4204 Determination of Extractables for Pharmaceutical Packaging Materials and Containers

Extractables of pharmaceutical packaging materials and containers refer to the substances released from the materials and containers when using specific extraction medium and extraction conditions. The determination of extractables is an important part of chemical property test of pharmaceutical packaging materials and containers. This method is applicable to the chemical analysis for extractables of pharmaceutical packaging materials and containers.

General principles for the test of extractables

Most of the analysis methods given in this method are non-specific. These methods and indicators are generally used for the control of product quality, and can be also used for preliminarily evaluation of chemical hazards in pharmaceutical packaging materials and containers.

Due to the difference in the biological risk levels of packaging materials and containers for drugs with different administration routes and properties, suitable extractable test and indicators shall be set based on the risk level of the packaged drug, combined with materials and processing technology.

Due to the possibility that long-time storage of the test solution may affect the results of some test, such as oxidizable substances, UV absorbance, conductivity, total organic carbon, etc., it is recommended to conduct the test within 4 hours after the preparation of test solution.

Preparation of test solution

The preparation of test solution is a complex process that is influenced by time, temperature, surface area (weight) to volume ratio, extraction medium, and phase equilibrium of the material.

Extraction container: The extraction shall be carried out in a clean, chemically inert, and closed container (e.g., borosilicate glass container) to ensure that the extraction container does not interfere with the extract.

Extraction medium: When selecting the extraction medium, full consideration shall be given to the properties of the pharmaceutical packaging materials and containers, and the composition characteristics of the packaged drug. The nature and type of extraction medium shall cover all application conditions as far as possible. Common extraction medium include:

a) water；

b) 65% alcohol；

c) *n*-heptane。

Extraction temperature and extraction time: The extraction temperature and extraction time shall be generally selected based on the process of pharmaceutical packaging materials and containers, as well as the worst conditions of production, transportation, storage and use, especially the sterilization process conditions, which also adapt to the extraction medium. The extraction temperature of polymers shall be below their glass transition temperature. If the glass transition temperature is lower than

the operating temperature, the extraction temperature shall be lower than the melting temperature. Common extraction temperatures and times include:

a) 58℃±2℃, 2h;

b) 58℃±2℃, 24h;

c) 70℃±2℃, 2h;

d) 70℃±2℃, 24h;

e) 100℃±2℃, 2h;

f) 110℃±2℃, 0.5h;

g) 121℃±2℃, 0.5h.

Extraction ratio: For the selection of extraction ratio, the shape and use of pharmaceutical packaging materials and containers shall be generally considered, so that all tested surfaces of the sample are immersed in the extraction medium. The materials can be cut into small pieces before extraction. The recommended cutting size is given in the following table. If a specific size is provided in relevant general chapters, it shall be performed according to the general chapter. Considering the potential difference in extraction performance between the intact surface and the cut surface, rubber closures, coated materials, composites, laminates, etc. shall be extracted as completely as possible. The effect of newly exposed surfaces (such as lumens or cut surfaces) shall be considered when cutting samples. The extraction is generally conducted according to the surface area. Samples in irregular shapes can be extracted according to the mass, and container-type pharmaceutical packaging materials and containers such as some bags, and bottles can be extracted according to the labeled content. Common extraction ratios include:

a) surface area/volume is 6cm^2/ml;

b) surface area/volume is 3cm^2/ml;

c) surface area/volume is 0.5cm^2/ml;

d) mass/volume is 0.2g/ml;

e) labeled content.

The commonly used methods for preparing test solutions for the determination of extractables of pharmaceutical packaging materials and containers are given in the following table.

Table Common methods for preparing test solutions for the determination of extractables of pharmaceutical packaging materials and containers

Serial No.	Preparation of test solution	Applicable Products
I	Take a flat part of the test sample, cut into 5cm×0.5cm or smaller pieces, and place in an extraction container. Add water at the surface area to volume ratio of 6cm^2/ml, shake and rinse, discard the water, and repeat the operation twice. Then add water of the same volume, close and heat in an autoclave at 121℃ ± 2℃ for 0.5 hour (extracted at 100℃ ± 2℃ for 2 hours if the material will be damaged when being heated to 121℃). Take out and allow to cool to room	It is applicable to regular plastic packaging systems and components for infusion.

