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GROUP STANDARD

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Synthetic Polyisoprene Rubber For Pharmaceutical Packaging

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PREFACE

The test method and performance index of synthetic polyisoprene rubber for medicinal packaging are specified in this standard.

Synthetic polyisoprene rubber for medicinal packaging refers to the production of rubber seals such as medicinal rubber plugs and gaskets for processing, with isoprene monomer 1,4-polyisoprene rubber for solution polymerization.

This standard is based on GB/T 1.1 rules.

The appendix to this standard is a normative appendix.

This standard is proposed by the China Medical Packaging Association.

This standard is returned by the China Medical Packaging Association.

The main drafting unit of this standard: Shandong Province Pharmacetical Glass Co., Ltd.

This standard participating drafting unit: Shanghai Food and Drug Packaging Materials Testing Institute, Qingdao University of Science and Technology high-performance polymer and molding technology teaching Department of Engineering Research Center, Maoming Luhua Chemical Co., Ltd., Fushun Yikesi New Materials Co., Ltd., Hubei Huaqiang Technology Co., Ltd., Shijiazhuang First Rubber Technology Co., Ltd., Jiangsu Bosheng Medical New Materials Co., Ltd., Jiangsu Hualan Pharmacetical New Materials Co., Ltd..

The main drafter of this standard: Yuan Hengxin, Lu Jiwei, Wang Jingju, Chen Dongmei, Cui Guangjun, Wu Guoxu, and Xie Haixian.

This standard was first released on May 11, 2016.

WARNING: Personnel using this standard should have the practical experience of working in a regular laboratory. This standard is not intended to involve the possibility of occurrence due to the use of this standard

The user is responsible for taking appropriate safety and health measures and ensuring compliance with the conditions stipulated in the relevant national regulations.

Synthetic Polyisoprene Rubber For Medicinal Packaging

1 Scope

This standard sets out the technical requirements,requirements for transportation and storage, test methods, inspection rules and marking, packaging, etc. of synthetic polyisoprene rubber for medicinal packaging.

This standard is suitable for the production of synthetic 1,4-polyisoprene rubber used in rubber seals such as medicinal rubber plugs and gaskets.

2 Normative reference document

The following documents are essential for the application of this standard. For reference documents with reference dates, only the version of the reference date applies to this standard.

The latest version(including all amendments) of any reference document not dated applies to this standard.

GB/T 1.1 Guidelines for Standardization Work Part I: Structure and Preparation of Standards

GB/T 528 Determination of tensile stress and strain properties of Vulcanized rubber or thermoplastic rubber

GB/T 1232.1 Determination of disc shear viscometers for unvulcanized rubber-Part 1: Determination of Mooney viscosity

GB / T 3516 Determination of Rubber Solvent Extraction

GB / T 4498 Determination of rubber ash

GB/T 6038 Rubber test ingredients, mixing and vulcanization equipment and operating procedures

GB/T 7764 Rubber Identification Infrared Spectrometry

GB/T 15340 Natural, synthetic rubber sampling and sample preparation method

GB / T 24131 Determination of volatile content of raw rubber

GB / T 30918 Evaluation Method for Polymerized Isoprene Rubber(IR)

GB/T 6682 Analysis Laboratory Water Specification and Test Method

GB/T 19187 Sample check procedure for synthetic gum

People's Republic of China Pharmacopoeia 2015 4th part general rule 0512: High Performance Liquid Chromatography

People's Republic of China Pharmacopoeia 2015 4th part general rule 0411: Inductively coupled plasma atomic emission spectrometry

People's Republic of China Pharmacopoeia 2015 4th part general rule 0406: Atomic Absorption Spectrophotometry

3 Technical requirements

Product technical indicators should meet the requirements of Table 1.

