Research Progress on the Process Optimization and Stability Improvement of Third-generation Cephalosporins

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Abstract The latest progress in the process optimization and stability improvement of third-generation cephalosporins in recent years was reviewed. The introduction of green chemistry, enzyme catalysis, nanotechnology, lyophilization, and nitrogen-filled packaging technologies can only improve production efficiency and reduce the generation of by-products, but also significantly extend the shelf life of drugs. In the future, process automation and intelligent technology will further optimize the large-scale production process, and the combination of nanotechnology and precision drug delivery will promote the improvement of effect in clinical applications.

Key words Third-generation cephalosporins, Process optimization, Nanotechnology, Green chemistry, Drug stability

1 Introduction

Antibiotics are the core weapon in the fight against bacterial infections, and especially in the face of gram-negative bacteria and multi-drug resistant bacteria, third-generation cephalosporins have become an important choice in the treatment of complex infections due to its broad spectrum antibacterial activity. Since the introduction, third-generation cephalosporins (such as cefotaxime, ceftriaxone, *etc.*) have remarkable efficacy in the treatment of sepsis, community-acquired pneumonia, complex urinary tract infections and meningitis, and have become an important choice in clinical treatment. However, with the large-scale use of antibiotics, the drug resistance of antibiotics is a growing problem, and it is estimated that by 2050, drug resistance may lead to 10 million deaths per year due to infections[1]. The production process of third-generation cephalosporins traditionally relies on multi-step chemical synthesis, and which can guarantee the yield, but there are some obvious shortcomings. First of all, the use of a large number of organic solvents not only increases production costs, but also brings the risk of environmental pollution. Secondly, the purity and stability of the drug are more difficult to control, and especially during storage and transportation, β-lactam ring is susceptible to external factors, such as humidity and temperature, leading to drug failure. With the progress of technology, emerging technologies such as green chemistry, nanotechnology and continuous flow reactor provide new ideas to solve these problems, and open up a new path for the process optimization and stability improvement of third-generation cephalosporins[2-4]. In this study, from the perspective of preparation process, the optimization technology in the production of third-generation cephalosporins was systematically reviewed, and the application of new technologies such as green chemistry, nanotechnology and stability improvement was mainly studied, aiming to systematically review the research progress of third-generation cephalosporins in the optimization of preparation process and improvement of drug stability in recent years, mainly analyze how these technologies can improve production efficiency, reduce environmental pollution, and improve the stability and safety of drugs in different environments.

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2 Enzymatic process

Enzymatic process is the key to improve the preparation efficiency and environmental protection. The application of green chemistry in the preparation of third-generation cephalosporins is mainly reflected in the aspects of reducing the use of harmful chemical reagents and waste discharge. Traditionally, the synthesis of cephalosporins relies on a large number of organic solvents and multi-step reactions, which not only increases production costs, but also causes environmental pollution. Chloroform, acetonitrile and other organic solvents commonly used in production have strong toxicity and volatility, and will cause serious impact on the environment in case of improper treatment. In recent years, enzymatic process has gradually replaced chemical catalysis and becomes a more environmentally friendly option[5]. Enzymatic reactions are usually carried out under mild reaction conditions, significantly reducing the use of organic solvents. Studies have shown that the synthesis steps of cefotaxime can be reduced to two steps by enzyme catalysis, which saves 40% of organic solvent compared with traditional methods[6]. In addition, the high selectivity of enzyme catalysis can effectively reduce the generation of by-products and improve the purity of the target product. In the last step of cephalosporin synthesis, β-lactamase was used to increase the reaction efficiency by 25% by increasing the reaction yield. Continuous flow reactor technology is another significant progress in the pharmaceutical industry in recent years. Compared with conventional batch reactors, continuous flow reactors can complete the reaction in a closed system, greatly reducing the risk of volatile solvent leakage during the reaction process. Studies have shown that the applica-

tion of continuous flow technology can not only shorten the reaction time, but also reduce the generation of by-products by more than 30%[7]. With the optimization of the production process of third-generation cephalosporins, the effect in clinical application has also been significantly improved. Through the application of enzyme catalysis technology, the purity of drugs has been enhanced, thus reducing the incidence of allergic reactions in patients and the occurrence of adverse reactions in the course of treatment. The introduction of continuous flow reactors makes the content of active ingredients of cephalosporins more uniform, ensuring the stability of drug release in patients, and prolonging the half-life of drugs in plasma, thereby reducing the frequency of administration and improving the medication compliance of patients. For patients with multi-drug resistant bacteria infection, the cephalosporins prepared by the optimized process show stronger antibacterial activity and better tissue penetration in vivo, which is expected to improve the cure rate, and it has more clinical application value especially for complex cases of serious infection.

