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Review Article

OUTLINE OF PHARMACEUTICAL PACKAGING TECHNOLOGY

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ABSTRACT

Packaging is the science, art, and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging is system or mean by which the product will reach from production center to the consumer in a safe & sound condition & with minimum overall loss. So many issues regarding the pharmaceutical product like stability, sell, patient compliance, etc are related with the packaging and in regard to this review is done on the various advancements in the packaging techniques and selection of packaging material.

KEYWORDS: Packaging**,** Packaging technologies, Pharmaceutical packaging

INTRODUCTION

Packaging is the science, art, and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging also refers to the process of design, evaluation, and production of packages. Package labeling is any written, electronic, or graphic communications on the packaging or on a separate but associated label. Packaging is a bridge connecting the production with marketing.[1]

It is an economical means of providing protection, presentation, identification, information and convinces for a pharmaceutical product from the moment of production until it is used or administered.[2] Packaging is system or mean by which the product will reach from production center to the consumer in a safe & sound condition & with minimum overall loss. A package or market package refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap).

OBJECTIVES OF PACKAGING

Packaging and package labeling have several objectives which are summarized below[3-6]:

Physical Protection - The objects enclosed in the package may require protection from, among other things, shock, vibration, compression, temperature etc.

Barrier Protection - A barrier from oxygen, water vapor, dust, etc., is often required. Package permeability is a critical factor in design. Some packages contain desiccants, or oxygen absorbers, to help extend shelf life.

Containment or Agglomeration - Small objects are typically grouped together in one package for reasons of efficiency. For example, a single box of 1,000 pencils requires less physical handling than 1,000 single pencils. Liquids, powders, and flowables need containment.

Information Transmission - Packages and labels communicate how to use, transport, recycle, or dispose of the package or product. With pharmaceutical, food, medical, and chemical products, some types of information are required by governments.

Marketing - The packaging and labels can be used by marketers to encourage potential buyers to purchase the product. Package design has been an important and constantly evolving phenomenon for dozens of years. Marketing communications and graphic design are applied to the surface of the package and (in many cases) the point of sale display.

Security - Packaging can play an important role in reducing the security risks of risks of shipment. Packages may include authentication seals to help indicate that the package and contents are not counterfeit. Packages also can include anti-theft devices, such as dye-packs, RFID tags, or electronic article surveillance tags which can be activated or detected by devices at exit points and require specialized tools to deactivate.

Convenience - Packages can have features that add convenience in distribution, handling, display, sale, opening, re-closing, use, and reuse.

SELECTION OF PACKAGE

The stability of drug shelf life depends on many factors and packaging is one of them. The selection of the package begins with the determination of the products physical and chemical characteristics, its protective need and its marketing requirement. The stability of the pharmaceutical product may be totally depends on proper functioning of package. Some of the selection criteria to be considred are as follows[7-9]:

It depends on the ultimate use of the product. The product may be used by skilled person in a hospital or may need to be suitable for use in the home by a patient.

It depends on the physical form of the product. For example solid, semisolid, liquids or gaseous dosage form.

It depends upon the route of administration. For example oral, parentral, external etc.

It depends on the stability of the material. Moisture, oxygen, carbon dioxide, light, trace metals, temperature or pressure or fluctuation of these may have a deleterious effect on the product.

It depends on the content. The product may react with the package such as the release of alkali from the glass or the corrosion of the metal and in turn the product is affected.

It depends on cost of the product. Expensive product usually justifies expensive packaging.

