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Study on the technology of sterilization water for injection in celine bottle

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Abstract. Manufacturers of penicillin bottled sterile injection water often encounter the problem of increased pH of the produced sterile injection water. The qualified range of pH for sterile injection water specified in the Chinese Pharmacopoeia is 5.0 to 7.0, while the actual results of stability testing for penicillin bottled sterile injection water in the near term are often close to the upper limit. This article mainly explores the production process of sterilized injection water in penicillin bottles. The penicillin bottles are pretreated under different conditions, and then sterilized injection water is filled. The effect of pretreatment of penicillin bottles on the pH value and conductivity of sterilized injection water is investigated. After sterilization with a 121 ℃ water bath for 45 minutes, the pH value and conductivity of the sterilized injection water can be reduced, and the stability is good. After processing the penicillin bottles, the injection water is packaged and sterilized. The production process is stable, the product quality meets the requirements, and the long-term and accelerated stability is good.

1. Page layout

At present, small capacity sterilized water for injection used for lyophilized product redissolution or concentrated product dilution is mostly used in ampoules, pre-filled syringes and cillin bottles. Among them, celine bottle sterilization water for injection is widely accepted because of its convenient use, cheap price and relatively simple production process. However, the stability of small-capacity cillin bottle sterilization water for injection is poor, especially the specification of 0.5 ml of Cillin bottle sterilization water for injection, which is in high demand in the vaccine industry. The poor stability of the water for injection is mainly due to the gradual increase in pH and conductivity of the water for injection during storage, which exceeds the standard requirements.

The bottled sterilized water for injection is the water for injection prepared according to the injection production process. The production process is that the water for injection is sterilized, divided into the bottled water for injection, and then prepared by plugging and pressing the cap. It is widely used in the pharmaceutical industry as a vaccine thinner. The pH and conductivity of water for injection will increase, which will affect the quality of water for injection [1].

The main reason for the increase in pH and conductivity of the bottled sterilized water for injection is that the boron, silicon and sodium oxides in the inner wall of the glass bottle will slowly precipitation, react with the water for injection, hydrogen ions and sodium ions exchange, and the ONa in the original skeleton transforms into OH, resulting in an increase in pH. In the leaching process, the leaching rate of boron and sodium in the glass is basically the same, at the same time, the content of silica in the glass has a direct effect on the increase of pH, the higher the content, the slower the leaching rate, the slower the pH increase. The study of reaction potential can explain the reaction between glass and water. Although 12 items such as acid resistance, alkali resistance and internal stress were tested according to the quality standard of Xilin bottle, the problem of increased pH could not be solved. In comparison, the structure and composition of glass are crucial. By exploring and studying the process of glass structure of reaction potential, the influence of water on glass structure and performance and the degree of corrosion of glass can be understood [2]. In addition, the firing temperature of the glass tube of the raw material of the glass tube injection bottle will also affect the leaching of the inner surface. Heat treatment has an important influence on the change of pH value. After heat treatment, Na leaching from glass slows down and the time becomes longer, which provides a solution for the pH increase of water for injection in Xylin bottle.

pH value and conductivity are important indicators for evaluating water for injection. pH value is a convenient way to express the activity of hydrogen ions in aqueous solution, which can be measured by pH agent (pH meter). Conductivity is a physical quantity that represents the electrical conductivity of an object, and its value is the reciprocal of the resistivity of the object, in uS /cm. The water molecules in pure water will undergo a certain degree of ionization to produce hydrogen ions and hydroxide ions, so the conductivity of pure water is very weak, but it also has a measurable conductivity. The conductivity of water is closely related to the purity

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of water, the higher the purity of water, the lower the conductivity, and vice versa. When gases such as carbon dioxide in the air dissolve in water and interact with water, corresponding ions can be formed, thereby increasing the conductivity of water. When the water contains other impurity ions, it will also increase the conductivity of the water. According to the Pharmacopoeia of the People's Republic of China (2020 edition), when the pH value of water for injection at 25℃ is 5.0-7.0, and the marked load is 10ml or less, the conductivity limit is 25μs /cm, and the measured conductivity value is not greater than the limit value, it is judged to be in compliance with the regulations [3].

The main reason for the increase in pH and conductivity of sterilization water for injection in Siling bottle was the material of Siling bottle. In this study, the Siling bottle was pretreated to remove salt ions from the inner wall of Siling bottle, reducing the possibility of salt ions separating from the inner wall of Siling bottle after subpacking sterilization water for injection, and the feasibility of subpacking sterilization water for injection after subpacking under different conditions was discussed.

