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Review Article

A REVIEW ON INNOVATIONS IN PHARMACEUTICAL PACKAGING

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ABSTRACT

Drugs need more care in their packaging than do most other products. Now a day's other than protection, presentation, identification, information and convenience; packaging must be tamper evident equally for primary and secondary packages. Tamper evident packaging having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visual or audible evidence to consumer that tampering has occurred. Packaging in Pharma Industry is an extensive, comprehensive and multi-faceted task. From containment and protection to convenience, identification and delivery, packaging's role in the market cannot be underestimated. It is a means of protecting and preserving items contained within, as well as communicating marketing and regulatory information to consumers. Pharmaceutical packaging industry must involve in the research and development activity to find out the solutions for the issues to produce the product in quality, safety, and effective way to consume. This review article focused on the Temper-Evident Packaging, Types of pharmaceutical packaging, Objectives of pharmaceutical packaging, Choice of packaging, Characteristics of Packaging Material, Innovations in Pharmaceutical packaging.

Key Words: Pharmacy, Packaging, Temper-Evident, Packing Materials.

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INTRODUCTION

Packaging is defined as a technique which allows containment of pharmaceutical product from the time of production in a unit till its use. Role of pharmaceutical packaging is to provide life-saving drugs, surgical devices, blood and blood products, nutraceuticals, powders, poultices, liquid and dosage forms, solid and semisolid dosage forms.[1] Packaging play an important role in communicating the image and identity of a company. In many countries it is fully integrated into government, business, institutional, industrial and personal use. The external image of the package give the clear information about the product like route of administration, storage condition, batch number, expiry date, manufacture name, address, license number New ideas of dynamic packaging, intelligent packaging, and nanotechnology offers arrangement which a play a vital part to improve or observing food quality.[2]

The World Health Organization (WHO) guideline defined packaging is a process that a bulk material must undergo to become a finished product. Packaging is not only protecting the drug from degradation but also contamination; it will become an important part of drug delivery system. [3,4] Hence, the manufacturer uses packaging as the tool to promote the products and to increase the degree of patient compliance. Moreover, smart pharmaceutical packaging depends on the nature of the drug, dosage form, route of administration, supply chain, and shelf life of the product.[4]

3] Temper-Evident Packaging:

Tamper evidence has been defined in the USA as the degree to which tampering is apparent to the observer. Tamper – evident packaging therefore is packaging that makes tampering apparent to the observer, to some degree. In its definition of tamper resistant packaging, the US Food and Drug Administration (FDA) have made it clear that for their purpose, the observer is the consumer. This is an important point, because consumer observers are less knowledgeable than observers who design, specify, make fill packages. Consumer observer may misinterpret some of the sign of tampering that would be clear to those who make and fill packages. For this reason, FDA has stated that tamper-proof probably cannot be achieved. Now there is the question of how resistant or evident tampering is?

Tamper-resistant packaging is term originated by the Food and Drug Administration (FDA) in 1983, with the first publication of the regulation, requiring such packaging for OTC drugs sold at retail in the USA. The term was never widely accepted by packaging makers and users. They preferred 'tamper-evident'. The FDA has recently proposed to change its terminology to tamper-evident, based on the idea that the tamper-evident might emphasize to consumers that they should be looking for evidence of tampering rather than assuming without looking, that there has not been any tampering to a resistant package.

The regulatory requirement for tamper –evident packaging is directed against what is known as malicious tampering. It was not established with the intent to provide any control on casual tampering, or grazing, it is called reduction of successful malicious tampering is the goal.

There is another kind or level, of tampering to consider. It used to be called 'pilfering'. A product is stolen opened and the contents partially removed during transit; but target of the regulation is the malicious tamperer, working on retail packages.