Table 1 Technical specifications for the synthesis of polyisoprene rubber for medicinal packaging

Item			Specification	Test method
Appearance			colorless, white to light yellow rubber block, uniform color, no impurities, oil	visual inspection
Mooney viscosityML（1+4）100℃/MU			Nominal value±5	GB/T 1232.1
*Identification (infrared spectroscopy)			Consistent with the Standard Atlas	GB/T 7764
Volatility /%			≤0.7	GB/T 24131
Ash/%			≤0.5	GB/T 4498
* Acetone extract/%			≤2.0	GB/T 3516
Metal elements	* Calcium /%		≤0.1	Appendix A
	* Iron /%		≤0.003	
	*Copper /%		≤0.0003	
	* Lead /%		≤0.0003	
	*Chromium /%		≤0.0003	
	* Cadmium /%		≤0.0003	
*Total antioxidant /%			≤1.0	Appendix B
*Type of antioxidant			The types of antioxidants added are in accordance with the European Pharmacopoeia, and no more than three antioxidants may be added to each isoprene	Appendix B
*Physical and mechanical properties		Tensile Strength/MPa	≥25	Appendix C
		Elongation at break/%	≥450	

4 Test method

Except as otherwise specified, the reagents used in this standard should be conformed to the relevant methodological requirements and the water used should be conformed to the analytic laboratory specifications and the test method(GB/T 6682).

4.1 Appearance

Take the appropriate amount of this product, remove the packaging, in the bright natural light, face the visual; The sample quantity of the whole batch of adhesive selection inspection shall meet the requirements of Table 2.

4.2 Mooney Viscosity

Test according to "Determination of Disc Shear Viscosity for Unvulcanized Rubber: Determination of Mooney Viscosity(GB/T 1232.1)".

4.3 Identification(IR method)

The infrared spectrum of rubber was determined by the rubber identification infrared spectrometry(GB/T 7764), and the Spectrogram should be in accordence with GB/T 7764.

4.4 Volatility

Testing for Volatile Discharge of Rubber should be according to method B (oven method) in Rubber raw-Determination of Volatile matter Content (GB/T 24131) .

4.5 Ash

According to content A in Rubber-determination of ash (GB/T 4498) to test the ash content of the raw rubber.

4.6 Acetone extract

The acetone extract of the raw rubber was tested according to Rubber-Determination of solvent extract(GB/T 3516), method B.

4.7 Metal Elements

Determination according to the method specified in Appendix A.

4.8 Antioxidant content

Determination according to the method specified in Appendix B.

4.9 Physical mechanical properties

Determination according to the method specified in Appendix C.

5 Test rules

5.1 Inspection classification and inspection items

5.1.1 Product inspection is divided into total inspection and partial inspection;

5.1.2 Items with "*" are partial inspection, and rubber manufacturers need to be inspected on a case-by-case basis;

5.1.3 All inspection items specified in this standard shall be full inspection items and shall be inspected by the rubber manufacturer as required.

5.1.4 Total inspection shall be performed if:

(1) When the product is registered or applied for a production license;

(2) When there is a major change in the raw and auxiliary materials, processes and equipment of the product;

(3) Reproduction of the product after a major quality accident has occurred;

(4)If there is a large deviation in the batch inspection data;

(5) During the normal production period, the whole inspection of the product is carried out every six months.

5.2 Group rules and sampling

5.2.1 Group approval rules:

The same quality and stability of the continuous production of polyisoprene rubber with the same raw materials, the same process, and the same time period

Brand products are a batch.

5.2.2 Sampling

During the quality inspection of the medicinal synthesis of polyisoprene rubber, samples are taken according to the provisions of GB/T19187.

5.3 Decision and re-inspection rules

If any of the inspection results does not meet the requirements of these standards, the sample shall be re-inspected, and the re-examination results still do not meet the requirements of these standards

When the required indicator is used, the batch is judged to be unqualified.

5.4 Inspection reports

The manufacturer shall provide the quality inspection report of the shipped products according to the requirements of the user.

The product quality inspection report shall indicate the name of the product, the brand number, the name of the production plant(company), the batch number of the production, the test items, and the test
The results, grades and other relevant contents shall be stamped with the special seal for quality inspection and the seal for inspectors(signature), and shall be subject to examination and approval.

