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Application and Feasibility Study of High-Pressure CO_2 Sterilization Technology in Chinese Medicinal Materials Sterilization

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Abstract: Aiming at the risks of excessive microorganisms and irradiation sterilization residues in the direct use of raw powder of Chinese medicinal materials, this paper took the production line of a Chinese patent medicine enterprise as the engineering research object to study the engineering application of high-pressure CO_2 sterilization technology. With the designed sterilization conditions of pressure 30–60 MPa and temperature 35°C–65°C, the raw powder sterilization of medicinal materials with different medicinal parts was completed, and a technical parameter system for industrial application was established. During the project implementation, key technical problems, such as equipment pressure-bearing design, process energy consumption control and multi-round sterilization capacity improvement, were solved. The sterilization effect meets the pharmacopoeia standards, realizing the industrial application goal, and providing a green and safe technical alternative for the sterilization of raw powder of Chinese medicinal materials.

Keywords: High-pressure CO_2 sterilization; Raw powder of Chinese medicinal materials; Engineering application

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1. Introduction

The direct use of raw powder of Chinese medicinal materials is a common method in the production of Chinese patent medicines. Raw powder raw materials generally contain a large number of microorganisms and pathogenic flora. Traditionally, ^{60}Co irradiation technology is used for sterilization. Although irradiation sterilization has strong penetrability and large processing capacity, it has potential safety hazards of nuclear ray irradiation residues, and high-energy rays may affect the active components of some heat-sensitive medicinal materials. With the continuous improvement of drug safety requirements, the development of new, environmentally friendly, safe and cost-effective sterilization technologies has become a major demand in the field of Chinese patent medicine production. As a low-temperature physical treatment method, high-pressure CO_2 extraction technology exhibits good mass transfer performance and biological activity inhibition effect in the supercritical state. Starting from engineering application, this paper selected the raw powder medication process involved in the key products of a Chinese patent medicine enterprise, deeply analyzed the technical feasibility of high-pressure CO_2 sterilization technology in industrial scenarios, and formed an overall technical scheme including process parameter design, equipment selection and configuration, and on-site implementation improvement,

providing practical basis for the upgrading of sterilization technology for raw powder of Chinese medicinal materials.

2. Engineering overview and technical basis analysis

2.1. Process characteristics and sterilization requirements of the production line

A Chinese patent medicine enterprise located at the foot of the Qinling Mountains has an advanced production line and a fully intelligent integrated production workshop. The core products of the enterprise adopt the raw powder medication process of Chinese medicinal materials, covering four major categories of medicinal materials: roots and rhizomes, flowers, leaves, and fruits and seeds, involving key medicinal materials such as *Salvia miltiorrhiza*, *Bupleurum chinense*, *Schisandra chinensis*, *Lonicera japonica*, *Isatis indigotica* leaves and *Ligustrum lucidum* fruit [1]. According to the microbial limit specifications of Table 3 "Non-sterile pharmaceutical raw materials and excipients" in the *Chinese Pharmacopoeia*, the total number of aerobic bacteria in pills shall not exceed 30,000 colony-forming units per gram ($CFU \cdot g^{-1}$), and the total number of molds and yeasts shall not exceed 10^2 colony-forming units per gram (the maximum acceptable number of bacteria is 200).

2.2. Technical principle and applicability demonstration of high-pressure CO_2 sterilization

High-pressure CO_2 sterilization technology relies on the strong diffusivity and low viscosity of supercritical CO_2 fluid, and destroys the microbial cell membrane structure through the combined action of pressure and temperature. When CO_2 is in a supercritical state with pressure exceeding 7.38 MPa and temperature exceeding 31.1°C, its density is close to that of liquid and its diffusion coefficient is close to that of gas, which can penetrate the tiny pores inside the medicinal material powder [2]. In the high-pressure CO_2 environment, microbial cells suffer from physiological inhibition, such as the extraction of cell wall lipids, a decrease in internal pH value and inactivation of important enzyme systems. For the treatment of raw powder of Chinese medicinal materials, this technology can achieve a sterilization effect in the temperature range of 35°C–65°C, avoiding the color change of medicinal materials and loss of volatile oil components caused by high temperature in the traditional dry heat sterilization method, and also solving the hydrolysis damage of active components of medicinal materials caused by the moist heat sterilization method. The technical applicability evaluation shows that this process has good applicability to the raw powder of Chinese medicinal materials with low water content (such as less than 12%), and can well adapt to the material characteristics of different medicinal parts, such as rhizomes, leaves and flowers.

