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药品泡罩包装应用指南

Application guidance for blister packaging of pharmaceutical

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Foreword

This standard is drafted in accordance with the rules given in the GB/T 1.1-2020.

This standard was proposed by China Pharmaceutical Packaging Association.

Introduction

Blister packaging is one of the main forms of pharmaceutical packaging, suitable for automatic packaging of tablet, capsule, pill, suppository and inhalation powder dosage forms. The blister for pharmaceutical packaging (hereinafter referred to as "blister") refers to a system in which a blister is formed by thermo or cold processing and then filled with pharmaceuticals, lidding materials are heat-sealed with blister-forming material.

The pharmaceutical blister packaging system generally consist of lidding material and blister material, which are usually single-unit (single dose) packaging. Blister is classified according to its barrier performance, forming method, opening method, light barrier performance, user requirements /clinical needs. It is necessary to select the appropriate blister packaging according to the characteristics of the pharmaceuticals when designing a blister packaging system for pharmaceuticals.

In the design of pharmaceutical blister system, it is necessary to consider the characteristics and expected benefits of the drugs in order to determine the size, lidding material, blister material and packaging methods. Reasonable optimization design for the blister packaging system not only conductive to quality assurance but also contributes to low-carbon environmental protection, cost reduction and increased efficiency.

This document lists some different combinations of pharmaceutical blister packaging systems and their key indicators and testing methods, which may not cover all types of blister packaging systems. Pharmaceutical manufacturers can refer to this document in the selection of materials and pharmaceutical R&D stage, and analyze and carry out relevant research in accordance with the actual situation.

This document aims to provide technical guidance for pharmaceutical manufacturers in designing blister packaging and selecting, using blister packaging materials and equipment so as to achieve expected protective, functional, safety and compatibility. It can also be used to guide the blister packaging materials and equipment manufacturers to produce materials and equipment that meet the pharmaceutical requirements. The relevant parties should use this document in compliance with current regulations.

This document, as application guidance of "blister packaging", is the first to propose this concept in China. In order to facilitate readers' comprehensive understanding of blister packaging, the drafting unit also compiled five aspects of content including pharmaceutical blister packaging process, pharmaceutical packaging equipment, pharmaceutical packaging materials, inspection methods for blister packaging system and professional terms with Chinese-English correspondence. In view of space limitations, these contents are placed after the main text in Appendix A~E.

Application guidance for blister packaging of pharmaceutical

1 Scope

This document provides the composition, classification, design and evaluation of blister packaging of pharmaceutical.

This document applies to the selection design materials and equipment for blister packaging of pharmaceutical, as well as critical quality control in the production process of preparation.

2 Normative references

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

GB/ T 22645 Aluminum and aluminum foil for blister packaging

T/ CNPPA 2005—2018 Folding cardboard boxes for pharmaceutical packaging

3 Terms and definitions

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

3.1

Blister packaging

Blister material is formed by filling the medicine in a blister cavity formed by thermoforming or cold forming, and then using a lidding material such as aluminum foil for medicine, within a certain temperature, pressure and time conditions (see Figure 1).

Note: Blister packaging for pharmaceutical, formerly known as bubble eye packaging, is one of the main forms of unit medicine packaging, which is convenient to carry and use.

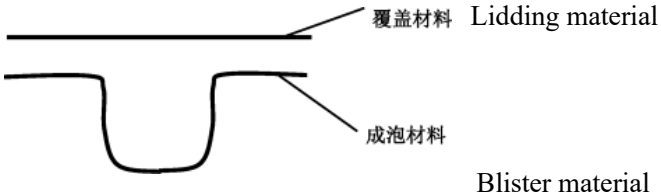

Figure 1 Classic blister packaging

3.2
Lidding material
The material covering the blister cavity, usually aluminum foil or composite aluminum foil, plastic, etc., plays the role of sealing and internal label, carries the text pattern information, and is a component of the blister packaging system.

3.3
Blister material

The material that makes up the blister cavity is usually a hard sheet composed of polyvinyl chloride, polyethylene, polypropylene, polyester hard sheet and related materials such as polyvinyl chloride/ polyvinylidene chloride, polyamide/aluminum/polyvinyl chloride, etc.

3.4
Thermo suction forming

Vacuum (negative pressure forming) is used to draw the heated softened hard sheet into the blister cavity of the forming mold to form a blister with a specific geometry forming method.

3.5
Thermo blow forming

Compressed air (positive pressure forming) is used to blow heated and softened hard sheets into the blister cavities of the forming mold, forming bubbles with specific geometric shapes hood forming method.

3.6
Plug-assist to the thermos blow forming

Use the punch to press the heated and softened hard sheet into the blister cavity of the molding mold. When the punch is fully pressed in, introduce compressed air to make the film tight Attach to the inner wall of the blister cavity to form a blister forming method with a specific geometry.

3.7
Coldform

At room temperature, a punch is used to press the blister material into the blister cavity of the forming die, causing it to undergo plastic deformation to form a blister with a specific geometric shape.

Note: Cold stamping is abbreviated as cold forming.

3.8
Single-unit packaging

A closed system used to hold a single patient for a single use, ready for immediate use upon opening, and capable of giving a single dose.

