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Standard of China National Pharmaceutical Packaging Association

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HDPE Non-woven Fabrics Iron Based Oxygen Absorbent Sachet for Infusion

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Table of Contents

Foreword

Appendix A to this standard is an appendix to this standard.

This standard is centralized by China National Pharmaceutical Packaging Association.

Drafting committee of this standard: Jiangsu Sud-Chemie Performance Packaging Material Co., Ltd., Nanjing Tianhua Science & Technology Development Co., Ltd. and Dupont (China) Research and Development Management Co., Ltd.

Draftsman of this standard: Zhao Guangtao, Chen Yujiang, Ying Danqing, Jin Hong, Cai Rong, Wu Ping, Luo Hongyu, Zhu Bilin, Qian Jun. This standard is the first edition.

This standard is drafted on the basis of GB/T 1.1.

Introduction

The HDPE non-woven fabrics iron based oxygen absorbent sachet stipulated in this standard is composed of ironbased oxygen absorbent and HDPE non-woven fabrics, which is suitable for infusion bag packaging.

The ironbased oxygen absorbent refers to the absorbent which is made of iron powder as the main raw material, can react with the oxygen, and may reduce the concentration of oxygen in the space between the inner bag and the outer bag of infusion bag within the specified time and maintain for a period of time.

HDPE non-woven fabrics are made with HDPE as the main raw material via the non-woven production process. They have multilayer continuous physical structure and balanced physical properties. Antistatic agent and fluorescent whitening agent must not be used. According to different requirements, it is necessary to study and evaluate the physical and chemical properties of HDPE non-woven fabrics, material specifications (mass per unit area), material cleanliness, particulate contamination, floc falling level, waterproof permeability, particle barrier, tensile strength, tear resistance, rupture resistance and surface performance etc.

The HDPE non-woven fabrics materials specified in this standard include glue-coated materials and non-glue-coated materials, which shall not release substances sufficient to cause health risks (see GB/T 16886.1 for biological evaluation and test). Where the material is coated with glue, the continuity of the coating shall be assessed. The sachets usually shall be made via the electric heating sealing process for glue-coated materials, and shall be made via the ultrasonic sealing process for non-glue-coated materials.

The manufacturers of pharmaceutical preparations must pay attention to the possible effects of bioburden of HDPE non-woven fabrics iron based oxygen absorbent sachet for infusion on the pharmaceuticals.

HDPE non-woven fabrics ironbased oxygen absorbent sachet for infusion bag preparation must be produced in the environment adaptive to the production environment of corresponding pharmaceutical. Proper measures shall be taken to prevent the dust of iron powder and other raw materials from contaminating the outer surface of the HDPE non-woven fabrics iron based oxygen absorbent sachet for infusion bag in the production process.

HDPE Non-woven Fabrics Iron Based Oxygen Absorbent Sachet for Infusion

1 Scope

This standard stipulates the HDPE non-woven fabrics iron based oxygen absorbent sachet for infusion (hereinafter referred to: as well as the requirements for product packaging, marking, transportation and storage of HDPE non-woven fabrics iron based oxygen absorbent sachet for oral solid preparation (hereinafter referred to as "iron based oxygen absorbent")

2 Normative References

The documents cited herein are indispensable to the application of this standard. For dated references, only the dated version applies. For undated references, the latest version (including all amendments) applies. The references are as follows:

Chinese Pharmacopoeia (Version 2015)

GB/T 455 Paper and Board Determination of Tearing Resistance

GB/T 2828.1 Sampling procedures for inspection by attributes - Part 1: Sampling Schemes Indexed by Acceptance Quality Limit (AQL) for Lot-by-lot Inspection

GB/T 4744 Textile Fabrics- Determination of Resistance to Water Penetration- Hydrostatic Pressure Test

GB/T 16886.1 Biological Evaluation of Medical Devices -Part 1: Evaluation and Testing within a Risk Management Process

YBB00122003-2015 Test for Welding Strength

YBB00262004-2015 Test for Infrared Spectrum of Packaging Materials

YBB00312004-2015 Test for Residual Solvent of Packaging Materials

3 Terms and Definitions

For the purpose of this document, the following terms and definitions apply.

