metabolic pathway. Therefore, when it is used in medicine and biomaterials, it will not have toxic and side effects. Of course, lactose deficiency is excluded. By adjusting the monomer ratio to change the degradation time of PLGA, this method has been widely used in biomedical fields, such as skin transplantation, wound suture [55], in vivo implantation [56], micro nanoparticles [57], etc. The commercially available Lupron depot for the treatment of advanced prostate cancer uses PLGA as a drug carrier.

PLGA has good biocompatibility and biodegradability, and the degradation rate is controllable. It is widely used in the field of Biomedical Engineering [58]. It has been made into artificial catheter, drug sustained-release carrier and tissue engineering scaffold material [59]. The preparation and application of various PLGA drug microspheres are often reported.

Conclusions to section 1

Biodegradable materials have unlimited potential in the field of medicine. As a carrier material, it can carry drugs, bioactive substances and other substances, and control the release of the substances in the body. At this point, it has become the focus of many researchers. For example, it can improve the bioavailability of drugs, have certain targeting and sustained-release effects, reduce the toxic and side effects of drugs or other substances, and even reduce the rejection of tissues and cells in vivo. These studies provide a strong guarantee for the search and development of new drug formulations.

In recent years, people have also developed various methods to prepare nano microspheres. For example, allemann and his collaborators developed salting out method and emulsion solvent diffusion technology. Salting out method uses the

principle of reversible expansion of polymer in solvent to precipitate polylactic acid and drugs to form nanoparticles. Drug loaded polylactic acid nanoparticles can be obtained by centrifugation and drying. The emulsion solvent diffusion technology is similar to the emulsion phase separation method. It is an aqueous solution of the mixture of drugs and polylactic acid dissolved in the water soluble part of the organic solvent and mixed with a prepared stabilizer in the water to form O/W emulsion. Dilute the emulsion with a large amount of pure water, so that the organic solvent can be diffused into the aqueous phase, separated and freeze-dried, and then the drug loaded polylactic acid nanoparticles can be obtained. It is also reported that nano particles can be prepared by supercritical fluid technology. Salting out / emulsification solvent diffusion technology and supercritical fluid technology are environmentally friendly. The prepared drug loaded particles have high purity, no solvent residue, little toxic and side effects on human body and high efficacy.

In this paper, PLGA drug loaded microspheres were prepared by emulsification, and the drug release behavior of drug loaded microspheres was studied. The material PLGA used in the preparation of microspheres has good biocompatibility and biodegradability, and the degradation products are harmless to human health. It is hoped that through the research of this subject, it is expected to establish a preparation technology of drug carrier integrating biocompatibility, degradability and controlled release, so as to make its practical application in the field of pharmaceutical preparations possible.

Section 2. Experimental preparation of microspheres loaded with simvastatin and determination of their properties

2.1. Experimental materials

Characteristics of drugs and reagents are presented in Table 2.1

Table 2.1 main drugs or reagents

Name of drug and	Manufacturer	Specifications

reagent		
PVA	Ti xi'ai (Shanghai) Huacheng Industrial Development Co., Ltd	Medium viscosity
DCM（AR）	Tianjin fufu Fine Chemical Co., Ltd	CH2Cl2 ≧99.5%
Simvastatin	Tianjin xiensi Biochemical Technology Co., Ltd Suzhou fulaizi Testing Technology Co., Ltd	≧98%
NaOH（AR）	Xilong Chemical Co., Ltd	NaOH≧96%
Sodium dodecyl sulfate (AR)	Tianjin siguangcheng Chemical Reagent Co., Ltd	
Sodium dihydrogen phosphate (AR)	Sinopharm Chemical Reagent Co., Ltd	≧99.0%
phosphate mixture	Shanghai Leici Chuangyi Instrument Co., Ltd	（pH=6.86，25℃）
Glycolic acid	DuPont Co., Ltd	
Zinc acetate dihydrate	Tianjin kemio Chemical Reagent Co., Ltd	
Stannous octanoate	Sigma Aldrich Chemical Reagent Co., Ltd	
Dodecanol	Shanghai McLean Biochemical Technology Co., Ltd	

lactic acid	Henan Jindan lactic acid Technology Co., Ltd

Note: all chemicals are of analytical grade and can be used without further purification.

The characteristics of the main instruments are presented in the Table 2.2

Table 2.2 main instruments involved in the experiment and relevant information

Name of experimental instrument	model	Manufacturer
Ultrasonic cleaner	Kq5200 type	Kunshan Ultrasonic Instrument Co., Ltd
Intelligent magnetic stirrer	ZNCL-BS140*140	Gongyi Yuhua Instrument Co., Ltd
Electronic balance	TE124S	Saidoris scientific instrument (Beijing) Co., Ltd
Electric blast drying oven	101type	Beijing Yongguangming Medical Instrument Co., Ltd
Glass instrument airflow drying oven		Henan Yuhua Instrument Co., Ltd
PH meter	PHS-3E	Shanghai Leici Chuangyi Instrument Co., Ltd
Ultraviolet visible spectrophotometer	UV-6000H	Shanghai Yuanxi Instrument Co., Ltd

Booster electric agitator	Jb50-d type	Made by Shanghai specimen model factory
Electric centrifuge	800type	Jiangsu Jintan Jiangnan Instrument Factory
Four purpose tester	Sy-3d type	Shanghai Huanghai drug inspection instrument Co., Ltd
Six tube disintegrator	LB-812A type	Shanghai Huanghai drug inspection instrument Co., Ltd
scanning electron microscope	BA210	Mcdio Industrial Group Co., Ltd
Nano particle size meter	Winner802	Jinan Weina particle instrument Co., Ltd

2.2. Stages of obtaining microspheres SIM-PLGA

The synthesis of glycolide is mainly divided into two steps: the first step is the multistage esterification of glycolic acid at 80 ~ 170 ℃ and under reduced pressure to dehydrate and polycondensate into oligomers. The second step is the thermal decomposition of oligomers at 200 ~ 280 ℃ and under high vacuum to form glycolide. Operation steps: (1) dehydration and condensation of glycolic acid, 1000ml of glycolic acid, 20g of zinc acetate and magnon are successively added to 2000ml flask by vacuum fractionation device, and the heating intensity is controlled under the condition of vacuum of about 40kpa to make the water generated by the reaction slowly flow out of the mother liquor, so as to let the esterification and dehydration of glycolic acid continue the reaction. Gradually raise the temperature to 140 ℃ within 1.0-1.5h.(2) Further dehydration condensation

Use 45 ° elbow, adjust the vacuum degree to the maximum, and gradually raise the temperature to 170 ℃ within 1.0h.The more sufficient dehydration in this

step, the higher the degree of polymerization of the product, and the less likely it is to splash in the next cracking reaction.(3) Oligomer cleavage into rings

First install the air condensing pipe, receiving pipe and receiving flask, check the vacuum tightness of the system, adjust the vacuum degree of the system to the maximum (greater than 95kpa), quickly raise the temperature to 170 ℃, and then raise the temperature evenly. The light yellow products condense and precipitate on the wall of the condensing pipe, and strictly prevent the mother liquor from splashing into the distillation head to pollute the products. When the temperature rises to 260 ℃, stop the reaction.

