Intelligent Optimization and Biocompatibility Evaluation of Nano-drug Delivery System

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Abstract: Nano-drug delivery system is of great significance in the field of modern medical drug delivery, and its intelligent optimization and biocompatibility evaluation are the key research directions. This paper discusses the intelligent optimization strategy and the evaluation method and index of biocompatibility around nano-drug delivery system. The intelligent optimization strategies such as environmental response, targeted modification and intelligent controlled release are expounded. With the help of cytotoxicity in vitro, blood compatibility evaluation, animal model experiment in vivo and toxicity evaluation of tissues and organs, the influence of intelligent optimization on biocompatibility was studied. Taking the nano-drug delivery system based on pH response and targeted modification as an example, the results showed that the survival rate of HepG2 cells was 85% when its in vitro concentration was 10 μg/mL. The hemolysis rate was 3%. In vivo experiments, the high-dose group showed mild inflammatory cell infiltration in the liver, and some blood biochemical indexes changed. It is not difficult to see from the research results that intelligent optimization can improve the performance, but the biocompatibility still needs to consider many factors to ensure safety.

1. Introduction

In the field of modern medicine, disease treatment faces many challenges. Efficient and safe drug delivery system is the key to solve these problems [1]. Nano-drug delivery system shows great potential in the field of drug delivery because of its unique nano-size effect, high drug loading and modifiability [2].

Nano-drug delivery system can wrap or adsorb drugs in nano-carriers, and then realize the effective transportation of drugs [3]. However, the traditional nano-drug delivery system is difficult to accurately control the behavior in vivo, and it is prone to problems such as early drug leakage and insufficient targeting [4]. It is very important to intelligently optimize the nano-drug delivery system based on this factor [5]. With the help of intelligent optimization, nano-drug delivery system can respond to specific stimuli in vivo and in vitro, such as changes in pH, temperature and enzyme concentration, so as to realize accurate drug release and targeted delivery.

The biocompatibility of nano-drug delivery system can not be ignored. Nano-drug delivery system with good biocompatibility can reduce the immune response of the body and reduce the side effects [6]. Comprehensive and accurate evaluation of the biocompatibility of nano-drug delivery system is the key prerequisite for its successful clinical application [7]. At present, although a variety of biocompatibility evaluation methods have been developed, how to comprehensively consider different factors and establish a more perfect evaluation system needs further study. At present, although some progress has been made in intelligent optimization and biocompatibility evaluation of nano-drug delivery system, it still faces many challenges. The main purpose of this study is to explore the intelligent optimization and biocompatibility evaluation of nano-drug delivery system, in order to provide valuable reference for the development of this field.

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2. Intelligent optimization strategy of nano-drug delivery system

(1) Environment responsive intelligent optimization

There are many unique physiological and pathological environmental factors in organisms, such as pH, temperature, enzymes, etc. The design of nano-drug delivery system based on these factors is an important intelligent optimization direction [8]. For example, the microenvironment of tumor tissue usually presents a low pH value (pH is about 6.5-7.2), which is significantly lower than that of normal tissue (pH is about 7.4). Using this characteristic, a pH-responsive nano-drug delivery system is designed, which can realize the accurate release of drugs in tumor sites. Such nanocarriers usually contain pH-sensitive chemical bonds, which undergo hydrolysis or structural transformation in acidic environment, thus releasing drugs.

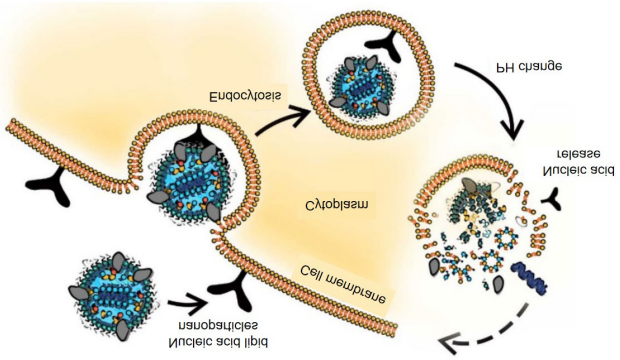

Figure 1 Working principle of Lipid Nanoparticle (LNP) delivery system

Figure 1 clearly shows the key steps of nano-drug delivery system, including the identification, internalization, pH response and final drug release of nanoparticles. LNP first enters the cytoplasm through the cell membrane. This process mainly depends on endocytosis, that is, cells wrap external substances through their membrane structures and ingest them into cells. Once in the cell, nanoparticles will undergo a change in pH, which usually occurs in endosomes or lysosomes. This change of pH value triggers the structural change of nanoparticles, resulting in the release of encapsulated nucleic acid molecules into cytoplasm, thus achieving effective drug delivery.

