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Review on Pharmaceutical Packaging

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Abstract

Packaging of the pharmaceutical product is associated with an integral part of the pharmaceutical process. Packaging plays a crucial role within the protection of the internal contents of a pharmaceutical product to take care of the standard of product. Packaging of a product is additionally needed to differentiate between the various products of various makers. The packaging of a product ought to be convenient and compliant throughout the complete product lifecycle. Packaging helps to guard the contents from environmental exposure like light/moisture and mechanical stress throughout transportation. Numerous styles of packaging materials square measure offered like glass, metal, plastic etc. handiness of varied packaging instrumentation has helped the business to satisfy today's needs of meeting the worldwide standards at a far quicker rate compared to ancient packaging. Container-closures also are necessary as they will act with the interior content directly. The foremost used material for closure is that the rubber-based closure system. Pharmaceutical packaging has a subject matter of continuous development continually and has undergone vital alterations from time to time attributable to the modernization of dose forms that need special packaging needs.

Keywords*: - Pharmaceutical Packaging, Categories of Packaging, Types of Packaging, Containers, Closures, Packaging Materials, Formulation aspects, Regulatory aspects.*

INTRODUCTION

In the present scenario, it is next to impossible to visualize the existence of any Pharmaceutical company without a packaging department (Rundh and Rundh, 2016).[1] Packaging is required to serve the primary necessity that the manufactured medicine Remains in its original form with all desired quality specifications throughout the specified Shelf life (Krishna et al., 2017).[2] Pharmaceutical formulations have three important components, i.e., active pharmaceutical ingredients, excipients, and packaging material. The active pharmaceutical ingredient is the pharmacologically active substance that is generally stabilized by excipients and packaged in a packaging material (Kumar, 2013).[3]

Packing: Packing consists of enclosing an individual item, or several items, in a container, usually for shipment or delivery. This process is mostly done by hand and machine.

Pharmaceutical Packaging:

Pharmaceutical packaging means the combination of components Necessary to contain, preserve, protect & deliver a safe, efficacious drug product, such that at any time point before the expiration date of the drug product, a safe & efficacious dosage form is available.

Packaging plays an essential role in the protection of a product. Product protection throughout its shelf life is the primary function of a packaging system. It protects the product from spoilage, leakage, microbial growth, and contamination, etc.

The packaging is also used for product identification and separates a particular product from a variety of products. This is an important feature required at all levels of use, such as from manufacturers, retailers, and consumers. Primarily, the products intended for different routes of delivery have different kinds of packaging systems. Based on the design and type of packaging container, a patient can identify its intended use. The packaging is important as it delivers protection of medical components (devices/drugs) from the environment and keeps them safe until opened by the consumer (Klimchuk and Krasovec, 2013).[4]

Nowadays, the packaging is an important tool to attract the customer (Raheem et al., 2014)[5] through various promotional activities such as television, print, and electronic media advertisements. Packaging also plays a crucial role in

several nanotechnology-based (Tekade et al., 2017b, 2017c, 2017d) [6] [7] [8] formulation, which are the matter of current scientific interest, especially for pharmaceutical product development.

History of Packaging:-

Since man began to hunt, collect and market his products, the use of packaging was established, with the purpose of transporting and protecting the product.

The first packages were made of sheets, skins and leather. Over time, these packages began to be made with grass and other natural fibers because they were more resistant and could store heavier products.

Nature can be considered the first inventor of the packaging due to the natural protections that some foods have, such as pod to protect the beans and peas, straw to wrap the corncob, eggshell and walnut shell. (Cavalcanti and Chagas, 2006).[9]

Until 1800, packaging was used only to store, protect and transport large quantities of merchandise. They were not intended to store the product for just one individual consumer(Twede, 2016).[10] It was only currently that one of the objectives of the packaging became to satisfy the great individual demand of modern marketing and the logistics of the commerce.