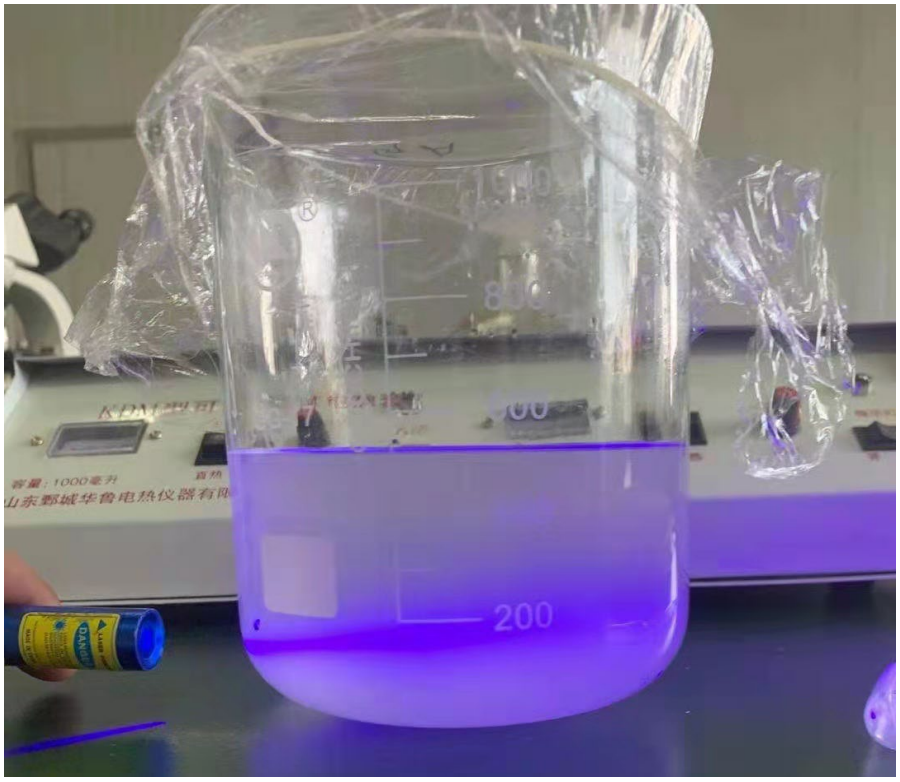

Figure 2.1- Ethyl lactide solution

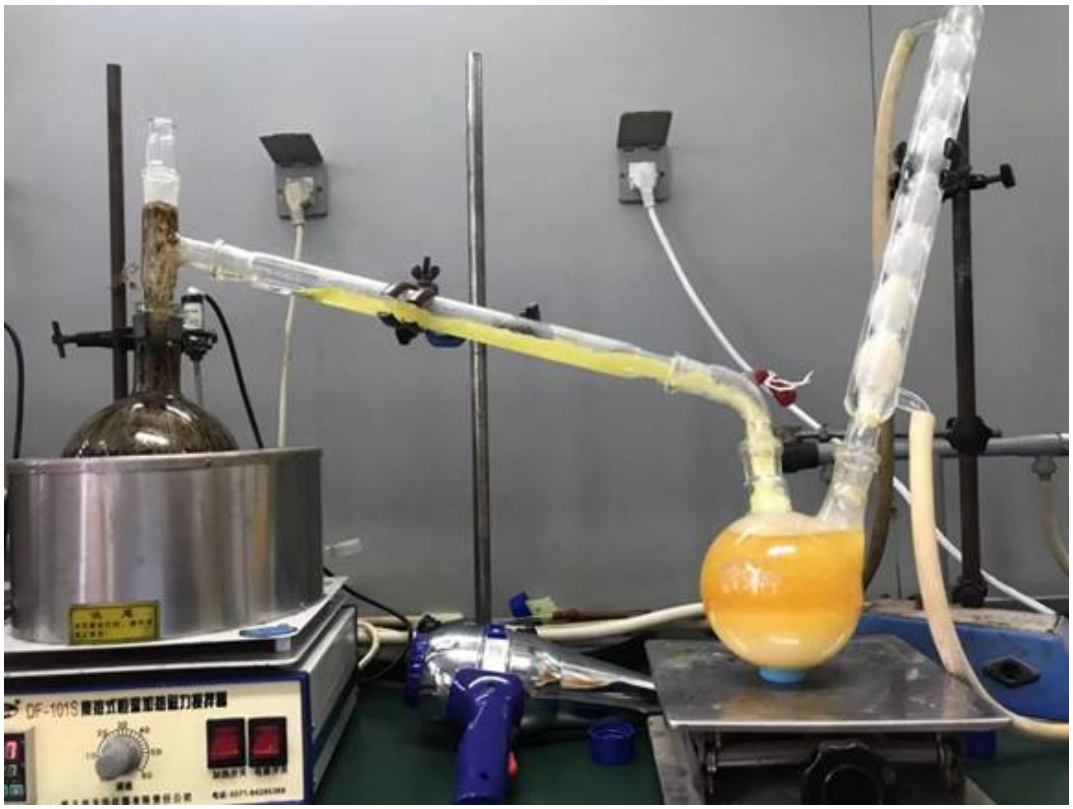

Figure 2.2 - Oligomer cleavage into rings

The evaporated light yellow crystal product is filtered with anhydrous ethanol Buchner funnel, recrystallized with anhydrous ethanol twice, and then precipitated with 300-500 ethyl acetate for recrystallization four times according to the amount of product. Finally, filter and weigh.

Fig. 2.3 - Buchner funnel suction filtration

Fig. 2.4 - Third and fourth recrystallization products

Preparation of PLGA. (1) Monomer pretreatment:

Take out the frozen high-quality L-lactide and glycolide one day in advance and put them at room temperature. Dodecanol will become solid below 25 ℃, so it needs to be placed in a 30 ℃ blast drying oven for constant temperature one day in advance. The next day, after fully grinding with a glass mortar in the super clean table, it is added into the flask. The rotary evaporator is vacuum dehydrated at 35 ℃ for no less than 2H.(at this time, the indoor temperature control is less than 25 ℃, the relative humidity is less than 30%, and there is no obvious dust floating in the room).The melting point of lactide was determined by melting point tester.

Precautions: wear masks and dust-free gloves throughout the process to reduce the contact time between lactide and air indoors. If possible, it is best to operate in the glove box. Lactide cannot contact with metal vessels and keep dry indoors.

Figure 2.5 - Crude lactide

Figure 2.6 - Melting point of lactide measured by melting point tester

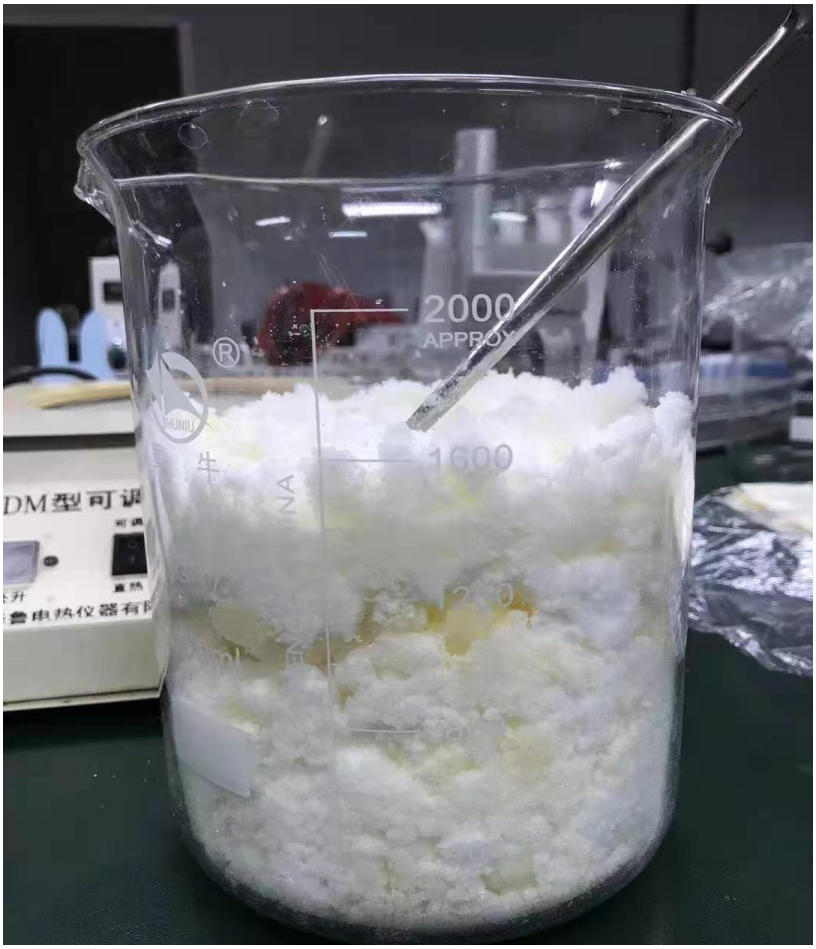

Figure 2.7 - Recrystallized purified lactide

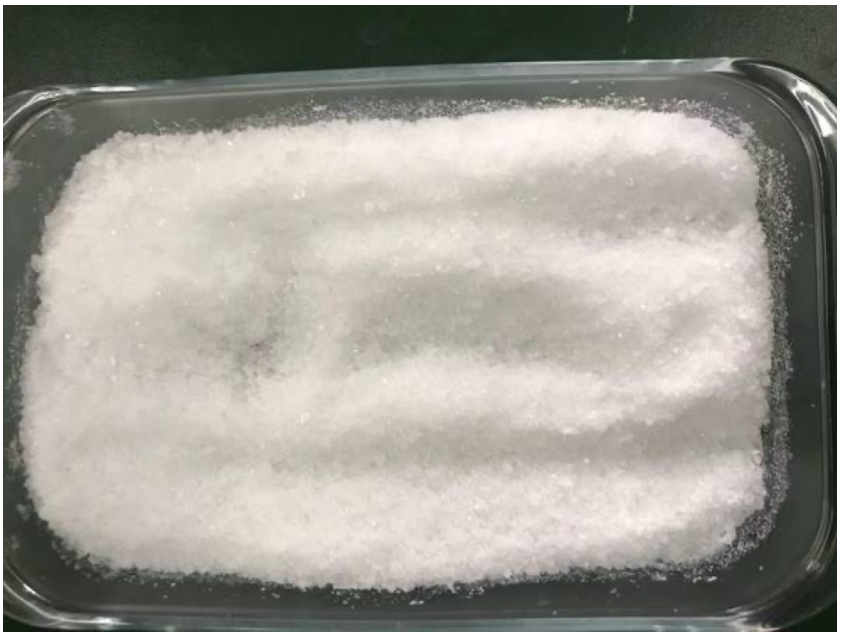

Figure 2.5 - Lactide

(2) Vacuum sealing pipe: Weigh accurately with a balance. Before each operation of the balance, clean the test bench and weighing bin, keep the balance horizontal, do not press the platform where the balance is located, close the doors, windows and air conditioning, and control the indoor temperature at 25 ℃ as far as possible. The balance shall be started up at least 0.5h in advance before use. The balance shall be corrected twice before each use, and the error can be used only when the error is within the standard range. Wear a mask when using the balance to prevent exhalation from affecting the measurement results.

Pretreatment of reaction kettle and glassware: all glassware shall be deeply cleaned with brush and detergent. Ultrasonic cleaner shall be used for 30min and tap water for 10min. After there is no stain on the surface, it shall be washed twice with purified water and twice with ethanol. It shall be dried at 105 ℃ for 3H in blast drying oven and adjusted to 40 ℃ for the next day.

On the second day, weigh an appropriate amount of 23.65 g of L-lactide, 6.35 g of glycolide, 0.0105 g of stannous octanoate and 0.3 g of dodecanol (if the catalyst is not required, the addition amount of dodecanol shall be 3.5% 00 of the weight of lactide, depending on the target molecular weight). At this time, try to reduce the contact time of catalyst and initiator with air and operate quickly. The lactide and glycolide after rotary evaporation dehydration and the beaker containing catalyst initiator to be added, the glass rod is evenly mixed and transferred to the vacuum reactor for many times. After five times of high-purity argon replacement, the vacuum pipe is sealed (5 * 5min + 1 * 30min vacuum pumping time, vacuum pump limit vacuum degree 6 * 10-2 PA).

(3) Polymerization: the sealed reactor is placed in a 160 ℃ oil bath to ensure the magneton rotation reaction for 24D.

Fig. 2.6 - 160 ℃ oil bath reaction

(4) Product purification: after the reaction is completed, take out the reaction bottle, open the reactor after placing it at room temperature, take out the product, place the product in a 2L beaker containing dichloromethane twice the product, magnetic stirring at room temperature for dissolution overnight, suction filtration with a sand core funnel to remove the insoluble matter, slowly drop the polylactic acid solution in 10 times absolute ethanol with a constant pressure dropping funnel under the condition of mechanical stirring, and suction filtration with a Buchner funnel quantitative filter paper, The product was extracted with absolute ethanol for 30min, and then placed in a Teflon tray. The product was dried in an electric blast drying oven at 30 ℃ for 48h, a vacuum drying oven at 40 ℃ for 24h, and vacuum sealed at minus 20 ℃.

Figure 2.7 - PLGA after drying

SIM-PLGA Preparation of drug loaded microspheres, by analyzing the physical and chemical properties of simvastatin, SIM-PLA drug loaded microspheres are prepared by emulsification method. The basic formulation and process are as follows.

