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white paper

PHARMACEUTICAL BLISTER PACKAGING: HOW BARRIER FILMS WORK

This paper outlines a simple approach to explain how packaging material works to provide barrier to moisture, oxygen, and gases and its applications in solid oral-dose packaging.

The pharmaceutical industry has gone through significant changes during the last years. On one side, exciting and valuable drugs have been developed which save peoples' lives, help them to get relief, and to cure serious diseases. On the other hand, the regulatory environment has changed leading to increased requirements for product safety and cost pressure due to changes in the healthcare systems. A clear example is the creation of the zone IV-b for stability testing. In order to provide a test condition that reflects the challenges of distributing drugs in the ASEAN countries, the WHO has proposed this new category for hot and very humid climates.

All these developments have a big influence on packaging requirements. Besides the best protection of the drug, the contribution of the packaging for greater efficiency and cost reduction has become a major criterion.



Blister packaging plays an important role especially for oral- and solid-dosage forms. Most packages are made from thermoforming polymers, but also the number of cold-form aluminum based packs is constantly growing. Individual protection of each dose; dial-in barrier; the support of child-resistance and senior citizen friendliness; and opportunities for the design of compliance packs are only some arguments for the use of blister packs. It is obvious that the aforementioned criteria also impact material requirements for blister packaging.

New generations of blister materials have been developed to comply with these demands and to provide maximum security and productivity. New services have been created to support packaging development, optimization, and acceleration of time-to-the market.

Pharmaceutical substances are getting more and more sophisticated, and also tend to get more and more sensitive to environmental influences like the attack of moisture and oxygen. Most active ingredients and compositions show sensitivity against moisture, but the number of drugs sensitive to oxygen is increasing. In addition, temperature is important due to hydrolysis and oxidation rates increasing with temperature.

The exposition of tablets and capsules to oxygen and/or moisture can have serious effects:

- Softening and disaggregation (mechanical corrosion)
- Chemical hydrolysis of the active ingredients (decrease of potency and/or forming of toxic compounds)
- Oxidation of the active ingredients (decrease of potency and/or forming of toxic compounds)

Worst case, fatality can be the result of missing medication or decomposition of the product. To avoid or reduce such negative influences, the drugs must be protected by an effective barrier packaging. Barrier packaging decelerates the intrusion of product affecting gases and/or the escape of volatile ingredients or protective gases.

TECHNICAL BACKGROUND

Generally speaking, the following materials can be used for pharmaceutical barrier packaging:

Metal (i.e. cold-form foil, CFF)

Inorganic glasses (bottles, vials)

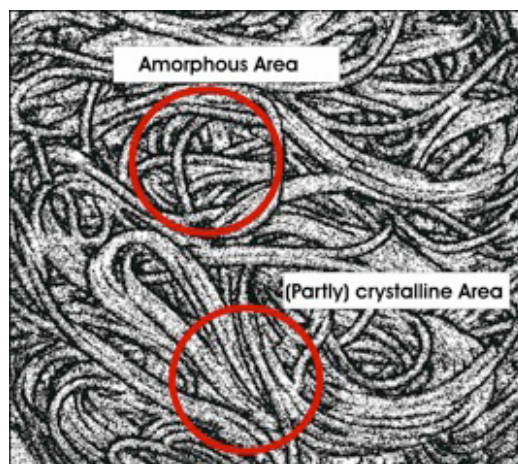
Polymers (bottles, blister packs)

These materials differ in their molecular structure and barrier properties:

Metals consist of a compact package of metal atom spheres with small interspaces. Metals are not transparent, the density is high, and the plastic forming of metals is limited. Only ductile metals like copper, gold, and aluminium can be formed at ambient temperatures without destruction. For cold-form-foil blister packs, aluminium is used, which is supported on both sides by thin polymer films as a forming and sealing aids. Because of limited formability, only relatively flat and wide cavities can be obtained.

Glass is an amorphous high viscous melt of silicates. It is composed of a network of silicate units with larger interspaces as compared to the metal grid. It is similar to a compact inorganic crystal structure. Because of its brittleness, glass can only be formed in the molten status and, thus, only bottle and vial containers are in use for pharmaceutical packaging purposes.

Polymers with linear molecular chains like PVC, PET, PE, etc. have random coil structures in their amorphous state and may have some crystalline regions which are formed by chain arrangement.