3.9
Virtual seal

The unsealed area around blister bags produced on certain machines. When the bubble hole diameter at the seal is larger than the bubble hole diameter at the forming mold. These need to be considered as the edges of the effective seal, rather than being counted into the seal distance.

3.10
Universal feeding or brush box feeding

The traditional feeding form usually consists of one or more sets of brushes, and the product is filled into the blister by the rotation and rolling of the brushes.

3.11
Channel feeding or vibratory feeding

The more widely used form of feeding 、usually consists of a hopper oscillating disc and a vertical track. The medicine enters the vertical track through the oscillating track, then fill into the blister through the vertical track.

3.12
Combined feeding

Add a distribution roller beneath the vertical track, and the medicine will first pass through the vertical track into the bubble of the distribution roller and then through the rotation of the distribution roller move into the forming blister. For the double- aluminum packaging form, the blister is larger and cannot be directly fed through the vertical track, a form derived from the track feeding.

3.13
Simultaneous tablet placement feeding; SimTap feeding

It mainly consists of a hopper oscillation bin blocking mechanism and a discharge port. The medicine enters the shaking chamber through the hopper, and then enters the blocking mechanism through the shaking chamber. There are multiple track tubes in the blocking mechanism, and each track tube releases one medicine in each working cycle, which enters the blister through the discharge port. Synchronized alignment for material cutting has a large fabric area and can achieve high cutting speed, suitable for ordinary blister packaging and aluminum blister packaging.

4 Composition and classification of pharmaceutical blister packaging system

4.1 Overview

A pharmaceutical blister packaging system is an unit pharmaceutical packaging formed by filling the medicine in a container formed with blister material and heat-sealing it with lidding material. The blister packaging processes are in Appendix A and the blister packaging equipment is in Appendix B.

4.2 Composition

The pharmaceutical packaging system consists of lidding material and blister material. The pharmaceutical packaging materials are in Appendix C, and professional terms are in Appendix E.
Lidding materials can be made of aluminum or plastic, etc. If aluminum foil for medicine is used, the aluminum foil substrate should comply with the requirements of GB/ T 22645, with a heat-sealing adhesive layer of ink (if any) applied on the inner side and a protective layer of primer coating. Ink is applied on the outer side as required. The aluminum foil has the property of being easily broken under pressure and is also called PTP aluminum foil.
The lidding material, depending on the function, is laminated with materials such as paper or polyester film on one side of the foil and coated with ink (if any) heat - sealing adhesive layer on the other side, known as medicinal composite foil.
Blister material can be plastic or other composite materials.
Single-layer foaming materials typically include polyvinyl chloride hard sheet, polypropylene hard sheet, polyethylene hard sheet, polyester hard sheet, etc.
Multilayer foamed materials are typically coated with polyvinylidene chloride or polyethylene film laminate, polyamide film, aluminum foil, and poly on a single layer of foamed material Trifluoro vinyl chloride film, etc.

4.3 Classification

4.3.1 This document classifies the blister packaging according to barrier performance, forming method, opening method, light barrier performance, user requirements and clinical needs.

4.3.2 Barrier properties are mainly divided into moisture barrier and oxygen barrier properties. Moisture barrier properties are classified as super high barrier, high barrier and low barrier according to the amount of water vapor passing through (see Table 1).

Table1 Classification of moisture barrier properties Water vapor transmission rate

Barrier performance	Water vapor transmission rate(mg/blister· d)
Super high barrier	< 0.01
High barrier	< 1.0
Low barrier	≥ 1.0
Test conditions: temperature at 40 °C, relative humidity at 75 %.	

4.3.3 Classified by forming method (see Table 2), it can be divided into thermo forming, cold form, thermo forming + coldform.

Table 2 Classification of forming methods and Common structures

Forming method	Common structures
Thermo forming	PVC, PP, PE, PET, COC, PVC/PE, PVC/PVDC, PVC/PE/PVDC , PVC/PCTFE, PVC/PVDC/PVC, PVC/ PCTFE/PVC
Coldform	AL/PE, PA/AL/PVC, PA/AL/PE
Thermo forming+ coldform[a]	PVC+PA/AL/HSL
[a] Also known as tropical type, it is mainly used for secondary packaging to improve barrier performance.	

4.3.4 Classified by opening method (see Table 3), It can be divided into direct push type, peel type, and peel-push type.

Table 3 Classification of opening methods and common structures

Opening method	Common structures
Direct push	OP/ AL/ HSL , OP/AL/ PVC
Peel	Paper/AL /HSL, PET/AL/ HSL, Paper/PET/AL/ HSL
Peel-push	Paper/AL/ HSL, PET/AL/ HSL, Paper/PET/AL/ HSL

4.3.5 Classified by light barrier performance (see Table 4), it can be divided into transparent, semi- transparent and opaque.

Table 4 Classification of Light barrier performance and Common structures

Light barrier performance	Common structures
Transparent	PVC, PP, PET, PE, PVC/PE, PVC/PVDC, PVC/PE/PVDC, PCTFE/PVC, PVC/PVDC/PVC
Semi –transparent [a]	Colored-PVC, PP, PET, PE
Opaque	AL/PE, PA/AL/PVC, PVC+ PA/AL/HSL
[a] Colorants, anti UV agents and other ingredients are added to the blister material to realize the barrier of visible light and ultraviolet light.	

