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Review Article

The significance of pharmaceutical packaging and materials in addressing challenges related to unpacking pharmaceutical products

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Abstract

The packaging of a medicine is very important during its production. It helps to protect the inside parts of the medicine and maintain its quality. Packaging plays a crucial role in distinguishing products manufactured by various companies. It is essential for the packaging to be functional and fulfill all the necessary criteria throughout the entire lifespan of the product. During transportation, the packaging serves as a shield, safeguarding the contents from potential damage caused by mechanical pressure and environmental factors such as light and moisture. There is a wide range of packaging materials, such as glass, metal, and plastic. The company has efficiently fulfilled the present requirements of meeting global standards in a significantly shorter time frame by utilizing diverse packaging equipment. Additionally, container closures play a vital role because they directly impact the contents within them. Closure system made of rubber are extensively used for sealing purposes. The pharmaceutical packaging industry is continuously progressing and has experienced notable transformations due to advancements in dosage forms and their specific packaging needs.

This review primarily focuses on elucidating the various categories of packaging materials and their composition in relation to dosage forms. The choice of packaging material is crucial in assessing the stability of the dosage form. Nowadays, biodegradable polymers are widely used in the production of packaging materials. The comprehensive composition of packaging materials encompasses glass, plastic, rubber, and numerous others, accompanied by detailed descriptions.

1. INTRODUCTION

Packaging encompasses the disciplines of science, art, and technology, which are utilized to enclose and protect goods for transportation, preservation, commercialization, and consumption. The entire procedure of designing, evaluating, and packaging is commonly known as packaging. Contemporary packaging serves multiple purposes, with its primary function being the efficient safeguarding of the product contents from loss, pollution, or harm [1]. Pharmaceutical packaging encompasses the cost-effective methods employed to ensure the presentation, protection, identification, information, convenience, compliance, integrity, and stability of the product. Protecting the product is arguably the most crucial role of pharmaceutical packaging. It is necessary to stop physical damage, chemical deterioration, changes caused by microbes, and weather-related dangers. The product and its packaging must work together. Modern packaging must also be tamper-evident and child-resistant. The complexity of testing needs has increased as a result of advancements in packing technology, necessitating a deeper understanding of both conventional and cutting-edge packaging techniques and materials [2].

Packaging plays a crucial role in ensuring that the manufactured medicine maintains its original form and desired quality specifications for the entire specified shelf life. Pharmaceutical formulations consist of three essential components: active pharmaceutical ingredients, excipients, and packaging material. The active pharmaceutical ingredient is a substance with pharmacological activity, which is typically stabilized by excipients and then packaged using suitable packaging material.

1.2. Packing: Packing is the process of placing a single object, or numerous items, in a container, usually for delivery or transportation. Packaging serves a crucial purpose in safeguarding products, involving a combination of manual and automated processes. Its primary function is to ensure the protection of the product throughout its shelf life. Apart from offering convenience, ease of use, hygiene, package integrity, and innovative dispensing methods to consumers, it also plays a vital role in preventing product deterioration, leakage, microbiological growth, and contamination, among other various factors. Compared to most other products, drugs require extra care in regard to packing because any flaws could cause the drug to change and produce side effects such as disease, injury, or even patient death.

Packaging plays a crucial role in product identification and differentiation from other products in the market. This feature is essential for all stakeholders involved in the supply chain, including manufacturers, distributors, retailers, and consumers [3].

1.3. Pharmaceutical Packaging: The collection of elements required to enclose, maintain, safeguard, and distribute a secure and effective medication, ensuring that a safe and effective dosage form is accessible at any time prior to the drug product's expiration date, is known as pharmaceutical packaging. Various packaging systems are utilized primarily for products intended for different delivery routes. Through the design and type of packaging container, a patient can easily

recognize and comprehend its intended purpose.

Packaging serves a vital role in safeguarding medical devices and drugs from external factors, ensuring their safety until they are used. It not only aids in product identification but also plays a crucial role in protecting the products. The use of biodegradable polymers in packaging materials is gaining popularity due to their eco-friendly nature. When biodegradable packaging decomposes, it enriches the soil. Hydrocolloids and lipids are commonly used biodegradable materials for packaging. Examples of biodegradable packaging materials include paper boards, cellulose, chitin, protein, gluten, zein, soy, casein, whey, gelatin, collagen, keratin, polylactic acid, and pollutants [4].

1.4. Criteria for Choosing Packaging Types and Materials: Many criteria for the selection of the packaging and the different packaging materials used in many pharmaceutical products are selected according to the following criteria:

- Regarding the available facilities, certain products, such as pressurized dispensers, require specialized equipment for filling purposes.
- When considering the ultimate use of a product, it is essential to determine whether it will be utilized by skilled individuals in a hospital setting or if it needs to be suitable for use by patients in their own homes.
- The physical form of the product should also be taken into account, as it can vary among solid, semisolid, liquid, or gaseous dosage forms.
- The route of administration is another crucial factor to consider, with options including oral, parenteral, and external routes.
- Additionally, the stability of the material must be considered. Factors such as moisture, oxygen, carbon dioxide, light exposure, trace metals, temperature and pressure, can potentially have detrimental effects on the product.

Additional factors to take into account when choosing a pharmaceutical packaging item include its ability to repel moisture, withstand corrosion from acids or alkalis, resist grease, shield against salt, fend off microorganisms, deter insects and rodents, endure temperature variations, guard against light exposure, fire hazards, and theft, retain or prevent odors, create a visually appealing effect, and overall cost [5].

1.5. Ideal Requirements for Packaging: The ideal requirements for the individual packing of the product are necessary for its stability and safety including other requirements, some of which are discussed in the following section:

- Ensure that the material does not react with the product, preserving its original identity.
- Safeguard the dosage form to prevent any potential damage or breakage.
- The preparation was protected from environmental conditions.
- Do not impart tastes or odor to the product.
- Nontoxic and FDA approved.

- Withstand with the high-speed packaging manufacturing machine.

1.6. Ideal Quality of Pharmaceutical Packaging: The ideal quality of pharmaceutical packaging encompasses several crucial aspects to ensure the safety, efficacy, and integrity of the products. First, it should provide adequate protection against environmental factors such as light, moisture, oxygen, and temperature variations, which can degrade the quality of pharmaceuticals. This includes using materials that are compatible with the specific medication and its storage requirements. The packaging should be designed for ease of use, with clear instructions and labeling that are legible and easy to understand for patients and healthcare professionals alike. Proper labeling should include essential information such as the drug name, dosage, administration instructions, expiration date, lot number, and manufacturer details. The packaging should also facilitate accurate dosing, whether through pre-measured doses or clear dosage indicators for liquid medications.