(2) Intelligent optimization of targeted modification

Targeted modification is the key strategy to realize accurate delivery of nano-drug delivery system. On the one hand, by modifying specific ligands, such as antibodies and peptides, on the surface of nanocarriers, they can specifically recognize and bind to receptors on the surface of target cells, thus realizing active targeting [9]. On the other hand, passive targeting can be achieved through enhanced penetration and retention (EPR) effect by using the size and surface properties of nanoparticles themselves. There is a large gap in the vascular wall of tumor tissue and the lymphatic reflux system is not perfect, so nanoparticles can be passively accumulated in tumor tissue by virtue of this feature.

(3) Intelligent controlled release optimization

Intelligent controlled release optimization aims at precise control of drug release. One of the important means is to construct a nano-valve structure, and control the opening and closing of the valve through external stimuli (such as light, magnetic field, etc.) or internal environmental changes (such as pH, enzymes, etc.), so as to accurately control the drug release rate [10]. In addition, the controlled release of drugs based on the degradation of intelligent carrier materials has also attracted much attention. Some degradable polymer materials, as nano-drug carriers, gradually degrade under specific conditions in vivo, slowly release drugs, and maintain the effective concentration of drugs in vivo.

3. Evaluation method and index of biocompatibility of nano-drug delivery system

3.1. In vitro biocompatibility evaluation

(1)Cytotoxicity assessment

Cytotoxicity assessment is an important means to detect the effects of nano-drug delivery system on cell survival, proliferation and metabolism. Commonly used cell lines include human hepatocellular carcinoma cell line (HepG2), human lung cancer cell line (A549) and so on, which can well simulate the cell environment in vivo. MTT assay and CCK-8 assay are common detection methods. MTT method is based on succinate dehydrogenase in mitochondria of living cells, which can reduce MTT to insoluble blue-purple crystal nail and deposit it in cells, but dead cells have no such function. The cell activity can be indirectly reflected by measuring the absorbance of nail enamel at a specific wavelength. The principle of CCK-8 method is similar to that of MTT method, but the products produced by CCK-8 reagent are more stable and easier to operate.

(2) Evaluation of blood compatibility

Nano-drug delivery system will first contact with blood components after entering the body, so blood compatibility evaluation is indispensable. The main evaluation indexes include hemolysis rate and platelet activation (see Table 1). The hemolysis rate reflects the damage degree of nano-drug delivery system to erythrocyte membrane, which is calculated by incubating nano-drug with erythrocyte suspension, centrifuging and measuring the absorbance of supernatant at a specific wavelength, and comparing with positive and negative controls. Platelet activation is evaluated by detecting the expression of platelet surface markers or platelet aggregation, such as the expression level of P- selectin on platelet surface by flow cytometry.

Table 1 Evaluation index and detection method of blood compatibility of nano-drug delivery system

Evaluation index	Test method	Principle
Hemolytic rate	Spectrophotometric method	After the nano-drug was incubated with red blood cells, the damaged red blood cells released hemoglobin, and the hemolysis rate was calculated by detecting the hemoglobin content in the supernatant.
Platelet activation	The expression of p-selectin was detected by flow cytometry.	When platelets were activated, the expression of P-selectin increased, and its expression level was quantitatively detected by flow cytometry.

3.2. In vivo biocompatibility evaluation

(1) Animal model selection and experimental design

Choosing a suitable animal model is the basis of biocompatibility evaluation in vivo. Rodents (such as mice and rats) are widely used because of their short reproductive cycle, low cost and similar physiological structure to humans. The experimental design needs to consider the administration route (such as intravenous injection, intraperitoneal injection, etc.), dosage, administration frequency and observation period of nano-drug delivery system.

(2) Toxicity assessment of tissues and organs

Toxicity evaluation of tissues and organs is a key link to judge the biocompatibility of nano-drug delivery system in vivo. Through histopathological examination, we can directly observe the morphological effects of nano-drugs on major tissues and organs (such as heart, liver, spleen, lung, kidney, etc.) and judge whether there are inflammation, necrosis and other diseases. At the same time, biochemical indexes in blood or tissues, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflecting liver function, creatinine (Cr) and urea nitrogen (BUN) reflecting renal function, were detected, and the effects of nano-drugs on the functions of tissues and organs were evaluated from the biochemical level.