The package passes through number of stages, beginning with the container manufacturer, then to the product manufacturer, wholesaler, retailer, and, finally, Consideration of the life history and the functions of the package shows that five basic qualities are required – Protection, Identification, Presentation, Convenience, Economical.[5,6]

4] Tamper Evident Packaging Systems

Some packages are inherently tamper proof, like a tin can hermetically sealed, an aseptically packed multilayer carton or a vacuum or the retort pack. The tamper evident packaging systems are:

a) Film wrappers :

A transparent film with a distinctive design is wrapped securely around a product or product container. The film must be cut or torn to open the container and remove the product. Substrates options include ultra-destructible films, voidable films that provides image when removed. e.g. solvent sensitive papers.

b) Shrink seals and bands :

Bands or wrappers with a distinctive design are shrunk by heat or drying to seal the cap and container union. The seal must be cut or torn to remove the product.

c) Breakable caps :

Such caps break when an attempt is made to open it. These caps provide external tamper evidence and can also be combined with the internal seals thereby providing double security.

d) Sealed tubes :

The mouth of the tube is sealed, and the seal must be punctured to obtain the product [7]

5] Types of pharmaceutical packaging

Pharmaceutical packaging is classified into three different types: they are

1. **Primary packaging system:** The primary packaging system contains the product and holds it that those package components actually come in contact with the product or those components that may have direct effect on the product shelf life. Example: Ampoules, IV containers etc .
2. **Secondary packaging system**: Secondary packaging system is outside the primary packaging which stores pharmaceutical packaging in it for their grouping. Example: cartons box etc.
3. **Tertiary packaging system**: Tertiary packaging system is used for bulk handling shifting of pharmaceutical packages from one place to another. Example: containers, barrels etc. [8]

5.1] Primarily two types of containers are used for packaging:

- **Glass Containers**
- **Plastic Containers [9]**
- **Metal**
- **Rubber**

A) Glass containers:

These need to be chemically inert, impermeable, strong and rigid proving FDA clearance. glass widely used as a drug packaging material. Glass composed of sand, soda ash, limestone and cullet.

Advantages:

- They are transparent
- They are non-reactive
- They can easily labelled

- Economical
- Superior protective qualities
- Available in a wide variety of sizes & shapes

Disadvantage:
- Glass is easily broken
- Heavy weight [10]

A . Type I-Borosilicate glass:

Highly resistant and chemically inert glass. Alkali's and earth cations of glass are replaced by boron and/or aluminium and zinc. These are used to contain strong acids and alkalis. [9]

▪ Eg: pyrex, borosil

▪ **Uses:** Laboratory glass apparatus, for water for injection [10]

b. Type 2-Treated soda-lime glass:

These are more chemically inert than Type I glass. The glass surface is de-alkalized by "Sulfur treatment" which prevents blooming/weathering from bottles.[9]

- **Uses:** For alkali sensitive products, Infusion fluids, blood, & plasma, large volume container.[10]

c. Type III- Regular soda lime glass :
- Untreated soda lime glass with average chemical resistance [9]
- **Uses:** Topical use, for oral use, not for ampoules[10]

d. Type IV- General Purpose soda lime glass:

Glass is not used for parenterals, used only for products intended to be used orally or topically.[9]

e. Coloured glas :

Colored glass is used to screen out Ultraviolet rays and is thus effective for protecting contents from light. Amber glass and red colored glass is used for this purpose.[9]

B.Plastic :

Plastic used for packaging pharmaceutical product. These packages are extremely resistance to breakage and leakage.

Advantages:
- low in cost
- It is unbreakable
- It is available in various size and shape.
- It has good protection power.
- Ease for transportation.
- It is light in weight.

Disadvantages:
- Plastic contain certain disadvantages like interaction, adsorption, absorption, lightness so it has poor physical stability.
- Main disadvantages is permeation. The atmospheric gases, vapors or liquid from environment easily migrate into plastic container.[10]

Types of Plastics There are two types plastic material
- **a. Thermoplastic type**
- **b. Thermosetting type**

a. Thermoplastic type:

This plastic can be softened by heating and harden by cooling.

e.g: Polyethylene, Polypropylene, PVC, Polystyrene, Nylon etc.

b.Thermosetting type:

When heated they become flexible but they do not become liquid.

e.g: Urea formaldehyde, phenol formaldehyde, Melamine formaldehyde.[10]

Primarily plastic containers are made from the following polymers:

Provides good barrier against moisture, relatively poor one against oxygen and other gases. High density polyethylene is used with density ranging from 0.91-0.96 leading to four basic characteristics of container

a) Stiffness
b) Moisturevapor transmission
c) Stress cracking
d) Clarity or translucency based on polymer density used.