Some of the key points for the quality of packaging are as follows:

- The container must endure high temperatures during the sterilization process.
- It must remain chemically inert to prevent any reaction with the stored contents.
- Sufficient mechanical strength is required to withstand handling, filling, closing, and transportation.
- The container should not release alkali into its contents.
- The inner walls of the container should not absorb the contents.
- Closure should not be toxic in nature and the containers should be chemically stable.
- The container should offer the necessary level of safeguard against environmental risks. The chosen material for constructing the container must be non-reactive and securely stored.

The packaging has caught the attention of the customer, serving as a crucial instrument. Consequently, marketing strategies like TV, print, and digital ads have gained popularity. Moreover, packaging is essential in nanotechnology-driven formulations, which are currently a subject of significant scientific curiosity, especially in the advancement of pharmaceutical goods.

2. THE CATEGORIES OF PHARMACEUTICAL PACKAGING

The pharmaceutical industry utilizes different types of packaging for various drugs, which are typically categorized into primary, secondary, and tertiary packaging levels.

- **Primary package system:** The packaging system consists of package components and subcomponents that directly interact with the product or could impact the product's shelf life.
- **Secondary or tertiary package system:** Includes cartons, corrugated shippers & pallets [7].

There are generally three categories of pharmaceutical packaging systems:

2.1. Primary Packaging: Primary packaging,

also known as a consumer unit, is the packaging that directly engages with a product. The primary objective of primary packaging is to enclose, safeguard, and/or preserve the final product, especially in the first layer where it is shielded from any possible contamination. Its design aims to ensure the integrity, sterility, and potency of pharmaceuticals.

Figure 1: Primary Packaging (United Packaging)

Primary packaging refers to the components and subcomponents of a package that directly touch the product or impact its shelf life. The primary packaging is the layer that comes into direct contact with the product formulation. Primary packaging containers include ampoules, vials, strips, blister packaging, dosing droppers, syringes, and various other types of containers. The types of containers that are used as primary packages are as follows:

A) Primary Package for Solid Dosage Forms:

- **Strip package:** The contents are securely enclosed within a packet, consisting of two layers of film. Within the packet, there is a strip that contains multiple pockets, with each pocket containing a single dose of medicine.
- **Blister package:** This particular packaging option offers enhanced protection compared to the strip package. The lid is made from either aluminium or paper foil. To seal the package, the lid and base are joined together using heat and pressure. The package itself consists of a base layer with compartments that hold the pharmaceutical product [8].

B) Primary Package for Liquid Dosage Forms:

- **Airtight containers:** These types of instruments protect containers from environmental dangers. If these containers are meant to be opened multiple times, they will still be airtight when resealed. These containers are also known as tightly sealed containers.
- **Closed containers:** These containers offer safeguarding against external contaminants and prevent any damage while being transported or sold.
- **Single dose containers:** This container contains a single dose of following

medication examples: Glass ampoules, vials, etc.

- **Light resistant containers:** The primary purpose of these containers is to shield the contents from harmful UV light. They are constructed using materials that effectively block the transmission of UV light to the contents. An example of such containers is amber colored glass containers.

C) P

rimary Packaging for Semi-Solid Dosage Forms: Creams, pastes, and ointments are examples of semisolid dosage forms. Collapsible tubes are commonly used as containers for these types of dosage forms. Plastic containers have recently gained popularity in recent times. Additionally, there are pressurized products available on the market. For such products, packages made of materials such as stainless steel are utilized. It is crucial for the package to possess sufficient strength to endure the pressure that builds up within the container.

2.2. Secondary Packaging: This type of packaging serves as a supplementary solution to gather a designated quantity of products into a stock-keeping unit, or SKU. Consolidating smaller items into a single package, simplifies their handling. Moreover, this packaging provides extra protection to maintain the integrity of the primary packaging. Additionally, it proves to be an excellent asset for e-commerce as it can double as a shipping container for small merchandise [8-9].

The secondary packaging often incorporates various elements such as boxes, padding, separators, reinforcements, bags, paper, and more. These components are commonly utilized in secondary packaging to ensure the safety and protection of the product. Furthermore, the secondary packaging has the potential to be tailored in order to improve the product's prominence and attractiveness in a warehousing environment. As an example, when it comes to cereal, the secondary packaging usually takes the form of a corrugated cardboard box that contains numerous individual cereal boxes.

Figure 2: The secondary packaging

Secondary packaging does not have direct contact with the product it contains. It is designed to be visible to the consumer and provides all the essential information such as

the product's name, instructions for use, ingredients, and more. The main objectives of secondary packaging are to protect the product and ensure the safety of the primary packaging container. Commonly used secondary packaging containers include paperboard, shoe boxes, corrugated fibers, cardboard boxes, plastic crates, and others. [9].

2.3. Tertiary Packaging: Tertiary packaging, often referred to as bulk or transit packaging, is utilized to transport a large quantity of SKUs from the manufacturing site to the point of sale. At this stage, products are treated as distribution units. This form of packaging enables the safe and secure transportation of heavy and bulky loads, simplifying the handling, storage, and transportation processes while also preventing damage. An instance of tertiary packaging is a stretch-wrapped pallet containing cereal boxes, accompanied by cardboard boxes (secondary packing) to enhance the efficiency of product transportation.

Figure 3: The representation of tertiary packaging

Tertiary packaging containers are essential for the efficient transportation of packaged goods from manufacturers to retailers or distributors. Although consumers are usually unaware of this packaging, it is routinely removed by retailers before displaying the products for sale. The main purpose of tertiary packaging is to protect the product and secondary packaging materials from any possible harm during transit. Various materials can be used for tertiary packaging, such as wooden boxes, shippers, carton boxes, and shrink wrap.

*Apart from *primary, secondary and tertiary packaging,* two main types of special packaging are currently in use, as follows;

- **Unit-dose packaging:** This packaging enhances medication safety by reducing errors and offers added convenience for patients. It has the potential to significantly improve treatment adherence and may be beneficial for products with shorter shelf lives.
- **Device packaging:** Packaging incorporating an administration tool is created to improve user experience and promote adherence. This packaging streamlines the medication administration process by offering a range of tools like prefilled syringes, droppers, transdermal patches, pumps, and aerosol sprays. These tools ensure

precise dosing, guaranteeing the accurate delivery of medication [10].