4. Effect of intelligent optimization on biocompatibility of nano-drug delivery system

4.1. The relationship between intelligent optimization factors and biocompatibility

Environment-responsive intelligent optimization: Taking pH-responsive nano-drug delivery system as an example, its original intention was to realize accurate drug release by using the low pH value of tumor microenvironment. However, this pH-sensitive property may affect biocompatibility to some extent. Under normal physiological pH conditions, nanocarriers need to be stable to avoid drug leakage in advance, but some pH-sensitive materials may slowly degrade in a neutral environment, and the degradation products may have potential toxicity to cells or tissues. On the other hand, when the drug is released rapidly in the slightly acidic environment of tumor, the sudden release of a large number of drugs may trigger a local high-concentration drug effect, which will have a certain impact on the surrounding normal tissues.

Intelligent optimization of targeted modification: Active targeted modification can achieve accurate delivery through ligand-receptor specific binding, which can theoretically reduce the distribution of nano-drugs in non-target tissues, thus reducing the damage to normal tissues and improving biocompatibility. For example, antibody-modified nanoparticles can specifically recognize tumor cell surface antigens, so that nano-drugs can be more enriched in tumor sites. However, some ligands may trigger immune response, especially after repeated administration, the body may produce antibodies against ligands, which will affect the biocompatibility of nano-drug delivery system.

Intelligent controlled release optimization: Intelligent controlled release can maintain a stable effective concentration of drugs in vivo, reduce the toxic and side effects caused by drug concentration fluctuation, and help improve biocompatibility. However, the realization of controlled release mechanism depends on specific carrier materials and structures, and the degradation speed of these materials, degradation products and physical and chemical changes in the process of controlled release may affect biocompatibility.

4.2. Case analysis

A nano-drug delivery system based on dual intelligent optimization of pH response and targeted modification was selected for analysis (see Table 2). The nano-drug delivery system takes polylactic acid-glycolic acid copolymer (PLGA) as the carrier, and the surface of the nano-drug delivery system is modified with monoclonal antibodies against epidermal growth factor receptor (EGFR) on the surface of tumor cells, and at the same time contains pH-sensitive chemical bonds.

Table 2 Optimization of biocompatibility evaluation results of nano-drug delivery system based on pH response and targeted modification

Evaluation index	In vitro experimental results	In vivo experimental results (mouse model)
Cytotoxicity (HepG2 cells)	MTT assay showed that the cell survival rate of untreated group was 100%, and the cell survival rate of the nano-drug delivery system was 85% when the concentration was 10μg/mL. At 50μg/mL, the cell survival rate was 70%.	Histopathological examination of heart, liver, spleen, lung and kidney showed that the low dose group (1mg/kg) was basically normal. In the high dose group (10mg/kg), there was slight inflammatory cell infiltration in the liver.
Blood compatibility	The hemolysis rate is 3% (lower than the safety standard of 5%); Platelet activation test showed that compared with the blank control group, the expression of P- selectin on platelet surface increased by 15% (the difference was statistically significant)	Blood biochemical indexes were detected at different time points after administration. There was no significant change in alanine aminotransferase (ALT) in the low-dose group, but it increased by 20% in the high-dose group. AST increased by 10% in the low dose group and 30% in the high dose group.

From the data in Table 2, it can be seen that the nano-drug delivery system shows good

biocompatibility to some extent, but it still affects some tissues and blood biochemical indexes when used in high dose. This shows that although intelligent optimization can improve the performance of nano-drug delivery system, biocompatibility still needs to consider a variety of factors to ensure its safety and effectiveness.

5. Conclusions

This study focuses on the intelligent optimization and biocompatibility evaluation of nano-drug delivery system. In the aspect of intelligent optimization strategy, environmental response, targeted modification and intelligent controlled release optimization provide effective ways to realize accurate drug delivery and release. Biocompatibility evaluation method covers multiple levels in vitro and in vivo, which lays the foundation for system safety evaluation.

Through the case analysis of intelligent optimization of nano-drug delivery system based on pH response and targeted modification, it can be known that intelligent optimization can enhance its targeting and controlled release performance, but it has complex effects on biocompatibility. The experimental data in vitro showed the changes of cell survival rate and blood compatibility related indexes at different concentrations. Histopathology and blood biochemical indexes were abnormal at high dose in vivo. This shows that while pursuing intelligent optimization of nano-drug delivery system to improve the therapeutic effect, its influence on biocompatibility must be fully considered. Future research should focus on balancing the relationship between intelligent optimization and biocompatibility, further improving the evaluation system of biocompatibility, and deeply exploring the long-term impact of intelligent optimization strategies on various systems in vivo, so as to provide a more solid theoretical and practical basis for the clinical application of nano-drug delivery systems.

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