3.1

Saturation oxygen absorbed capacity **saturation oxygen absorbed capacity**

It refers to the actual amount of oxygen absorbed by each sachet of ironbased oxygen absorbent.

3.2

Deoxidize time **deoxidize time**

It refers to the time required for each sachet of iron-based oxygen absorbent to reduce the percentage volume of oxygen concentration in the container to less than 0.1% under confined conditions with specified volume for the first time.

4 Requirement

4.1 Identification

The HDPE non-woven fabrics sachet material shall be determined with the fourth method in YBB00262004-2015.

4.2 Specification and Dimension

The specification and dimension of iron basedoxygen absorbent sachet shall be in accordance with Table 1.

Table 1 Specification and Dimension

Specification and Dimension[a]	Overall Dimension[b] (mm)		Weight of Inclusions [c] (g)		Test Method
	Central Value	Tolerance Range	Central Value	Tolerance Range	
30ml	30×40	±3	0.9	-10%/+15%	**A.1**

(continued)

Specification and Dimension[a]	Overall Dimension[b] (mm)		Weight of Inclusions [c] (g)		Test Method
	Central Value	Tolerance Range	Central Value	Tolerance Range	
50ml	35×45	±3	1.4		
100ml	35×55	±3	2.8		
200ml	50×60	±5	5.6		
300ml	50×70	±5	8.5		
a: The specific indicators of other specifications and models may be determined by the seller and the buyer through consultation according to the filling requirements. b: The indicator of overall dimension is only for reference. c: The indicator of weight of inclusions is only for reference.					

4.3 Appearance

The appearance defects of iron basedoxygen absorbent sachet shall comply with the provisions in Table 2.

Table 2 Appearance

Defects	Description	Inspection Level	Acceptance Quality Limit (AQL)	Test Method
Sachet breaking	Breaking of HDPE non-woven fabrics sachet for various reasons, resulting in iron basedoxygen absorbent leakage	General inspection level I	0.04	**A.2**
Empty sachet	Iron based oxygen absorbent missing		0.04	
Dirt	The surface of iron basedoxygen absorbent sachet is contaminated, and is prone to falling off		0.65	
Printing	The pattern of iron basedoxygen absorbent sachet is not printed or incomplete, resulting in the loss of function		0.65	
	A part of the pattern on the iron basedoxygen absorbent sachet is blurred, causing the pattern to be illegible		1.0	
	A part of the pattern on the iron basedoxygen absorbent sachet is blurred, but the pattern is legible		4.0	
Printing ink	Due to printing, there are extra ink marks on the surface of the iron based oxygen absorbent sachet, which are easy to be wiped off or fall off		0.65	
	Due to printing, there are ink marks on the surface of the ironbased oxygen absorbent sachet, which are not easy to be wiped off or fall off		4.0	
Color difference	There exists color difference between different iron basedoxygen absorbent sachets due to packaging materials or production process		4.0	

4.4 Physical and chemical indicators

The physical and chemical indicators of iron based oxygen absorbent sachet shall comply with the provisions of Table 3.