Basic prescription:

Sim (simvastatin) 0.1g, 0.3g, 0.5g (model drug)

PLGA (polylactic acid glycolic acid copolymer) 0.5g (carrier material)

1% PVA (polyvinyl alcohol) solution 20ml (aqueous phase, emulsifier)

Dichloromethane 5ml (oil phase)

Process:

(1) Preparation of aqueous phase

Accurately weigh 10 g of polyvinyl alcohol (PVA), pour it into a 1000 ml beaker, add magnet, stir it at 50 ℃ until it is dissolved, and prepare 1%.Polyvinyl alcohol solution

(2) Preparation of oil phase

Accurately weigh 0.5g of polylactic acid glycolic acid copolymer (PLGA) and 0.1g, 0.3g and 0.5g of simvastatin (SIM) drugs with different mass respectively, put them into a beaker containing 20ml DCM, seal them with fresh-keeping film, weigh them, stir them at room temperature for 24h to fully dissolve them, weigh them regularly and make up the evaporated dichloromethane.

(3) Preparation of drug loaded microspheres by emulsion solvent evaporation method

The 20mL water phase is accurately measured and placed in 50mL (to prevent subsequent emulsification, excessive foaming and overflow, as far as possible to pick up a bigger beaker) flask. Place the prepared oil phase in a constant pressure dropping funnel. In the ultrasonic cleaning machine, add proper amount of ice and water to maintain the water temperature at about 0-5 degrees Celsius. In the ultrasonic cleaning machine, add PLGA and SIM of DCM solution (oil phase) to the PVA containing water solution (water phase), add a strong stirring speed of 30 min, and make it into a super fine and uniform emulsion. After the emulsion was formed, the emulsion was removed, stirring at room temperature for 12 h, and DCM was evaporated. After the mixing is stopped, the emulsion is removed, and then the supernatant is poured out. The solid obtained is washed with distilled water, then centrifuged and separated. Finally, the solid obtained by centrifugation is pre frozen and then dried in a vacuum drying oven until the weight of solid powder does not increase.

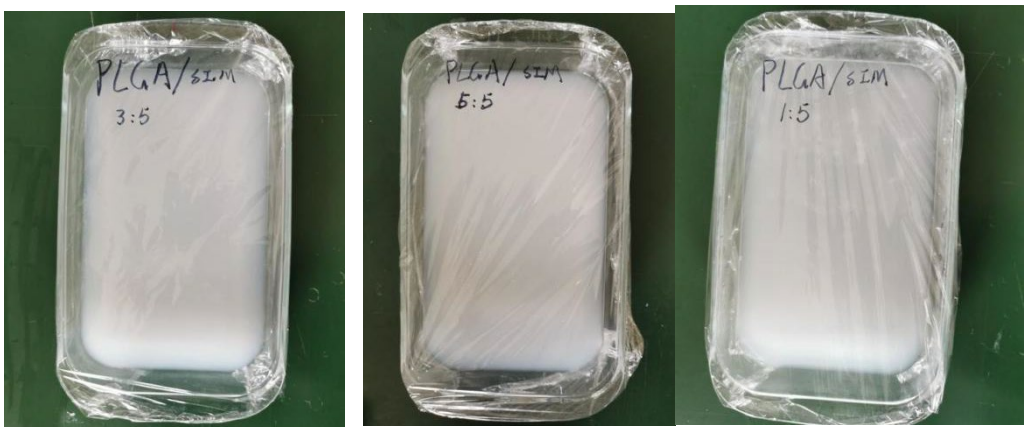

Fig. 2.8 - Emulsion morphology of various proportions

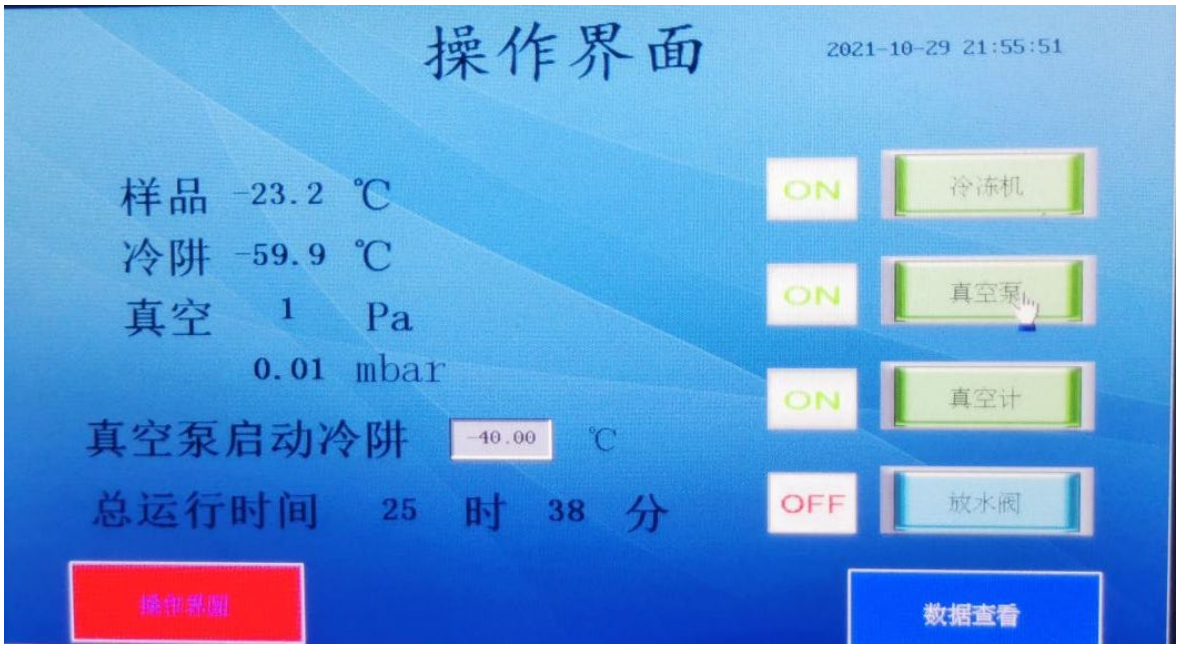

Fig. 2.9 - Operation interface of freeze dryer

Determination of simvastatin content included the following steps**:**

(1) Preparation of 0.01 mol / ml sodium dihydrogen phosphate buffer solution

Precise weighing Place 5.00 mg sodium dodecyl sulfate (surfactant) and 1.3609 g sodium dihydrogen phosphate in a beaker, add water to dissolve them, then transfer them to a 1000 ml volumetric flask, dilute them to the scale with water, and shake the volumetric flask to make them uniform. Then transfer to a 2000 ml beaker to obtain 1000 ml of sodium dihydrogen phosphate buffer solution (0.01 mol / ml).Finally, adjust the pH value of the solution to 7.0 with NaOH solution (50%).

(2) Determination of detection wavelength

Accurately weigh 5.00 mg of SIM model drug, put it into a 100 ml volumetric flask, dissolve it with sodium dihydrogen phosphate buffer solution (0.01 mol / ml), dilute it to the scale, shake the volumetric flask to make it uniform, and use it as mother liquor for standby (50%)μg/mL. Use a pipette to take out 48 ml

and transfer it to a 50 ml volumetric flask, dilute it to the scale with sodium dihydrogen phosphate buffer solution, shake the volumetric flask to make it uniform, and the concentration is 48μG / ml standard solution. Sodium dihydrogen phosphate buffer solution was used as the blank control solution, detected by ultraviolet spectrophotometer, and the standard solution was scanned at the wavelength of 200-800 nm to determine the maximum wavelength of simvastatin.

Accurately weigh a small amount of polylactic acid and dissolve it in sodium dihydrogen phosphate buffer solution. After several hours of treatment by ultrasonic cleaning machine, polylactic acid still does not dissolve. Considering that polylactic acid does not interfere with the content determination of simvastatin model drug.

(3) Preparation of standard curve

Accurately measure 2, 4, 6, 12, 18, 24 and 48 ml of standard solution respectively, transfer them to a 50 ml volumetric flask, fix the volume to the scale with sodium dihydrogen phosphate buffer solution (0.01 mol / ml), shake the volumetric flask to make it uniform, and prepare the concentrations of 2, 4, 6, 12, 18, 24 and 48 respectively μG / ml series solution. Use sodium dihydrogen phosphate buffer solution as the blank control solution, detect it with ultraviolet spectrophotometer, select the wavelength of 238nm, scan the series of solutions and determine the absorbance (a).The concentration of simvastatin model drug (C,μG / ml) is the abscissa (x) and absorbance (a) is the ordinate (y). Linear regression of absorbance to concentration is carried out to obtain the standard curve equation of y = 0.0685x + 0.0631 r = 0.9986.

2.3. Characteristics of the obtained microspheres

The surface morphology, microstructure and particle size of PLGA loaded simvastatin microspheres were characterized by scanning electron microscope and nano particle size analyzer.

Determination of drug release, entrapment efficiency and drug loading of microspheres in vitro. Prepare three dissolution cups of the same size, adjust the stirring paddle to the same height (10 mm from the bottom of the dissolution cup) and fix it, pour 200 ml sodium dihydrogen phosphate buffer solution as the dissolution medium, cover the dissolution cup, insert the sampling needle to fix it at the same height, adjust the water bath temperature in the jacket to 37.5 ℃, and set the speed of the dissolution instrument to 100 R / min, Start stirring and heating.

Accurately weigh 100 mg of simvastatin loaded microspheres containing different masses. When the temperature of the dissolution instrument reaches the set temperature, add the drug loaded microspheres (containing 0.1g, 0.3g and 0.5g SIM drugs of different mass) into the dissolution cup and start timing. Samples were taken after 15 min, 30 min, 1, 2, 4, 8 and 14 h respectively. Take out 5 ml of dissolution solution with a disposable syringe each time and put it into a centrifuge tube. Supplement 5ml of sodium dihydrogen phosphate buffer solution, centrifuge and take the supernatant. The absorbance was measured with an ultraviolet spectrophotometer at the wavelength of 238 nm.

2.4. Experimental Results and Discussion

Oil in water (O / W) emulsion was prepared by mechanical ultrasonic emulsification with DCM solution containing PLGA as oil phase and PVA as emulsifier. Under the microscope, it can be seen that the emulsion droplets will not break and fuse within 15 min, and have good thermodynamic stability. Due to low boiling point and high saturated vapor pressure of dichloromethane, rapid evaporation will lead to rapid precipitation of PLGA, which is not conducive to the preparation of microspheres with uniform particle size. Therefore, in the experiment, low temperature is used to play slowly to overcome the influence of rapid evaporation of solvent on particles. Simvastatin is easy to dissolve in oil phase and difficult to dissolve in water phase, which is conducive to improve the drug entrapment efficiency of drug loaded particles.