6 Marking, packaging, transport and storage

6.1 Marking

After packaging, the product should clearly indicate the product name, specification, brand number, batch number, production date, trademark, net content, implementation standards, and
The name and address of the production unit.

6.2 Packaging

The product should use two or more suitable packaging materials, the packaging should be easy to peel off, or use the fluidity but not to the product pollution
Dyeing materials; The outer packing shall be strong and durable for protection during storage, transportation and handling.

6.3 Transport

During transportation, dry and clean carriages should be used for shipment. Cover the tarpaulin to prevent sun exposure, rain wet, damaged packaging, and debris from mixing.

6.4 Storage

The product should be stored in a warehouse with light, cleanliness, dryness, good ventilation and suitable temperature, and it is strictly forbidden to pile in the open air; The product is at least 1m away from the heat source.

7 Quality assurance period

The quality assurance period of the product is 2 years from the date of production.

Appendix A
(Normative appendix)
Determination of metallic elements
(Inductively coupled plasma emission spectrometry(ICP-AES) or atomic absorption spectrophotometry(AAS))

A. 1 Principle

After burning the sample and dissolving the acid, the metal elements were determined by inductively coupled plasma emission spectrometer or atomic absorption spectrophotometer
The content of metal elements can be determined quantitatively according to the characteristic spectral lines and strength of the elements.

A. 2 Instruments and Appliances

A. 2.1 Inductively coupled plasma emission spectrometer(ICP-AES) or atomic absorption spectrophotometry(AAS)
A. 2.2 Analytical balance, Muffle furnace, crucibles, etc...
A. 2.3 Capacity bottles(25mL, 50mL), Pipette, etc...

A. 3 Reagents

Except for special provisions, the reagents used in this standard are analytic pure reagents, and the water used is High Purity deionized water(resistivity reaches or exceeds
18.2 MΩ · cm) or quite pure water.
Hydrochloride acid: GR

A. 4 Operational steps

A. 4.1 Preparation of sample solution

Precise determination of the sample 5G, placed in a crucible, 350 ℃ in Muffle furnace, to smoke-free production(about 6h, should avoid flame generation), and then rise

Warm to 550 ℃, continue to burn 30 min. To be cooled to room temperature, add hydrochloric acid(1 +3) 15mL, plus crucible cap, 60 ℃ water bath heating

For 30 minutes, cool to room temperature, transfer to a 50mL bottle, and set the capacity with hydrochloric acid(1 +3) to obtain a test sample.

A. 4.2 Determination of metallic elements

Take solution and use ICP-AES according to "People's Republic of China Pharmacopoeia 2015 4th part general rule 0411: Inductively coupled plasma atomic emission spectrometry, determination of metallic elements calcium, copper, iron, lead, Chromium, cadmium; Or use atomic absorption spectrophotometer(AAS), according to the "People's Republic of China Pharmacopoeia 2015 4th part general rule 0406: Atomic Absorption Spectrophotometry" to detect the above metal elements.

A. 5 Results

As the following formula to calculate the element content:

$$P_x = \frac{C_{sample} \times V_{sample}}{M_{sample}} \times 10^{-4}$$

In the formula

Px-The percentage content of metal elements in the sample, Wt. %;

C_{sample}-test value of metallic elements in sample, μg / mL;

V_{sample}-sample volume, mL;
M_{sample}-sample quality, g.

Appendix B
(Normative appendix)
Determination of Antioxidant Content(High Performance Liquid Chromatography)

B. 1 Principle

Soluble the glue in a mixed solution of cyclohexane / dichloromethane, settle it with methanol, and the antioxidant in the rubber is dissolved in a mixed solution of methanol / cyclohexane / dichloromethane, determined by liquid chromatography(HPLC), Quantitative analysis by internal standard method(This method is described with three examples of antioxidant BHT, 1010 and 1076, and the actual detection types are not limited to these three antioxidants; When transferring, confirming, or testing the three kinds of antioxidants described in this standard, the methodology shall be verified according to the requirements of the Chinese Pharmacopoeia or other appropriate standards.)