I) Polypropylene (PP):

Polypropylene has features of polyethylene in addition it does not stress-crack in any condition. Hot aromatic or halogenated solvents soften the package. It has high melting point making it suitable for boilable packages and products needed to be sterilized. Brittleness at low temperature is its major disadvantages.

II) Polyvinyl Chloride (PVC):

Can be produced with crystal clear clarity, will provide good gaseous barrier and stiffness. Reduction in residual vinyl chloride monomers had further enhanced PVC quality. PVC is used as coating on glass bottles providing shatter resistant coating.

III) Polystyrene:

Rigid and crystal clear plastic. Not useful for liquid products. Polystyrene has high water and gaseous

permeability also these are easily stretchable and breakable. To increase their strength and quality for permeability polystyrene is combined with rubber and acrylic compounds. Base on the composition these are classified as intermediate impact, high impact and super impact packages.

IV) Nylon (polyamide):

Many dibasic acids and amines combine to provide numerous varieties of nylon. Nylon is extremely strong and is quite difficult to be destroyed by mechanical means. Nylon provides resistance to wide range of acids and alkali only disadvantage of it is being permeable to water vapor for some amount this can also be dealt with coating of PE over the container. Not used for long term storage of products.

V) Polycarbonate:

Has an ability to be sterilized repeatedly. It has immense rigidity and is a possible replacement for glass, vials and syringes. It has qualities like high dimensional stability, high impact strength, resistance to strain, low water absorption, transparency, and resistance to heat and flame. Polycarbonates have impact strength five times greater than any other common packaging plastics.

VI) Acrylic multipolymers (Nitrile Polymers):

These are polymers of acrylonitrile or methacrylonitrile monomers. These provide for packaging of those products which are not packed in usual packages as they provide for high gas barrier, good chemical resistance, and good strength

VII) Polyethylene terepthalate (PET):

Condensation polymer formed by reaction of terepthalic acid or dimethyl terepthalic acid with ethylene glycol. It has excellent strength and provides barrier for gas and aroma making it as a useful package for cosmetics, mouth washes and other products.[8]

C. Metals:

Metals are used for construction of container. The metals used for aluminum, tin plated steel, stainless steel, tin and lead.

Advantages:

- Metal holders are solid, generally unbreakable opaque
- Resistance to chemical attack.
- Labels can printed directly on their surface
- They are impermeable to light, moisture, and gases
- They are strong.

Disadvantages:

- They are expensive
- This are costly metal among tin, lead, aluminium & press
- They react with certain drug or chemicals and produce toxic product

Aluminium

Aluminum is commonly used because of its light weight. They are attractive in nature. Thickest aluminum is used for rigid container such as aerosols cans and tubes for effervescent tablets. Thinnest aluminum is used in flexible foil that are component of laminated packaging material.

Advantages

- Aluminum tube offer shipment cost of the product is less because of their light weight.
- They provide attractiveness of tin at somewhat lower cost.

Disadvantages

- As a result of corrosion process H2 may evolve
- Any substance that react with the oxide coating can cause corrosion .[11]

Uses: Aluminum ointment tubes, Screw capes.

Lead

Advantages

Lead has lowest cost of all metals used in pharmaceutical containers. It is soft in nature.

Disadvantages

Lead never be used alone for anything taken internally because of the risk lead poison. Use: with internal linings lead tubes used for products such as chloride tooth paste.

Iron

Advantages:

Iron is not used for pharmaceutical packaging, large quantities of tin combines the strength of steel with corrosion resistance of tin.

Use: fabrication of milk containers, screw caps and aerosol cans, creation of drain holders [12]

D. Rubber:

Natural elastic comprises of long chain polymers of isoprene units connected together within the cis portion. Its most important source is the tree Heave Brazilians from which latex, containing 30 to 40% of rubber in colloidal suspension, exudes when shallow cuts are made within the bark.

a. Butyl rubber :

These are co polymer of isobutylene with 1-3% of butadiene [11]

Advantages:
- Permeability to water vapor
- Water absorption is very low
- They are relatively cheaper as compared to other synthetic rubbers.