4.3.6 Classified by user requirements/ clinical needs (see Table5), typically including anti-counterfeiting, volatile drug corrosion resistance, child safety, senior friendly, etc.

Table 5 Classification of user requirements/ clinical needs and Common structures

User requests/ clinical needs	Common structures
Anti-counterfeiting	OP/anti-counterfeiting printing AL/HS L
Volatile drug corrosion resistance	OP/AL/Special HSL
Child safety	OP/AL/PVC, Paper /AL/HSL a, PET/ AL/ HSL, Paper/ PET/ AL/ HSL , transparent/opaque blister
Senior friendly	OP/printing AL/HSL with reminder function, lidding material containing paper

a There are three forms of this structure: peel off the paper firstly and then directly push open the aluminum , directly push type, directly peel type.

5 Design of pharmaceutical blister packaging system

5.1 Blister Size and Standardization

The cost reduction and efficiency increase of blister size standardization in terms of fixed assets investment of daily running molds and conversion parts is reflected in reducing packaging costs and combining molds of different specifications to reduce mold costs and reduce switching time. Three sizes of blister plate are recommended: small, medium, and large. The typical dimensions of blister card are shown in Table 6.

The size of the blister plate should also refer to T/CNPPA 2005-2018.

Table 6 Typical size of blister plate

Size	Length/mm	Width/mm
Small	79.0~124.0	30.0~45.0
Medium	125.0~135.0	46.0~60.0
Large	125.0~135.0	61.0~90.0

Figure 2 provides a typical example of blister size in a typical pressure plate blister machine setup, where the wide edge of the projected area falls in the direction of machine.

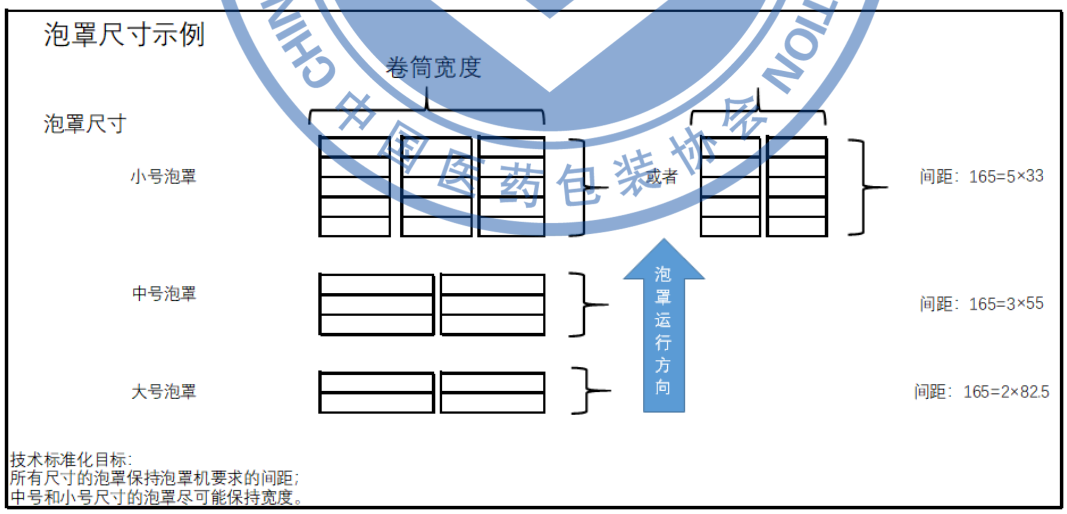

Figure 2 Example of blister size

Blister size standardization can provide convenience for the next process such as cardboard packaging and automated standardization of cardboard packaging. Different types of transportation packaging can keep the width and length of the cardboard box unchanged, only changing the height.

To ensure maximum utilization of packaging materials, it is necessary to choose smaller plate

types to control the area of blister plate and avoid the use of reinforcing ribs.

5.2 Lidding Material

The hardness of the tablets and deformation of the capsules of the drug should be evaluated during the medicine development phase to ensure that the medicine will not be damaged when the pushing the lidding film. If the medicine may be damaged when pushing through the aluminum foil, the easy-to-peel lidding material is preferred.
On the premise of satisfying the robustness, the lidding material can be selected for stability testing.

5.3 Blister Material

Select blister materials with corresponding barrier performance based on the sensitivity of medicine to environmental factors such as humidity and light.
According to market and medicine promotion needs, transparent forming materials are usually used. Some drugs, based on the purpose of protecting children's safety, reduce children's interest and try to use opaque forming materials to conceal the color and shape of the medicine.
When using blister materials containing PVDC, please note that the material will age and discolor under UV irradiation.
Based on the above applications, when designing blister material formulations, additives that meet pharmaceutical requirements can be added according to the specific performance needs of the drug and the processing needs of the blister material, such as stabilizers, enhancers, antioxidants, UV inhibitors, sunshades, colorants, lubricants, etc. The requirements for the limited use of additive varieties, specific migration amounts, or maximum residue amounts, specific migration total amounts, etc. can refer to relevant standards.

5.4 Blister Plate Stacking

In order to cope with the situation of multi plate blister packaging (such as 4-plate box~10 plate box), and to avoid the outer box being too large due to too many plates, refer to Figure 3 to stack the blister on both sides to save some paper box volume.

