YY

PHARMACEUTICAL INDUSTRY STANDARD

OF THE PEOPLE'S REPUBLIC OF CHINA

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YY/T 0308-2015

Replacing YY/T 0308-2004

Medical sodium hyaluronate gel

医用透明质酸钠凝胶

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Foreword

This Standard was drafted in accordance with the rules given in GB/T 1.1-2009.

This Standard replaces YY 0308-2004 *Medical sodium hyaluronate gel*. Compared with YY 0308-2004, the main technical changes are as follows:

- Added terms, definitions and requirements for shear viscosity, elasticity, viscoelastic and weight average molecular weight (see 3.2~3.5, 5.8, 5.9, 5.10.2 of this edition);
- Deleted dynamic viscosity's terms, definitions and requirements (3.2 of this edition; 5.8 of 2004 edition);
- Modified requirements for effective usage (see 5.2 of this edition; 5.2 of 2004 edition);
- Modified requirements for light transmittance (see 5.5 of this edition; 5.5 of 2004 edition);
- Modified requirements for protein content (5.11 of this edition; 5.10 of 2004 edition);
- Added requirements for refractive index (see 5.13 of this edition);
- Modified ethanol residues indicator (see 5.15 of this edition; 5.13 of 2004 edition);
- Modified bacterial endotoxin Indicator (see 5.17 of this edition; 5.15 of 2004 edition);
- Deleted description on biological test methods (5.17.2~5.17.7 of 2004 edition);
- Modified method for the determination of sodium hyaluronate (see Appendix A of this edition; Appendix A of 2004 edition).

Please note that some of the content of this document may involve patents; the issuing agency of this document does not undertake the responsibility for the identification of these patents.

This Standard was proposed by China Food and Drug Administration.

This Standard shall be under the jurisdiction of Shandong Food and Drug Administration of China Food and Drug Administration.

Introduction

Sodium hyaluronate is a naturally occurring linear polysaccharide; it is a disaccharide structural unit composed of (1→4) -β-D-glucuronide and (1→3)-2-acetamido-β-D-glucose. Medical sodium hyaluronate gel made after deep processing based on the characteristics of sodium hyaluronate is a non-toxic, water-soluble and biocompatible new biomaterial which shall be used for eye surgery, intra-articular lubrication, postoperative tissue adhesion after preventive surgery.

When medical sodium hyaluronate gel is used for intra-articular injection, it shall require molecular weight closer to sodium hyaluronate in normal human synovial fluid. In eye surgery, the high shear viscosity value is especially important for surgical procedures. When it is used for postoperative tissue adhesion after preventive surgery, it mainly relies on biological barrier effect generated by high viscoelastic. Since shear viscosity values are closely related to measured temperature and shear rate, this Standard chooses shear viscosity at low shear rate (i.e. surgical instruments are operating under viscoelastic agents of anterior chamber). Meanwhile, considering ophthalmic viscoelastic and intra-articular injection products, its elasticity is also closely related to the clinical application.

Sodium hyaluronate, as an implantable biomedical materials, the content of all kinds of impurities must be strictly controlled, so as to ensure the safety and effectiveness of the use of the product. Considering that the drying and purification of sodium hyaluronate in the production process requires the use of organic solvents, but sodium hyaluronate is a difficult dry polymer material, and the organic solvent is difficult to completely evaporate; trace organic solvent in sodium hyaluronate causes the product have varying degrees of stimulation to patients during the use. Therefore, in order to minimize the adverse effect of the product on the patient, taking into account the current level of technology production, it is necessary to define a reasonable residual amount of ethanol. Considering that some manufacturers may use organic solvents besides ethanol, it must make appropriate technical requirements and test methods.

Some sodium hyaluronate is extracted from animal tissue or organ, so there may be the risk of carrying the virus and infectious agents. The manufacturer shall take effective measures to control and effectively remove or inactivate animal tissues or organs for viruses and infectious agents.

NOTE: Control measures on viruses and infectious agents in animal tissues shall refer to YY/T 0771 standards.

Some sodium hyaluronate is prepared by microbial fermentation. During the fermentation process, strain may produce metabolite by itself. The

Medical sodium hyaluronate gel

1 Scope

This Standard specifies the classification, requirements, inspection rules, marks and packaging of medical sodium hyaluronate gel.