The three main categories of packing used in the pharmaceutical industry, *primary, secondary and tertiary packing*, are shown in **Fig. 4**:

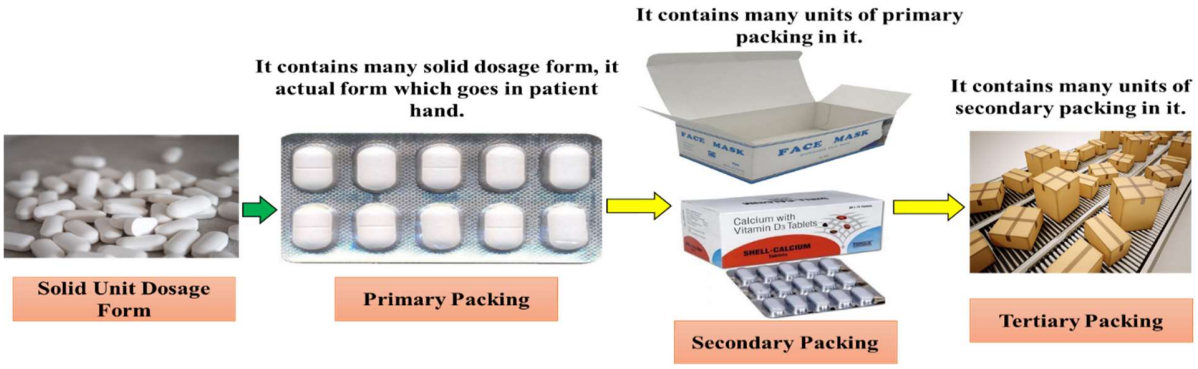

Figure 4: The different stages pharmaceutical product packaging

The above figure describes about how the particular product package first into primary packaging than respectively in secondary and tertiary packaging for further distribution and transportation. Wholesalers receive the tertiary package from manufacturers and then distribute it to stores. This package consists of multiple unit packages. Retailers open these packages and deliver the contents to patients based on the prescription provided by a registered medical practitioner [11].

3. PACKAGING COMPONENTS & MATERIALS

The container closure system of a pharmaceutical product encompasses both primary and secondary components that are responsible for maintaining the sterility and integrity of the medication. Primary packaging components include vials, stoppers, blisters, bottles, screw caps, closure liners, and other items that directly interact with the pharmaceutical product. On the other hand, secondary packaging refers to elements that do not have any direct or indirect contact with the drug product.

The external packaging containing the product bottle or blisters is commonly known as secondary packaging, encompassing labels, user guides, and booklets. This type of packaging is often labeled as "essential" or "practical" secondary packaging due to its role in ensuring the product's stability, integrity, and protection. Examples include an outer aluminium bag or pouch, a light protective label on a clear glass vial, and a crimp seal on vials [12]. Tertiary packaging refers to items like shrink wrap, wooden pallets, carton shippers, etc. that are used to store a number of finished products together. The different packaging materials are used in *primary, secondary and tertiary packaging* components. The most commonly used packaging materials can be found in **Table 1** as below followings:

Table 1: Raw materials used as packaging materials for pharmaceutical products

Sr. No.	Material Type	Uses in Pharmaceutical Products
01.	Cardboard	Boxes and display units.
02.	Paper	Labels and leaflets.
03.	Glass	Ampoules, bottles, vials, syringes and cartridges.
04.	Plastic	Closures, bottles, bags, tubes and laminates with paper or foil.
05.	Metal e.g., aluminium	Collapsible tube, rigid cans, foils, needles, gas cylinder etc.
06.	Rubber	Closures including plungers.

The materials used in packaging vary widely depending on the product, its properties, and environmental considerations. The common packaging materials include plastics, glass, metals, paperboard, and corrugated board. The each material offers unique characteristics such as durability, barrier properties, recyclability, and aesthetic appeal, allowing manufacturers to choose the most suitable option for their packaging requirements.

4. BROADLY USED MATERIALS FOR PHARMACEUTICAL PRODUCT PACKAGING

Historically, the majority of medications (51%) have been administered orally in the form of tablets or capsules. These are typically stored in plastic pharmaceutical bottles or blister packs, which are particularly favored in Europe and Asia (especially in the USA). In addition to solid forms, oral medications can also be consumed as liquids, pastilles, and powders. Nevertheless, there is a growing trend towards alternative methods of medication administration. This encompasses inhalation (17%), transdermal (3%), and parenteral or intravenous (29%) routes.

5. TYPES OF PACKAGING MATERIALS

There are several factors to take into account when choosing packaging materials for pharmaceutical products. These factors encompass the nature of the drug product, the level of protection needed, the filling technique, sterilization requirements, compatibility between the drug and packaging material, patient convenience, and packaging cost. Considering these aspects, a variety of materials can be utilized to create the packaging. Moreover, there are diverse options for packaging materials and closures specifically designed for pharmaceutical products.

- Glass
- Metal
- Plastic
- Rubber
- Paper and board
- Cotton
- Adhesive and inks

- Closures

The several packing material used in the commonly pharmaceutical product such as glass, plastic, rubber and other things such as used in the packing. In which the some of them below discussed:

5.1. Glass Container: Glass containers are widely utilized for the storage of pharmaceutical products. These containers are specifically designed to directly interact with pharmaceutical substances. The different figure for shown the glass container used in the pharmaceutical packaging as **Fig. 5** as follows:

Figure 5: The glass Containers as pharmaceutical packing material

Glass Container Composition: Glass consists of silica along with different metal oxides, limestone, and cullet. Cullet, which is primarily broken glass, serves as a bonding agent. Pharmaceutical glassware often includes cations like silicon, zinc, boron, alumina, Na^+, K^+.. Oxygen is the only anion that is present [12–13]. The composition of glass container shown in the given below **Fig. 6** as follows:

Figure 6: The representation of Glass container compositions

Types of Glass: Based on their degree of chemical resistance against water contact (i.e., resistance against hydrolysis), glass containers are classified into four types of glasses:

- **Type I – Borosilicate Glass**
- **Type II – Treated Soda-Lime Glass**

- **Type III– Regular Soda-Lime Glass**
- **Type NP – General Purpose Soda-Lime Glass**

The data of all categories of glasses are shown in the given **Table 2** as follows:

Table 2: The list of type of glass, test and their limits

Sr. No.	Types of Glasses	General description of glass type	Types of tests involving Glass	Limits size in ml	Limits (ml or 0.20N)
01.	**I**	Highly resistant borosilicate glass.	Powdered glass test.	**All**	**1.0**
02.	**II**	Treated soda lime glass.	Water attack.	**100 or less**	**0.7**
03.	**III**	Soda-lime glass.	Powdered glass.	**Over 100**	**0.2**
04.	**IV**	General-purpose soda lime glass.	Powdered glass.	**All/all**	**8.5/15.0**