Figure 3.1 - Appearance of drug loaded microspheres

The suspension of PLGA loaded SIM drug microspheres was evenly dispersed and milky white. With the increase of SIM content, the suspension loaded with 0.5 g SIM microspheres showed light yellow. The appearance of the microspheres obtained after vacuum drying is shown in Figure 3.1. The microspheres containing SIM are in the shape of light yellow loose powder, and the color is slightly darker with the increase of SIM content.

The yield of drug loaded microspheres is shown in Table 3.1. With the increase of drug loading, the yield increases, showing that simvastatin has better hydrophobicity than PLGA. The maximum yield was obtained when the material ratio of drug to PLGA was 3:5.

Table 3.1 - Yield of PLA loaded SIM microspheres

Serial number	Simvastatin / g	Polylactic acid / g	Mass of prepared microspheres / g	Yield /%
1	0	0.5	0.3783	75.67
2	0.1	0.5	0.4224	70.41
3	0.3	0.5	0.7145	89.32
4	0.5	0.5	0.8749	87.49

The morphology of the prepared drug loaded microspheres was observed by electron microscope, as shown in Figure 3.2. The particle size of PLGA microspheres without drug was about 100μm. There are depressions on the surface of some particles.

With the addition of drugs, the particle size of microspheres increases, and when the amount of drugs is high, the sphericity of particles becomes worse and the particle size distribution becomes wider. When the dosage of the drug was 0.1 g (sample 2), it showed an obvious core-shell structure, which may be due to the phase separation between the drug and PLGA in the particles, and the drugs with better hydrophobicity existed in the core of the microspheres; With the increase of drug addition, the core-shell structure disappears, and the drug crystals are physically embedded in the PLGA matrix. For example, when the drug addition is 0.5 g (sample 4), a large number of drug crystals can be obviously observed on the surface of the microspheres.

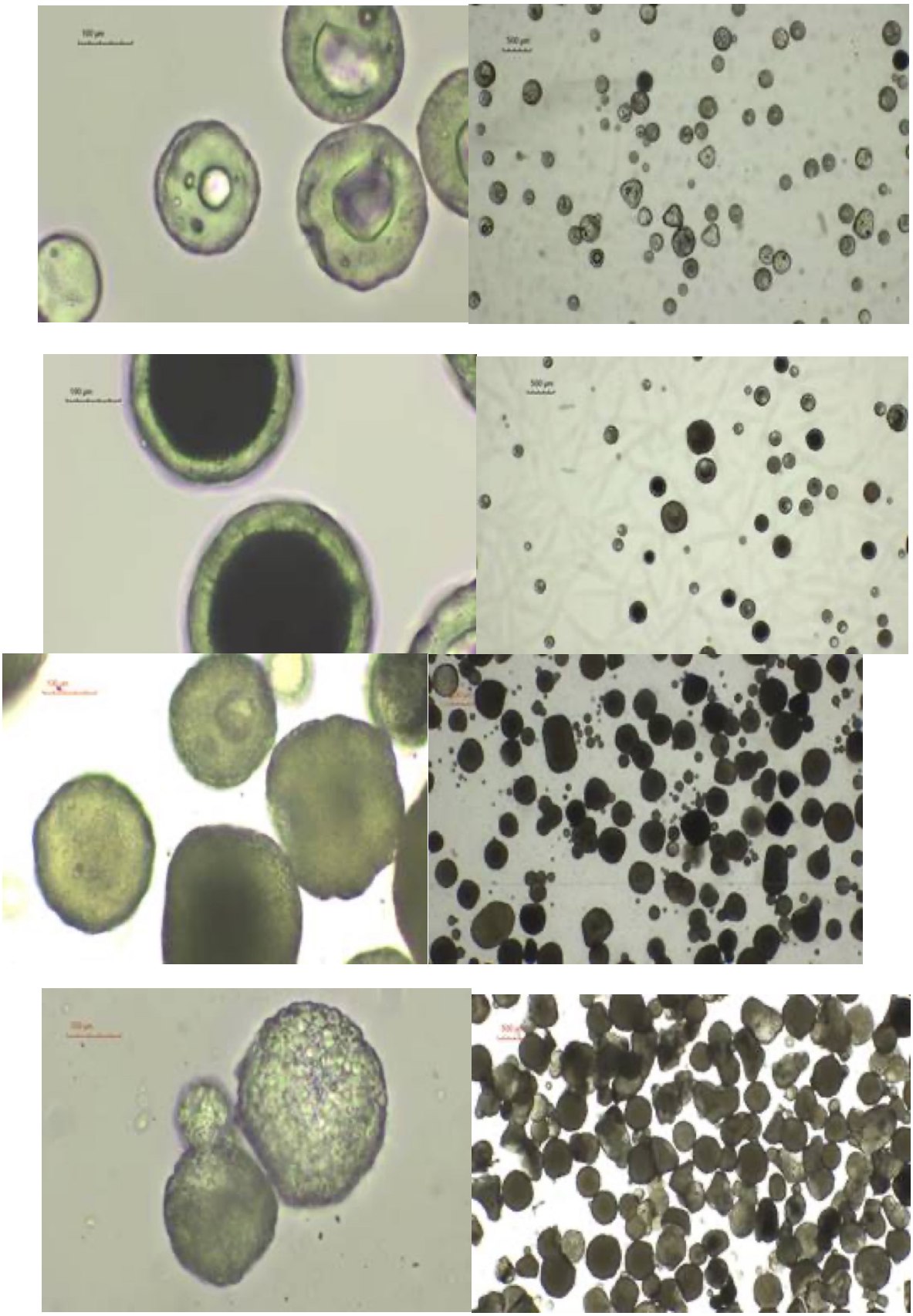

Fig. 3.2 - Electron microscopic observation of drug loaded microspheres. The amount of drug added in the preparation process is 0 g (1 row);1 g (2 rows);3 G (3 rows);5 g (4 rows)

7.26ppm is the characteristic peak of deuterated chloroform solvent; Methyl and - CH groups belonging to lactide repeat units at 1.56 ppm and 5.17 ppm respectively; 4.81ppm is the - CH2 - proton peak of glycolide repeat unit; The methylene proton peaks of initiator dodecanol are at 1.26ppm and 3.71ppm. The peak areas at 5.17ppm and 4.81ppm are 3.12 and 1.22 respectively, so it can be calculated that the molar ratio of lactide and glycolide is about 72 / 28, which is basically consistent with the feed ratio.

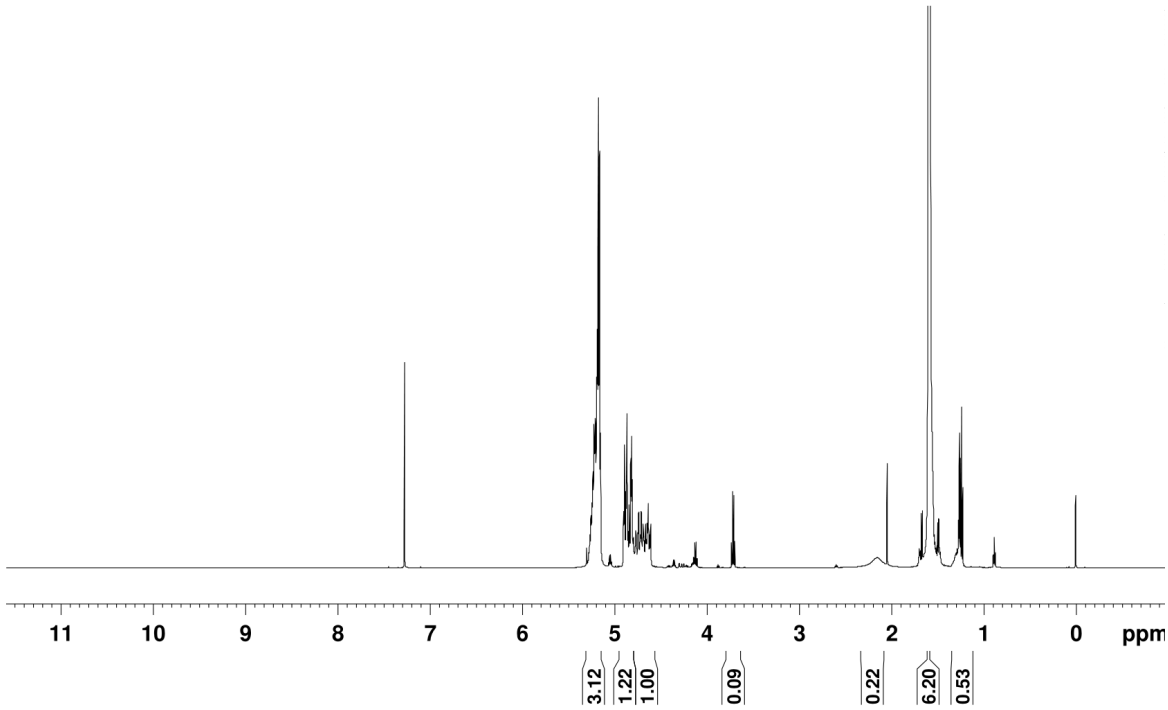

Figure 3.3 - Nuclear magnetic diagram of PLGA

The molecular weight of PLGA was determined by GPC. The weight average molecular weight was 15285 and the polydispersity index (MW / Mn) was 2.07.