Disadvantages:
- Slow decomposition takes place above 130°c
- Oil and solvent resistance is not very good.

b. Nitrile rubber:

Advantages:

Oil resistant due to the polar nitrile group. Heat resistant.

Disadvantage:

Absorption of bactericide and leaching of extractives are considerable.

c. Chloroprene rubber:

These are polymers of 1:4 chloprene.

Advantages
- This rubber is oil resistant.
- Heat stability is good

d. **Silicon rubbers :**

Advantages:
- Heat resistance (up to 2500c)
- Extremely low absorption and permeability of water
- Poor tensile strength. [6]

Disadvantage:

They are very expensive [10]

6] Objectives of pharmaceutical packaging

Containment:

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging: not to leak, nor allow diffusion and permeation of the product, to be strong enough to hold the contents when subjected to normal handling and not to be altered by the ingredients of the formulation in its final dosage form.

Protection:

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as light, moisture, oxygen, biological contamination, mechanical damage and counterfeiting/ adulteration.

Information transmission:

Labels and packages help to provide adequate information related to the drugs and communicate how to use, transport, dispose and recycle of the product. For pharmaceuticals, medical, chemical and food products, some types of information are required by governments.

Identification:

The printed packs or its ancillary printed components serve the functions of providing both identity and information.

Convenience:

The convenience is associated with product use or administration e.g. a unit dose eye drop which both eliminates the need for preservative and reduces risks associated with cross infection, by administering only a single dose.[13]

7] Choice of packaging

The choice of packaging for any specific pharmaceutical product is dependent on the following principle factors
- The nature of product itself- its chemical activity, moisture sensitivity, effect oxygen and its compatibility with possible packaging materials
- The type of patient- e.g. Child, elderly adult, male or female, ethnic origin
- The form of the dose- free flowing granules, aqueous solution, cream, ointment, inhalation etc.
- Method and site of administering the medication oral, topical, parenteral, ear, eye, nose, skin etc. whether a dispensing devices is to be used e.g. syringe, dropper etc.
- Method of distribution- Ethical through pharmacies and hospitals through retail outlets.
- Capacity of the packaging needed-small bulk pharmacies, OPD, unit dose etc.
- Required shelf life and likely sales areas.

Analysis of many stages in the life history of a package shows that hazards can be divided into two main groups mechanical and environmental. The only exception is theft, which can be a serious risk with drugs and may demand special protection in certain cases.[14]

8] Characteristics of Packaging Material

1. It must be a non –toxic
2. It must be a FDA approved
3. It must be not reactive with the product
4. Material must be protect the preparation from environmental condition
5. It must be not impart to the odor or taste to the product[10]

9] Innovations in Pharmaceutical packaging:

Innovations in pharmaceutical packaging have experienced so little reinvention or change over the last few decades especially the prescription drugs. While

other packaging categories have enjoyed progressive modifications, there is little variation in the packs of pharmaceutical products from 1950s and 60s and the packs of today. However, the key role packaging plays in acquainting consumers about the contents & the risks involved in taking any prescription or over the counter drugs, there is an opportunity for modern pharmaceutical packaging to be depicted by smart info graphics.While on one hand there is a challenge of making packaging easy to open for people aged over 55, who reflects for about three quarters of all medicine users, the industry also has to create packs that are child-resistant. The external image of package must not only compliment product confidence, but provide clear & concise product identification & other feature.

Cypak's advanced medication monitoring and report card systems:

This is an advanced packaging technology can enable patients to communicate with healthcare professionals through printed technology. This record the time and data that a pill was taken based on when it is removed from its blister pack. This allows the patients to log their feedback on side-effects and treatment efficacy and upload it.

This technology holds significant potential for new levels of patient-doctor interface to workout best treatment plan. Sensor-based packaging concepts are best applied in clinical trials. This helps in drug development to establish whether a drug is ineffective or simply not being taken properly.