Table 3 Physical and chemical indicators

Items	Units	Indicators	Test Method
Saturation Oxygen Absorbed Capacity and Deoxidize Time			
Saturation oxygen absorbed capacity(25±2℃)	ml	≥ 3 time of specification volume	**A.3**
Deoxidize time(25±2℃)	h	≤ 48	
Dropping Resistance	—	The iron basedoxygen absorbent sachet shall not be broken and the iron based oxygen absorbent shall not leak	**A.4**
Physical and Chemical Properties of HDPE Non-woven Fabrics Sachet			**A.5**

(continued)

Items		Units	Indicators	Test Method
Decolorization test		—	The soaking solution shall not be darker than the blank solution	**A.5.1**
Fluorescence of HDPE Non-woven Fabrics Sachet		—	Shall comply with the provision	**A.5.2**
Residue on ignition	Including opacifying agent	%	≤ 3.0	**A.5.3**
	Excluding opacifying agent	%	≤ 0.1	
Residual solvent content	Total amount	mg/m^2	≤ 5.0	**A.5.4**
	Benzene	mg/m^2	No content shall be detected	
	Benzole	mg/m^2	No content shall be detected	
Heavy metal		—	The content shall not exceed 1 ppm	**A.5.5**
Heat-sealing strength (longitudinal sealing and transverse sealing)	Non-coated	N/15m	≥5	**A.5.6**
	Coated	N/15m	≥3	
Hydrostatic pressure		mm	≥1 000	**A.5.7**
Tearing strength		mN	≥1 000	**A.5.8**

4.5 Microbial limit

The microbial limit shall comply with the provision of Table 4.

Table 4 Microbial limit

Items	Units	Indicators	Test Method
Total number of aerobic bacteria	cfu/ sachet	≤100	**A.6**
Total number of molds and yeasts	cfu/ sachet	≤100	
Escherichia coli	—	No content shall be detected	

5 Inspection Rule

5.1 Lot

A lot shall be the products which are produced continuously for a period of time under the conditions of same raw material formula, same specification & variety, same technology and same equipment or otherwise agreed in the contract.

5.2 Sampling

After the external packaging is inspected, a certain number of packages shall be randomly selected from the same lot of products according to Table 5 for sampling.

Table 5 Quantity of packages sampled

Quantity of packages sampled from each lot of products	Quantity of packages sampled
2 ~15 pieces	2 pieces
16 ~ 50 pieces	3 pieces
51 ~ 150 pieces	5 pieces
151 ~ 500 pieces	8 pieces
> 500	13 pieces

Then, the above packages shall be sampled for inspection according to Sampling Procedures for Inspection by Attributes- Part 1: Sampling Schemes Indexes by Acceptance Quality Limit (AQL) for Lot-by-lot Inspection (GB/T 2828.1.

5.3 Inspection

The dropping resistance inspection items, inspection level and acceptance quality limit (AQL) shall comply with the provisions of Table 6.

Table 6 Inspection

Inspection Items	Inspection Level	Acceptance Quality Limit
Dropping Resistance	Special Inspection Level S-3	4.0

6 Acceptance Rule

If any technical indicator cannot reach the requirement when the receiving party carries out acceptance inspection, it shall conduct the joint inspection for the defective item together with the manufacturer; the joint inspection result shall be based to judge the compliance.

7 Packaging and shelf life, marking, transportation, storage

7.1 Packaging and shelf life

The packaging form and material of iron basedoxygen absorbent sachet will directly affect the shelf life of iron based oxygen absorbent sachet. For example: For the iron based oxygen absorbent sachet packaged in the “polyester/aluminum/polyethylene” medicinal composite film sachet, the shelf life will 2 years as of the production date under the premise that it is unopened.

For other packaging forms and materials, the shelf life shall be determined by both parties through negotiation. According to customer needs, the oxygen indicating card can be placed in the package.

7.2 Marking

The product marking shall comply with the relevant requirements of applicable national laws and regulations.

7.3 Transportation

The products shall be protected from pressure, sunshine, moisture and heat in the process of transportation. Products must not be shipped along with toxic or spoiled materials

7.4 Storage

The product must be sealed and stored in a room temperature, dark, clean, dry and ventilated warehouse.

Appendix A

(Normative)

Test Method

A.1 Specification and Dimension

A.1.1 Overall Dimension

Take appropriate amount of the product, and use the vernier caliper with accuracy of 0.01mm to measure the length.