Visualization of amorphous and crystalline regions of a polymer with linear chains

The permeation of gases and small molecules through a solid material is enabled by diffusion processes. Diffusion is the transport of single molecules by means of thermal movement of these particles. Opposite to diffusion, the macroscopic transport of matter through pinholes and pores has its origin in convective processes. In principle, permeation of oxygen, water, aromas, and other molecules can occur with all materials, but diffusion through metals and glasses is strongly hindered or even impossible because of the small interspaces. Plastics can be combined and easily processed to build barrier structures to different permeants. This kind of customization is becoming extremely popular in the pharmaceutical solid oral-dose packaging.

The Transmission Rates (quantity of mobile substance (gas) that permeates per time and surface area through the stationary phase (i.e. polymer film)) depends of the following factors:

- Medium pathway of the mobile molecules through the stationary phase (influenced by the thickness, crystallisation level, content of additives, and filling material)
- Fraction of free volume in the stationary phase and size of the mobile molecules (influenced by the chemical composition and structure, crystallisation level, content of additives)
- Chemical affinity of mobile and stationary phase

Usually, polymers show, because of their chemical structure, different barrier performance in relation to permeating gases. That means often polymers have good barrier against water vapor and low barrier performance for oxygen and vice versa. Only a few polymers show good barrier against oxygen and water vapor at the same time. This makes it very important to find the right polymer film for the right application.

As an indication, the following table might help to categorize the single polymers with regard to their oxygen and water vapor barrier performance.

POLYMER	INTRINSIC WATER VAPOR BARRIER	INTRINSIC OXYGEN BARRIER
PVC	o	o
PET	o	o
PVdC/PVdC new generation	++/+++	+++
PCTFE (ACLAR®)	+++	o
EVOH	--	+++
PA	-	o
PP	+	---
COC	+	---
HDPE	+	---
A/MA/B	-	+

The Intrinsic Transmission Rates are characteristic for each polymer (grade) and represent the thickness independent barrier performance (commonly said “the Transmission Rate of a one micron thick film”). In numbers, these categories might be defined to be approximately as follows:

CATEGORY	INTRINSIC WATER VAPOR TRANSMISSION RATE (range, @ 38°C/90%r.h.), g µm/(m² d)	INTRINSIC OXYGEN TRANSMISSION RATE (range, @ 23°C/0%r.h.), cm³ µm/(m² d bar)
Very low barrier level (---)	More than 5,000	More than 30,000
Medium barrier level (o)	500–800	1,000–3,000
Very high barrier level (+++)	Lower than 10	Lower than 50

Usually, the incremental barrier ranges of a barrier film portfolio are generated by variation of the thicknesses of the barrier layers. Also, combinations of two or more different barrier polymer layers lead to tailor-made barrier film solutions.

INTRODUCTION TO PHARMACEUTICAL BARRIER FILMS

The use of rigid PVC as a means of providing protection to pharmaceutical products has been established for many years. Used in blister packaging, PVC offers a wide range of benefits to the consumer, such as product visibility, barrier and mechanical protection, ease of use, and compliance. Homo-polymer mono-layer PVC films are typically found in less demanding applications, such as small tablets and shallow form requirements. In more demanding applications such as large tablets (deep or precipitous cavities), the use of copolymer grades of PVC could be recommended. For some applications such as suppository films or packaging of ampoules/unit dose, the use of high copolymer PVC films may be necessitated. Addressing requirements such as ingredient performance and compliance, such as child resistance and product protection against UV, PVC films can be pigmented with titanium dioxide and other colorants to provide a suitable solution.

As an alternative to PVC mono films, Pentapharm® kpVantage® films based on polyester present similar optical and mechanical properties as PVC. Pentapharm® kpVantage® films form at lower temperature while reducing the wear and tear on tools and heating plates on the machine. Barrier to oxygen and moisture is less than PVC, but enough to cover the low end of the spectrum. A switch to Pentapharm® kpVantage® film does not require machine modifications nor a tool change. All other properties like UV resistance, opacity, or color can be customized as easily as PVC. In child resistance tests, Pentapharm® kpVantage® films scored as high as PVC.



To provide the pharmaceutical market with greater moisture barrier protection, a number of enhanced properties can be added to the PVC, polyester, or other polymer substrates such as a PVdC (a copolymer based on vinylidene chloride) coating that will provide high-moisture barrier protection. Typically available in the market place are 40g, 60g and 90 g/m² coating weights offering Water Vapor Transmission (WVTR) rates of 0.6 g/m² down to 0.2 g/m² (38°C, 90% r.h.).

With the advent of new drug delivery systems, new dosage formulations, and a trend to testing at accelerated ICH conditions (40°C – 75% RH), the requirement for additional barrier properties has been steadily growing.