2. Materials and methods

2.1. Materials

Water for injection; Celine bottle; Washable rubber plug; Aluminum-plastic composite cover.

2.2. Experimental method

2.2.1 Study on sterilized water for injection in untreated Cillin bottle

The bottles were taken and produced according to the normal production process, that is, the bottles were cleaned, dry roasted and then divided into 0.6ml/ bottle of sterilized water for injection. After the packaging, plug and cap were added, and pH and conductivity of the finished products were tested. Long-term (room temperature) and accelerated (40℃) stability of the samples were studied. pH value and conductivity were tested in accordance with the Pharmacopoeia of the People's Republic of China (2020 edition).

The bottle was dried and sterilized in a dry hot oven at 320℃ and then used. The non-washing rubber plug was packed with a double-layer breathing belt and sterilized by wet heat at 121℃ in a pressure cooker for 60 minutes.

Sterilized water for injection was first sterilized at 121℃ for 60min, and then filtered by 0.2μm filter element.

2.2.2 Study on sterilized water for injection in pre-treated cillin bottle

The bottle was pretreated first, and the treatment conditions were as follows: (1) 121℃ water bath for 15min; (2) Treatment with 121℃ water bath for 45min; (3) 121℃ water bath treatment for 60min; (4) Treatment with 121℃ water bath for 90min. The treated cillin bottles were cleaned and dry roasted, and then sterilized injection water was subpacked with 0.6 ml/ bottle and the filling range was controlled within ±5%. After subpacking, plug and cap were added, and pH and conductance of the finished products were tested. According to the above conditions, the optimal processing conditions are determined.

The bottle was dried and sterilized in a dry hot oven at 320 °C and then used. The disposable rubber plug was packed with a double-layer breathing belt, and the pressure cooker was sterilized at 121 °C for 60 min with wet heat. The water for injection was sterilized at 121 °C for 60 min, and then filtered through a 0.2μm filter.

According to the above treatment conditions, 3 groups of sterilized water for injection were prepared continuously, and the stability was investigated. pH value and conductivity were tested in accordance with the Pharmacopoeia of the People's Republic of China (2020 edition).

2.3 Test instrument

PH meter, conductivity meter, pressure cooker, dry heat oven, super clean table, handheld gland.

3. Test result

3.1. Experimental results of sterilized water for injection in untreated cillin bottle

3.1.1 Long-term pH stability of untreated celine bottled sterilization water for injection

Table 1. Long-term pH stability of untreated cillin bottled sterilized water for injection at 12 months.

Long-term Stability (pH)	0Month	3Month	6Month	9Month	12Month
WCL001	6.5	6.8	6.7	6.7	6.9
WCL002	6.5	6.9	6.7	6.7	6.9
WCL003	6.5	6.8	6.9	6.9	7.0

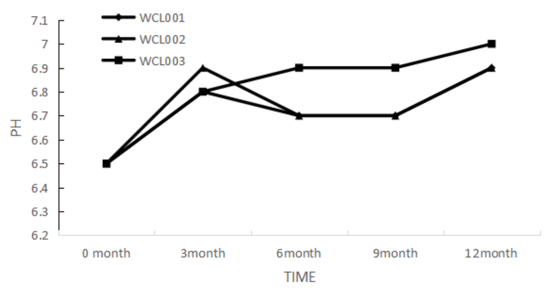

Fig. 1. Long-term pH stability curve of untreated cillin bottled sterilized water for injection at 12 months.

As can be seen from Table 1 and FIG. 1, the long-term stability of pH value of the three groups of samples showed an upward trend after cleaning and drying the untreated cillin bottles and filling sterilization water for injection, and the rise rate was faster in the first three months.

3.1.2 pH accelerated stability of untreated celine bottled sterilization water for injection

Table 2. pH accelerated stability of untreated Cillin bottled sterilized water for injection at 6 months.

Accelerated stability (pH)	0 Month	1 Month	2 Month	3 Month	6 Month
WCL001	6.5	6.8	6.9	6.7	7.1
WCL002	6.5	6.9	7	7	7.2
WCL003	6.5	7	7	7	7.1

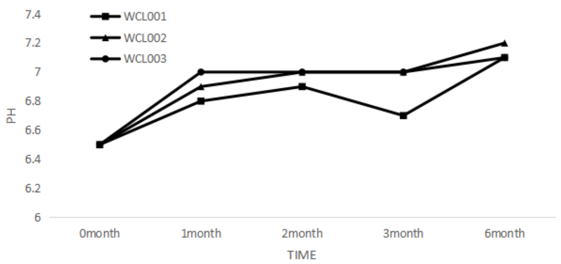

Fig. 2. pH accelerated stability curve of untreated cillin bottled sterilized water for injection for 6 months.