PACKAGING DEVLOPMENT

Anti- Counterfeit Technologies

There are distinct aspects to deciphering and de-complexifying the counterfeit pharmaceutical supply chain. One that is probably more in use today by almost all pharmaceutical companies worldwide is the product-based tracking methodology which incorporates the use of high technology systems to identify counterfeit products in the market. These technologies include tamper-evident packaging, holographics, bar codes and the more recent RFID[10-15]. The purpose of an anti-counterfeit feature is primarily to enable the authentication of healthcare products. The second function may be to act as a deterrent to anyone considering counterfeiting a product based on the difficulty or cost involved set against the likelihood of detection, and therefore prosecution. It is true that security devices on packaging components provide no assurance as to the authenticity of the contents, which may have been substituted or adulterated. Security devices alone do not reduce counterfeits, but are designed to make them easier to detect.[16-17]

Classification of anti-counterfeit technologies

Overt (Visible) Features

Overt features are intended to enable end users to verify the authenticity of a pack. Such features will normally be prominently visible, and difficult or expensive to reproduce.

i) Holograms

For security, anti-counterfeiting, promotion & brand protection holograms can't be counterfeited. The transfer of the protective hologram from one entity to another is impracticable. Because of a good

combination of these qualities with high aesthetic properties, holograms have emerged and taken up important positions in the market of protective as well as promotional technologies. Different types of holographic pack are shown in Figure 1

ii) Optically variable devices (OVD)

OVDs also include a wide range of alternative devices, similar to holograms, but often without any 3D component. Generally they involve image flips or transitions, often including colors transformations or monochromatic contrasts.

Like holograms, they are generally made up of a transparent film which serves as the image carrier, plus a reflective backing layer which is normally a very thin layer of aluminum. Extra security may be added by the process of partial de-metallization; where by some of the reflective layer is chemically removed to give an intricate outline to the image.

iii) Colour shifting security inks and films

These can show positive changes in colors according to the angle viewing angle, and can be effective either as an overt graphic element or by incorporation in a security seal. Colors shifting pigments are finely ground metallic laminates which need to be laid down in a thick opaque film to achieve the optical effect, and are therefore better suited.

iv) Security Graphics

Fine line colors printing incorporating a range of overt and covert design elements such as line modulation and line emboss. They may be used as background in a discrete zone such as an overprint area, or as complete pack graphics, and can be printed by normal offset lithography or for increased security by intaglio printing.

v) Sequential Product Numbering

If printed visibly, it provides a semi-overt means of authentication by reference to a secure database, because duplicates or invalid numbers will be rejected. The main disadvantage of sequential numbering is that the sequence is predictable and easily replicated and end users require some means of access to the database. The more secure option is serialization by means of a pseudo-random non-repeating sequence.

vi) On-product Marking

On-product marking technologies allow for special images or codes to be placed on conventional oral dosage forms. These overt technologies can be difficult to replicate and offer a security technology at the high level. This added layer of security is effective from the original package.

Covert (Hidden) Features

The purpose of a covert feature is to enable the brand owner to identify counterfeited product. The general public will not be aware of its presence nor have the means to verify it. If compromised or publicized, most covert features will lose some security value.

i) Invisible Printing

Using special inks, invisible markings can be printed on almost any substrate, and which only appear under certain conditions, such as via UV or IR illumination. They can be formulated to show different colures with illumination at different wavelengths.

ii) Embedded Image

An invisible image can be embedded within the pack graphics which can only be viewed using a special filter, and cannot be reproduced by normal scanning means.

iii) Digital Watermarks

Invisible data can be digitally encoded within graphics elements and verified by means of a reader and special software. The data can be captured using webcam, mobile.

iv) Hidden marks and printing

Special marks and print may be applied in such a way that escapes attention and is not easy to copy. Their effectiveness relies on a combination of secrecy and subtlety; they may be applied to product packaging as a background tint.

v) Laser coding

The application of batch variable details by lasers coding requires special and expensive equipment, and results in recognizable art effects which may be difficult to simulate. Laser codes can be applied to cartons and labels, and plastic and metal components.

vi) Substrates

There are many ways of incorporating covert markers within a substrate, such as visible or UV fluorescing fibers, or chemical reagents in carton board or paper. Watermarks can be embedded in leaflet paper, or metallic threads interwoven in the base material, possibly including an overt OVD feature. These require a dedicated supply source and large volume production, which, if affordable, results in a very effective option.

vii) Anti-copy or anti-scan design

Fine line background patterns appear as uniform tones, but when scanned or copied reveal a latent image which was not previously visible. Commonly used on secure documents to prevent photocopying, they may be applied to product packaging as a background tint.

viii) Odour

Micro-encapsulated distinctive odors can be applied as an additive to an ink coating to provide a novel covert or semi-overt feature.