This Standard is applicable to medical sodium hyaluronate gel. The application of medical sodium hyaluronate gel includes viscoelastic agents for eye surgery, lubricants for intra-articular injection and barriers for surgical operation.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

GB/T 16886.1 *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*

Pharmacopoeia of the People's Republic of China 2010 English Edition, 2 Volumes

3 Terms and definitions

The following terms and definitions apply to this document.

3.1 medical sodium hyaluronate gel

Gel-like solution formulated with sodium hyaluronate and for human.

3.2 shear viscosity

Ability to resist deformation rate of fluid by shear force.

NOTE 1: Quantitatively, shear viscosity is shear stress divided by shear rate under constant shear rate.

NOTE 2: Shear Viscosity is represented in Pa•s or usually in mPa•s.

NOTE 3: Shear rate refers to fluid velocity gradient, in s^{-1}.

Try to take out the content in each single package in normal used method. After accurately weighed, it is divided by medical sodium hyaluronate gel density (ρ = 1.01 g/mL), the obtained value shall not be less than 93% of the labelled amount, and the average value shall not be less than the labelled amount.

5.3 Identification

Medical sodium hyaluronate gel shall have the following reactions:

a) Product a purple red solution according to the method in Appendix A;

b) Take 0.1g of medical sodium hyaluronate gel. Use distilled water for 10-fold dilution. Add 2~3 drops of cetyl pyridinium chloride (1→20) to generate white flocculent precipitate;

c) Take 0.1g of medical sodium hyaluronate gel. Use distilled water for 10-fold dilution. Use platinum gold to burn, and the flame is yellow.

5.4 Content

Determine it according to the method stipulated in Appendix A and the sodium hyaluronate content should be 90.0%~120.0% of the labelled mass concentration.

5.5 Light transmittance

Use sodium chloride solution of which the concentration is 9 g/L for 10-fold dilution of medical sodium hyaluronate gel. Take preparation solution as blank control. Determine it according to the method stipulated in Appendix IV A of *Pharmacopoeia of the People's Republic of China 2010 English Edition, 2 Volumes*. Record the spectral transmittance within 300 nm ~ 800 nm. Draw a line graph of light transmittance to wave length. At a wavelength within a range of 300 nm ~ 800 nm, the transmittance shall not be less than 98.0%.

5.6 pH

Use distilled water for equivalent mass ration dilution of medical sodium hyaluronate gel. Determine pH according to the method stipulated in Appendix VI H of *Pharmacopoeia of the People's Republic of China 2010 English Edition, 2 Volumes*, and pH shall be within 6.8~7.6.

5.7 Osmotic pressure

Make direct sampling. Determine it according to the method stipulated in Appendix IX G of *Pharmacopoeia of the People's Republic of China 2010 English Edition, 2 Volumes*, and the osmolarity of medical sodium hyaluronate gel shall be 270 mOsmol/kg ~ 350 mOsmol/kg.

5.11 Protein content

Determine in the method stipulated in Appendix C. The protein content in sodium hyaluronate shall not be greater than 0.1% (mass fraction).

5.12 UV absorption

Use sodium chloride solution of which the concentration is 9 g/L for 10-fold dilution of medical sodium hyaluronate gel. Determine in the method stipulated in Appendix IV A of *Pharmacopoeia of the People's Republic of China 2010 English Edition, 2 Volumes*, and the sodium hyaluronate solution concentration shall be 1/10 of the original concentration during determination of UV absorption. The results need converting to the absorption value at the original labelled concentration. The absorbance at 280nm and 260nm of wavelengths shall not be greater than 1.0.

5.13 Refractive index

At (25±2)°C, determine in the method stipulated in Appendix VI F of *Pharmacopoeia of the People's Republic of China 2010 English Edition, 2 Volumes*, and the refractive index of medical sodium hyaluronate gel for ophthalmic use shall be 1.32~1.35.

5.14 Heavy metal content

Determine in the third method in Appendix VIII H of *the People's Republic of China 2010 English Edition, 2 Volumes*. Take and put 1.0 g of medical sodium hyaluronate gel into a sample tube, 1.0 mL of standard lead solution in a standard control tube; the heavy metal content shall not be greater than 10 μg/g.

5.15 The residual amount of ethanol

Determine in the method stipulated in Appendix D. The residual amount of ethanol in medical sodium hyaluronate gel shall not be greater than 200 μg/g.

NOTE: Ethanol is one of the more commonly used purified sodium hyaluronate solvents. If other solvents are used, it shall determine the suitability of the selected solvent and stipulate the indicators and methods for the residual amount.