A.1.2 Weight of Inclusions

Take appropriate amount of the product, and use the analytical balance with accuracy of 0.1mg to measure the weight.

A.2 Appearance

Take appropriate amount of this product, place in the bright place with natural light and conduct visual inspection.

A.3 Saturation Oxygen Absorbed Capacity and Deoxidize Time

As shown in Figure A.1, take 1 sachet of the product, fix the product on the top of bracket, then turn the measuring cylinder upside down in the beaker containing water and fix it by the supporting pad, keep the measuring cylinder perpendicular to the water surface, then quickly adjust the water column to the height (h_0) corresponding to the initial volume of the reaction chamber (Table A.1), and record the height (h_0) of the water column and time (t_0). Record the height of water column every 1h until the height of water column does not rise further (for 3h, and continuously observe that the height of water column remains on a scale), and record the height (h_k) of the water column and time (t_k).

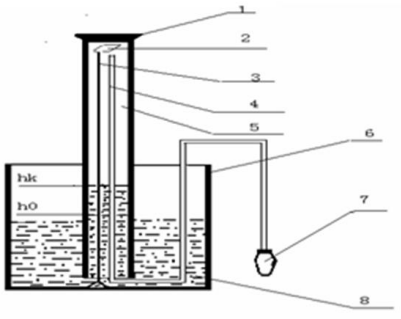
Repeat the above test steps for n times (n≥4, try to discharge the remaining gas in the measuring cylinder, fill it with fresh air, put it into the beaker vertically, and adjust it quickly to scaleh0), and record the initial and final heights (h_{0i}, h_{ki}) of the water column.

Calculate by the following formula,

$$\text{Deoxidize time (h)} = t_k - t_0 \qquad \text{……(A.1)}$$

Calculate by the following formula,

$$\text{Saturation oxygen absorbed capacity (ml)} = [(h_0 - h_k) + \sum_{i=1}^{n} (h_{0i} - h_{ki})] \qquad \text{……(A.2)}$$



Where:

1 Measuring cylinder;
2 Sample;
3 Bracket;
4 Air suction pipe;
5 Reaction chamber;
6 Beaker;
7 Air suction ball
8 Water.

Figure A.1 Test Equipment for Saturation Oxygen Absorbed Capacity and Deoxidize Time

Table A.1 Initial Volume of Reaction Chamber

Specification/Model	Initial Volume of Reaction Chamber
30ml	150ml
50ml	250ml
100ml	500ml
200ml	1 000ml
300ml	1 500ml

A.4 Dropping Resistance

Take appropriate amount of the product, and drop onto the horizontal, rigid and smooth surface freely from the height of 1.2m.

A.5 Physical and Chemical Indicators of HDPE Non-woven Fabrics Sachet

A.5.1 Decolorization test

Take 5 sachets of the product, remove the Oxygen Absorbent, put them in 50ml water for soaking (60℃±2℃, 2h), and take the solvent of the same lot as the blank solution for comparison .

A.5.2 Fluorescence of HDPE Non-woven Fabrics Sachet

Take 10 sachets of the product, cut off the heat-sealed part, take out the oxygen absorbent, clean the surface of HDPE non-woven fabrics sachet, place the surface of sachet in contact with the pharmaceutical under the UV lamp with the wavelength of 365nm and 254nm for inspection; there shall be no flake fluorescent.

A.5.3 Residue on ignition

Take appropriate amount of the product, remove the oxygen absorbent, weigh 2g HDPE non-woven fabrics sachet and determine in accordance with the General Rules0841 of Part IV, Chinese Pharmacopoeia 2015.

A.5.4 Residual solvent content

(Apply to the ironbased oxygen absorbent sachet with painting) Take several HDPE non-woven fabrics sachets with ironbased oxygen absorbent removed (internal area is about 0.02m2) and determine in accordance with the method I in YBB00312004-2015.