Forensic Markers

There is a wide range of high-technology solutions which require laboratory testing or dedicated field test kits to scientifically prove authenticity of the products[18].

i) Chemical Taggants

Trace chemicals which can only be detected by highly specific reagent systems, but not normally detectable by conventional analysis.

ii) Biological taggants

A biological marker can be incorporated at extremely low levels in product formulations or coatings, or invisibly applied to packaging components. At such low levels they are undetectable by normal analytical methods, and require highly specific "lock and key" reagent kits to authenticate.

iii) DNA taggants

Highly specific DNA "lock and key" reagent systems can be applied to packaging by a variety of printing methods. They require a "mirror image" recombinant strand to effect the pairing, and this reaction is detectable by a dedicated device.

iv) Isotope ratios

Naturally occurring isotopes can be highly characteristic of the source of a compound, and accurately determined by laser fluorescence or magnetic resonance techniques. These can provide a "fingerprint" of one or more of the product constituents. Detection requires highly specialist laboratory equipment.

v) Micro-taggants

Micro-taggants are microscopic particles containing coded information to uniquely identify each variant by examination under a microscope. This may take the form of alphanumeric data depicted on small flakes or threads or of fragments of multi colored, multi layered laminates with a signature color combination. These can be embedded into adhesives, or directly applied to packaging components as spots or threads.

Serialization/Track and trace Technologies

A number of Track and Trace applications are under development for the pharmaceutical sector. These involve assigning a unique identity to each stock unit during manufacture, which then remains with it through the supply chain until its consumption[19,20].

i) Serialization

In itself the Track and Trace label may not be immune to copying or falsification, but its security is greatly enhanced by the inclusion of unique and apparently random serialization, or non-sequential numbering, ideally at individual item level. If the serialization was sequential, then the level of security would

be very low as the sequence is predictable, whereas random serialization using a highly secure algorithm or method of encryption overcomes this.

ii) Radio Frequency Identity (RFID) tagging

An RFID tag comprises of an antenna with a microchip at its centre. This contains item-specific and batch information which can be interrogated at a distance, and without requiring line of sight (unlike bar codes). Some systems are able to capture multiple records for a mixture of different products, but there are some issues around orientation of the tags and absorbance of the radio signal by liquids and foils. But one clear advantage of RFID is that it has the potential to be fully automated in warehouses and even through to pharmacies, without requiring manual intervention.

iii) Unique Surface Marking or Topography

There are several methods for applying a pseudo-random image to each item in a batch, such as a pattern of lines or dots in one area of the carton, and then scanning the signature into the batch database via secure algorithms, for later authentication. Alternatively, the pack surface provides a unique fingerprint when scanned by a dedicated laser device, which enables each pack to be registered into the database at batch manufacture, and which is impossible to replicate or falsify.

CLOSED VIAL TECHNOLOGY

The closed vial has been developed to improve aseptic filling quality and to reduce process complexity. A ready-to-fill closed vial consists of a sterile vial provided with the stopper secured in place. The vial is filled by inserting a non coring needle through the stopper, which is then resealed by laser[21,22].

The principle of the closed - vial concept can be summarized as follows:

The body of the closed plastic vial is made of cyclo olefin copolymer (COC), a plastic material that can be molded into shapes that are not feasible with glass and that allow for tighter seals between parts of the vial, thus improving closure integrity.

Closed vials are clean and do not require washing before filling .The vial body and the stopper are molded and assembled in Class 100 environment, leading to extremely low particle levels inside the container.

The vial is sterile. After assembly, the closed vial is sterilized in a gamma- irradiation unit to secure the absence of vial contamination, eliminating the vial washing and dehydrogenization step in the filling line.