The different types of glasses which are majorly used in the pharmaceutical packaging such as explained in the given above **Table 2**, remaining such as follow:

1. **Type I-Borosilicate Glass:** Borosilicate glass is known for its high resistance and is made by replacing alkali and earth cations with boron, aluminum, and zinc. Compared to soda-lime glass, borosilicate glass is typically more chemically inert. It is commonly used to contain strong acids, alkalies, and various solvents. The composition of borosilicate glass includes approximately 6% boron, which helps reduce the leaching effects of other materials used.
2. **Type II-Treated Soda-Lime Glass:** Glassware of this type is usually stored for several months, especially in environments with high humidity or significant temperature fluctuations. When the surface becomes wet due to condensed moisture, salts are dissolved from the glass materials. This process is commonly referred to as blooming or weathering, often leading to the formation of fine crystals on the glass. The sulphur treatment of empty bottles is a de-alkalizing procedure used to remove surface alkali from commercial soda-lime glass, which is the material used in making these Type II containers.
3. **Type III-Regular Soda-Lime Glass:** This particular type of glassware consists of untreated containers made from commercial soda-lime glass, which offers average or higher chemical resistance. However, it is not advisable to use this glass for parenteral preparations due to

certain concerns regarding its impact on the formulations.

4. **Type NP-General Purpose Soda-Lime Glass:** Typically, soda lime glass containers of NP type are provided for non-parenteral products, specifically for oral or topical applications.

Advantages of Glasses: The various advantages under the using glass as the material in the pharmaceutical product preparation, they are used having lots of merits in which the sum of advantages such as following:

a) They can be easily sealed, which can provide hermetic sealing.

b) They are impermeable to water vapors, air etc.

c) They have an elegant appearance than plastic containers and it available in various sizes and shapes.

d) They are transparent so the contents can be easily seen from outside for e.g., in case of parental products [13-14].

5.2. Plastic Containers: Plastics, which are high molecular weight synthetic polymers, exhibit sensitivity to heat and can undergo melting or softening at certain temperatures. Despite this, plastic containers are advantageous due to their lightweight nature, making them easier to handle. However, it is important to note that only a limited number of plastic materials possess exceptional thermal resistance and can be autoclaved, thus being suitable for pharmaceutical packaging purposes. Example of these polymers are, but not limited to, *PVC, polyvinylidene chloride, polystyrene polypropylene, polycarbonate, polypropylene and polyethylene terephthalate (PET),* etc. The composition in plastic shown in the given **Fig. 7** as followings:

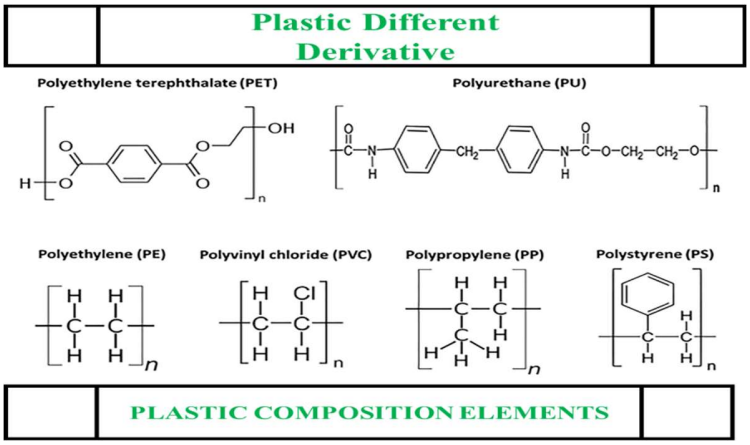

Figure 7: The plastic containers composition chemically

The plastic containers shown in the given **Fig. 8** which used as the primary material in the pharmaceutical packaging such as:

Figure 8: The plastic used as packing material in pharmaceutical

Types of Plastics: Plastics are classified into two groups according to their behaviour when heated.

1. Thermoplastic type: When subjected to heat, these substances undergo a change and become a thick liquid, returning to their initial hardness upon cooling. Some instances of such substances encompass polyethylene, polypropylene, polyvinylchloride, polystyrene, nylon (polyamide), polycarbonate, acrylic multi-polymers, and polyethylene terephthalate.

2. Thermosetting type: When subjected to heat, these materials have the ability to become pliable, but they do not transform into a liquid state. Typically, their form remains intact until they reach the temperature at which decomposition occurs. Due to a significant amount of cross-linking, these substances tend to be rigid and fragile when at room temperature. Examples of such materials include phenol-formaldehyde, urea formaldehyde, and melamine formaldehyde.

Additives of Plastics: Polymers are formed by combining monomers to produce plastics. While plastics can be utilized independently to manufacture the final product, it is customary to blend them with additional substances to enhance stability or performance during use. These substances include stabilizers, antioxidants, pigments, fillers, plasticizers, and other agents such as cross-linked agents, curing agents, activators, and accelerators.

Advantages of Plastic Containers: Plastic is an ideal material for pharmaceutical packaging due to its cost-effectiveness and lightweight properties. Additionally, it is durable, tactile, odorless, chemically inert, unbreakable, and maintains its shape over time.

5.3. Metal Containers: Metals are very commonly used as packaging material for pharmaceutical containers. These are resistant to heat fluctuation. Samples of metals used for this purpose embody chiefly *metallic element, lead, tin* etc. The metal containers can be prepared by particular material such as *Aluminium, tin and lead* etc. The containers of metal as material of pharmaceutical packaging generally, shown in the given **Fig. 9** as follows:

Figure 9: The representation metal as material in packing

Types of Metal Containers:

1. **Collapsible tube:** These solid preparations are made from either tin or lead, which are metallic elements. Aluminium packs are used for storing toothpaste and creams. Metallic element tubes are specifically designed for dispensing these products. Lead is not utilized in pharmaceutical purposes due to the potential risk of lead poisoning. On the other hand, aluminium collapsible tubes may have a minimal risk of contamination in the remaining content of the tube due to the absence of a suck back mechanism.
2. **Metal container for solid dosage form:** Aluminum is predominantly employed for this specific purpose. Consequently, the containers for tablets and capsules are lightweight and sufficiently robust.
3. **Metal foil:** Individual suppositories or pessaries are wrapped using these foils. Primarily, aluminum foil is utilized for this specific application. Additionally, metal foil is employed for strip and blister packaging of tablets and capsules [15-16].