From Table 2 and FIG. 2, it can be seen that the untreated penicillin bottles were washed and dried before being filled with sterilized injection water. The pH values of the three groups of samples accelerated (40 °C) and showed an upward trend in stability. The pH value exceeded the pharmacopoeia standard in the sixth month.

3.1.3. Long-term stability of conductivity of sterilized water for injection in untreated cillin bottles

Table 3. Long-term stability of 12-month conductivity of untreated cillin bottled sterilized water for injection.

Long-term stability (conductivity)	0 Month	1 Month	2 Month	3 Month	6 Month
WCL001	5	11	12	14	18
WCL002	4	11	12	16	18
WCL003	5	11	11	14	18

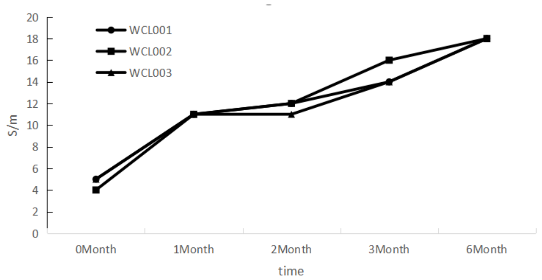

Fig. 3. Accelerated conductivity stability curve of untreated cillin bottled sterilized water for injection for 6 months.

As can be seen from Table 3 and FIG. 3, the long-term stability of the electrical conductivity of the three groups of samples showed an upward trend after cleaning and drying the untreated celine bottles and filling sterilization water for injection, and the increase rate was faster in the first three months.

In summary, from FIG.1, 2, and 3, it can be seen that the long-term stability of pH and conductivity of injection water after packaging has shown an upward trend, and the long-term stability of pH value of injection water has reached the upper limit of 7.0 specified in the Pharmacopoeia, which poses a risk of exceeding the quality standard. After accelerating for 6 months, the pH value of injection water has exceeded the upper limit of 7.0 specified in the Pharmacopoeia.

3.2. Study on bottled sterilized water for injection of cillin treated under different conditions

3.2.1. Accelerated test results of pH value after treatment with cillin bottle water bath

Table 4. pH at 121°C for different pretreatment times 0 and 1 month.

Processing time	0 days pH	1 month pH
15min	6.5	6.9
45min	6.4	6.6
60min	6.3	6.6
90min	6.4	6.6

3.2.2. Conductivity acceleration test results after treatment with Silene bottle water bath

Table 5. Conductivity of pretreatment at 121°C for 0 days and 1 month.

Processing time	0 days	1 month
15min	4	11
45min	3	8
60min	5	8
90min	4	7

As can be seen from the table 4 and Table 5, the accelerated test results of 121°C water bath for 45min, 60min and 90min for 1 month have little change, but they are all better than 121°C water bath for 15min, so the pretreatment method of 121°C water bath for 45min is adopted for the next study.

3.3. Study on the stability of cillin bottle after pretreatment

After treatment at 121 °C for 45 min, three groups of filling were carried out to investigate the 12-month long-term stability and 6-month accelerated stability, and the average data of the three groups of untreated and pre-treated sterilization water for injection of Cillin bottle were compared.

3.3.1 Comparison of the mean value of pH long-term stability data of pre-treated and untreated cillin bottles

Fig. 4. Comparison trend of the mean value of long-term pH stability results of pre-treated and untreated cillin bottles.

As can be seen from FIG. 4, the mean pH long-term stability results of the three samples of the Cillin bottle treated with 121 ℃ water bath for 45 minutes after filling sterilization water for injection were lower than those of the untreated Cillin bottle at month 0, month 3, month 6, month 9 and month 12. Long-term pH stability data improved.

3.3.2 Comparison of the mean value of pH acceleration stability data of pre-treated and untreated Cillin bottles

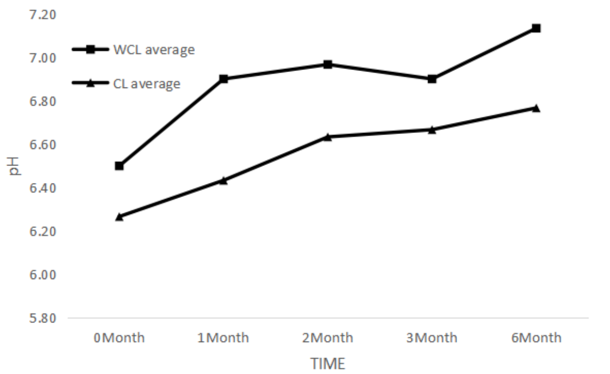

Fig. 5. Comparison trend of the mean value of pH acceleration stability results of pre-treated and untreated Cillin bottles.