Table 1. Microbial background value and sterilization target of medicinal raw materials in the project

Sample Name	Total aerobic bacteria (cfu/g)
Mixed coarse powder of *Salvia miltiorrhiza*/*Schisandra chinensis*	Uncountable
Mixed coarse powder of *Salvia miltiorrhiza*/*Schisandra chinensis* (1st round sterilization)	7000
Mixed coarse powder of *Salvia miltiorrhiza*/*Schisandra chinensis* (2nd round sterilization)	1000
Ligustrum lucidum fruit	12000
Ligustrum lucidum fruit (1st round sterilization)	1200
Isatis indigotica leaves	53000
Isatis indigotica leaves (1st round sterilization)	21000
Lonicera japonica	18000
Lonicera japonica (1st round sterilization)	2000
Bupleurum chinense	Not studied

3. Design of engineering application scheme for high-pressure CO_2 sterilization

3.1. Sterilization process route and pressure parameter configuration

The project adopted the batch-type high-pressure autoclave sterilization method, equipped with two vertical high-pressure sterilization autoclaves with a capacity of 1000 liters. The working pressure was designed to be 60 MPa and the temperature was 70℃. Each autoclave can load 800 kg of coarse medicinal material powder, and the powder particle size is kept in the range of 40 to 60 meshes to enhance the penetration effect of CO_2 fluid [3]. The process pressure parameters are set in an adjustable range of 30 MPa to 60 MPa and adjusted according to different types of medicinal materials: a higher pressure condition of 55 MPa is used for roots and rhizomes, a medium pressure condition of 40 MPa for flowers and leaves, and a medium-high pressure condition of 50 MPa for fruits and seeds. The sterilization cycle is 3 hours per round, including 30 minutes of pressure rise, 150 minutes of pressure holding for sterilization and 30 minutes of pressure relief and exhaust. The multi-round sterilization scheme is adjusted according to the microbial detection results, and the basic scheme is two rounds of treatment.

3.2. Design of CO_2 fluid circulation and temperature control system

The system is equipped with a CO_2 circulation and recovery device to control the operation cost, adopting a closed circulation mode of compressor pressurization and condenser liquefaction. The capacity of the CO_2 storage tank is set to 5 cubic meters, the storage pressure is kept at about 6 MPa, and the storage temperature is normal room temperature [4]. The pressurization system uses a three-stage piston compressor to compress liquid CO_2 to the process pressure and send it to the sterilization autoclave. Temperature regulation is completed by the jacketed heat exchanger of the autoclave body, with a 60℃ hot water circulation system as the heat source and a 5℃-ethylene glycol solution circulation system as the cold source. Hot CO_2 fluid at 60℃ is introduced during the pressure rise stage, so that the temperature in the autoclave reaches the target sterilization temperature of 35℃–65℃ within 15 minutes. During the pressure holding stage, the temperature fluctuation range is controlled within ± 2℃ by a proportional regulating valve to ensure the stability of the sterilization process.

3.3. Design of equipment, material and sealing structure

The main material of the high-pressure sterilization autoclave is S30408 austenitic stainless steel; the inner diameter of the cylinder is 800 mm, and the wall thickness is set to 45 mm according to the strength requirements. The head of the autoclave body adopts a standard elliptical head with a major-minor axis ratio of 2:1 and the same thickness as the cylinder. The sealing method adopts a double wedge ring self-sealing structure, and the sealing material is polytetrafluoroethylene composite material, which can bear a pressure range of 0 to 70 MPa [5]. The design life of the equipment is about 15 years, and the corrosion allowance is about 1.5 mm. Three layers of perforated clapboards are arranged in the autoclave, and the loading height of each layer is not more than about 200 mm to ensure the uniformity of the longitudinal flow of CO_2 fluid. The pressure relief pipeline is equipped with a muffler and a CO_2 recovery interface, and the pressure relief rate is controlled at no more than about 2 MPa per minute to avoid powder entrainment with the air flow.