5.4. Rubber: Natural rubber consists mainly of long chain polymers of isoprene units linked in the cis-position. The primary source of natural rubber is the Hevea brasiliensis tree, which yields latex with 30 to 40% rubber in colloidal suspension when the bark is gently incised. This rubber is frequently used in making stoppers and bulbs for dropper assemblies. The examples of rubber for pharmaceutical products includes as follows:

1. Natural rubber
2. Neoprene rubber
3. Nitrile rubber
4. Butyl rubber
5. Chlorobutyl rubber
6. Bromobutyl rubber
7. Silicone rubber

The chemical composition of natural as well as synthetic rubber some of shown in the given below **Fig. 10** as following:

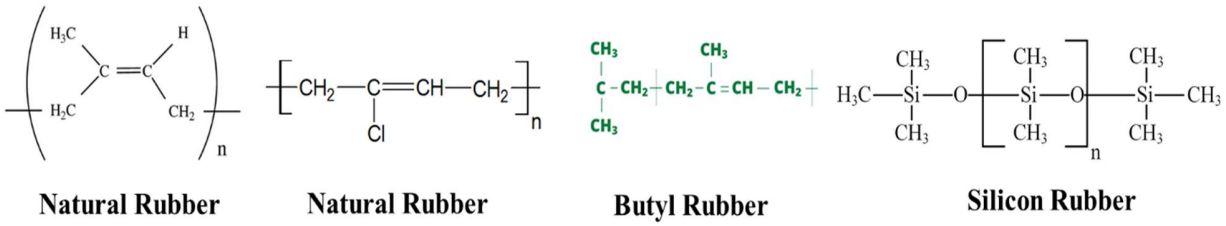

Figure 10: The chemical composition of different rubber as packing material

Compounding rubbers: Raw rubber is not ideal for producing many rubber items due to its limited elasticity and vulnerability to temperature variations. The characteristics of rubber can be transformed through the incorporation of certain additives.

Vulcanizing agent: Natural rubber exhibits low elasticity, resulting in weak strength. It solidifies in cold temperatures and turns pliable and adhesive in warm conditions. It is soluble in numerous solvents. The process of vulcanization significantly enhances the material's elastic properties across a wider spectrum of stress and temperature [17].

5.5. Cotton: Pharmaceutical cotton is mainly composed of 100% purified, absorbent cotton, being easy to use and aesthetically pleasing. It is a traditional filler for tablet packaging.

The natural cotton fibers are chosen for cleanliness to provide a safe, non-toxic, easily-cut filler for the packaging of pharmaceutical items. They are most frequently used for bottling tablets and cottons. It mainly contains moisture content is approx. *NMT 8.0%* and it is biodegradable.

5.6. Adhesives and Inks: Some materials, like cements and lacquers utilized as label adhesives, are not water-based emulsions. Instead, they are commonly dissolved in organic solvents such as toluene, alcohol, naphtha, methyl ethyl ketone, or naphtha. The solvent could potentially allow adhesive components to migrate into the formulation when this adhesive is applied on plastics or elastomers. Hence, it is crucial to conduct proper testing to ascertain if adhesive and ink components migrate through the container.

5.7. Closures: The container's most crucial element is its closure system. A well-designed closure system plays a vital role in preventing material loss, environmental contamination, and the entry of microbes into the container.

In the pharmaceutical industry, closures, commonly referred to as stoppers or bungs, are of utmost importance in the final packaging of sterile pharmaceutical preparations. Elastomeric closures, in particular, are widely used in this context. These advancements have greatly influenced the packaging industry, leading to a growing need for customized packaging solutions that guarantee the effectiveness of medications. The different types of closures used as material in pharmaceutical packaging, it may

show as description given below section such as:

1. **Lug cap:** Lug caps and thread caps differ in the presence of continuous threads in thread caps and intermittent threads in lug caps. Another distinction is that lug caps only require a quarter turn to secure. Lug caps are primarily used for storing food items.
2. **Threaded screw cap:** These closures are composed of aluminum, tin, or plastic materials. As their name suggests, they feature threads that securely fasten with the threads found on the container's neck. Such closures provide a robust seal that effectively protects the product from chemical and physical reactions.
3. **Roll on closures:** The roll-on closure comprises of an aluminum roll-on cap that can be effortlessly sealed, opened, and closed. These closures are offered in resealable, non-sealable, and pilfer-proof variations. They are suitable for application on glass or plastic bottles and jars used in the food, beverage, chemical, and pharmaceutical industries.
4. **Crown caps:** These metallic caps are frequently utilized for sealing beverage bottles, ensuring an efficient seal that cannot be easily opened by hand. Once opened, they cannot be resealed
5. **Pilfer proof closures:** The extended length below the threaded portion acts as a bridge, which breaks when the closure is taken off, allowing the extra piece on the neck of the container to remain in place and expose the opening. [18].

The all are shown in the given **Fig. 11** for the better explanation about the all types of closures of pharmaceutical packing.

Figure 11: The different Types of closures used as packing material

6. THE APPLICATIONS OF PHARMACEUTICAL PACKAGING

Pharmaceutical packaging is of utmost importance in the healthcare sector as it guarantees the safety, effectiveness, and

excellence of medications. It encompasses the creation, manufacturing, and distribution of containers and packaging materials for pharmaceutical products. The main objective of pharmaceutical packaging is to safeguard medicines from external elements like light, moisture, oxygen, and any potential harm during storage, transportation, and utilization. Additionally, pharmaceutical packaging also provides information about the drug, including dosage instructions, expiration dates, and safety warnings, facilitating proper usage by patients and healthcare professionals. The some of them explained in the given **Fig. 12** as below followings:

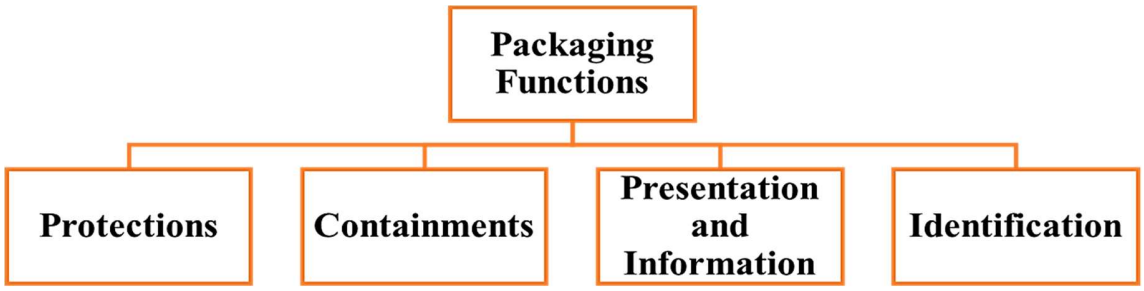

Figure 12: The functions of Pharmaceutical Packaging

1. **Containment**: Packaging for medicinal products serves as a vital means to guarantee the containment of the product. When creating packaging of superior quality, it is imperative to take into account the product's specific requirements, as well as the manufacturing and distribution processes. This involves ensuring that the packaging remains leak-proof, prevents any diffusion or permeation of the product, and possesses the necessary strength to withstand regular handling while securely holding its contents.
2. **Protection:** It is essential to protect the product from detrimental external elements such as light, moisture, oxygen, biological contamination, mechanical damage, and tampering to ensure its quality and effectiveness.
3. **Presentation and Information:** Packaging plays a crucial role in providing vital information about medicinal products. Patients can rely on labels and package inserts to access this valuable information.
4. **Identification**: The both identification and information are provided by the printed package and its auxiliary printed components [19].

In conclusion, pharmaceutical packaging plays a vital role in ensuring the safety, efficacy, and quality of medicines in the healthcare sector. By protecting medications from external factors, providing essential information to users, and incorporating safety features, pharmaceutical packaging contributes significantly to patient well-being and medication adherence. The continuous innovation and development in packaging technologies further enhance the efficiency and effectiveness of pharmaceutical packaging, ultimately benefiting both patients

and healthcare professionals in their efforts to improve healthcare outcomes.

7. DIFFERENT TYPES OF PACKAGING OF SOLID DOSAGE FORM

The various types of packaging of solid dosage forms discussed as below followings:

- Blister package
- Strip package
- Alu-Alu packaging

7.1. The Blister Package: 1. The Blister Package is produced by heating a thermoplastic resin sheet until it becomes pliable, then shaping the softened plastic sheet into a mold using vacuum-forming techniques. After cooling, the sheet is taken out of the mold and transferred to the filling station of the packaging machine. The semi-rigid blister is subsequently filled with the product and sealed using a heat-sealable backing material, usually peelable heat-seal-coated aluminum foil.

The blister packaging material needs to be coated with a suitable substance on the foil to ensure proper sealing, providing protection for the product and preventing tampering. Materials commonly used for thermo-formable blisters are poly vinyl chloride (PVC), PVC/polyethylene blends, polystyrene, and polypropylene. In tropical areas, blister packs with an aluminum membrane are employed to increase protection against high humidity levels. Blister packaging is a popular type of pre-formed plastic packaging used for individually packaging pharmaceutical products such as tablets, capsules, or lozenges.

Blister packs consists of two principal components:

01. The cavity made from either plastic or aluminium.

02. The lid, which can be made from paper board, paper, plastic, or aluminum, is used to seal the product in the package. The cavity holds the product inside. Two methods of forming the cavity in the base web sheet are thermoforming and cold forming.

03. Thermoforming: In the process of thermoforming, a plastic film or sheet is unwound from the reel and guided through a pre-heating station along the blister line. The pre-heating plates, positioned both above and below, are adjusted to a specific temperature that enables the plastic to soften and acquire a pliable state.

04. Cold Forming: In cold forming, a laminate film made of aluminum is pressed into a mold using a stamp. This process elongates the aluminum and ensures that it retains its shape. The cold form foil blister has a significant advantage as it provides a nearly impenetrable barrier against water and oxygen due to the use of aluminum, thereby extending the expiration date of the product [23].

7.2. Strip Packages: Strip packaging is a widely used method of packaging tablets and capsules in individual doses. This technique involves passing two flexible film webs that can be heat-sealed through a heated crimping roller or reciprocating plate. The purpose is to create separate compartments where the

medication is placed and then securely sealed. The desired length of the continuous strip of packets, usually consisting of multiple packets, is achieved by cutting it. Strip packaging utilizes different packaging materials, and a popular option for high-barrier applications is a paper/polyethylene/foil/polyethylene lamination [22].

Figure 13: The strip packing

7.3. Alu-Alu Packaging: Aluminum foil is a superior multilayered design intended for extremely delicate pharmaceutical and generic medications that are highly susceptible to moisture or light exposure and cannot be adequately protected by barrier plastic films. Alu-Alu packaging involves aluminum foil on both the top and bottom of the package. Each box contains a total of one hundred units of dosage forms. The breakdown may differ depending on the product or type of dosage form. The first ten units represent individual strips within a box, while the second ten units represent tablets/capsules/dosage forms within a strip or package [20].

Strip Packing is the process of wrapping pharmaceutical items like lozenges, tablets, and capsules with two layers of heat-sealable foil, such as paper-poly and aluminum-poly. The last stage involves sealing the products in pockets created between the two foil sheets that are in constant motion.

Figure 14: The Alu-Alu packaging

The Alu-Alu machine utilizes Aluminum film composite material known for its superior moisture and light protection. It employs a unique cooling mold for shaping, making it a cutting-edge packaging solution in the pharmaceutical sector. This versatile machine is capable of packing objects with both Aluminum-Aluminum and Aluminum-Plastic configurations by simply changing the mold.

Procedure of Alu-Alu Packaging: Inspect the cleanliness of the machine and activate the compressed air supply. Activate the main electrical supply. Activate the cooling unit and

switch on the sealing heaters, setting the temperature between 180 to 200°C. Adjust the knob to the starting speed. Activate the electrical supply by turning on both of the clear buttons. After the machine has reached the desired operating temperature, initiate it and verify that the punching unit is both clean and properly lubricated prior to inserting the aluminum foil for sealing. Proceed by inserting the sealed web into the punching unit and carefully inspect the web tension behind the indexing roller. Commence the machine and make necessary adjustments to the idler roller of the BCP unit in order to achieve consistent and even over-printing. After a satisfactory batch printing, activate the tablet filling unit and open the gate for filling tablets after 2 revolutions of the blister format roller [21].

Advantage Alu-Alu packing: Stringent quality inspections are conducted at every phase to provide assurance and ensure safe usage without any risks. Enhanced security measures and extended durability are guaranteed. Consistency, reliability, and cost-effectiveness are maintained for creating deep drawing blister holes with high malleability. The packaging is sealable with standard aluminum foil and features a VMCCH base package with robust counterfeit protection.