As can be seen from FIG. 5, the mean pH accelerated stability results of the three samples of the Cillin bottle treated with 121 ℃ water bath for 45 minutes after filling sterilization water for injection were lower than those of the untreated Cillin bottle at month 0, month 1, month 2, month 3 and month 6 after filling sterilization water for injection. The pH accelerated stability data increased at a slower rate, and the pH accelerated stability data for all three groups at 6 months did not exceed the 7.0 required by the pharmacopeia.

3.3.3 Comparison of the mean value of long-term stability data of conductivity of treated and untreated Cillin bottles.

As can be seen from FIG. 6, the average curves of the electrical conductivity data of the three groups of samples after pretreatment were below the curves of untreated Cillin bottles, and the mean values at month 0, month 3, month 6, month 9 and month 12 were all lower than those of untreated Cillin bottles, and the water for filling and sterilization for injection after water bath treatment. Long-term conductivity stability has improved.

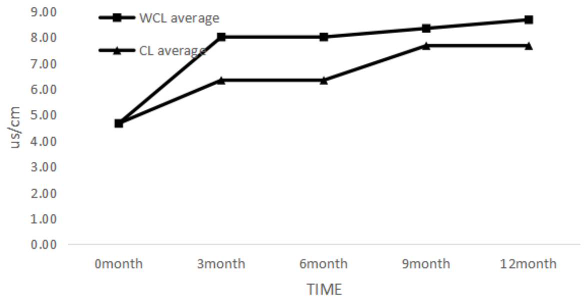

Fig. 6. Long-term stability of the conductivity of water for injection after pretreatment of cillin bottle for 45min

3.3.4 Comparison of mean value of conductivity acceleration stability data of treated and untreated Cillin bottles

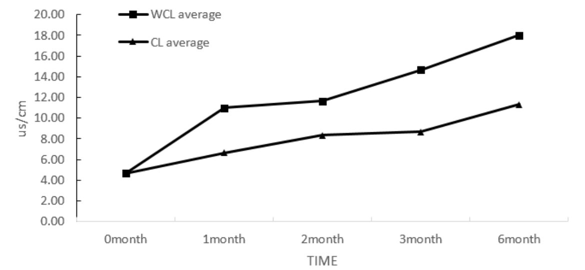

Fig. 7. Accelerated stability of conductivity of injection water after pre-treatment with penicillin bottles for 45 min.

As can be seen in FIG. 7, the mean values of accelerated conductivity data of the Cillin bottle treated with 121 ℃ water for 45 min and filled with sterilized water for injection were lower than those of the untreated Cillin bottle at month 0, month 1, month 2, month 3 and month 6, and the conductivity data of the Cillin bottle treated with water bath and refilled with sterilized water for injection were significantly improved.

4.Outlook

The pH of cillin bottle sterilized water for injection increased to different degrees after subpacking. In the Cillin bottle treated with 121 ℃ water bath for 45 minutes, the pH and conductivity of the refilling water showed a slow increase trend. Compared with the Cillin bottle not treated with water bath sterilization, the rise rate was significantly slower. And the long-term stability of 12 months and accelerated stability of 6 months pH and conductivity are in line with the quality standards of sterilization water for injection. Therefore, the water bath sterilization pretreatment at 121 ℃ for 45min can improve the pH and conductivity of the sterilized water for injection, effectively solve the problem that the pH of the sterilized water for injection exceeds the quality standard during the validity period of the product, and provide solutions for the pH increase of the sterilized water for injection.

Pharmaceutical packaging materials play an important role in ensuring the stability of drugs, so pharmaceutical packaging materials will directly affect the safety of drugs. Packaging materials and containers that come into direct contact with drugs are part of drugs. Especially in pharmaceutical preparations, some dosage forms themselves exist dependent on packaging, so it is necessary to carry out research on the compatibility of drugs with glass bottles, rubber seals and PVC composite films [4]. Meanwhile, the compatibility research of pharmaceutical packaging materials and drugs has been written into regulations [5]. Compatibility research is an effective way to ensure the quality of pharmaceutical packaging materials, and it is also an important content of drug quality and safety evaluation. It is believed that the continuous in-depth research on the compatibility of pharmaceutical packaging materials under the leadership of regulatory departments and scientific research institutions will promote the continuous improvement of the production level of pharmaceutical packaging materials in China faster.

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