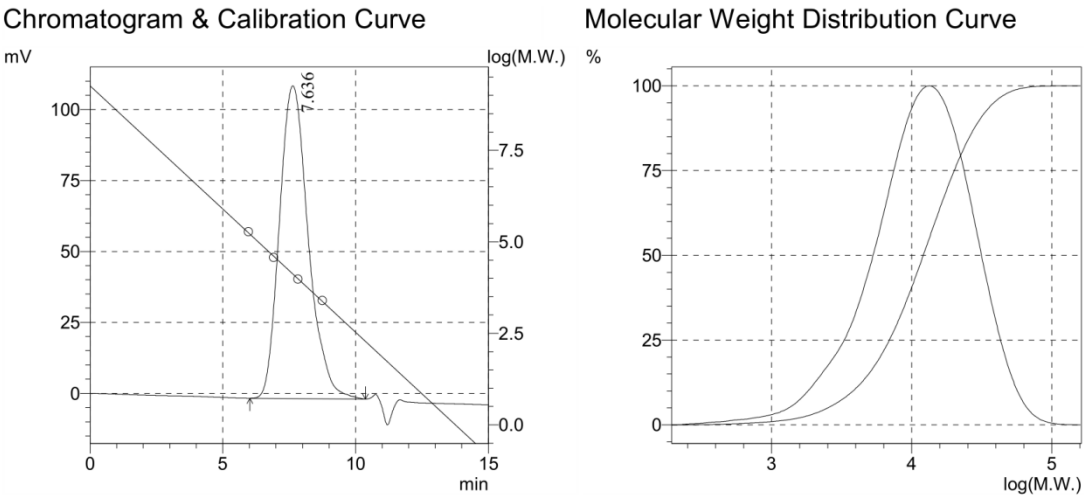

Figure 3.4 - GPC determination of PLGA

Determination of detection wavelength. (1) The UV scanning spectra of SIM drug solution and PLGA material solution are as follows. It can be seen from figure 3.3 that the maximum absorption peak of SIM is at 238nm wavelength, while the PLGA material solution has no absorption peak at 238nm wavelength, which does not interfere with the determination of simvastatin. Therefore, 238nm is selected as the detection wavelength.

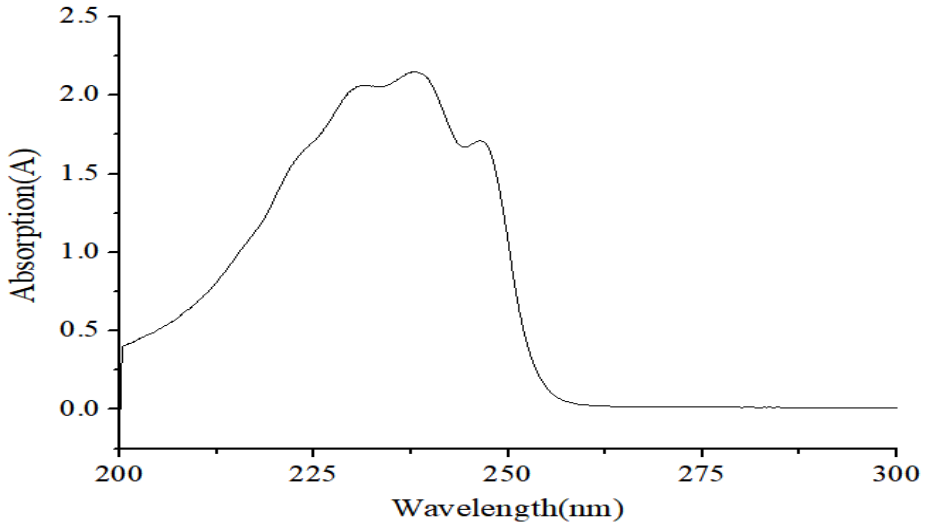

Fig. 3.3 - UV scanning spectrum of Simvastatin

（2）Establishment of standard curve

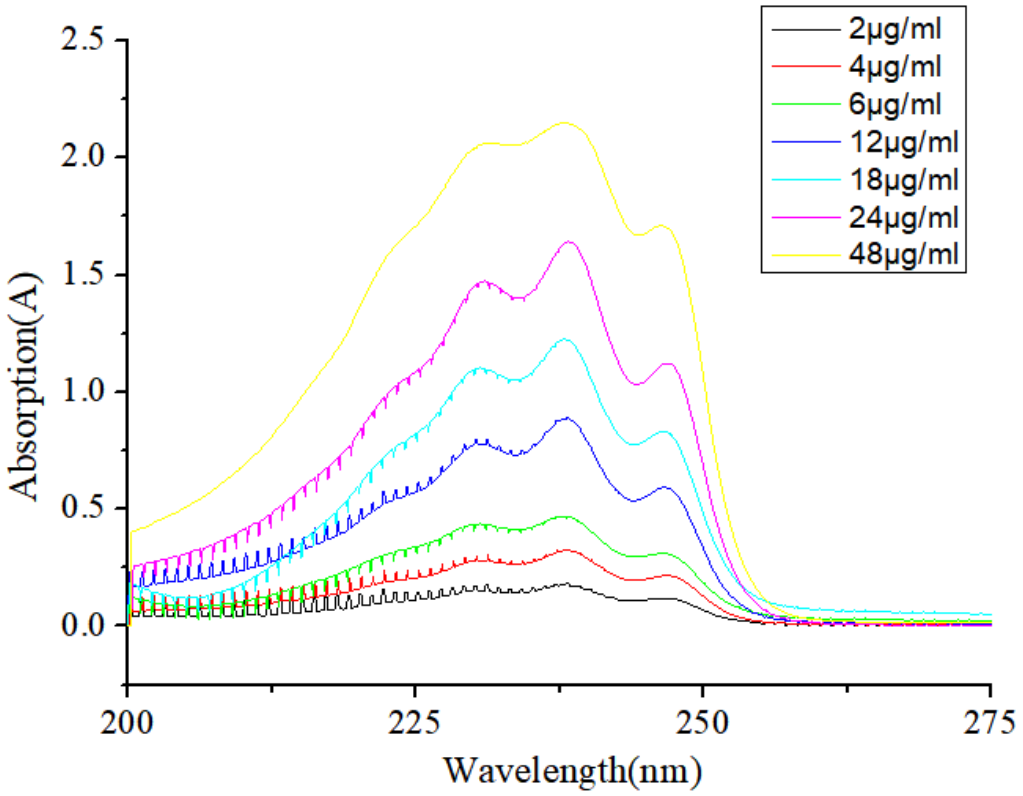

Fig. 3.4 - UV scanning spectra of simvastatin with different concentrations

Table 3.2 - Absorbance of different concentrations of simvastatin at 238 nm wavelength

Concentration C（μg/mL）				2	8	4	8	
Absorbance a (ABS)	.1747	.3225	.47	.8871	.2258	.6391	.1474	

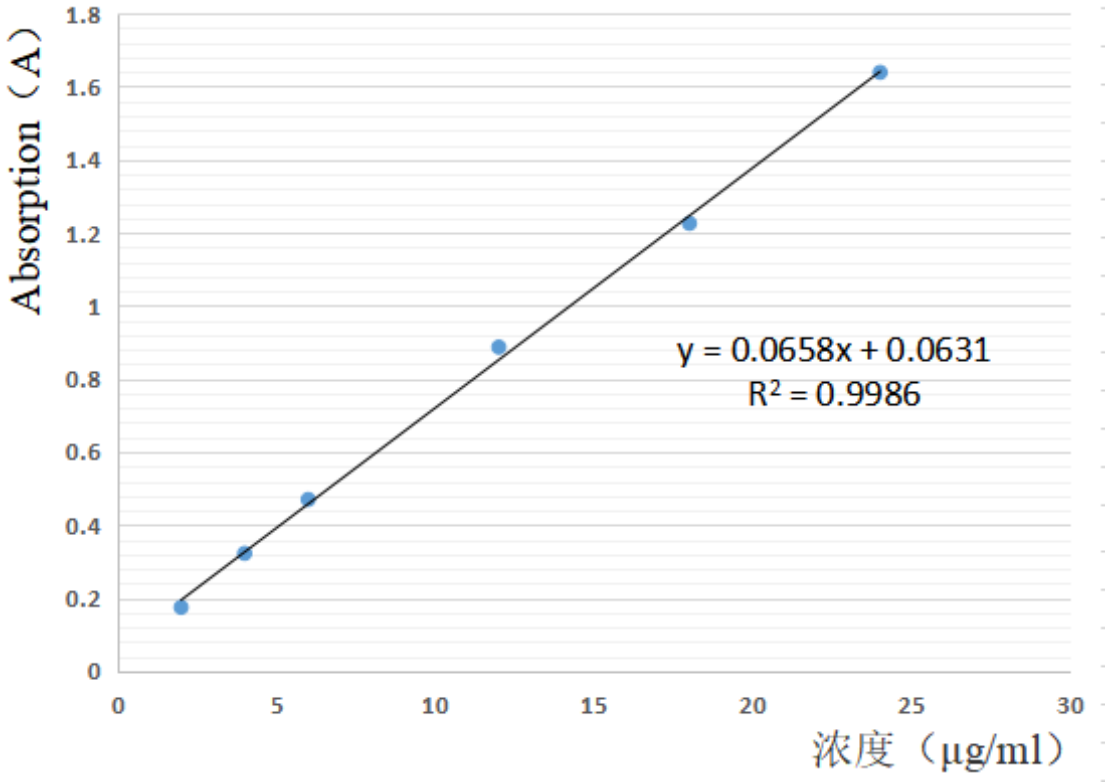

Figure 3.5 - Standard curve of simvastatin content

The concentration C was measured by absorbance a (absorption)（μG / ml) to obtain the standard curve equation of y = 0.0685x + 0.0631 R2 = 0.9986.The results showed that SIM drugs were in 2-24μWithin the concentration range of g / ml, there is a good linear relationship between absorbance and concentration.

In vitro drug release properties of microspheres. Simvastatin is insoluble in water, so phosphate buffer containing 0.5% sodium dodecyl sulfate is used as dissolution medium. As a surfactant, sodium dodecyl sulfate is positively adsorbed at the interface of microspheres and plays the role of wetting agent. On the other hand, as a drug solubilizer, it increases the solubility of drugs in dissolution medium. The volume of dissolution medium is 900 ml, which makes the dissolution test meet the conditions of leakage tank. The drug release properties of drug loaded microspheres are shown in table 3.4.It can be seen that in the first 30 min, the drug of the microspheres with low drug loading (sample 2) was not released, showing the limiting effect of the shell (as shown in Fig. 3.1) on the drug diffusion; High drug

loading microspheres (samples 3 and 4) have sudden release effect, which is consistent with the existence of a large number of drug crystals on the surface of drug loading microspheres shown in Figure 3.2.The drug release performance is gentle, showing the slow-release performance of drug diffusion control. At 14 h, the drug release was basically complete. Considering the slow degradation rate of PLGA and the drug release not controlled by degradation, it is inferred that some drugs in the microspheres may not be released.