B. 2 Instruments and Appliances

B. 2.1 Liquid chromatograph

B. 2.2 Analysis of scales

B. 2.3 Transfer tubes(5mL, 20mL), bottle capacity(50mL, 100mL, 200mL), threaded mouth sample tubes(60mL), syringes(without rubber seals), filters(0.45 μm filters)

B. 3 Reagents

Except for special provisions, the reagents used in this standard are analytical pure reagents, and the experimental water used is distilled water, deionized water, or fairly pure water.

B. 3.1 Methanol

B. 3.2 Cyclohexane

B. 3.3 Dichloromethane

B. 3.4 Antioxidant BHT: Standard

B. 3.5 Antioxidants 1010: Standard

B. 3.6 Antioxidants 1076: Standard

B. 3.7 Antioxidants 3114: Standard

B. 3.8 Isopropyl alcohol: Chromatography pure

B. 3.9 Acetonitrile: Chromatography pure

C. 4 Operational steps

B. 4.1 Preparation of internal standard solutions

Take 1,3,5-tri(3,5-di-tert-butyl-4-hydroxybenzyl) isocyanurate(antioxidant 3114) about 10 mg, precisely, set in a 100mL bottle, dissolved in appropriate amount with methylene chloride, plus methylene chloride to scale, Shake evenly to give an internal standard solution with an antioxidant 3114 concentration of 0.1 mg/mL.

B. 4.2 Preparation of standard test solutions

Take the antioxidant BHT, the antioxidant 1010, and the antioxidant 1076 each 100mg, respectively, precisely, to the 100mL capacity bottle, add the appropriate amount of methylene chloride, shake and dissolve, add the methylene chloride to the scale, mix, A mixed standard solution with each antioxidant concentration of 1.0 mg/mL was obtained and further diluted with methylene chloride to a mixed standard solution with concentrations of 0.5, 0.2, 0.1, 0.05, and 0.02 mg/mL, respectively. Each of the mixed standard solutions with precision intake series concentrations is 5mL. In the 60mL thread mouth sample tube, the inner standard solution is precisely added 5mL, cyclohexane 5mL is added, methanol 15mL

is added, the methanol is tightened and screwed, and the shake is mixed. Some solution was absorbed with a syringe without rubber seal and filtered by 0.45 μm filter to obtain a series of standard concentration test solutions.

B. 4.3 Preparation of sample test solutions

Take the appropriate amount of raw glue, cut it into 1 to 2 mm particles, precisely call 0.25 g, set the 60mL thread mouth sample tube, accurately add the inner standard solution 5mL, add cyclohexane 5mL, add 5ml dichloromethane(increase dissolution speed), tighten the cover, Shake for about 3 hours until completely dissolved, add methanol 15mL, tighten the lid, shake violently about 1min, absorb part of the solution with a syringe without a rubber seal, and filter it through a 0.45 μm filter to obtain a sample test solution.

B. 4.4 Chromatographic conditions(recommended conditions, which may be adjusted as applicable)

The chromatographic column is an 18-alkyl silicon bonded silica gel as a filler(Agilent XDB C18, 5um, 4.6 ×150mm). The flow phase A is water, and the B phase is a mixed solution with a volume ratio of isopropanol and acetonitrile of 1:1; The flow rate is 1.5 mL/min; Elution gradient: The B-phase starting ratio is 70 %, maintaining 1 min, increasing the B-phase ratio linearly to 84 % at 7min, increasing the B-phase proportional linear to 95 % at 18min, and increasing the B-phase proportional linear to 96 % at 24min. At 25min, the B-phase proportional linear decrease to 70 %, Hold on 2 min. The sample volume is 10 μL. The detector is an ultraviolet detector with a wavelength of 280 nm. The sample storage temperature is 5 ℃ and the column temperature is room temperature.