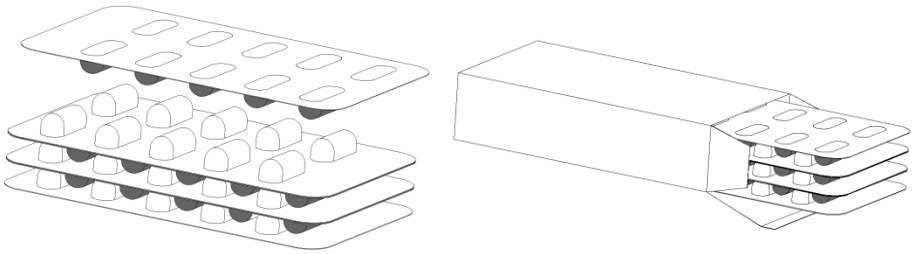

Figure 3 Schematic diagram of stacking and boxing of blister plates in both directions

5.5 Child Protection

If it is assessed that the dosage of the packaging contents may pose potential harm to children, or if there are relevant regulations [such as the Poison Prevention Packaging Act (PPPA) in the United States], it is advisable to use lidding materials that are difficult for children to open. The solution and guiding principles are as follows:

a) The headspace of blister cavity should be as less as possible, make it difficult for children to bite or tear to open;

b) In an ideal situation, the distance between the blister cavity and the edge of blister board should be 5 mm; for plates with the size of a wallet, the minimum distance should be 4 mm, making it more difficult for children to come into contact with the pills through biting;

c) Most packaging requires secondary handling, placing the blister in the design of child safety packaging, and more blister handling makes it difficult for children to open.

5.6 Sealing Area

5.6.1 Minimum Sealing Area

The minimum sealing area width must leave sufficient redundancy distance between the cavities, the cavity and the plate edge, the cavity and the perforated line and reinforcing rib to ensure the sealing performance of the blister

5.6.2 Virtual Sealing Size

The design of virtual sealing size should pay attention to the following:

a) Excessive cavity size on the mold can lead to excessive virtual sealing size;

b) The coding area for "Three Dates" (production date, expiration date, batch number) should avoid being close to the blister cavity to prevent it from affecting the sealing of the blister;

c) The perforation/tear line should be kept at a sufficient distance from the blister cavity to avoid the size of the virtual seal affecting the sealing of the blister.

5.6.3 Blister Design Dimensions and Sealing Area

The basic dimensions and allowable deviations of blister design should meet the design requirements listed in Table 7. Generally, the distance between blister cavities should not be less than 3 mm, the distance between blister cavities and edges should not be less than 4mm, and the minimum sealing area width should not be less than 2.5mm.

The sealing area is shown in Figure 4.

Figure 7 Basic dimensions and allowable deviations for blister design

Items	Basic Dimensions(mm)	Allowable deviations(mm)
Thinnest part of cavity	≥0.05	-----
Length of plate	-----	±0.3
Width of plate	-----	±0.3

A: distance between cavities	≥2.5	±0.3
B: distance between cavity and plate edge	≥2.5	±0.3
C: distance between cavities and pressing area	≥2.5	±0.3
D: distance between cavity and reinforcement rib	≥2.5	±0.3
distance between cavity and perforation line	≥2.5	±0.3