	temperature, separate the solution from the sample and use as the test solution. Prepare a blank solution in the same manner as for the test solution except the same batch of water is used without test sample.	
II	Place a suitable number of complete test samples in an extraction container, add water at the surface area to volume ratio of 0.5cm^2/ml, boil for 5 minutes, cool, and rinse with water of the same volume for 5 times. Transfer to another extraction container, add water of the same volume, close and heat in an autoclave at 121℃ ± 2℃ for 0.5 hour. Take out and allow to cool to room temperature, separate the solution from the sample and use as the test solution. Prepare a blank solution in the same manner as for the test solution except the same batch of water is used without test sample.	It is applicable to (halogenated) butyl rubber and polyisoprene rubber closures.
III	Take a suitable amount of the test sample, cut into appropriate sizes, and place in an extraction container. Add water at the mass to volume ratio of 0.2g/ml, shake and rinse, discard the water, and repeat the operation twice. Then add water of the same volume, close and heat in an autoclave at 121℃ ± 2℃ for 0.5 hour. Take out and allow to cool to room temperature, separate the solution from the sample and use it as the test solution. Prepare a blank solution in the same manner as for the test solution except the same batch of water is used without test sample.	It is applicable to irregular plastic packaging systems and components for infusion.
IV	Take a flat part of the test sample, cut into 3cm×0.3cm or smaller pieces, and place in an extraction container. Add water at the surface area to volume ratio of 6cm^2/ml, shake and rinse, discard the water, and repeat the operation twice. Then add water of the same volume, close and extract at 70℃ ± 2℃ for 24 hours. Take out and allow to cool to room temperature, separate the solution from the sample and use as the test solution. Prepare a blank solution in the same manner as for the test solution except the same batch of water is used without test sample.	It is applicable to regular plastic bottle systems and components for eye drops.
V	Take a suitable amount of the test sample, cut into appropriate sizes, and place in an extraction container. Add water at the mass to volume ratio of 0.2g/ml, shake and rinse, discard the water, and repeat the operation twice. Then add water of the same volume, close and extract at 70℃ ± 2℃ for 24 hours. Take out and allow to cool to room temperature, separate the solution from the sample and use as the test solution. Prepare a blank solution in the same manner as for the test solution except the same batch of water is used without test sample.	It is applicable to irregular plastic bottle systems and components for eye drops.
VI	Take a flat part of the test sample, cut into 5cm×0.3cm or smaller pieces, and place in an extraction container. Add water at the surface area to volume ratio of 6cm^2/ml, shake and rinse, discard the water, and repeat the operation twice. Add the same volume of water, 65% ethanol, 50% ethanol and *n*-hexane respectively after drying at 30℃-40℃, close and weigh. Then extract respectively at 70℃ ± 2℃, 70℃ ± 2℃, 70℃ ± 2℃ and 58℃ ± 2℃ for 24 hours. Take out and allow to cool to room temperature, make up to the original weight with the same batch of extraction medium. Separate the solution from the sample and use as the test solution. Prepare the corresponding blank solution in the same manner	It is applicable to regular plastic composite pipe systems and components for topical ointment, plastic bottle systems and components for topical liquid preparation, and plastic bottle systems and components for oral preparation.

	as for the test solution except the same batch of extraction medium is used without test sample.	
Ⅶ①	Take a suitable amount of the test sample, cut into appropriate sizes, and place in an extraction container. Add water at the mass to volume ratio of 0.2g/ml, shake and rinse, discard the water, and repeat the operation twice. Add the same volume of water, 65% ethanol, 50% ethanol and *n*-hexane respectively after drying at 30℃-40℃, close and weigh. Then extract respectively at 70℃ ± 2℃, 70℃ ± 2℃, 70℃ ± 2℃ and 58℃ ± 2℃ for 24 hours. Take out and allow to cool to room temperature, make up to the original weight with the same batch of extraction medium. Separate the solution from the sample and use as the test solution. Prepare the corresponding blank solution in the same manner as for the test solution except the same batch of extraction medium is used without test sample.	It is applicable to irregular plastic composite pipe systems and components for topical ointment, plastic bottle systems and components for topical liquid preparation, and plastic bottle systems and components for oral preparation.
Ⅷ①	Take a flat part of the test sample, cut into 3cm×0.3cm or smaller pieces, and place in an extraction container. Add water, 65% ethanol, and *n*-hexane at the surface area to volume ratio of 6cm^2/ml respectively, close and weigh. Then extract respectively at 70℃ ± 2℃, 70℃ ± 2℃ and 58℃ ± 2℃ for 2 hours. Take out and allow to cool to room temperature, make up to the original weight with the same batch of extraction medium. Separate the solution from the sample and use as the test solution. Prepare the corresponding blank solution in the same manner as for the test solution except the same batch of extraction medium is used without test sample.	It is applicable to laminated films and pouches for oral preparation.
Ⅸ②	Take a flat part of the test sample, cut into 3cm×0.3cm or smaller pieces, and place in a extraction container. Add water, 65% ethanol, and *n*-hexane at the surface area to volume ratio of 3cm^2/ml respectively, close and weigh. Then extract respectively at 70℃ ± 2℃, 70℃ ± 2℃ and 58℃ ± 2℃ for 2 hours. Take out and allow to cool to room temperature, make up to the original weight with the same batch of extraction medium. Separate the solution from the sample and use as the test solution. Prepare the corresponding blank solution in the same manner as for the test solution except the same batch of extraction medium is used without test sample.	It is applicable to sheet for oral solid preparation.
Ⅹ	Place a suitable number of complete test samples in a extraction container, add water at the mass to volume ratio of 0.05g/ml, boil under a reflux condenser for 5 hours. Then allow to cool to room temperature, separate the solution from the sample and use as the test solution. Prepare a blank solution in the same manner as for the test solution except the same batch of water is used without test sample.	It is applicable to silicone rubber closures.