3 Enhancement technology of drug stability

3.1 Lyophilization Lyophilization is a common method for improving drug stability, and is especially applicable to heat-sensitive drugs that are easily degraded. The hydrolysis of beta-lactam rings can be effectively avoided by rapidly freezing drug solution at low temperatures and then subliming it under vacuum to remove the water to transform the drug into a dry solid form[8-9]. Studies have shown that lyophilization significantly improves the stability and shelf life of cephalosporins[10-11]. After cefotaxime is treated by lyophilization, its stability at room temperature can be increased by more than 50%, and its efficacy is effectively maintained under different temperature and humidity conditions. Besides, the freeze-dried drug can still maintain its original activity after reconstruction, and is more stable during storage and transportation, which is suitable for long-distance transportation and inconvenient storage. In order to further optimize the lyophilization process, the effects of freezing and sublimation rates, vacuum degree, and solvent selection on the crystalline form and stability of drugs can be studied.

3.2 Nitrogen-filled packaging technology Oxidation is another important factor affecting drug stability. Especially when the drug is exposed to air, oxygen will accelerate the degradation reaction of β-lactam ring[12]. Nitrogen-filled packaging technology means replacing oxygen in the air by filling the package with the inert gas nitrogen, thereby reducing the oxidative degradation of the drug and significantly extending the shelf life of the drug. Modern multi-layer composite materials can better prevent gas penetration and maintain a stable concentration of internal nitrogen. Using this material with high barrier properties, the shelf life of the drug can be effectively extended, ensuring the stability of the drug throughout the storage and transportation process. Studies have shown that the rate of oxidative degradation of ceftriaxone packed with nitrogen is reduced by more than 40%, and the shelf life is extended by 30%. This technology is especially suitable for those drugs that are sensitive to oxygen, and can effectively improve the storage stability of drugs. It is also found that the advantage of nitrogen-filled packaging is more obvious under the low-temperature storage condition. In low-temperature environment, the chemical reaction rate of drugs will be reduced, and the oxidation and hydrolysis reactions will be further slowed down. Especially in temperature-sensitive antibiotic preparations, by combining nitrogen-filled packaging and refrigeration or freezing conditions, the storage stability of drugs can be greatly improved, and the degradation of active ingredients can be reduced. Nitrogen-filled packaging technology, as an effective means to improve drug stability, not only prevents oxidation and hydrolysis, but also combines with other technologies such as freeze-drying and low-temperature storage to maximize drug activity. With the advancement of packaging material technology and the optimization of nitrogen-filled equipment, nitrogen-filled packaging will play a more important role in drug storage, transportation and long-term use, especially in improving the safety and efficacy of antibiotic drugs.

3.3 Nanotechnology Nanotechnology shows great potential in drug development, especially in improving the absorption and delivery efficiency of third-generation cephalosporins *in vivo*. By combining cephalosporins and polymer nanoparticles can not only significantly improve the antimicrobial activity of drugs, but also achieve targeted delivery, and reduce the toxicity to healthy tissues[13]. Such nanoparticles can optimize the release rate of drugs and prolong its action time in the body to reduce the frequency of administration, which is particularly important for patients with long-term treatment. Nanotechnology also shows great advantages in improving drug stability[14]. Studies have shown that cephalosporins wrapped in polymer nanoparticles can effectively protect the β-lactam ring of drugs and delay its degradation under high-temperature and high-humidity conditions[15]. Wrapping drugs in nanoparticles can effectively isolate the contact between drugs and the external environment and prevents degradation caused by light, heat or humidity[16]. By changing the size and shape of nanoparticles, the dissolution rate of drugs can be effectively controlled, and its degradation in the body can be reduced. In traditional drugs, the β-lactam ring of cephalosporins is easily degraded in unstable environments such as high temperature and high humidity, so that their efficacy is reduced. The stability of drugs is significantly improved by being encapsulated in nanoparticles. Studies have shown that the stability of coated cefotaxime improved by about 25% at room temperature, and it showed strong anti-degradation ability in high-temperature and high-humidity environment. Cephalosporins can be active for a long time under more demanding storage conditions, so that their shelf life is extended, and the safety during transportation and storage is improved[17-18]. This research not only enhances the efficacy of drugs, but also provides a new idea for the development and application of antibiotics.

3.4 Optimization of excipients In pharmaceutical prepara-

tions, excipients are not only as a filler, but also can significantly affect the stability of drugs. Appropriate excipients can effectively improve the antioxidant, moisture and light resistance of drugs[19]. In cephalosporin preparations, the addition of antioxidant excipients such as sodium ascorbate and sodium thiosulfate can effectively reduce the oxidative degradation of drugs. When a small amount of antioxidants was added to the formulation of ceftriaxone, the stability of the drug in light was increased by 15% , while the shelf life was also significantly extended. Water is an important factor leading to drug hydrolysis, and especially the β-lactam ring of cephalosporins is very sensitive to water. The addition of anti-moisture excipients such as microcrystalline cellulose and silicon dioxide in the preparation can effectively adsorb the water in the package to prevent the contact between the drug and water and then delay the hydrolysis reaction. After microcrystalline cellulose was added to cefotaxime, its stability in high-humidity environment was increased by 20% – 30%. The selection and optimization of excipients is still an important direction in the improvement of drug stability. By studying the interaction of different excipients and the compatibility between excipients and drugs, the comprehensive stability of drugs can be further enhanced. In addition, reasonable design of the proportion and use conditions of excipients can ensure the stability of drugs and reduce the impact on drug absorption, solubility and so forth.