4. Analysis of technical difficulties in project implementation

4.1. Fluctuation of multi-batch sterilization efficiency

During the commissioning stage of the project, the detection results of the total number of aerobic bacteria in the mixed powder of *Salvia miltiorrhiza* and *Schisandra chinensis* showed obvious differences between batches, with 7000 CFU per gram measured in a certain batch after the first round of sterilization. The analysis found that the uneven bulk density of the coarse medicinal material powder in the autoclave led to poor flow of CO_2 fluid and channeling in some areas, resulting in incomplete sterilization. The bulk density measurement results showed that the value varied from 0.35 to 0.42 liters per kilogram, which was different from the uniform accumulation expected in the equipment design. Similarly, the

water content of medicinal materials harvested in different seasons varied from 8% to 15%, and the increase in water content caused the change of CO_2 fluid solubility, thus interfering with the lipid extraction effect of cell membranes [6]. The temperature field distribution detection found that the temperature difference between the upper and lower parts of the autoclave body reached 5°C in some cases, exceeding the temperature stability requirements for microbial sterilization kinetics. The experimental data on the sterilization effect of coarse *Bupleurum chinense* powder showed that its initial microbial content was 4000 colony-forming units per gram. After one process of high-pressure CO_2 sterilization, the microbial content decreased to 100 colony-forming units per gram, a reduction of 97.5% in the number of microorganisms [7]. After the second process of sterilization, the microbial content further decreased to less than 10 colony-forming units per gram, with an overall reduction ratio of more than 99.75%, meeting the limit standard of not more than 100 colony-forming units per gram specified in the *Chinese Pharmacopoeia* [8]. This indicates that the high-pressure CO_2 sterilization process has a significant microbial killing effect on medicinal materials containing volatile oil components such as *Bupleurum chinense*, and can meet the relevant compliance requirements of the pharmacopoeia after two rounds of treatment. At the same time, this process can avoid the damage of heat-sensitive active components caused by the traditional high-temperature sterilization method, which reflects the technical advantages of this process in ensuring the quality and safety of medicinal materials.

4.2. Hidden danger of fatigue cracks in equipment pressure-bearing components

After three months of project operation, fine cracks were found in the weld-adjacent area of the sealing surface of the quick-opening blind plate during the tank opening inspection of the sterilization autoclave. Nondestructive testing confirmed that the cracks were stress corrosion cracks, caused by the combined action of water in the high-pressure CO_2 environment and residual stress on the equipment surface. The material of the main cylinder met the strength requirements, but frequent pressure cycle loading led to fatigue cracks in local stress concentration areas. The polytetrafluoroethylene composite material of the sealing structure showed a cold flow phenomenon in the high-pressure environment, and needed to be replaced when the service life was only about 60% of the design life. The wear rate of the piston ring in the high-pressure stage of the compressor exceeded the expectation, and the fine powder particles carried by CO_2 caused abrasive wear during the compression process, reducing the volumetric capacity to about 85% of the design value.

5. Project optimization and technical solutions

5.1. Powder fluidized loading and multi-round process optimization

Aiming at the problem of unstable sterilization capacity, the technical transformation of powder fluidized uniform loading was carried out. A vibrating feeder and a distributor were equipped at the feeding port of the autoclave body, so that materials such as coarse *Bupleurum chinense* powder were evenly filled in a layered accumulation mode, and the thickness of single-layer loading was controlled at 180 mm with stainless steel wire mesh support laid between layers. A differentiated sterilization scheme based on the initial colony count was established: when the initial total number of molds and yeasts of medicinal materials such as *Bupleurum chinense* exceeds 4000 CFU per gram, a four-round sterilization process is adopted with a pressure of about 55 MPa, a temperature of 60°C, a pressure holding time of about 2.5 hours and a total processing time of no more than 12 hours [9]. For relatively clean plant medicinal materials such as *Lonicera japonica* in the initial state, two rounds of sterilization are carried out with a pressure of 40 MPa, a temperature of 45°C and a pressure holding time of 3 hours. The online rapid microbial detection technology is adopted to shorten the culture detection time from 48 hours to 8 hours, realizing flexible adjustment of the number of sterilization rounds and avoiding over-treatment.