New PVdC-grade development allows the processor to reduce the coating mass of PVdC to attaining the equivalent barrier of previously standard coating weights respective offering high barrier against moisture, gases, oxygen, or aroma. Today, it is possible to achieve barriers of less than 0.1 g/m²d with the new generation PVdC-coated blister films.

PCTFE laminate (commonly known as “ACLAR®”) structures provide the potential for super high-barrier solutions. They cover the high-end range of water vapor barrier materials. Products such as PCTFE have been making a strong resurgence in the marketplace and new emerging technologies such as COC (Topas®) have been offering new polyolefin based barrier structures.

In new drug delivery systems such as controlled/sustained release and especially rapid dissolve system, PCTFE film laminated with PVC has found a growing market. Unsurpassed in its barrier properties, PCTFE film laminates offer WVTR protection from 0.42 g/(m² d) to as low as 0.038 g/(m² d) with the graduated thicknesses of 15, 20, 23, 51, 76, 102, and 152 microns PCTFE – in addition PCTFE films provide process performance and excellent clarity.

New polymers such as Cyclic Olefin Copolymers (COC) are providing the end-user with exciting new alternative barrier materials for blister packaging. Based on norbornenes and ethylene, COC is free of chlorine, fluorine, and other halogens. Available in a number of laminations, COC can be combined with a range of substrates such as PP, PVC, polyester, and APET. A complete range of barrier substrates can be provided to offer the user the best barrier cost performance. COC films show excellent barrier and process performances.

Hybrid solutions combining different barrier polymers have been developed for customized solutions and unsurpassed properties can be provided. The newest kp development is the combination of PVC, ACLAR®, and PVdC with the structure PVC/ACLAR®/PVdC/PVC 127/102/150/127. This laminate offers



the best water vapor and oxygen barrier values available for transparent thermoformable polymer films absolute and in combination: The Water Vapor Transmission Rate is less than 0.035 g/(m² d) (38°C/90% r.h.) in a unique combination with an Oxygen Transmission Rate below 0.18 cm³/(m² d) (23°C/50% r.h.). The pseudosymmetrical structure with PVC skins on the outside of the laminate result in a very good thickness distribution in the blister cavity, low coefficient of friction, and an outstanding blister barrier (formed film barrier).

Another example of hybrid barrier laminates is a combination of PVC, ACLAR®, and EVOH. With the structure PVC/PE-EVOH-PE/ACLAR® and PVC/PE-EVOH-PE/ACLAR®/PVC, moisture transmission rates of 0.06 g/(m² d) and oxygen barriers of less than 0.25 cm³/(m² d) can be achieved. These laminates offer best thermoformability, a very good oxygen/moisture barrier combination, and a crystal clear appearance.

TRENDS IN BLISTER PACKAGING

More and more high sophisticated drugs have been developed with a high value for patient's quality of life, but also with a high monetary value because of their dedication to individual needs and special diseases. These high-value drugs require maximum protection.

Products have become more sensitive. To ensure a quick and controlled release of the active substances, the active ingredient has to be well protected until the moment the patient will take it. Therefore, an optimum barrier has to be provided by the packaging.

New OTC drugs have been introduced to the market exploring the use of alternative materials to PVC like Pentapharm® kpVantage® films. Either laminated to PCTFE or PVdC, alternative materials are becoming very popular.

Time-to-market continues to be essential for the pharmaceutical companies for new product introductions. It is essential that the packaging does not hinder the timely product launch and offers the utmost reliability.

Products are more and more developed for the global markets and delivered to the various regions through a global production network. Global standardized packaging solutions contribute to easy production transfers.

Continuous improvement programs have also become key for the pharmaceutical industry. Line efficiency, sustainable production, and waste reduction are some of the criteria. These targets need to be supported by state-of-the art packaging materials.

New drug delivery systems for an increased convenience and effectiveness play an important role in the actual R&D programs of the pharmaceutical companies. This has to be accompanied by innovative packaging solutions.

SELECTING THE RIGHT BARRIER

Understanding how packaging material works to provide a barrier to moisture, oxygen, and gases provides the basis for selecting the right barrier for a particular solid oral-dose package. In summary, the characteristics of plastic blister films are influenced by the different properties of the polymers. Using different base films gives opportunities for structures other materials to achieve the best property combination. For blister films, PVC is the most common base material. The unsurpassed machine performance and the polymer specifics combined with a valuable contribution to environmental sustainability make it to the ideal material for this application.

Without the necessity to change package design, tooling, and production line setup, it is possible to adjust the barrier over the life cycle in accordance with long-term tests results to ensure the best product shelf-life. Plastic blister films are available from low- to high-barrier against moisture and oxygen. Selecting the right film from the beginning provides the maximum security for a successful new product introduction.

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