Under the above chromatographic conditions, three different antioxidants can be determined: antioxidant BHT, antioxidant 1010 and antioxidant 1076.

B. 4.5 The first method is generally used, unless otherwise provided.

B. 4.5.1 First method(control method)

The corresponding standard test solutions were prepared according to the type and content of the antioxidants in the raw glue, and the standard test solutions and sample test solutions were each 10 μL, injected with liquid chromatography, and recorded chromatographic charts. The peak area of the relevant antioxidants was recorded respectively. And the peak area of the internal standard chromatography.

B. 4.5.2 Second method(standard curve method)

Precise absorption of 10 μL of controlled test solutions at different concentrations, injection of liquid chromatography, and recording of chromatographic charts, respectively, record the peak area of the relevant antioxidant chromatogram and the peak area of the internal standard chromatogram, and the ratio of the peak area of the chromatogram to A standard x/A. The internal standard is the X axis, The standard curve is drawn with different levels of antioxidants(mg) as the Y axis.

Precise sampling test solution 10 μL, injection liquid chromatography, record chromatography, record the peak area of the relevant antioxidant chromatogram and the peak area of the internal standard chromatogram, respectively, and calculate the ratio of the peak area of the chromatogram to the A sample x/A internal standard, The content of the relative antioxidant(MG) in the sample solution is obtained from the standard curve.

B. 5 Results

B. 5.1 Results of the first method

Press the following formula to calculate the relative percentage content of the related antioxidant:

$$P_x = \frac{W_{standardX} \times \frac{R_{sampleX}}{R_{standardX}}}{1000 \times M_{sample}} \times 100 = \frac{W_{standardX} \times R_{sampleX}}{10 \times M_{sample} \times R_{standardX}}$$

In the formula：

P_x—relative percentage of relative antioxidant（%）

$W_{standard\ X}$—content of related antioxidants in standard solution（mg）

M_{sample}—the weight of sample（g）

$R_{standardX} = \frac{A_{standardX}}{A_{interstandard1}}$， $A_{standard\ X}$—standard solution related antioxidant chromatographic peak area，

$A_{inter\ standard1}$ is standard solution within the standard peak area

$R_{sampleX} = \frac{A_{sampleX}}{A_{interstandard2}}$，$A_{samole\ x}$—standard solution within the standard peak area，$A_{inter\ standard2}$ is the sample solution within the standard chromatographic peak area

B.5.2 The results of the second method

Calculating the relative percentage content of the antioxidant according to the following formula to：

$$P_X = \frac{W_{sample}}{1000 \times M_{sample}} \times 100 = \frac{W_{sample}}{10 \times M_{sample}}$$

In the formula：

P_x—relative percentage of relative antioxidant（%）

W_{sample}—The content of relative antioxidant in sample solution was obtained on the standard curve（mg）

M_{sample}—the weight of sample（g）

Appendix C
(Normative appendix)
Testing of physical and mechanical properties

C. 1 Scope

This appendix specifies the standard materials, standard test formulas, equipment and operating methods used to synthesize the tensile stress and strain properties of the polyisoprene rubber sulfide.

C. 2 Principle

Standard mixing formula, mixing equipment and mixing procedure were used to prepare the mixing rubber sample, then standard vulcanization equipment and vulcanization method were used to prepare the vulcanization test piece, and then the vulcanization test piece was made into a certain tensile sample, and the tensile stress and strain properties were tested on the tensile test machine.

C. 3 Equipment

C. 3.1 Electronic balance: range 1000g, accuracy 0.01 g

C. 3.2 Ovens: maximum temperature 250 ℃, temperature control accuracy 1 ℃

C. 3.3 Open rubber machine

C. 3.4 Sulphurization equipment

C. 3.5 Tension tester

C. 4 Reagents

C. 4.1 Stearic acid

C. 4.2 Zinc oxide: indirect method

C. 4.3 Sulphur

C. 4.4 Industrial reference carbon black(N330)

C. 4.5 Vulcanization accelerator TBBS: The product should be powdered and the initial methanol insoluble mass fraction should be less than 0.3 %; It should be stored in a closed container at room temperature and checked for methanol insoluble content every 6 months. If it exceeds 0.75 %, it should be discarded.