A.5.5 Heavy metal

A.5.5.1 Preparation of leaching solution

Take appropriate amount of the product, remove the desiccant, take 600cm^2 (internal surface area) of HDPE non-woven fabrics sachet (cut into small pieces with length of 5cm and width of 0.3cm), put them in conical flask with cover, add appropriate amount of water, shake to wash the small pieces, discard the water and repeat the operations twice. Soak in (70℃±2℃) 200ml water for 24h after drying at 30℃-40℃, then take out and cool down to room temperature, supplement to the original volume with the aqueous solution for test from the same lot as the leaching solution and use the water from the same lot as the blank solution.

A.5.5.2 Detection of heavy metal

Measure out 20ml leaching solution precisely, add acetate buffer (pH3.5), and determine in accordance with the method I in General Rules 0821 of Part IV, Chinese Pharmacopoeia 2015.

A.5.6 Heat-sealing strength

Take appropriate amount of HDPE non-woven fabrics sachets with oxygen absorbent removed, and determine according to YBB00122003-2015.

A.5.7 Hydrostatic pressure

Take appropriate amount of materials for HDPE non-woven fabrics sachets, and determine according to GB/T 4744.

A.5.8 Tearing strength

Take appropriate amount of materials for HDPE non-woven fabrics sachets, and determine according to GB/T 455.

A.6 Microbial limit

Take 10 sachets of the product, put them in conical flask, add 100ml sodium chloride injection-peptone buffered solution (pH7.0), and shake out by 1min to obtain 1:10 solution for testing product. 10 供试品溶液。 Determine according to the General Rules 1105 and 1106 of Part IV, Chinese Pharmacopoeia.

Drafting Instruction Standard for HDPE Non-woven Fabrics Iron Based Oxygen Absorbent Sachet for Infusion

I. Overview

With the rapid development of infusion bag market, the quality control of ironbased oxygen absorbents for infusion becomes more and more important. However, there has not been a complete standard in line with the development of modern pharmaceuticals for their on based oxygen absorbent manufacturers and users. The present standard has been unable to meet the development needs of ironbased oxygen absorbents for the field of infusion. At present, the dominant iron based oxygen absorbent sachets are packaged with HDPE non-woven fabrics in Europe and America. For the iron based oxygen absorbent sachet, the part that comes into direct contact with the pharmaceutical is the HDPE non-woven fabrics sachet whose materials and characteristics will directly affect the quality of the pharmaceutical, thus causing harm to the pharmaceutical users.

Such HDPE non-woven fabrics are made of 100% high density polyethylene as raw material. The high density polyethylene (HDPE) has been widely applied both at home and abroad as the raw material for pharmaceutical packaging material. It is non-toxic, tasteless, odorless, high in crystallinity and relatively high in density; relative molecular weight is often several hundred thousand to hundreds of thousands; the range of melt flow rate is narrow; it has relatively high rigidity and toughness, excellent mechanical strength and heat resistance, and good solvent resistance. The excellent performance of high density polyethylene provides favorable conditions for the production of ironbased oxygen absorbent sachets; for example, the melt index is moderate, the processing temperature is not high, it has the performance satisfying the pharmaceutical packaging requirement including non-toxicity, tastelessness, odorlessness, good toughness and surface hardness, tensile strength, stiffness and other mechanical strength etc., and complies with the requirement of the FDA and the European Union.

The content of oxygen absorbent is made of iron powder as the main raw material, and its reaction principle is as follows:

The formula of oxygen absorbent is prepared according to neutralization and alkaline, in which the iron powder will undergo the following rusting deoxygenation reaction:

$2Fe + 2H_2O + O_2 \rightarrow 2Fe^{+2} + 4OH^- \rightarrow 2Fe(OH)_2$

$2Fe(OH)_2$ is unstable in the oxygen bearing medium and will be oxidized further to ferric iron salts:

$2Fe(OH)_2 + H_2O + 1/2\ O_2 \rightarrow 2Fe(OH)_3$

Finally, the iron powder is oxidized to form reddish brown rust, thus achieving the purpose of oxygen absorption.