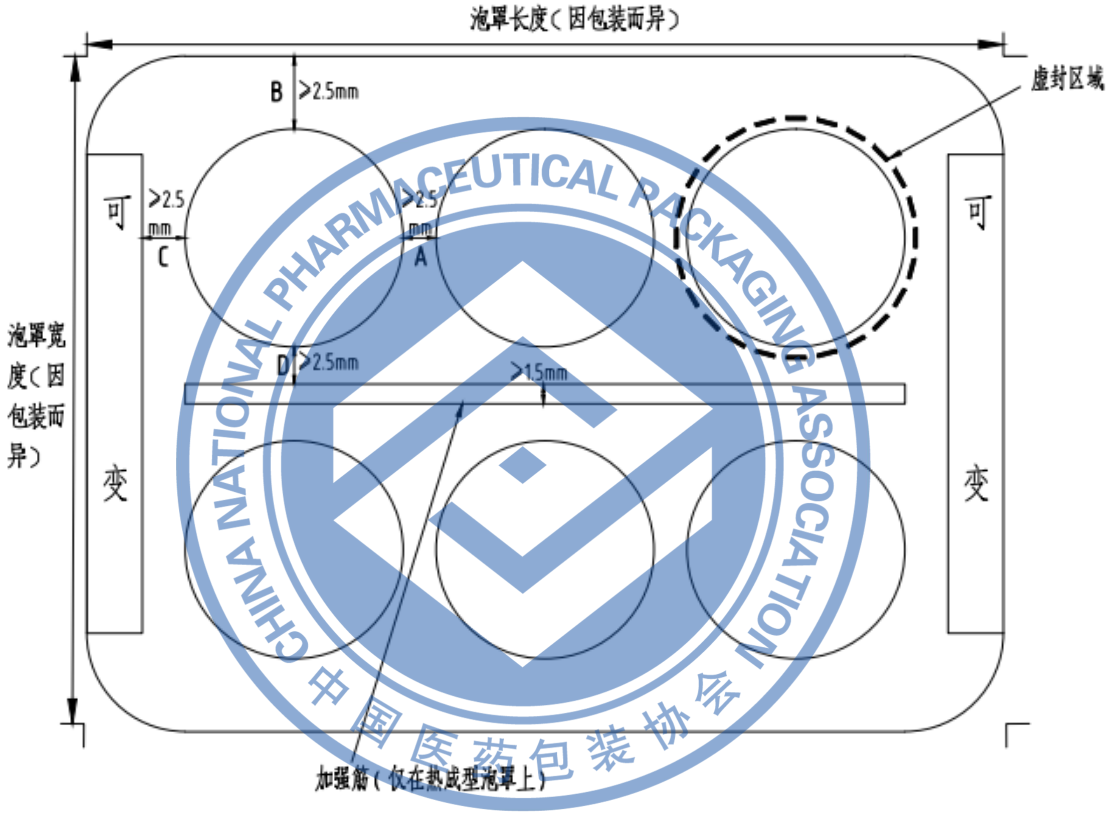

Figure 4 Sealing area diagram

5.7 Blister Cavity Volume

The shape of cavity is decided by tablet and capsule shape. Normally the headspace between tablet and lidding material should be no less than 0.5mm. The design of cavity volume should pay attention to the following:

a) Cavity volume design matches the volume of packaged tablets and capsules;

b) The cavity size and volume should be bigger when using cold-form blister;

c) The mold angle 7° ~ 10° is more conducive to demolding.

Typical cavity designs are shown in Figure5 and Figure 6.

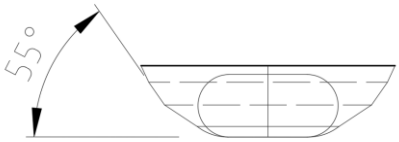

Figure 5 Example of cold-form cavity

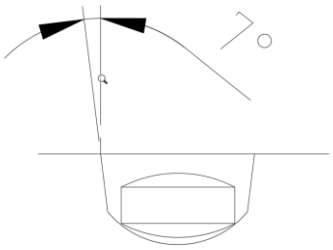

Figure 6 Example of thermoforming cavity

5.8 Blister Layout

The layout of blister should consider the following:
a) Minimum sealing critical area
b) Feeding direction of tablet/capsule
c) Type of tablet/capsule
d) Size of blister cavity
e) Size of blister plate

5.9 Tear line

When selecting the blister with easy-tear / fold line, it should be easily and quickly torn or simply folded in half twice to break apart.

5.10 Variable information

After the formation of the blister system, <Pharmaceutical Manufacturing Quality Management Practice> requires the labeling of relevant information, which is variable data, such as production date, expiration date, production batch (batch specific code), and other information. Variable information is usually printed on lidding material or both sides of forming material using methods such as steel stamping, laser coding, ink spraying, etc.

5.11 Printing on Lidding Material

On the premise of complying with <Regulations on the Administration of Pharmaceutical Instructions and Labeling>, considering brand/marketing factors, the text and printing patterns on the lidding materials should be as simple and easy to print as possible.
If a QR code is printed on the lidding material, it should meet the requirements of minimum height and blank area, and try to use the dark side printing of aluminum foil for easy automatic reading.

6 Evaluation of blister packaging systems

6.1 Overview

When choosing a blister package, pharmaceutical companies should be based on the characteristics of the product itself in order to ensure that the quality of the drug can be controlled to meet the clinical requirements and usage safety. The barrier performance should be established such as water vapor transmission, the pharmaceutical is particularly sensitive to oxygen and there should be corresponding research and control over its oxygen barrier performance.

6.2 Dimensions and deviations

It shall comply with the requirements of 5.6.3.

6.3 Appearance

It shall comply with the requirements of Table 8.

Table8 Appearance quality of blister

Items	Requirements
Overall	No scratches, wrinkles, damages, foreign objects, dirt, or other defects.
Graphic and Text Information	Graphic and text information (such as name, specifications, patterns, etc.) must have no errors, omissions, printing marks, or obvious color differences.
Variable information	production date, expiration date, batch number must be clear, complete and identifiable
Heat Sealing of Blister and Aluminum Foil	Must be tight, smooth, with clear mesh patterns, and no wrinkles are allowed.
Mesh Pattern Penetration	Not allowed
Separation of Aluminum Foil and Blister at Corners	Not allowed (except easy-to-peel blister and special applications)
Blister	Must be intact, smooth, and rigid
Missing Pieces (Grains), Broken Pieces (Grains), Dirty Pieces (Grains)	Not allowed

6.4 Sealing performance of blister

The appropriate test conditions should be selected according to blister size, opening method, quantity of blister per board, sealing width, virtual sealing area, lidding material, etc.
In general, no liquid should penetrate into the blister under vacuum condition of -80kPa ±13kPa for 30 seconds. The pass rate of blister sealing shall be 100%, and the test method is shown in Appendix D.

6.5 Moisture barrier performance of blister

It should meet the requirement of moisture-proofing of the pharmaceutical contained in the blister.

Appendix A

(Informative)

Process of pharmaceutical blister packaging

A.1 Form stage

The forming methods of blister are mainly divided into thermo forming and cold forming.

Thermo forming mainly includes thermo suction forming, thermo blow forming and plug-assist to the thermo blow forming.