Disadvantage Alu-Alu packing: Aluminum foil's main drawback lies in its limited resistance to acid, which is why acidic products like fruit juice are typically not stored in direct contact with the foil. This precaution is taken to prevent the acid from corroding or breaking down the foil layer.

PACKAGING MATERIALS FOR VARIOUS DOSAGE FORMS

It contains lots of packing in solid unit dosage form as well as other dosage form packing such as:

Containers for Semi Solid and Pressurized Products:

8.1. Collapsible Metal and Plastic Tubes:

- The narrow opening of the container prevents any significant contamination of the unused portions of its contents. This helps to maintain the integrity of the product.
- By having a small orifice, the chances of the patient removing an excessive amount of the product are minimized, resulting in reduced wastage.
- Unlike conventional containers, the expulsion of a portion of the product does not result in the introduction of an equal volume of air. This unique feature effectively safeguards against microbial contamination and degradation of the remaining contents.
- Nozzle type applicators can be affixed to the container to aid in the administration of substances into body cavities such as the nose or vagina.
- Collapsible tubes can be manufactured using a range of materials including tin, lead, tin coated lead, and plastics. However, the most prevalent material used for these tubes is aluminium. The reason behind this preference is the exceptional corrosion resistance offered by aluminium tubes, thanks to the protective oxide film present on their surface.

8.2. Glass Plastic Pots: Glass or plastic

containers with a broad opening and short, cylindrical design can serve as viable options. These containers usually feature a plastic screw cap or sometimes a metal one, or in the case of plastic containers, a slip-on cap. Glass containers are available in colorless, transparent, amber, or opal white options. Glass is a stable and hygienic material that is inert. Moreover, its clear nature enables effortless viewing of the contents [25].

8.3. Aerosols: The expulsion of the product from pressurized packages is facilitated by a valve. When choosing packaging for various products, it is crucial to take into account the pressure required for the product to be expelled. In the context of therapeutic active ingredients, they are enclosed within pressurized systems. Aerosols utilize the power of compressed or liquefied gas to expel the contents from their containers. This guarantees the extraction of a dose without any possibility of material contamination.

8.4. Containers for liquids/ Parenteral: Injectable formulations are typically housed in containers constructed from either plastic or glass. These containers include ampoules, syringes, vials, bottles, and cartridges. Ampoules are crafted from glass, while bags are typically made from plastic. Rubber components such as rubber stoppers in vials and bottles, rubber plungers, and rubber seals in syringes and cartridges are commonly used. Irrigation solutions are commonly kept in glass bottles sealed with aluminum screw caps. A unit-dose container is created to contain a precise amount of medication for one dose, and once unsealed, cannot be sealed again to maintain sterility. Instances of such containers include fusion-sealed ampoules, prefilled syringes, and cartridges.

- **Single unit packages:** These packages contain a specific amount of the product meant for one-time or multiple uses in a single administration.
- **Multi-unit packages:** These are airtight containers that allow for the removal of multiple portions of the product without compromising its strength, quality, or purity (such as vials). The dispensing device typically has a volume of 5 ml, such as spoon or cup.

Properly sealed containers safeguard the product from being contaminated by unwanted foreign substances and prevent any loss of contents during usage [26].

8.5. Airtight containers: Air tight containers ensure the complete impermeability of solids, liquids, and gases throughout regular storage and usage. In the event that the container needs to be opened multiple times, it is crucial for it to maintain its airtightness upon resealing.

8.6. Light-resistant containers: Many pharmaceutical items require packaging that is resistant to light. Usually, containers made from premium amber glass or light-resistant opaque plastic can effectively reduce light exposure to protect light-sensitive pharmaceuticals. UV absorbers may also be added to the plastic to decrease the transmission of short UV rays. 1. The latest progress in plastic packaging involves a two-layer, high-density polyethylene bottle with coextruded black polyethylene on the inside and white polyethylene on the outside. This innovative container provides better light resistance than amber glass, as well as

moisture protection. It is becoming more popular for packaging tablets and capsules to protect them from radiation with wavelengths between 290 nm and 150 nm [27].

8.7. Suppositories Package:

1) Strip packing in pouch form utilizes a combination of 4 poly materials (Poly+Aluminium+Poly+Paper, with the inner layer being poly and the outermost layer being paper). This type of packaging is considered superior to blister packs in three distinct ways.
2) Unlike blister packs, strip packs ensure that the product, such as a suppository, can be easily removed without any risk of breakage, which is a common occurrence with blister packs.
3) While blister packs often require refrigeration to prevent any deformities in shape, strip packs do not have this requirement. They maintain their shape and integrity without the need for refrigeration.
4) Strip packs consist of a 4-ply material that incorporates aluminum, enhancing its ability to prevent moisture penetration. Consequently, the product maintains a higher level of stability compared to blister packs, which are typically composed of PVC. Liposome packaging often utilizes hermetically sealed containers.

8.8. Transdermal (TDDS) Patches Packaging:

Backing Film: Occlusive films with different compositions and/or thicknesses.

Adhesive: The adhesive layer contains the active ingredient and utilizes silicone, acrylic, and/or polyisobutylene adhesive formulas.

Release Liner: A removable coated film or polymer-based protective layer.

9. REGULATORY ASPECT OF PHARMACEUTICAL PACKAGING

The regulatory aspect of pharmaceutical packaging plays a vital role in guaranteeing the safety, effectiveness, and quality of pharmaceutical products. Pharmaceutical companies are obligated to adhere to strict guidelines and requirements set by regulatory agencies like the FDA in the United States and the EMA in Europe throughout the packaging process. These regulations cover various aspects such as labeling accuracy, tamper-evident packaging, child-resistant packaging for certain medications, expiration date visibility, and ensuring that packaging materials are compatible with the stored product. On October 10, 1998, the International Organization for Standardization (ISO) released a compilation of global standards related to packaging. The initial section of the list features the primary four standards, followed by the subsequent standards in sequential order. Among the key standards is the quality systems model, which serves as a framework for ensuring quality in various stages such as design, development, production, installation, and servicing.

International Standard ISO 9001-1994; Quality systems: Model for quality assurance in production, installation and servicing.

International Standard ISO 9002-1994; Quality systems: Model for quality assurance in final inspection and test.

International Standard ISO 9003-1994; Quality management and quality systems elements.

- **Part 1:** Guidelines

International Standard ISO 9004-1-1994. Quality management and quality systems elements.

- **Part 2:** Guidelines for service [28].

These regulations are essential for preventing contamination, ensuring product stability, and protecting the health of consumers. Pharmaceutical companies must stay updated with evolving regulatory standards to maintain compliance and market their products effectively.