Table 3.3 - Cumulative release rates of SIM microspheres with different contents

Sim content / g	0.1	0.3	0.5
15 min cumulative release rate	0	40.59%	47.58%
30min cumulative release rate	0	51.33%	58.59%
1H cumulative release rate	2.10%	64.15%	71.07%
2H cumulative release rate	20.13 %	74.89%	83.84%
4h cumulative release rate	40.32 %	86.56%	92.89%
8h cumulative release rate	69.01 %	96.26%	97.40%

	14h cumulative release rate	79.98 %	96.82%	99.99%

The drug entrapment efficiency and drug loading of drug loaded microspheres were calculated according to the cumulative drug release, the calculation formula is as follows:

Entrapment efficiency (%)= (Drug content in microspheres/The total amount of medicine added) *100%

Drug loading (%)=(Drug content in microspheres/The total weight of the microsphere) *100%

The results of entrapment efficiency and drug loading are shown in table 3.4. The entrapment efficiency is about 18%, and the drug loading increases with the increase of drug addition in the preparation process, but it is also low (the maximum drug loading is about 8.66%).In the experiment, we also measured the drug concentration in the aqueous phase during the preparation process, and calculated the entrapment efficiency of the drug by the reduction method, which is consistent with the low solubility of the drug in PVA aqueous solution. The low entrapment efficiency calculated by cumulative release may be that the drug release in PLGA particles is incomplete in a limited time (14 h), which needs to be further investigated in future experiments.

Table 3.4 entrapment efficiency and drug loading of SIM microspheres with different contents

Sim content / g	0.1	0.3	0.5

Encapsulation efficiency /%	19.376	17.014	17.755
Drug loading /%	3.440	6.380	8.657

Conclusions to section 2

In this paper, PLGA microspheres loaded with SIM drugs were prepared by mechanical emulsification solvent evaporation method with PLGA and DCM solution of simvastatin as oil phase and PVA aqueous solution as aqueous phase. The preparation process and morphology of drug loaded microspheres were studied, the quantitative analysis method of drugs was established, and the drug dissolution properties of drug loaded microspheres were measured. The surface is smooth and the particle size is about 100μm. Drug loaded microspheres with uniform particle size and sustained-release performance.

The material PLGA used in the preparation of drug loaded microspheres has good biocompatibility and biodegradability, and the degradation products are harmless to human health. There are also many deficiencies in the experiment, such as the existing form of drugs in particles, the reasons for the difference of particle morphology with different drug loading, whether the drug release is complete, etc. there are still questions, which need to be further studied in future experiments.

Section 3. Manufacturing and Quality Control of drugs with System of sustained and controlled release

3.1. System of sustained and controlled release of drugs

With the progress of society, people are facing more and more fierce competition in work, study and life, and bear more and more pressure. Human health has also become one of the main topics in the field of medicine. In order to treat various diseases, corresponding drugs are needed, so the safety of drug use has also attracted people's attention. In the traditional mode of administration, the drug reaches the maximum release in a very short time after entering the human body, which may lead to excessive drug concentration in human tissue or blood, exceeding the maximum tolerated dose of patients, resulting in large toxic and side effects; Moreover, after reaching the maximum release amount, it is difficult to maintain the effective concentration in the body for a long time. When its concentration in the body tissue or blood is lower than the effective dose, it can not play its corresponding therapeutic role, so the use efficiency of the drug is reduced. If multiple low-dose administration is adopted, the above problems can be solved, but this method increases the complexity of doctors; work and brings inconvenience to patients. In this case, an ideal drug controlled release system came into being.

Drug slow and controlled release, as the name suggests, is to make the drug release slowly in the body or control the drug release, so as to achieve the predetermined release rate or release it at a specific site, so as to achieve the purpose of treating a certain disease [64-67]. The ideal drug release system has obvious advantages compared with the traditional drug delivery method, as shown in Table 1 [68].

Table 1 - Comparison between ideal drug delivery system and traditional drug delivery mode

Traditional administration	Drug sustained and controlled release system
The drug concentration is too large and too small	The blood drug concentration at the drug required part shall be maintained within the required range
The drug has no targeted release function	Only delivered to the treatment target
Low drug use efficiency	High drug use efficiency
The drug has great toxic and side effects	The drug has little toxic and side effects, and is safe and reliable
Taking medicine many times brings inconvenience to patients	Reduce the number of medication, which is easy for patients to accept

Basic requirements of drug sustained and controlled release system. In order to make the drug slow and controlled release system have the above functions, the requirements for carrier materials are very strict. The basic requirements for drug carrier materials are:

（1） Good biocompatibility and degradability to avoid human rejection or carrier material residue in the body.

（2） Stable physical, chemical or biological properties

（3） Very low toxicity

（4） Controlled drug release rate.

Microsphere refers to a small spherical entity formed by the dissolution or dispersion of drugs in the matrix of polymer materials. The common microsphere particle size range is generally between two, which belongs to matrix skeleton

particles. The early research on microspheres has been carried out since the mid-1990s. So far, great progress has been made in the research of microspheres, and its development speed is very rapid. After the drug is prepared into microspheres, the drug in the particles has a certain slow-release property when released, and it has a certain targeting to specific organs and some tissues. Therefore, drug microspheres have become a hot field in the research of controlled-release dosage forms in recent years and a new type of drug carrier with great development and research value. At present, the research on preparation technology, physiological process in vivo and clinical application is becoming more and more in-depth in China. Microsphere drug carriers have been used in many drug delivery routes, such as nasal, injection, oral, local administration and so on. It is expected that this technology will be applied in clinic in the near future and will be used by mankind as a new and effective weapon to overcome diseases.

There are many ways to deliver the appropriate dose of drugs to the corresponding injured tissues, such as oral medication, injection medication, inhalation medication, mucosal medication such as eye, oral cavity and nasal cavity and implantable medication. Only some existing preparation technologies can not meet the requirements. Therefore, some new processes and technologies have been continuously applied to the preparation and production process. After the drug is encapsulated in polymer, the following purposes can be achieved

(1) It can reduce some compatibility changes of compound drugs

(2) When used, it can inhibit the reaction of the drug in the stomach and prevent its inactivation, so as to reduce the first pass effect of the drug

(3) Reduce the effect of external environment and drugs, and then improve the stability of drugs

(4) So that the drug can be effectively concentrated in the target area

(5) One time administration can control the release of active components to specific sites at the best dose and rate.

It is noteworthy that some valuable new drugs developed by investing huge human and material resources have been abandoned because of their low oral activity or short half-life for injection. However, if polymer encapsulated microspheres or microcapsules are used for controlled-release administration, the effect of oral activity will be eliminated, and the half-life of the drug will be prolonged in vivo. This will make many drugs that were considered unusable in the past become new drugs with application value. Therefore, polymer microspheres have broad prospects for the research and development of drugs.

Many types of oral liquids and injections can be prepared by dispersing polymer microspheres into aqueous or non-aqueous solvents. The excipients can be mixed to form patches, tablets, sprays, capsules and so on. Because of its good biocompatibility, targeting characteristics and controlled release, it plays a very important role in drug delivery technology, so it has become a hot issue in the research of controlled-release and sustained-release preparations in recent years.

Compared with the traditional microcapsule drug carrier system, drug loaded microspheres have the following advantages: the drugs are evenly distributed in the particles, so it will not lead to the sudden release of drugs similar to microcapsule products due to the dissolution or rupture of their shell. In the whole process of drug release, the polymer materials will gradually degrade, so the drug permeability will gradually accelerate, This will offset the decrease of diffusion rate caused by the decrease of drug concentration, so that the drug can be released evenly. The application of polymer microspheres in some non gastrointestinal tissues is often limited by biological acceptability. Reducing the particle size of microspheres for injection can effectively improve the biological acceptability. Taking advantage of the specificity of the distribution of particles with different particle sizes in the body and the biocompatibility to avoid being recognized by the immune system, the drug can be delivered directly to the lesion site and then released slowly, so as to increase the local drug concentration, so as to realize the controlled release and targeted administration of the drug at the disease site in the human body.

Nano microspheres are solid colloidal particles. Drugs can be dissolved or encapsulated in nano microspheres, which can be used as an excellent intravenous drug carrier. Nanoparticles have the characteristics of controlled release, targeting and high efficiency, and can enter the body through oral administration, transdermal absorption and intravenous injection. After entering the body, nanoparticles can prevent being swallowed by macrophages of human reticuloendothelial system. They can pass through the cell gap, further pass through the capillaries and blood-brain barrier in the body, and finally be absorbed by cell tissue. Nanosphere drug carrier system will have a broader prospect in the research and application of anti-inflammatory drugs, antiviral drugs, controlled release of antitumor drugs and gene carrier.

At present, there are not many applications of microsphere drug carriers in commercial products. Due to the complexity of its drug release mechanism, it is not very mature compared with the study of drug microencapsulation. Some existing problems need to be solved, such as the low efficiency of drug loading, difficult to control drug release, sudden release or incomplete release. However, for this kind of new drug carrier with great development potential and application value, there has been an increasingly in-depth research on the preparation, application and release mechanism at home and abroad.

Targeting: through passive distribution, active targeted combination or magnetic attraction, it can improve the local effective concentration of drugs in the body and reduce the drug concentration in other parts, so as to reduce the systemic toxicity and adverse reactions of drugs.

Sustained release and long-term effect: it can reduce the frequency of administration times and reduce the peak valley fluctuation of blood drug concentration. Biodegradable microspheres also have long-term effect.

Embolic: the particles are directly guided through the arterial tube and blocked in the tumor blood vessels. The microspheres can block the tumor feeding and the

drugs released by the drug loaded microspheres can inhibit and kill tumor cells and play a dual anti-tumor role.

Others: cover up the bad smell and taste of drugs to reduce local irritation; Improve the stability of the drug and reduce gastric irritation; It is conducive to the solid state of liquid drugs and is convenient for storage and transportation.

3.2. Technology for the production of tablets containing microspheres

Tablet refers to the preparation made by mixing drugs and pharmaceutical excipients. Since William Brockendon first applied for the invention patent of tablet press in the world in 1843, it has developed rapidly as a drug dosage form. In recent years, the research on its forming theory has been gradually deepened, a variety of new excipients have been developed and applied, and the high-efficiency tablet press has been upgraded, so that the continuous mass production of tablets has been realized. The quality of tablets has been greatly improved, and the varieties of tablets are diversified.

Characteristics of tablets. Advantage：

（1）The dosage is accurate and the content is uniform.

（2）The chemical stability is good, and light, high temperature and high humidity have little effect on it; Unstable drugs can be protected by coating or packaging.

（3）Easy to carry.

（4）The equipment used is mature and can be mass produced, so the cost is low.