Thermo forming is the process in which the sheet passes through a heated plate and the positively pressured. Normally the heating temperature for PVC is 100 ℃ ~ 150 ℃, the temperature for PVDC is 100 ℃~ 140 ℃. The forming pressure is 0.4MPa~0.8MPa.

If there are special requirements for the barrier performance of packaging materials (light water, oxygen), and if the residual heat after forming has a certain impact on the preparation, it is suitable to use cold press forming. The double-aluminum packaging material is selected for cold stamping and forming

When designing a forming mold, the ratio of blister width to depth is controlled to approximately 3:1, or computer-aided design can be used to obtain the optimum ratio.

A.2 Fill stage

There are 4 automatic filling methods, including universal feeding, channel feeding, combined feeding and simultaneous tablet placement feeding.

A.3 Seal stage

In the sealing stage, the formed and filled blister cavity sealing with the lidding material by heated rollers or heat-sealing plates under pressure to form the sealing cavity that makes up the blister packaging system. Typical sealing temperatures are shown in Table A.1.

Table A.1 Typical heat seal temperature for 20μm Aluminium Foil and Common Blister Materials

℃

Heat Sealing Method	Heat Sealing Surface	
	Typical structure of PVC: PVC PVC/PVDC/PVC PA/AL/PVC PCTFE/PVC	Typical structure of PVDC: PVC/PVDC PVC/PE/PVDC
Roll Type	180~240	170~230
Plate Type	150~210	150~200

A.4 Post-processing stage

The post-processing stage includes steel stamping, laser printing, inkjet printing, perforation, and die-cutting.

Steel stamp, laser printing and inkjet printing can be used for "three dates" (production date, expiration date and batch number) on packaging. They must be clear, complete and identification. Usually, high-speed blister packaging machines are equipped with heating functions at the steel stamp batch number station. In general, the heating temperature of the steel stamp batch number station is 80 ℃ ~140℃

A.5 Others

Online printing can be used on packaging production lines. There are many different ink chemical systems for online printing, and the print primer of pharmaceutical aluminum foil should adapt to the adopted online printing ink chemical system.

Appendix B

(Informative)

Equipment of pharmaceutical blister packaging

B.1 Blister packaging machine

At present, blister packaging machine includes fully automatic, automatic and semi-automatic blister packaging machine. The structure mainly consists of packaging machine body, unwinder, heater, forming section, feeding section, heat sealing section, conveying device, printing device, punching control system, etc.

B.2 Unwinding form

The unwinding device of a blister packaging machine basically has two forms:

a) Manual splicing of roll film: After using the blister film, stop the machine for 3~5min, and manually splice the film roll.

b) Automatic splicing of roll film: After use, the blister film is automatically spliced inside the equipment.

B.3 Heating form

There are two forms of heating forming structures for blister packaging machines:

a) Overall molding heating method: The room temperature film passes through double-layer heating plates, and is heated several times to reach the effective forming temperature, then enters the forming mold to be formed.

b) Localized heating and forming method: after the room temperature film is rolled into the forming position, it is heated and formed at a single position corresponding to the blister cavity. Compared with the overall molding heating method, the blister plate after localized heating and forming molding is more flat and straight.

B.4 Heat sealing form

There are two forms of heat sealing structures for blister packaging machines:

a) Roll type: The blister sealing is achieved through roll pressing, which is continuous;

b) Plate type: The blister is sealed by a flat plate, and this sealing method is intermittent.

B.5 Online control technology and methods

B.5.1 Online monitoring control system

Blister packaging equipment can use computerized systems to monitor and control process parameters. Based on current regulations for data integrity, the control system should also provide functions such as user management logic security and permission electronic record audit tracking.

B.5.2 Imaging inspection technology

Online imaging inspection of blisters is realized by integrating computer technology with imaging techniques. The system counts the defective blisters according to the requirements for substandard finished products, which is used for the rejection of these defective blisters. Usually, 1 ~3 vision

inspection systems can be configured on a blister packaging machine.

B.5.3 Automatic rejection

The equipment is able to automatically reject abnormal blisters detected by monitoring functions, or products produced under abnormal conditions. The configurable rejection confirmation function can automatically confirm the rejection results; if the rejection is unsuccessful, the signal can be transmitted to the control system to trigger an alarm and stop the machine.

Appendix C

(Informative)

Materials of pharmaceutical blister packaging

C.1 Lidding material

C.1.1 Aluminium foil for medicine

C.1.1.1 Process introduction

The production of Aluminium foil for medicine is based on industrial aluminum foil. The process involves printing and coating technology using a flexographic plate as well as applying protective coatings to the surface of the aluminum foil and hot seal coatings to the other side.

C.1.1.2 Composition

Aluminium foil for medicine is generally composed of protective layer/ (printing layer)/aluminum foil layer/ (printing layer)/heat sealing layer, and its key materials are protective coating, ink, aluminum foil and heat sealing coating

C.1.1.3 Process control

The process controls are as follows:

a) The quality of semi-finished products is controlled by key process parameters such as temperature, speed, air volume, tension, viscosity and pressure;

b) The appearance quality of products is controlled by detecting appearance defects such as pinholes, foreign objects, printing, etc. by on-line or off-line inspection.

c) The quality of products is controlled by manually testing the coating amount, the heat resistance of the protective layer, heat sealing strength of coating layer.