Notes: ① 50% ethanol is only applicable to plastic bottle systems and components for topical liquid preparation. In addition, if the printing on the surface of the material affects the extractable test results of plastic composite pipe systems and components used for external ointments, water, 65% ethanol, and *n*-hexane can be added respectively, at the inner surface to volume ratio of 3cm^2/ml. Air inside the pipes shall be expelled as far as possible. Heat seal the tail of the pipes and prepare the test solution according to the above conditions.

② The composite films containing paper can be prepared into a suitable number of

pouches with three sides sealed and an inner surface (excluding heat sealing edges) of about 150cm^2 (for pouches, it is calculated according to the inner surface of the actual sample size). Water, 65% ethanol and *n*-hexane can be, respectively, added at the inner surface to volume ratio of 3cm^2/ml. Air inside the pouches shall be expelled as far as possible. Heat seal the fourth side and prepare the test solution according to the above conditions.

Analysis methods for extractables

Clarity: Carry out the method for clarity of solution *<0902>*, using aqueous test solution.

Colour: Carry out the method for colour of solution *<0901 method 1>*, using aqueous test solution.

pH change value: Add 1ml of potassium chloride solution (1→1000) to 20ml of the aqueous test solution and blank solution, respectively, measure the pH value *<0631>*, and record the pH value or calculate the difference.

Acidity/alkalinity: Add 0.1ml of bromothymol blue solution (dissolve 50mg of bromothymol blue in a mixture of 4ml of 0.02 mol/L sodium hydroxide and 20ml of ethanol and dilute to 100ml with water) to 20ml of aqueous test solution. If the colour of the solution is yellow, titrate with sodium hydroxide (0.01mol/L) VS until a blue colour appears; if blue, titrate with hydrochloric acid (0.01mol/L) VS until a yellow colour appears; if green, no titration is required. Perform a blank determination and make any necessary correction.

Absorbance: Filter the test solution through a 0.45μm membrane filter if necessary. Measure the absorbance within the specified wavelength range *<0401>*.

Oxidizable substances: To 20ml of aqueous test solution, accurately measured, add accurately 20ml of 0.002mol/L potassium permanganate solution and 1ml of dilute sulfuric acid TS. Boil for 3 minutes. Cool. Add 0.1g of potassium iodide, and allow to stand in the dark for 5 minutes. Titrate with sodium thiosulfate (0.01mol/L) VS until a light yellow appears. Add 5 drops of starch IS and continue to titrate until the solution turns colourless. Perform a blank determination and make any necessary correction. The content of oxidizable substances is expressed as the difference of the volume of sodium thiosulfate (0.01mol/L) VS consumed by the test solution and the volume of sodium thiosulfate (0.01mol/L) VS consumed by blank solution, calculated by the following expression:

$$V=\frac{(V_0-V_S)\,C_S}{0.01}$$

where V is the difference of the volume of sodium thiosulfate (0.01mol/L) VS consumed by the test solution and the volume of sodium thiosulfate (0.01mol/L) VS consumed by blank solution, ml;

V_S is the volume of sodium thiosulfate (0.01mol/L) VS consumed by the test solution, ml;

V_0 is the volume of sodium thiosulfate (0.01mol/L) VS consumed by blank solution, ml;

C_S is the actual concentration of sodium thiosulfate (0.01 mol/L) VS, mol/L;

0.01 is the concentration of sodium thiosulfate (0.01 mol/L) VS specified in the standard, mol/L.

Non-volatile matter: Transfer 50ml of the test solution and the blank solution respectively to two evaporating dishes previously dried to constant weight, and evaporate to dryness on a water bath. Weigh after drying at 105□ to constant weight or verified drying time, and then calculate the difference.

Conductivity: Rinse the measurement electrodes several times with water, and then at least twice with blank solution. Measure the conductivity of the blank solution. It shall be no more than 3.0 μS/cm (20℃±1℃). Rinse the measurement electrodes at least twice with aqueous test solution and then measure the conductivity. If the measurements are not taken at the temperature of 20℃±1℃, temperature corrections shall be made.

Ammonium ion: Transfer 10ml of aqueous test solution to a 25ml Nessler cylinder. Transfer 10ml of ammonium chloride standard solution with specified concentration to another 25ml Nessler cylinder. To each of the Nessler cylinder, add 2ml of alkaline mercuric potassium iodide TS, allow to stand for 15 minutes, and then compare the colour visually.

Ammonium chloride standard stock solution: Dissolve 0.297g of ammonium chloride in a quantity of water in a 100ml volumetric flask, dilute with water to volume (each ml is equivalent to 0.1mg of NH_4).

Ammonium chloride standard solution: Before use, dilute the ammonium chloride standard stock solution to the required concentration.

Total organic carbon (TOC): Determine the TOC content of aqueous test solution and blank solution <*0682*>, and calculate the difference between them. The method used to perform the TOC test shall have a limit of detection of 0.2mg/L and shall have a linear dynamic range from 0.2 to 20mg/L (a linear range with a higher upper concentration can be used if the linearity is established). If the test solution exceeds this upper linear range, it can be diluted appropriately for analysis.

[Notes] In TOC test, potassium hydrogen phthalate or sucrose can generally be used as the reference substance to prepare calibration solutions.

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