This standard is formulated for the purpose of effectively strengthening the quality control of iron based oxygen absorbent sachet, ensuring the quality of pharmaceutical, and facilitating pharmaceutical enterprises to use desiccant sachet more confidently.

II. Description of standard project establishment and requirements

1. Name According to the preparation requirements of standard, the standards for pharmaceutical packaging materials shall be classified as per the materials, wherein one standard shall be prepared for each (variety) material and each purpose; the standard name shall follow the sequential format of administration route, pharmaceutical form, application and material. Therefore, the name of this standard is proposed as “HDPE Non-woven Fabrics Iron Based Oxygen Absorbent Sachet for infusion bag”.

2. Appearance The appearance, which shall be described according to the production requirements of the product and in combination with the actual situation of the sample, can reflect the external quality of the product directly and comprehensively.

3. Saturation oxygen absorbed capacity and deoxidize time The saturation oxygen absorbed capacity and deoxidize time are important indicators to inspect the oxygen absorbent. In order to ensure the use effect in the future, this item is specified. The oxygen permeability of the HDPE non-woven fabrics sachets foriron based oxygen absorbent has a certain influence on the saturation oxygen absorbed capacity and deoxidize time; therefore, it is tested together with HDPE non-woven fabrics sachets.

4. Dropping resistance The iron based oxygen absorbent sachets are placed between the inner bag and the outer bag of infusion bag when they are used. If they drop during transportation, storage and use, the iron basedoxygen absorbent sachets without certain fastness will be damaged and the iron based oxygen absorbent will

leak out, causing contamination to the pharmaceuticals for infusion. This standard specifies a "dropping resistance" item to evaluate the product endurance.

5. “Fluorescence of HDPE non-woven fabrics sachet”, “residue on ignition” and “heavy metal” In this standard, HDPE non-woven fabrics are used as the raw material for packaging bag of iron based oxygen absorbent sachets. This standard specifies three items, namely, “fluorescence of HDPE non-woven fabrics sachet”, “residue on ignition” and “heavy metal”, to test the performance of HDPE non-woven fabrics material.

6. “Heat-sealing strength” and “tearing strength” In order to prevent the contamination to the infusion pharmaceuticals caused by iron based oxygen absorbent leakage, this standard specifies two items “heat-sealing strength” and “tearing strength” to test the performance of HDPE non-woven fabrics sachet materials.

7. “Hydrostatic pressure” In order to prevent the liquid water containing other substances from seeping from the iron based oxygen absorbent sachets, thus causing contamination to the infusion pharmaceuticals, this standard specifies “hydrostatic pressure” item to test the performance of HDPE non-woven fabrics sachet materials.

8. “Residual solvent content” and “decolorization test” Considering that the wording “请勿食用” and “DO NOT EAT” are printed on the outside of the ironbased oxygen absorbent, this standard specifies two items “residual solvent content” and “decolorization test” to test the performance of HDPE non-woven fabrics sachet materials.

9. Microbial limit In order to ensure that the iron based oxygen absorbent sachet will not contaminate the infusion pharmaceuticals, this standard adopts the method specified in the Chinese Pharmacopoeia to test the microbial limit of the iron based oxygen absorbent sachet. Since the bioburden of iron based oxygen absorbent sachet has certain effect on infusion pharmaceuticals, this standard requires that the total number of aerobic bacteria shall not exceed 1,00cfu/sachet; the total number of molds and yeasts shall not exceed 100cfu/sachet; no escherichia coli shall be detected in each bag.

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Secretariat of China National Pharmaceutical Packaging Association

Address: 2nd Floor, No. C23 Nanlishi Road, Xicheng District, Beijing Postal Code: 100045

Tel: 010-62267180 Fax: 010-62267098

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