Cypak's advanced medication technology is used in targeting clinical trials market, as poor date resulting from non-compliance can be financially devastating in this context.[15]

Burgopak's sliding CR blister pack :

Burgopak healthcare and technology won the award for the "Most Innovative Child Resistant Packaging Design" at the Pharmapack Paris exhibition. The Burgopak‟s sliding CR blister pack can only be opened by applying force at two different points on the packaging. The blister pack & leaflets are coordinated with the outer box, which insures the product is never packaging. [1]

Ecoslide–RX sustainable compliance packaging:

The pack is made from 100% recycled material using unbleached paperboard and clay coated surface designed to house blister packaging with a low of unsustainable film and foil. The slide package is very useful and it meets modern expectations for child resistance and accessibility for seniors. It doesn't require heat sealing in the manufacturing process that reduces both cost and energy usage.[1]

Syreen prefilled syringe design:

Environmental awareness is even starting to extend to the syringe market. It replaces glass with cyclic olefin polymer (COP). This material has allowed secondary packaging altogether as the COP design forms its own outer shell. The ability of packed syringes to clip into place eliminates the need for packing materials like cardboard.[1]

Fig.1 Cypak's advanced medication monitoring and report card systems.

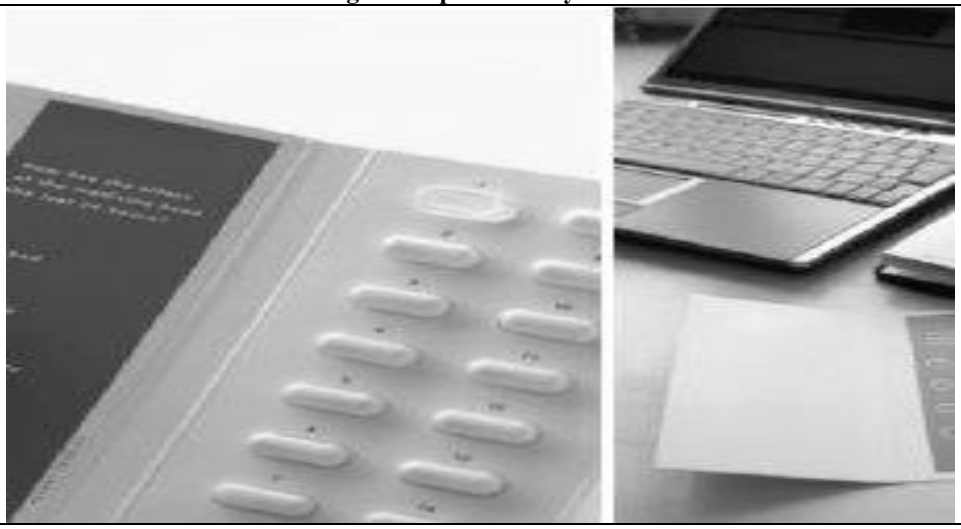

Fig.2 Burgopak's sliding CR blister pack

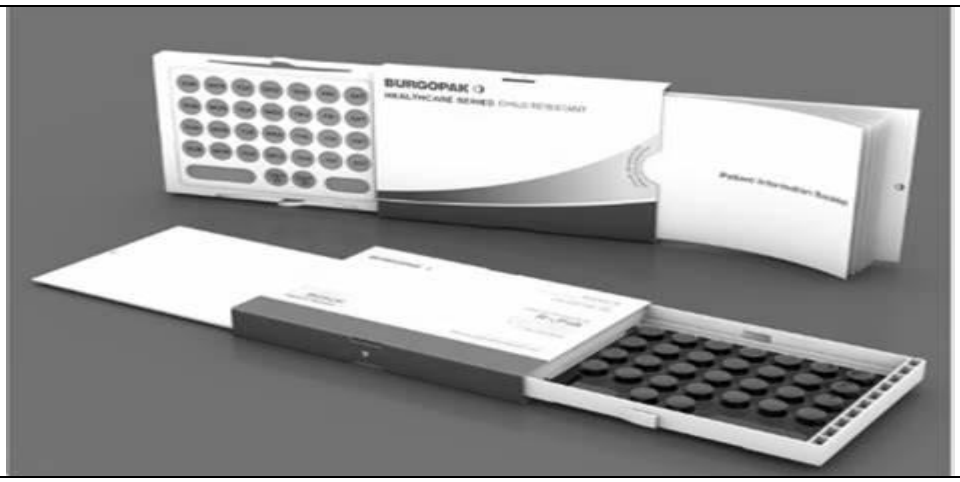

Fig.3 Ecoslide–RX sustainable compliance packaging

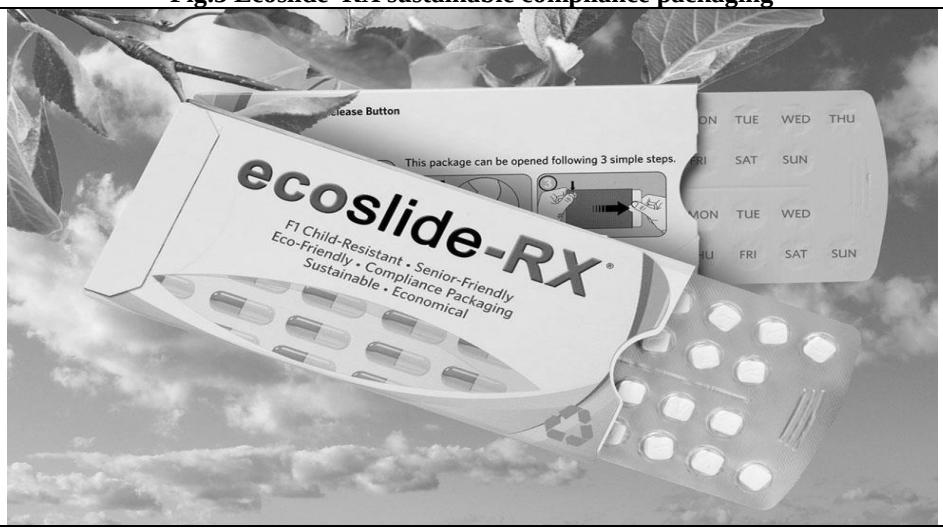

Fig.4 Syreen prefilled syringe design

Major trends in pharmaceutical packaging material

1. Fine print of serialization:

Many suppliers now-a-days introduced different technologies to enable serialized printing on primary packaging material as well as on the final dosage form. This new technique included printing of 2D barcodes on the vials as well as on the pills and capsules. Print is getting even more smaller due to the direct printing on the dosage form, but it is quite challenging one. This technique is adopted in the countries like Japan and America.

2. **Varying global standards require flexibility:**