（5）Various types meet various needs of clinical treatment. Effervescent tablets, sustained-release tablets, dispersible tablets, enteric coated tablets, chewing tablets, etc. are commonly used.

The preparation methods of tablets can be divided into two categories: particle tablet pressing method and direct tablet pressing method. At present,

particle tablet pressing method is the most widely used. Particle pressing method can be divided into wet granulation pressing method and dry granulation pressing method.

Making granules. Because pressing tablets after making granules can improve the fluidity and compressibility of materials, so making granules is often the process before pressing tablets.1. The purpose of granulation (1) to increase the fluidity of materials;(2) Reduce the air absorbed and stored by fine powder to reduce the looseness and crack of tablets;(3) Avoid powder delamination;(4) Avoid flying fine powder.

Granulation method:

(1) wet granulation: it refers to the method of adding medicine materials into wetting agent or adhesive to make soft materials and particles. It is divided into fluidized spray granulation, extrusion granulation, rolling granulation and spray drying granulation.

(2) Dry granulation: refers to the method of making particles without wetting agent or liquid adhesive. The utility model is characterized in that the materials do not undergo wet and heat treatment, which can not only shorten the working hours, but also improve the quality of wet and heat sensitive drug products. It is divided into rolling method and heavy pressing method.

(3) Wet particle drying: the particles made by wet method shall be dried in time to avoid agglomeration or compression deformation. The drying temperature depends on the nature of raw materials, generally 60 ℃ ~ 80 ℃.The drying temperature of drugs containing volatile and glycosides or unstable in case of heat shall be controlled below 60 ℃.

(4) Quality requirements for dry granules

① main drug content: determined according to the inspection method of the finished tablet.

② Water content: the water content of dry granules for traditional Chinese medicine tablet pressing is generally 3% ~ 5%;The water content of dry chemical granules is 1% ~ 3%, but individual varieties can be an exception.

③ Particle size and tightness: the particles are too hard, and the tablet is easy to produce pitted surface; Loose particles are easy to break into fine powder, and loose pieces, cracks, etc. are easy to occur when pressing.

(5) Treatment of dry particles before tablet pressing

① whole particles;

② Add volatile oil or volatile drugs;

③ Add lubricant.

Tabletting. The general preparation process of tablet pressing is as follows:

treatment of raw materials → addition of auxiliary materials → mixing → particle preparation → drying → whole particle → tablet pressing (coating) → quality inspection → packaging.

Tablet pressing methods. Tablet pressing methods are generally divided into wet granulation tablet pressing method, dry granulation tablet pressing method and powder direct tablet pressing method. Single punch tablet press or rotary tablet press are commonly used in tablet pressing.

(1) Wet granule method: it is applicable to the preparation of tablets that cannot be pressed directly and cannot change in case of humidity and heat.

(2) Dry particle method: it refers to the method of making particles without wetting agent or liquid adhesive for tablet pressing.

(3) Powder direct tablet pressing method refers to the method of directly tablet pressing without particle preparation after mixing drug powder with appropriate excipients.

Preparation process screening. The national drug standard stipulates that the raw material of simvastatin should be sealed, nitrogen filled and stored in a cool place, indicating that the raw material is unstable in case of heat. The preparation

process should try to avoid involving heating, drying and other preparation processes, especially wet granulation, which requires a relatively long heating and drying process. Therefore, in the study of prescription, the preparation process of granulating excipients first and then mixing with the main drug is selected

However, in the two preparation methods, the tablets prepared by powder direct compression have great differences in particle fluidity and tablet weight, and the tablet yield is low. Therefore, the preparation process of simvastatin tablets (plain tablets) is to dry the blank particles by wet method, and then mix and press the tablets with drugs.

Film coating process of plain tablets. The conventional film coating process was adopted, and the weight gain of plain tablets was 3%. The dosage of coating powder is about 3% of the tablet core weight, and the dosage of purified water is about 82% of the dosage of coating powder minus the dosage of coating powder. Add the required amount of purified water into the stainless steel barrel with peristaltic pump for stirring, and slowly add the weighed coating powder into the vortex. At the beginning, the speed should be fast, do not make the coating powder agglomerate, reduce the speed after adding, maintain the vortex and stir evenly. The tablet core is placed in the coating machine. After all preparations are completed, start the coating, start the peristaltic pump, and then spray the slurry according to the "spraying", slowly adjust the rotating speed of the coating machine to about 8 R / min as appropriate, and control the air outlet temperature between 45 ~ 55 ℃ during spraying. During the spraying process, the operator shall carefully observe whether the nozzle is blocked, whether the temperature is normal, whether the tablets are adhered, and whether the tablet surface is dense, smooth and flat. Finally, cool and take out the tablets to obtain smooth film coated tablets.

3.3. Method of quality control in the production of tablets

In the process of industrial production, there may be quality problems in the production of tablets due to some reasons. Discuss these possibilities, and then put forward corresponding solutions.

Common problems in granulation process. Granulation plays a key role in the whole tablet preparation process. The effect of granulation directly determines the quality of subsequent processes. Therefore, the preparation of qualified particles is the core of tablet production.

Table 2 - Common quality problems and Solutions

Serial number	Common quality problems	terms of settlement
1	The particle size does not meet the requirements: the particle is too thick, the fluidity is poor, and the weight difference of the pressed tablets is large;The particles are too fine, the hardness of the extruded tablets is too small, and the vacuum cleaner of the tablet press absorbs too much dust, resulting in low yield.	If the particle is too coarse, reduce the amount of adhesive or reduce the granulation speed and time;If the particles are too fine, appropriately increase the amount of adhesive or prolong the granulation time.
2	The particle viscosity does not meet the requirements, and the viscosity is too large or too small.	If the viscosity is too large, reduce the amount of adhesive or reduce the granulation speed and time;If the viscosity is too small, appropriately increase the amount of adhesive or prolong the granulation time.

3	The moisture content of particles does not meet the requirements: The score is too high.The tablet pressing process is easy to stick and punch;The moisture is too little, the particle viscosity is poor, the hardness of the pressed sheet is too small, and it is easy to crack and loose.	If the water content is too low, it shall be appropriately reduced Temperature and time;If the moisture is too high, reduce the drying temperature and time appropriately.
4	The uniformity of particle content does not meet the requirements.	Adjust the method and dosage of lubricant;Adjust the speed and time of mixing.

Common quality problems in tablet pressing process. Lobes. The tablet is shaken and splits from the middle of the tablet or from the top of the tablet.

Table 3 - Causes and solutions of tablet cracking

Serial number	**Common quality problems**	**terms of settlement**
1	The pressure of the tablet press is too high or the speed is too fast, and the air in the particles is not discharged in time.	Properly reduce the pressure or slow down the machine speed.
2	There are too many oil components in the prescription and the particle viscosity is poor.	Adjust the prescription, replace or add absorbent.

3	The ambient temperature and humidity are too low.	Properly increase the temperature and humidity of the air conditioning system.
4	The particle has too little water content and poor viscosity.	Reduce the temperature or time of the drying process.
5	The hardness of the upper and lower parts of the pressed tablets is different due to large difference in particle size or too much fine powder.	Some coarse particles and fine powder can be properly screened.
6	The amount of adhesive or wetting agent is insufficient, and the particle viscosity is poor.	Appropriately increase the amount of adhesive or wetting agent.

Pine flake. After the tablet is formed, the hardness is too low, and it will break when pinched gently by fingers; After the tablets are bagged, a little shaking will produce burrs or fragmentation.

Table 4 - Causes of looseness and Solutions

Serial number	**Common quality problems**	**terms of settlement**
1	Insufficient amount of adhesive or wetting agent.	Appropriately increase the amount of adhesive or wetting agent.
2	The moisture content of particles is too low.	Reduce the temperature or time of the drying process.
3	Tablet press, pressure is too low or running speed is too fast.	Increase the pressure of the tablet press or reduce the running speed.
4	Large agglomerates or particles block the filler and blanking port, affecting the filling amount.	Regroup or remove large particles and lumps.
5	The length of the die is different or individual dies are too tight, and the pressure on the tablet is different.	Check the die quality and clean the die hole in time.

6	The prescription contains more volatile oil.	Adjust the prescription and increase the absorbent.
7	Poor particle fluidity and filling amount in die hole. Not enough.	Add flow aids appropriately.

Stick punch. The surface of the tablet is stuck with a thin layer or a small part by the punch, resulting in one-sided roughness or dents.

Table 5 - Causes and solutions of one-sided roughness or dent

Serial number	**Common quality problems**	**terms of settlement**
1	The moisture content of particles is too high.	Adjust the drying time or temperature appropriately.
2	Insufficient or uneven amount of lubricant.	Reduce the temperature or time of the drying process.
3	Appropriately increase the amount of lubricant or adjust the mixing parameters.	Appropriately increase the amount of lubricant.
4	There are oil or water stains on the surface of the punch.	Clean the surface of the punch.

Lachong. Due to the influence of powder in the tablet pressing process, the upper and lower dies can not run freely, resulting in jamming.

Table 6 - Causes and solutions of Caton

Serial number	**Common quality problems**	**terms of settlement**
1	The die is worn after being used for a long time, and the powder enters the gap between the die and the die hole, hindering the up and down movement of the die.	Replace the die.

2	When the suction of the vacuum cleaner of the tablet press is too small or fails, the excess powder will be on the toilet surface of the lower die, hindering the up and down movement of the die.	Clean the powder in the vacuum cleaner in time and repair the vacuum cleaner
3	The viscosity of the particle itself is too large.	Time for adjusting braking force; Adjust the dosage or variety of absorbent; Adjust the amount or variety of adhesive

Common problems and solutions in coating process. The surface of solid preparations such as tablets, granules and pellets is evenly wrapped with appropriate pharmaceutical excipients to form a stable coating layer to achieve the desired effect. This process is called coating. The coating can improve the stability of the drug, cover the bad taste of the drug, control the release of the drug, and improve and beautify the appearance.

Adhesive sheet. Because the flow rate of the coating solution is greater than the drying capacity, the coating liquid fails to dry in time and accumulates on the surface of the tablet, resulting in mutual adhesion. The adhered chip cores are separated from each other during the continuous rotation of the coating pot, so that the film at the adhesion is broken.

Table 7 - Causes and solutions of film rupture

Serial number	Common quality problems	terms of settlement
1	The speed of the coating pot is too low.	Increase the rotating speed of the pot body.
2	The liquid injection flow rate is too fast.	Reduce the injection flow rate.
3	The spray gun is too close to the tablet bed.	Increase the distance between the spray gun and the tablet bed.