C.1.1.4 Key technical indicators

The key technical indicators of aluminium foil for medicine mainly include pinhole, protective layer heat resistance, heat seal strength and bursting strength, etc.

C.1.2 Composite aluminum foil for medicine

Composite aluminum foil for medicine is mainly used for functional blister packaging of drugs that require child resistance and resistance to corrosion by volatile drugs. Several typical structures include: OP/AL/PVC, Paper/AL/HSL, PET/AL/HSL, and Paper/PET/AL/HSL. The process control and key technical indicators of composite aluminum foil for medicine are similar to those of aluminum foil for medicine, but composite products should pay more attention to solvent residue.

C.2Typical blister material

C.2.1 Polyvinyl chloride (PVC) solid pharmaceutical hard sheet

C.2.1.1 Composition and process

Polyvinyl chloride (PVC) solid pharmaceutical hard sheet is a blister material that meets pharmaceutical requirements by PVC resin with certain amount of auxiliary materials (such as stabilizers, reinforcing agents, processing aids and lubricants), through extrusion, calendering and other processes.

C.2.1.2 Performance indicators

Safety performance: VCM residue, heavy metal, microorganism, etc.

Barrier performance: water vapor, oxygen permeability, etc.

Processing performance: tensile strength, heating shrinkage rate, etc.

Protective performance: transparent, semi-transparent, opaque and anti-UV, etc.

C.2.2 Solid pharmaceutical hard sheet of PVC/PVDC, PVC/PE/PVDC, PVC/PVDC/PVC

C.2.2.1 Composition and process

PVC/PVDC, PVC/PE/PVDC and PVC/PVDC/PVC solid pharmaceutical composite film is a kind of composite blister material which meets the requirements for pharmaceutical use. It is produced by coating and compounding processes using PVC pharmaceutical base materials PVDC emulsion, PE film and adhesive etc.

C.2.2.2 Performance indicators

The performance indicators of composite film are similar to those of PVC film, and more attention should be paid to solvent residue in composite products.

C.3 Polytrifluorochloroethylene (PTFCE) solid pharmaceutical hard sheet

C.3.1 Composition and process

The product structure mainly includes PCTFE/PVC, PVC/PCTFE/PVC. It is made of two raw materials, PCTFE film and PVC hard sheet, which are laminated once or twice by a dry lamination machine, then matured and cut into products with required width and length by a slitting machine. PCTFE has excellent transparency and moisture resistance, stable biochemical performance and chemical resistance.

C.3.2 Process control

The process controls are as follows:

a) The quality of semi-finished products is controlled by key process parameters such as temperature, speed, air volume, tension, viscosity and pressure;

b) The appearance quality of products is controlled by detecting appearance defects such as pinholes, foreign objects, printing, etc. by on-line or off-line inspection;

c) The quality of products is controlled through monitoring composite adhesive coating amount, appearance width thickness solvent residue content between different materials.

C.3.3 Barrier performance

The barrier performance indicators are shown in Table C.1.

Table C.1 Typical barrier indicators of PCTFE/ PVC composite sheet

Structures	Water Vapor Transmission Rate g/m2•24h，≤ 38℃, 90%RH	Oxygen Transmission Rate cm3/（m2•24h•0.1MPa），≤ 23℃, 50%RH
PCTFE15 μm/PVC250 μm	0.370	20.2
PCTFE20 μm/PVC250 μm	0.290	
PCTFE23 μm/PVC250 μm	0.233	
PCTFE51 μm/PVC250 μm	0.109	
PCTFE76 μm/PVC250 μm	0.078	
PCTFE102 μm/PVC250 μm	0.062	
PCTFE152 μm/PVC250 μm	0.038	
Note: The testing method refers to the relevant testing methods in ChP. For the PVC/PCTFE/PVC, if the thickness of the PCTFE layer is the same as that in the two-layer structure, the typical value data for the flat film will be the same(The barrier data will be different due to the different thickness and stretching after forming)		

C.4 Cold-formed aluminum: cold-formed foil for solid preparation

C.4.1 Composition

It is mainly used for pharmaceutical packaging with high requirements on barrier performance, and it is suitable for the packaging of solid dosage forms such as tablets, capsules, pills and powder inhalation preparations.

The typical structure of cold-formed aluminum is PA/ AL/ PVC, other structures such as PA/AL/PA/PVC, PVC/PA/AL/PA/PVC, PA/AL/PE(halogen-free), PA/AL/CPP(halogen-free), PE/PA/AL/PA/PE(halogen-free) have also been developing, it is necessary to select the appropriate structure according to the characteristics of the packaged pharmaceutical and the local laws and regulations.

C.4.2 Typical production process of cold-formed aluminum

The process of using adhesive to laminate polyamide (Nylon), soft aluminum foil and PVC into a whole unit, aging them so that interlayer peeling strength meets corresponding standards, and then slitting them into different specifications.

C.4.3 Key technical indicators

The key technical indicators of cold-formed aluminum mainly include peeling strength, barrier performance, heat sealing strength, residual solvent, vinyl chloride monomer leaching products, microorganisms and abnormal toxicity.