The sterile, ready-to-fill vial is delivered uncapped (left). After filling, the vial is capped (middle) inside an isolator. To use the vial, the central part of the flip-top cap is removed (right), exposing the large puncture area that has been kept sterile by the circular rib. (Figure 2)

Because of its advantages, the closed – vial technology is likely to become a standard for pharmaceutical aseptic filling processes. The technology not only improves quality for the patient, but also significantly reduces the complexity and cost of filling operations for manufacturers.

The closed-vial, freeze-drying concept

To maintain optimal sterility assurance, an opening in the vial is required but has been limited in this particular process. The vial actually remains closed most of time, especially between the filling station and the freeze dryer's shelf. The opening and closing of the vial is generated by rearranging the movements of the freeze dryer shelves. When the cycle is finished, the vial closes again before the freeze dryer's door is opened and stays closed until the vial is resealed with a laser and capped.

This process has several advantages over traditional glass-vial processing:

The closed vial content is not exposed during its movement from the sterilization tunnel to the freeze dryer (no half-seated stopper).

There is no risk of product spillage on the vial track to the freeze dryer or on the shelves themselves. Moreover, the plastic vials are shock resistant and nearly unbreakable.

The stoppers do not stick to the upper shelf.

There is no risk of incomplete reseating of the stopper or stopper pop-up after the stoppering step; closure integrity is maintained throughout the process.

When required, this process has the capability of inspecting for particles of the liquid before freeze-drying, provided that the inspection machine is compliant with a Class 100 environment. The vial's bottom ring enables it to be held from the bottom only for the rotation, without an upper spindle above the vial. Its slightly elevated bottom allows for a perfect view on the critical bottom part of the content.

BLOW-FILL-SEAL TECHNOLOGY

A variety of polymers may be used in the process, low and high-density polyethylene and polypropylene being the most popular. The innate ability to form the container/closure during the actual aseptic packaging process allows for custom design of the container to meet the specific needs of the application. This flexibility not only improves container ease of use, but provides a means of interfacing with many of today's emerging drug delivery technologies, most notably in the field of respiratory therapy[23].

Recent advancements in machine design allow for insertion of pre-molded, pre-sterilized components to be molded into the container creating additional design options to create multi-use and inject able product containers. Furthermore, the blow-fill-seal process flow is normally impacted by only two raw materials, product and polymer, that are each processed inline, thereby making the process amenable to large uninterrupted batch sizes, some in excess of 500,000 units, and fill durations of up to 120 hours. The net effect is routinely an increase in production efficiency and a subsequent decrease in operational costs for the user[24].

Blow-Fill –Seal Process

Container Molding

Thermoplastic is continuously extruded in a tubular shape (see Figure 3a). When the tube reaches the correct length, the mould closes and the prison is cut (see Figure 3b). The bottom of the prison is pinched closed and the top is held in place with a set of holding jaws. The mould is then transferred to a position under the filling station.

Container Filling

The nozzle assembly lowers into the prison until the nozzles form a seal with the neck of the mould (see Figure 3c). Container formation is completed by applying a vacuum on the mould-side of the container and blowing sterile filtered air into the interior of the container. The patented electronic fill system delivers a precise dosage of product into the container. The nozzles then retract into their original position.

Container Sealing

Following completion of the filling process, the top of the container remains semi-molten. Separate seal moulds close to form the top and hermetically seal the container (see Figure 3d). The moulds open and the container are then conveyed out of the machine.

The process reduces the amount of the amount of product-contacting components, there is limited operator intervention and the critical fill-zone is physically isolated under a continuous flow of filtered air. Since blow-fill-seal is a completely automated technology that allows for remote operation it is an ideal system for examining the relationship between the level of airborne micro-organisms in the environment and the product contamination rate. A series of published studies have been conducted to investigate and quantify this relationship and potentially provide a means for predicting sterility assurance levels.