At the beginning of the period 1800–1890, the use of sheet metal in the production of individual packages was reduced due to its high cost and manual production, so the use of glass, paper and cans were more used because they cost less and were more affordable(Twede, 2016).[10]

It was only in the period between 1920 and 1940 that the packaging began to be used as a way of advertising the product and to sell the product directly to the consumer. In 1928, people came to know the brands of the products they bought, and therefore they began to buy from the brands(Franken and Larrabee, 1928).[11] In addition, the packaging became individualized and intended for the consumer, since the population stopped buying a product in bulk (Twede, 2016).[10]

Packaging is the most manufactured item in the world since food, perfume, pharmaceutical, hygiene and cleaning industries use at least one type of packaging in their products (Cavalcanti and Chagas, 2006).[9] Polyethylene was already used in the insulation of telephone cables and submarine cables, but it was only after the war that plastic became used

in the production of food packaging. One of the first successes in the use of plastics in packaging was the development of containers with precise covers, the Tupperwares, widely used until today.(Finnen, 1966;[12] Cavalcanti and Chagas,2006[9]).

Ideal requirements for packaging:-

- It should be non-reactive with the product and so does not alter the identity of the product.
- Protect the dosage form from damage or breakage.
- Protect the preparation from environmental conditions.
- Does not impart tastes or odors to the product.
- Non-toxic
- FDA approved
- Withstand with the high-speed packaging manufacturing machine.[13]

Ideal quality of pharmaceutical packaging-

- The container must bear the heat when it is to be sterilized.
- It should not react with the contents store in it.
- It should have enough mechanical strength so as to withstand handling, filling, closing and transportation.
- It should not leach alkali in the contents.
- The contents of the container should not be absorbed by the inner container wall.
- Closure should not toxic in nature and chemically stable with container contents.
- It should provide the desired degree of protection from environmental hazards.

The material used for making a container should be inert with the contents which going to be store in it.[14 15]

Function of pharmaceutical packaging:-

1. Protecting Function:-

A good package protects the instrumentation from static and dynamic force throughout transportation and storage. Vibration is principally liable for cracking of emulsion, which may be suppressed by mistreatment smart package. It conjointly protects the contents from biological hazards. It defends the instrumentation from wetness, temp, environmental gases, humidness etc. lightweight, sensitive materials are often protected against lightweight by mistreatment primary packing of amber coloured bottles.

2. Identification Function:-

A packaging gives data related to a product like date of producing, ending date, use, batch no., warnings, if any etc. It conjointly gives associate degree simple establish the merchandise for e.g., coloured fluted bottles area unit used for external packaging preparation.

3. Storage and transport Function:-

Packaging plays a vital role in the storage and transportation of the product. Package form ought to be such it is handled simply. It should be thus designed that they'll be keeping in an economical manner i.e., safely one on top of the opposite. The size of package ought to be in line with the pellets.

4. Other functions:-

Other functions of package include protection from theft, compression, impact etc., patient compliance, effective tool for marketing.[16 17 18]

CATEGORIES OF PHARMACEUTICAL PACKAGING SYSTEM:-

There are generally three categories of the pharmaceutical packaging system as follows:

1) Primary packaging
2) Secondary packaging
3) Tertiary packaging

1) Primary packaging:-

It is made up of those package components & subcomponents that come into direct contact with the product or those that may have a direct effect on the product shelf life.

Primary packaging is the term used to designate the layer of packaging in immediate contact with the formulation. As this container is in direct contact with the product, the stability of the formulation mainly depends on its material (Campbell and Vallejo, 2015).[19]

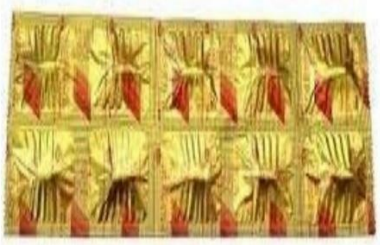
Few examples of primary packaging containers are ampoules, vials, strips, blisters, etc.

Types of containers which are used as a primary package are as follows:-

{1} Primary package for solid dosage forms:-

#1) Strip package:-

In this, the contents square measure sealed in a very packet. The package is formed of 2 layers of film. A strip containing several pockets and every pocket contains a single dose of medicine.

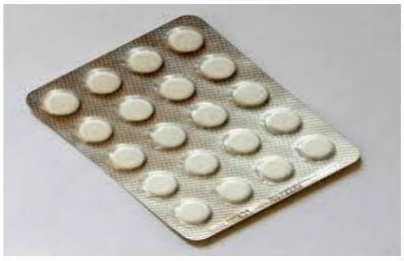


Strip package

Air tight containers

#2) Blister package:-

This type of package provides larger protection than the strip package. The lid is formed of Al or paper foil. The package is sealed by combining lid and base with the applying of warmth and pressure. It's created of a base layer with cavities that contain the pharmaceutical product.