Appendix D

(Informative)

Inspection method of pharmaceutical blister packaging

D.1 Dimensions and deviations

It measured using a vernier caliper having a precision of 0.02mm.

D.2 Appearance

Visual inspection.

D.3 Seal performance

D.3.2 Test equipment

As shown in Figure D.1, the test container is a sealed container that can withstand more than 0.1 MPa. The container has a vacuum gauge of grade 2.5 installed on it. It also has an exhaust pipe connected to the vacuum pump with a valve and an air inlet tube connected to the atmosphere. There is also a water supply pipe for supplying water. Inside the container there is a pressing plate whose diameter is slightly less than the inner diameter of the container.

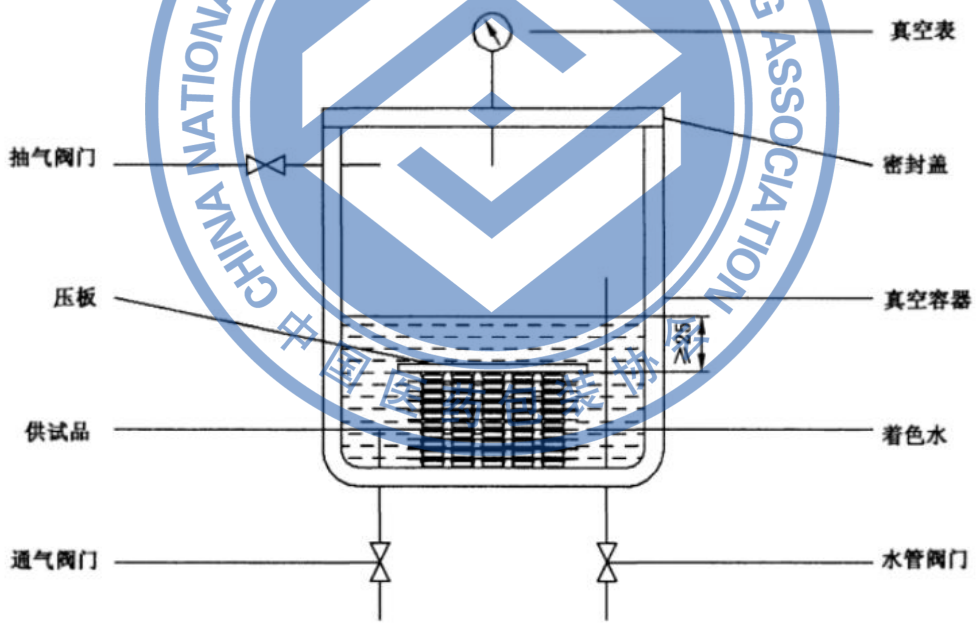

Figure D.1 Test equipment of sealing performance

D.3.2 Procedure

The sealing test procedures of blister packaging system are as follows:

a) Take 100 plates from the test sample and divide them into 4 groups, 25 plates in each group as samples;

b) Place the sample in the above container, close the sealing lid tightly ,close the venting valve, turn on the vacuum pump and keep the vacuum at -80kPa ± 13 for 30s, then inject the colored

water with the water surface not less than 25mm above the surface of the specimen, and return to atmospheric pressure.

c) Remove the sample and observe whether there is any liquid penetration into the blister and sealing layer after wiping it clean with clear water after 10 min.

D.3.3 Calculation of blister seal pass rate

Calculate the blister seal compliance rate according to the formula D.1:

$$S = \frac{n4}{100} \times 100\% \quad \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \quad (D.1)$$

Wherein:

S——the pass rate of blister sealing;

n4——the number of qualified blister plates

Note: method is derived from JB/T 20023-2016.

D.4 Moisture barrier properties of blister

It can be tested according to the method of water vapor permeability determination [the first method 1, weight gain method (2), container method in the Pharmacopoeia of People's Republic of China 4010]. Other suitable methods may also be selected based on measurement characteristics.

Appendix E

(Informative)

Professional terms in Chinese and English

The professional terms in Chinese and English used in this document are shown in E.1.

Table E.1 Professional terms in Chinese and English

Chinese	English	Abbreviation
药用铝箔（推破式盖膜）	aluminium foil for medicine （push through packaging）	OP/AL/HSL PTP
热封层	heat seal lacquer	HSL
聚氯乙烯	polyvinyl chloride	PVC
聚偏二氯乙烯	polyvinylidene chloride	PVDC
聚酰胺	polyamide	PA
铝	aluminum	AL
聚三氟氯乙烯	polytrifluorochloroethylene	PCTFE
聚丙烯	polypropylene	PP
聚酯	polyethylene glycol terephthalate	PET
环~~状~~烯烃共聚物	cyclic olefin copolymers	COC
保护层	over printing	OP
纸张	paper	Paper
低密度聚乙烯	low-density polyethylene	LDPE
聚四氟乙烯（特氟隆）	polytetrafluoroethylene	PTFE（TEFLON）
氯乙烯单体	vinyl chloride monomer	VCM
甲基丙烯酸甲酯-丁二烯-苯乙烯共聚物	methyl methacrylate-butadiene-styrene	MBS
聚乙烯	polyethylene	PE

References

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[4] Good Manufacturing Practice for Pharmaceutical Products (Revised in 2010)
[5] Pharmacopoeia of the People's Republic of China (2020 Edition)