4 Continuous production process

In recent years, continuous production process has shown great advantages in the preparation of antibiotics. Traditional batch production process often faces the problem of low output and high energy consumption, while continuous production technology can effectively improve the output and reaction control accuracy[20]. In the process of synthesizing cephalosporins, the mass and heat transfer efficiency of reactions can be greatly improved by reducing the reaction system to a micro-scale environment, thus shortening the reaction time and improving the purity of products. When cefotaxime was synthesized by a microreactor, the reaction time was reduced by 30% , and the purity of drugs was increased by 15% – 20%. The application of traditional batch reactors in pharmaceutical industry often leads to limited production capacity and complicated process. By introducing a continuous flow reactor into the production of cephalosporins, efficient continuous production of drugs can be achieved under automated conditions. Especially in mass production, the continuous process can reduce downtime and improve the utilization of the production line. With precise flow and reaction control, continuous production can better control reaction conditions and avoids the generation of by-products due to incomplete or excessive reaction. Due to the precise control of reaction conditions, continuous production process can significantly reduce the differences between batches and ensure the purity and stability of the final product. Compared with traditional batch production, continuous production can save a lot of energy and materials, reduce waste emissions, and thus decrease production costs. In the process of ceftriaxone production by Kockmann *et al*. using a continuous flow reactor, the temperature and pressure of the reaction could be precisely controlled, and the by-products of β-lactam ring degradation were greatly reduced, thus improving the yield and quality of the drug[21].

5 Process automation and intelligent manufacturing

For complex cephalosporin synthesis, the application of process automation system can effectively reduce manual operation errors and improve production efficiency and quality control[22]. In the production process of cephalosporins, the precise control of temperature, pressure, reaction time and other parameters is very important to their quality. The introduction of automatic process control system such as PLC (programmable logic controller) system in the modern process can realize real-time monitoring and automatic adjustment of each production link. During the synthesis of cefotaxime, the process control system can accurately monitor the temperature and pH of key reaction steps, thereby effectively preventing the formation of by-products and greatly improving the purity of the drug. The research of intelligent production line combines the technology of automation control, robot operation and data analysis, which can greatly improve the flexibility and production efficiency of the production line. Through the introduction of intelligent production lines in the preparation process of third-generation cephalosporins, the production of drugs can be completed in a shorter time, and the consistency and quality of products are effectively guaranteed[23-24].

6 Summary and prospects

Third-generation cephalosporins have been widely used in clinical practice, but still face many challenges especially in coping with the continuous development of drug-resistant strains and improving production efficiency[25]. The combination of nanotechnology with other technologies enhancing stability (such as lyophilization and nitrogen-filled packaging) will bring new breakthroughs in drug preparation processes[26]. The combined application of nanoparticle encapsulation, lyophilization and nitrogen filling can further extend the shelf life of drugs and ensure their stability and efficacy in extreme environments. In addition, the surface modification of nanomaterials and the reasonable proportion of different materials can optimize the bioavailability of drugs and promote the development of precision medicine[27]. By further promoting green chemistry technology and enzymatic reaction, pharmaceutical companies can reduce energy consumption and environmental pollution while improving drug output and purity[28]. For example, enzymatic technology can achieve efficient reactions under mild conditions and reduce the formation of harmful by-products. Besides, the application of continuous flow reactors and automated control systems has promoted the development of pharmaceutical industry towards large-scale and stable production, and further ensures the uniformity and consistency of drug quality, laying a solid foundation for achieving higher standards of drug quality[29]. In the fu-

ture, the automation and intelligence of pharmaceutical process will become the mainstream trend, and the introduction of AI and machine learning technology will further optimize reaction conditions and real-time monitoring of the production process to ensure the stability of drug quality and the safety of the production process[30]. At the same time, combined with nanotechnology and intelligent delivery systems, third-generation cephalosporins have the potential to achieve precise targeted delivery and targeted treatment for complex infection sites, and maximize drug efficacy and reduce side effects. With the development of environmentally friendly storage technology, the introduction of active packaging technology, such as intelligent temperature and humidity control materials, will also further improve the storage conditions and stability of drugs, and provide a stronger guarantee for the promotion and use of third-generation cephalosporins worldwide. In conclusion, future research should focus on improving the preparation process and drug stability of third-generation cephalosporins to deal with the increasingly serious problem of antibiotic resistance. Technological innovation and optimization can not only improve production efficiency, but also ensure the efficacy and safety of drugs. Technological innovation can improve drug efficacy and address the growing problem of drug resistance, thus providing strong safeguards for the treatment of complex infections.

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