For the manufacturers producing medicines for multiple countries on a single processing line, serialized data need to be vary accordingly. New specialized softwares can reduce this complexity. The another notable trend is quality assurance through advanced vision and inspection system. This system included advances from pill forming to the proper assembly of capsule to improvements in vial sealing.

3. **New biologics driving packaging changes:**

The rising popularity of new biological medicines continues to fuel some unaccepted packaging challenges. These new drugs may have the interactions with packaging material. The glass vials, prefilled syringe are the examples of the format that is undergoing changes that reflects market requirement and demand. Now a days tungsten free syringes are getting more attention for the research.

4. **Small is beautiful:**

Years back the pharmaceutical industry was engaged in handling the bigger dosage forms. But now they have focused in the smaller dosage form. The filling lines for the smaller dosage form are smaller, more modular, and flexible with shorter lead time. [16]

SELECTION OF PACKAGING MATERIAL

The ideal characteristics of packaging material should comply following properties.

- They must protect the preparation from environmental conditions.
- They must not be reactive with the product,
- They must not impart tastes or odours to the products,
- They must be non-toxic,
- They must be FDA (Food & Drug Administration) approved,
- They must meet applicable tamper-resistance requirements
- They must be adaptable to commonly employed high-speed packaging equipment. and
- They must have reasonable cost in relation to the cost of the product. [17]

Conclusion:

Pharmaceutical packaging is important technique in pharmaceutical industries. Packaging of the pharmaceutical products is very important to its stability, acceptance to patient, transport, etc. Packaging provide the valuable information to the patient. Packaging play important role for the protection of the pharmaceutical product. Now a days eco-friendly packaging are used which are biodegradable in nature. This review article focused on the material used for the packaging and types of packaging.

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