The calculation formula and process verification are as follows. The calculation formula of sterilization efficiency η is:

$$\eta=\frac{N_0\text{-}N_t}{N_0}\times 100\%$$

where N_0 represents the initial colony number and N_t represents the colony number after sterilization treatment. Taking the second round of sterilization of coarse Bupleurum chinense powder as an example, the initial number of molds and yeasts N_0 is 4000 CFU per gram, and the number after sterilization treatment N_t is 10 CFU per gram. Substitute the values into the formula for calculation:

$$\eta=\frac{4000\text{-}10}{4000}\times 100\%=99.75\%$$

The calculation results show that two rounds of high-pressure CO_2 treatment can inactivate a large number of microorganisms, meeting the requirements specified in the pharmacopoeia.

5.2. Equipment structure strengthening and material upgrading scheme

Aiming at the fatigue crack problem of pressure-bearing components, the material and structure of the equipment were improved: the material of the quick-opening blind plate was changed from S30408 to S31603, a polytetrafluoroethylene anti-corrosion coating with a thickness of about 2 mm was added to reduce the corrosion rate of CO_2 aqueous solution; the sealing groove structure was redesigned, adopting a combined sealing form of O-ring and wedge ring to improve the anti-cold flow capacity of the sealing part under high pressure; more flow guide devices were added inside the cylinder to make the CO_2 fluid distribution more uniform and reduce the wear of the vessel wall caused by local turbulence; a life evaluation model based on the number of pressure cycles was established and an annual maintenance plan was formulated, adopting a combination of magnetic particle testing and ultrasonic testing for integrity evaluation; the compressor system was equipped with an inlet filter and a buffer tank with a filtration accuracy of 5 microns to prevent medicinal material dust from entering the compression chamber.

5.3. Optimization of process parameter boundary and efficacy protection strategy

A balanced control method of sterilization intensity and component preservation was established, and the pressure-time critical values of various medicinal materials were determined by single-factor experiments. For medicinal materials containing volatile oil components such as *Bupleurum chinense*, the sterilization pressure was reduced from 55 MPa to 45 MPa, the temperature was kept at 40℃, and the pressure holding time was extended to 4 hours to make up for the sterilization intensity [10]. CO_2 fluid saturation control technology was adopted, and a CO_2 mixed fluid containing saturated water vapor was introduced in the pressure rise stage to weaken the dissolution and extraction effect on fat-soluble components. For fruits and seeds, the pressure difference cycle process was adopted, with a pressure change of about 0.5 MPa every half hour during the pressure holding stage to enhance the penetration effect of CO_2 fluid on cell membranes, achieving the same sterilization effect at a lower pressure, and the retention rate of active components was increased to more than 98%. A medicinal material classification and coding system was formulated, and the most suitable combination of process parameters was selected according to the medicinal parts and component characteristics.

6. Conclusion

Taking the production line of raw powder preparation of a Chinese patent medicine enterprise as an engineering example, this paper studied the engineering application approach of high-pressure CO_2 sterilization technology, designed the sterilization conditions with a pressure range of 30 to 60 MPa and a temperature range of 35℃ to 65℃, and solved the technical problem of replacing irradiation residues in raw powder of Chinese medicinal materials. During the project implementation, relying on the transformation of powder fluidized loading, improvement of equipment materials, optimization of process parameter range and configuration of heat energy recovery system, the main technical

problems, such as unstable sterilization capacity, equipment wear and cracks, loss of active components and high energy consumption, were solved. Practice shows that this technology has universal application value for medicinal materials of roots and rhizomes, flowers and leaves, and fruits and seeds, and can meet the microbial limit standards of the *Chinese Pharmacopoeia* after process improvement. With the characteristics of low-temperature treatment, advantages of no chemical residues and recyclable operation, high-pressure CO_2 sterilization technology provides an environmentally friendly and safe technical scheme for the sterilization of raw powder of Chinese medicinal materials, and has the potential for large-scale industrial application.

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Disclosure statement

The authors declare no conflict of interest.

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