C. 5 Preparation of gelatin samples

C. 5.1 Overview

The ingredients, mixing and vulcanization equipment and operating procedures for the test adhesive are performed according to GB/T 6038.

C. 5.2 The standard test formulation is shown in table C. 1.

Table C. 1 Mixing basic and mixing formulations

Material Name	Basic Formula, phr
Isoprene rubber	100.00
Stearic acid	2.00
Zinc oxide	5.00
Sulphur	2.25
Industrial reference carbon black （N330）	35.00
TBBS	0.70
Total	144.95

C. 5.3 Mixtures and Ingredients

Carbon black should be heated 1h in an oven at 125 ℃ ±3 ℃ before use. During the adjustment process, the carbon black depth does not exceed 10mm. The adjusted carbon black should be stored in a closed moisture proof container before mixing.

C. 5.4 Mixing equipment

Front and rear roller speed ratio 1:1.35, front and rear roller diameter 160mm open rubber machine.

C. 5.5 Mixing procedures

During the entire mixing process, the surface temperature of the roller of the furnace is adjusted to always maintain 70 ℃ ±5 ℃. During the mixing period, a good accumulation gum should be maintained. If the

specified roller distance is not released, the roller distance should be slightly adjusted. The specific mixing procedures are shown in table C. 2.

Table C.2

No.	Operation	Holding Time (min)	Cumulative Time (min)
1	The raw glue passes between the rollers with a roll distance of 0.5 mm twice, does not wrap the roll, and then gradually adjusts the roll distance to 1.4 mm, wrap the roll.	2	2
2	Add stearic acid and perform a 3/4 cutter from each side of the smelter.	2	4
3	Add zinc oxide and sulphur and perform 3/4 cutter twice from each side of the smelter.	3	7
4	Add half charcoal black and perform 3/4 cutter twice from each side of the smelter.	3	10
5	Add the rest of the charcoal black and the charcoal black scattered in the plate, and perform 3/4 cutter three times from each side of the smelter.	5	15
6	Add the accelerator TBBS and perform 3/4 cutter three times from each side of the smelter.	3	18
7	Take off the glue from the smelter. The pitch of the roll is adjusted to 0.5 mm so that the roll adhesive passes vertically through the roller 6 times.	2	20
8	Make a film with a thickness of about 6mm and check the quality of the adhesive. If the difference between the adhesive quality and the theoretical value is greater than 2.90 g or less than -8.70 g, discard the adhesive and remix.	/	/
9	The adhesive is made into a film about 2.2 mm thick for the preparation of the test film.	/	/

C.6 Environmental regulation of blended gum

The resulting mixing film shall be adjusted in accordance with the provisions of GB / T 6038　8.1 before vulcanization.

C. 7 Preparation of rubber sulfide samples and testing of tensile stress and strain properties

C. 7.1 The vulcanization equipment shall comply with the provisions of Article 8.2 of GB/T 6038. The vulcanization process shall comply with the provisions of Article 8.3 of GB/T 6038.

C. 7.2 The sample was vulcanized at 135 ℃ with a vulcanization time of 30 min.

C. 7.3 The vulcanization tablets should be adjusted to 16h ~ 96h at a standard laboratory temperature of 23 ℃ ±2 ℃ before testing.

C. 7.4 The tensile stress and strain properties of Vulcanized rubber were determined according to GB/T 528, and the specimen was prepared by a dumbbell type 2 cutter.

Synthetic Polyisoprene Rubber For Pharmaceutical Packaging

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Secretariat of China Pharmaceutical Packaging Association,

Address: second floor, No.C 23 Nanlishi Road, Xicheng District, Beijing

Postcode:100045

Tel: 01062267180 Fax: 01062267098

Website: www.cnppa.org

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