5.16 Sterility

Inspect in the method stipulated in Appendix XI H of *the People's Republic of China 2010 English Edition, 2 Volumes*. Medical sodium hyaluronate gel should be sterile.

5.17 Bacterial endotoxin

Use bacterial endotoxin test water to dilute the medical sodium hyaluronate gel.

e) Expiration date;

f) Storage conditions.

7.2 The following marks shall be on the small packaging or accompanying documentation:

a) Product's name;

b) Manufacturer's name and address;

c) Classification and specification;

d) Production batch or date;

e) Expiration date;

f) Labelled mass concentration of sodium hyaluronate, in mg/mL;

g) Words or graphics of "Sterile", "Sterilization method", "Disposable", "It must NOT be used when packaging is damaged";

h) Storage conditions;

i) Shear viscosity, elasticity, and the average molecular weight.

NOTE: It shall use graphical symbols in YY/T 0466.1 to meet the aforementioned requirements.

8 Packaging

It shall use a dose packaging for the small packaging of medical sodium hyaluronate gel shall use. Packaging design of convenient use is preferred.

NOTE: Appropriate packaging: for example, put it into a glass syringe, put the protective cap on the syringe cone and seal it in a single packaging container (bag or plastic blister).

Syringe plunger shall be made by butyl rubber.

Take an appropriate amount of medical sodium hyaluronate gel (accurate to 0.1 mg). Add distilled water to dilute it till about 50 μg of sodium hyaluronate is contained in per milliliter. Mix and shake it thoroughly till it is completely dissolved. Extract 1 mL and put it in the test tube.

A.5 Procedures

A.5.1 Prepare glucuronide standard solutions according to Table 1.

A.5.2 Place test tubes of standard solutions and sample tube in an iced water bath. Gradually add 5 mL of 0.025 mol/L sulfate sodium tetraborate in each tube (store it in a 4°C refrigerator for at least 2 h before use). Well shake it while adding. After adding and thorough mixing, put it in a boiling water bath to boil for 15 min. Then take it out and cool in the iced water bath. Add 0.2 mL of carbazole ethanol solution into each test tube. After thorough shaking, heat it in a boiling water bath for 15min, then cool it to room temperature. Use #0 test tube as reference. And use spectrophotometer to determine the absorbance of each standard tube and sample tube at 530 nm.

Table A.1 Glucuronic acid (GA) standard solution concentration

Tube No.	0	1	2	3	4	5
GA standard solution / mL	0	0.2	0.4	0.6	0.8	1.0
Distilled water /mL	1.0	0.8	0.6	0.4	0.2	0
GA content / (μg/mL)	0	10	20	30	40	50

A.5.3 Use standard tube to draw the absorbance - concentration curve. Based on the absorbance of sample tube, check glucuronic acid content in sample tube from the standard curve.

A.6 Result calculation

Calculate mass concentration of sodium hyaluronate c, in milligrams per milliliter, according to equation (A.1):

$$c = 2.07\ \rho_1 \frac{m_2 \times d_1}{m_1 \times d_2} \qquad \text{.....(A.1)}$$

Where,

m_1 - Medical sodium hyaluronate gel mass, in micrograms (μg);

m_2 - Medical sodium hyaluronate gel and distilled water mass, in milligrams (mg);

d_1 - Medical sodium hyaluronate gel density, 1.01 g/mL;

Appendix B

(Normative)

Determination of weight average molecular weight and molecular weight distribution coefficient

B.1 Principle

Light scattering method is a method of measuring absolute molecular weight of polymers. Polymer solution can be regarded as inhomogeneous. When light passes through it, the incident light scattering will occur. The scattered light intensity is much higher than the pure solvent and closely related to the molecular chain of polymer morphology, concentration, light scattering angle and refractive index increment (dn/dc). Therefore, scattered light intensity (I_0) of different concentrations (c) of the polymer solution at different scattering angles (θ) shall be obtained. And its weight average molecular weight (M_w) shall be calculated. In order to obtain the molecular weight distribution coefficient, it shall use laser light scattering - gel permeation chromatography (LLS-GPC)[1)].

B.2 Apparatus

Analytical balance, laser light scattering instrument, differential detector, HPLC pump, column oven, guard column, chromatographic column used SD805 / 806, TSK 5000pw-TSK6000[2)]) or other suitable chromatographic columns, and injector ring.