CONCLUSION

Packaging plays a crucial role in enhancing pharmaceutical elegance and improving patient compliance, thereby boosting the marketing of pharmaceutical products. It is an essential component in the pharmaceutical industries for packaging various categories of pharmaceutical products. The pharmaceutical packaging market has been steadily growing, with an annual growth rate of at least 5% over the past few years. Packaging plays a crucial role in safeguarding pharmaceutical products and conveying essential details to patients. The packaging of oral medications is specifically crafted to fulfill various needs, such as convenient dispensing, child safety, ease of use for seniors, functionality, and sometimes airtight sealing. While pharmaceutical packaging offers numerous advantages, it has certain limitations. It is imperative to obtain FDA approval before launching a new packaging design in the market, and any alterations made after approval must be authorized by the FDA beforehand. This review article provides a comprehensive description of pharmaceutical packaging and its various types.

ABBREVIATIONS:

FDA: Food and Drug Administration;

ISO: International Organization for Standardization; SKU: stock-keeping unit.

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REFERENCE

01. Zadbuke N, Shahi S, Gulecha B, Padalkar A, Thube M. Recent trends and future of pharmaceutical packaging technology. J Pharm Bioallied Sci. 2013 Apr;5(2):98-110. doi: 10.4103/0975-7406.111820. PMID: 23833515; PMCID: PMC3697200.

02. Rundh, B., Rundh, B., 2016. The role of packaging within marketing and value creation. Br. Food J. 118 (10), 2491-2511.

03. Kunal C Mehta, D. Akhilesh and Shyam Kumar. Recent Trends in Pharmaceutical Packaging: A Review. International Journal of Pharmaceutical and Chemical Sciences,2012;1(3): 933-934.

04. A. Singh, P.K. Sharma and R. Malviya: Eco Friendly Pharmaceutical Packaging Material. World Applied Sciences Journal, 2011;14(11): 1703-1716.

05. Kerry, J.P., 2014. New packaging technologies, materials and formats for fast-moving consumer products, Innovations in Food Packaging, second ed. Elsevier.

06. S.J Carter, Cooper and Gunn's Dispensing for Pharmaceutical Students, CBS Publishers and Distributors, Delhi,2005.

07. L. Lachman, H.A. Lieberman and J.L. Kanig, The theory and practice of industrial Pharmacy, Delhi, CBS Publisher & Distributors P Ltd, 2008.

08. Nasa, P. A review on pharmaceutical packaging materials. WORLD JOURNAL OF PHARMACEUTICAL REASEARCH, 3 (Issue-5), 345,347-350,352.

09. Schaut, R.A., Weeks, W.P., 2017. Historical review of glasses used for parenteral packaging. PDA J. Pharm. Sci.Technol. 71 (4), 279-296.

10. Donald C. Liebe, Packaging of Pharmaceutical Dosage Form, Modern Pharmaceutics by G.S.Banker, Marcel Dekker, p 681-725.

11. R.M Mehta. Dispensing Pharmacy, Containers and closures for dispensed products. (4th ed.), Delhi, Vallabh Prakashan: 2009, pp.57-58.

12. Campbell, G.A., Vallejo, E., 2015. Primary packaging considerations in developing medicines for children: oral liquid and powder for constitution. J. Pharm. Sci. 104 (1), page no. 52-62.

13. Mehta R.M. Dispensing Pharmacy, Containers and closures for dispensed products. (4th ed.), Delhi, Vallabh Prakashan, 2009; 49-50.

14. Kunal C M, Akhilesh D, Kumar B. Recent Trends in Pharmaceutical Packaging: A Review. International Journal Of Pharmaceutical And Chemical Sciences, 2012; 1(3): 933-934.

15. Singh A, Sharma P.K, Malviya R: Eco Friendly Pharmaceutical Packaging Material. World Applied Sciences Journal, 2011; 14(11): 1703-1716.

16. Mehta K, Akhilesh D and Shyam KB: Recent trends in pharmaceutical packaging: A review. International Journal of Pharmaceutical and Chemical Sciences, 2012; 1(3): 933-943.

17. Pilchik R: Pharmaceutical Blister Packaging, Part I: Rationale and Materials. Pharm Technol, 2000; 24(11): 68-78. 8.

United State Pharmacopoeia. Appendices. pp.no. 2653, 2654, 2558, 2580.

18. Indian Pharmacopoeia. Vol I. The Controller of Publication. New Delhi, 1996; 9-10. 10. Cooper and Gunn's. Tutorial pharmacy. Edited by Carter SJ. Delhi: CBS publisher &distributors, Delhi. 6th edition, 2005.

19. Council of Europe, European Pharmacopoeia, 5th ed., Strasbourg: Council of Europe, 2004.

20. Jenke DJ et al. Pharm Sci Technol, 2002; 56: 332-71

21. Croce, C., Fischer, A., and Thomas, R.H. Packaging materials science, in Lackman, L, Lieberman, H. A, and Kang, J.L, Eds. The Theory and practice of Industrial Pharmacy, 3rd ed., Lea and Febiger, Philadelphia, Chapter 24. 1986

22. Patel Chirag J, Satyanand Tyagi, Patel Jaimin, Patel Pinkesh, Tarun Parashar, Soniya. Pharmaceutical Packaging: Containers & Closures Journal of Biomedical and Pharmaceutical Research. J of Biomed and Pharm Res. 2012. 1(3): 23-32 P.

23. Dean, D. A., Evans, E. R., & Hall, I. H. (Eds.). (2005). *Pharmaceutical packaging technology*. CRC Press.

24. Zadbuke, N., Shahi, S., Gulecha, B., Padalkar, A., & Thube, M. (2013). Recent trends and future of pharmaceutical packaging technology. *Journal of pharmacy & bioallied sciences*, *5*(2), 98.

25. Pareek, V. I. K. A. S., & Khunteta, A. (2014). Pharmaceutical packaging: current trends and future. *Int J Pharm Pharm Sci*, *6*(6), 480-485.

26. Das, P. S., Saha, P., & Das, R. (2018). Pharmaceutical packaging technology: a brief outline. *Research Journal of Pharmaceutical Dosage Forms and Technology*, *10*(1), 23-28.

27. Nasa, P. (2014). A review on pharmaceutical packaging material. *World Journal of Pharmaceutical Research*, *3*(5), 344-368.

28. Kumar, S., & Gupta, S. K. (2012). Applications of biodegradable pharmaceutical packaging materials: a review. *Middle-East Journal of Scientific Research*, *12*(5), 699-70.