CONCLUSION

As the packaging of the pharmaceutical products is very important with regard to its stability, acceptance to patient, transport, etc here we can conclude that to met all these important regards the new techniques like blow off seal, closed vial technology, etc seems to be promising for both sterile and non-sterile pharmaceutical products.

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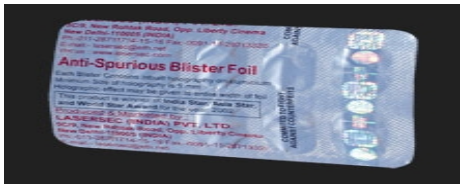
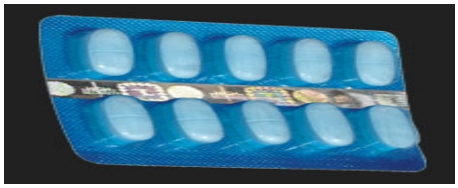


a) Holographic Hard Aluminums Foil for Blister Pack



b) Holographic PVC for Blister Pack

c) Holographic Soft Aluminums Foil for alu pack

d) Holographic Paper labels & cartons

Figure 1: Different types of Holographic Pack

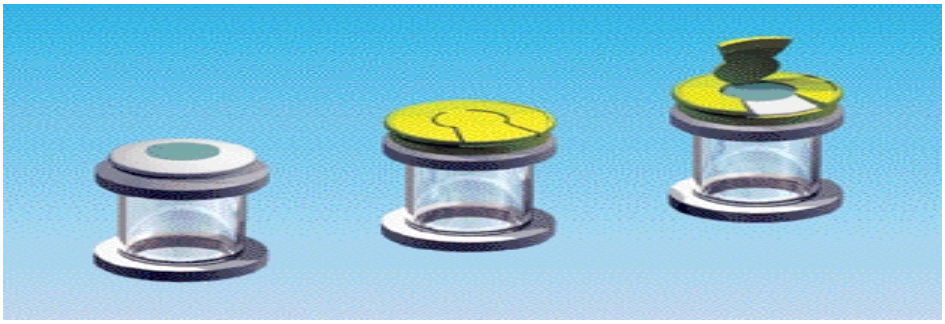


Figure 2: The sterile, ready-to-fill vial

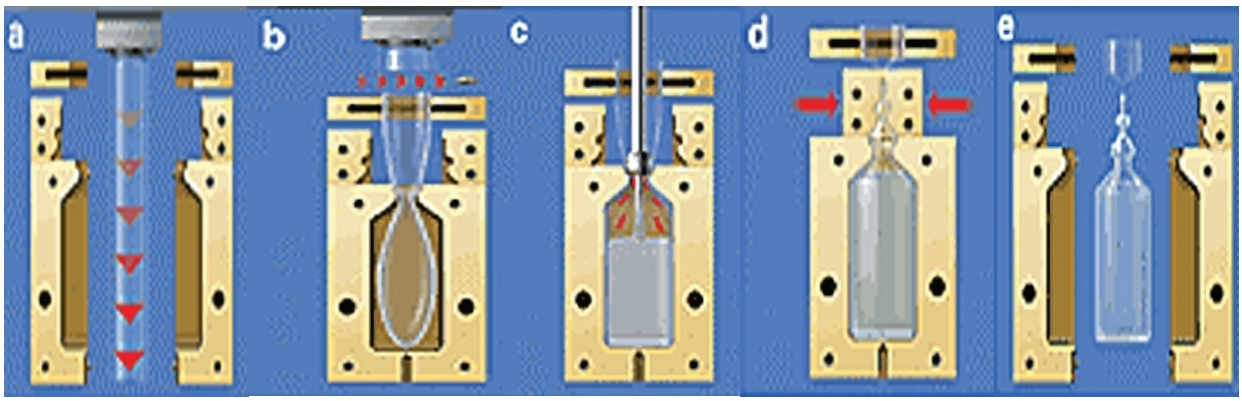


Figure 3: Container Moulding, Filling and Sealing