B.3 Solution preparation

B.3.1 The mobile phase (recommended): 0.1mol/L sodium nitrate - 0.02% sodium azide: accurately prepare 0.1mol/L sodium nitrate - 0.02% sodium azide, and use 0.22 μm filter membrane to filer.

B.3.2 Sample solution preparation: accurately weigh sample and use the aforementioned mobile phase to dissolve and dilute it to appropriate concentration. Use 0.22 μm filter membrane to filer.

B.4 Procedures

B.4.1 Refractive index increment (dn/dc): use mobile phase to dilute sodium hyaluronate gel to different concentration gradients; use laser to detect the same wavelength measurement at room temperature.

B.4.2 Connect chromatographic column with laser light scattering instrument

Appendix C

(Normative)

Determination of protein content

C.1 Principle

Colored reaction shall occur between Folin phenol test solution with protein in solution and its color intensity shall be proportional to the concentration of protein.

C.2 Apparatus

Analytical balance, spectrophotometer or equivalent device, swirl mixer or equivalent device.

C.3 Solution preparation

Test solution shall be prepared as follows:

a) Reagent A: weigh 1.0 g of hydrated copper sulfate ($CuSO_4 \cdot 5H_2O$) and add water to dissolve and dilute it to 100 mL.

b) Reagent B: weigh 2.0 g of hydrated potassium sodium tartrate ($KNaC_4H_4O_6 \cdot 4H_2O$) and add water to dissolve and dilute it to 100 mL.

c) Reagent C: weigh 25.0 g of anhydrous sodium carbonate and 5 g of sodium hydroxide, and add water to dissolve and dilute it to 250 mL.

d) Reagent D: before use, mix Reagent A and Reagent B of same amount.

e) Reagent E: before use, mix one Reagent D and 10 Reagent C.

f) Reagent F: before use, take Folin phenol solution (Folin - phenol test solution) for 10-fold dilution.

NOTE: All experimental reagents used are of analytical grade.

C.4 Preparation of standard solution

C.4.1 Accurately weigh 50 mg of bovine serum albumin reference vacuum dried by phosphorus pentoxide. Add water to dissolve and dilute to 250 mL (about 200 μg/mL).

C.4.2 Accurately pipette 1.0 mL, 2.0 mL, 4.0 mL, 5.0 mL, and 10.0 mL of the

Appendix D

(Normative)

Determination of the residual amount of ethanol (gas chromatography)

D.1 Principle

Separate the ethanol for test and other components by headspace gas chromatography. Use hydrogen flame ionization detector to detect. Compare the obtained ethanol peak and the ethanol peak obtained from external standard.

D.2 Apparatus

D.2.1 Gas chromatograph equipped with hydrogen flame ionization detector and capillary column system. It requires that the signal generated by the determined ethanol under the minimum detection concentration 2 times instrument noise.

D.2.2 Chromatographic data processor

D.2.3 Capillary column: selection of a suitable capillary column

D.2.4 Micro-injector

D.2.5 Thermoelectric oven or headspace automatic sampler

D.3 Preparation of ethanol standard solution

Put an appropriate amount of HPLC grade ethanol in a measuring flask. Accurately weigh it. Use purified water to dilute to scale. Well shake it and make a standard stock solution of which 1 mL contains 1 mg. Store it at 4°C. The validity is 1 month. Before use, take the aforementioned standard stock solution and dilute it to 20 μg/mL ~ 200 μg/mL standard solution.

D.4 Operating conditions

D.4.1 Column temperature: 60°C, maintaining for 2 min.

D.4.2 Gasification chamber temperature: 200°C; testing room temperature: 250°C.

D.5 Procedures

Take 1 g of medical sodium hyaluronate gel. Accurately weigh it and place in a

References

[1] YY 0033 Good manufacture practice for sterile medical devices

[2] YY/T 0287 Medical devices - Quality management systems - Requirements for regulatory purposes

[3] YY/T 0466.1-2009 Devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements

[4] YY/T 0771.1-2009 Medical devices utilizing animal tissues and their derivatives Part 1: Application of risk management

[5] YY/T 0771.2-2009 Medical devices utilizing animal tissues and their derivatives Part 2: Controls on sourcing, collection and handling

[6] YY/T 0771.3-2009 Medical devices utilizing animal tissues and their derivatives Part 3: Transmissible spongiform encephalopathy (TSE) confirmation of factor removal and inactivation

[7] ISO 13408-1 Aseptic processing of health care products - Part 1: General requirements

[8] ISO 13408-2 Aseptic processing of health care products - Part 2: Filtration

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