4	The drying temperature is too low.	Properly increase the drying temperature.
5	The inlet air volume is too low.	Properly increase the inlet air volume.

Rough surface. Due to poor atomization effect and thick coating, the sprayed droplets are heated unevenly or concentrated unevenly, resulting in rough coating film.

Table 8 - Causes and solutions of film roughness

Serial number	Common quality problems	terms of settlement
1	The coating solution concentration is too high.	Reduce the amount of coating powder in the coating solution.
2	The atomization effect of coating solution is not good.	Increase atomization pressure, reduce liquid injection speed Increase the distance from the spray gun to the tablet bed.

Coating film peeling. After coating, the coating film is partially or positively peeled off.

Table 9 - Coating peeling

Serial number	Common quality problems	terms of settlement
1	Mechanical strength of coating film.	Select the coating solution formula with strong adhesion.
2	The atomization effect of coating solution is not good.	Increase atomization pressure or reduce liquid injection speed.
3	The surface engraving is too complex, too thin or too shallow.	Adjust lettering.

4	There are too many hydrophobic components in the core prescription.	Increase hydrophilic components in the prescription.

Uneven color of coated tablets. After coating, the color of the coating film is uneven or the coating film fails to completely cover the core.

Table 10 - Coating problems

Serial number	Common quality problems	terms of settlement
1	Improper selection of colorants.	Adjust the type of colorant, often choose non water-soluble colorant.
2	The mixing effect of the coating machine is not good and there are dead corners.	Improve the structure and distribution of the guide plate of the coating pot.
3	The speed of the coating pot is too low.	Increase the rotating speed of Baoye pot.
4	The atomization range of the spray gun is inappropriate.	Adjust the spacing of spray guns. The spacing is not too large or too small. On the premise of ensuring that the atomization area does not overlap, shorten the spacing of spray guns.
5	The covering power of the coating material is not good.	The coating material with appropriate color shall be selected for pre coating.

After coating, the lettering part of the chip core is blurred or completely covered by the coating film.

Table 11 - Lettering partially blurred or completely covered up

Serial number	Common quality problems	terms of settlement
1	The adhesion of the coating film is not good.	Select the coating solution formula with strong adhesion.

2	The atomization effect of coating solution is not good.	Increase the atomization pressure or reduce the liquid injection speed.
3	The surface engraving is too complex, too thin or too shallow.	Adjust lettering.
4	There are too many hydrophobic components in the core prescription.	Increase hydrophilic components in the prescription.

Conclusions to section 3

Simvastatin is one of the first choice drugs for the treatment of hyperlipidemia. It has good therapeutic effects on primary hyperlipidemia, homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, hyperlipidemia with fatty liver, hypercholesterolemia in the elderly and nephrotic syndrome. It is a synthetic derivative of the fermentation product of Aspergillus terrestris.

It is an inhibitor of hydroxymethylglutaric ugly coenzyme reductase. It inhibits the synthesis of endogenous cholesterol by inhibiting the rate limiting enzyme of cholesterol synthesis by reductase hepatocytes, and is used to control the content of cholesterol in blood.

At present, the related products on the market mainly include APIs, tablets, capsules and dropping pills. Because the drug needs to be taken for a long time, it is very inconvenient to use. At present, several dosage forms on the market can not solve this problem well. Therefore, developing a new drug dosage form and making it into sustained-release tablets can change the inconvenience of the original dosage form. Reduce the times of taking medicine and improve the adaptability of patients. It will provide more choices for clinical medication.

Conclusion

Biodegradable materials have unlimited potential in the field of medicine. As a carrier material, it can carry drugs, bioactive substances and other substances, and control the release of the substances in the body. At this point, it has become the focus of many researchers. For example, it can improve the bioavailability of drugs, have certain targeting and sustained-release effects, reduce the toxic and side effects of drugs or other substances, and even reduce the rejection of tissues and cells in vivo. These studies provide a strong guarantee for the search and development of new drug formulations.

The material PLGA used in the preparation of microspheres has good biocompatibility and biodegradability, and the degradation products are harmless to human health.

In this paper, PLGA microspheres loaded with SIM drugs were prepared by mechanical emulsification solvent evaporation method with PLGA and DCM solution of simvastatin as oil phase and PVA aqueous solution as aqueous phase. The preparation process and morphology of drug loaded microspheres were studied, the quantitative analysis method of drugs was established, and the drug dissolution properties of drug loaded microspheres were measured. The surface is smooth and the particle size is about 100 μ m. Drug loaded microspheres with uniform particle size and sustained-release performance.

The material PLGA used in the preparation of drug loaded microspheres has good biocompatibility and biodegradability, and the degradation products are harmless to human health. There are also many deficiencies in the experiment, such as the existing form of drugs in particles, the reasons for the difference of particle morphology with different drug loading, whether the drug release is complete, etc. there are still questions, which need to be further studied in future experiments. It is hoped that through the research of this subject, it is expected to establish a preparation technology of drug carrier integrating biocompatibility, degradability and controlled release, so as to make its practical application in the field of pharmaceutical preparations possible.

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МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
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MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
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ЗБІРНИК НАУКОВИХ ПРАЦЬ
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2021

SIMVASTATIN-LOADED PLGA MICROSPHERES FOR DRUG DELIVERY

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Abstract

In this paper, simvastatin-loaded poly(L-lactide-co-glycolide) (PLGA) microspheres, with a uniform size about 35 μm and loading simvastatin amount about 18%, were prepared by emulsion-solvent evaporation method. The drug release behavior was determined in mimic sink condition, which shows an obvious burst release about 40.59% in the first 15 min, and then slowly released for over 14 h. This simvastatin-loaded microsphere may have potential application in bone regeneration and repair field by injection.

1. Introduction

Simvastatin can induce the expression of BMP-2 gene in osteoblasts and bone marrow cells, which can promote osteogenesis. [1] Oral preparation shows low bioavailability due to first-pass effect in liver, resulting in failing to promote the formation of new bone tissue at defect site. Moreover, high dosage simvastatin will have serious toxicity and side effects on liver, muscle and other tissues. Therefore, it is important to develop a new simvastatin delivery system. Injectable bio degradable microspheres have been extended studied as drug carrier and tissue engineering scaffolds. One side, drug-loaded biodegradable microspheres can release drug slower at injection site, on the other side the microspheres can promote cell growth, proliferation and tissue repair. [2] Herein, Simvastatin-loaded PLGA microspheres were prepared by emulsion-solvent evaporation method, and microspheres morphology and drug release behavior were studied.

2. Materials and methods

2.1 Materials

Simvastatin and medium viscosity polyvinyl alcohol (PVA) were purchased from Aladdin Chemical Reagent Co., Ltd. (Shanghai, China). Poly(L-lactide-co-glycolide) (glycolide/L-lactide=25/75, mol/mol, Mw=100000 Da) was synthesized in our lab.

2.2 Preparation of Simvastatin-loaded PLGA microspheres

Simvastatin (1 g) and PLGA (1 g) were dissolved in 10 mL dichloromethane to obtain homogeneous oil phase solution. The oil phase solution was poured into 1% PVA aqueous solution (40 mL) precooled at 4°C, and then stirred at 5000 rpm for 10 min by a emulsifier to obtain O/W emulsion. Finally, the emulsion was transferred into an open beaker, and mechanically stirred overnight at 600 rpm at room temperature to remove the organic solvent. Simvastatin-loaded PLGA microspheres were collected by centrifugation, and then lyophilized to obtain drug-loaded microspheres.

2.3 Characterization

Microsphere morphology was observed by optical microscope (Smartzoom 5, Germany), and its size distribution was determined by Laser particle size analyzer

(Zetasizer Nano ZS90, USA). 100 mg drug-loaded microspheres were dispersed in 900 mL dissolution medium of sodium dihydrogen phosphate buffer solution (0.01 mol, pH 7.0) with 4.5 mg sodium dodecyl sulfate stirred at 100 rpm at 37 °C. The medium of 5 ml was taken out and replaced with the same volume fresh dissolution medium at preset time intervals to mimic sink condition, and simvastatin concentration in dissolution medium was determined at 238 nm by a UV-vis spectrophotometer and calculated according to standard curve (y=0.0685x+0.0631 R^2=0.9986). Drug loading amount was calculated as total release simvastatin.

3. Results and discussion

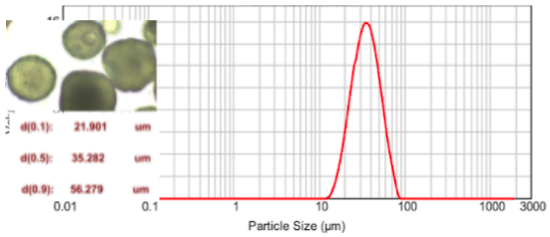

Fig. 1 Simvastatin-loaded PLGA microsphere morphology and size distribution

As shown in Fig 1, The simvastatin-loaded microspheres showed spherical structure, and obvious drug crystallization could be observed on its surface. The microsphere shows uniform size distribution, and the median particle size was about 35 μm, indicating injection can be administered by a very fine needle.

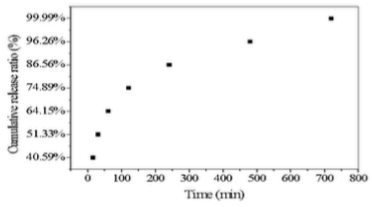

Fig.2 Cumulative release of simvastatin from the drug-loaded PLGA microspheres

Cumulative release ratio of simvastatin from drug-loaded microspheres is shown in Fig 2. In the first 30 min, an obvious burst release was observed, which was mainly ascribed to the drug crystals on the microsphere surface. Simvastatin was fully released from the microspheres after 14 h. Considering the slow degradation rate of PLGA,[3] it can be concluded that the release rate of simvastatin was mainly controlled by diffusion. Simvastatin is difficult to dissolve in water, but the encapsulation ratio and loading amount of simvastatin are low (~18%). This may be ascribed to the presence of PVA in water phase that increases the solubility of drugs,

resulting in drug loss during the preparation of microspheres by emulsification and solvent evaporation method.

4. Conclusion

Simvastatin-loaded microspheres can be prepared by emulsion-solvent evaporation method. The microsphere shows uniform size distribution with a median particle size about 35 μm. Loading amount of simvastatin in the biodegradable microspheres is about 18%, which can be slowly released for over 14 h.

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