Blister package

{2} Primary package for liquid dosage form:-

#1) Air tight containers:-

These sorts of instrumentations defend the container from environmental hazards. If these containers square measure supposed to be opened on quite one occasions then they remains airtight once re-closure. These also are called tight sealed containers.

#2) Well closed containers:-

These types of containers provide protection from foreign particles and loss during transportation, sale etc.

Closed containers

#3) Single dose containers:-

This container contains a single dose of medicament example are: Glass ampoules, Vials, etc.

Single dose containers

#4) Multi-dose containers:-

These types of containers hold more than a single dose and their contents are

withdrawn at various intervals. For e.g. Vials etc.

Multi-dose containers

#5) Light resistant containers:-

These containers protect the contents from light (UV light). These are made up of the materials that do not allow the UV light to pass from them to contents. For e.g., Amber colored glass containers.

Light resistant containers

{3} Primary packaging for semi-solid dosage forms:-

Semi-Solid dosage forms include creams, pastes, ointments etc. Semisolid dosage form containers include collapsible tubes etc. Plastic Containers are also very popular now a day. Another type of products is also available in market for e.g., Pressurized products. For these types of products, the packages made up of stainless steel, etc. are used. The package used must be strong enough to withstand pressure built up in the container.[15 13 14 20]

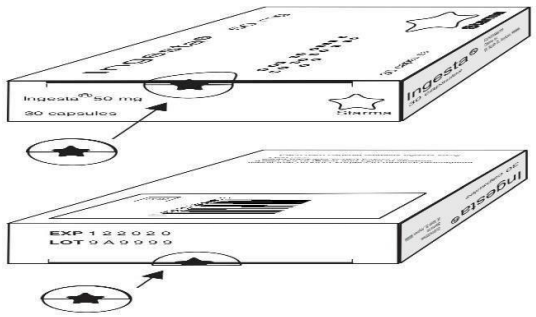
2) Secondary packaging:-

Secondary packaging material never comes in direct contact with the product it is holding. This packaging is visible to the consumer and hence contains the required information, such as labeling with name, usage direction, ingredients, etc.

Secondary packaging container is intended to have two purposes: one is to protect the drug product and the second is to protect the primary packaging container (Kassarjian et al., 2014).[21]

The secondary package chiefly contains shippers or cartons that offer physical protection to the first package. It's prepared by polyose fibers to get from woods. Paperboards are used as a secondary package that is thicker than paper and significant in weight. Samples of paperboards are whiteboard, solid board, Chipboard, fiberboard. These boards are chiefly laminated exploitation

polythene or waxes. Plank is obtained from recycled paper. Bleached salt boards are the e.g. of solid boards that are laminated with polythene.[22 23]



Paper board package with seal consideration

It is important that the seal is firmly fixed across the end flap in such a manner that it cannot be removed without leaving evidence. This is usually accomplished with an aggressive adhesive that damages the underlying carton when the label is removed.

Common examples of secondary packaging containers include Paper board, show box, cardboard box, plastic crates, etc.

3) Tertiary packaging:-

A tertiary packaging container has a crucial role during the transportation of packaged products from the manufacturer to retailers or distributors. This packaging is typically not seen by consumers since it is usually removed by retailers before products are displayed for sale. It protects the product and secondary packaging material from damage, which may occur during transportation (Kerry, 2014).[24] Examples of tertiary packaging materials are wooden box, shippers, carton box, shrink wrap, etc.

The above figure describes about how the perticular product package first into primary packaging than respectively in secondary and tertiary packaging for further distribution and transportation. It is the tertiary package that is received by the wholesalers from manufacturers and delivered to retailers and contains many unit packages inside. Retailers open these packages and the contents are delivered to patients as per the prescription of a registered medical practitioner.

The package is a container-closure system for a drug product or chemical that holds a quantity of the preparation suitable for at least two or more doses. A sealed package is a container-closure system for a pharmacopoeial article closed by fusion of the material of the container. The tamper-evident package is a container closure system for a drug product or chemical fitted with a device or mechanism that reveals irreversibly whether the container has been opened(Dellevigne et al., 2016).[25]

TYPES OF PACKAGING MATERIALS:-

Depending on the type of drug product, required degree of protection, the suitability of product filling method, sterilization requirement, compatibility between a drug product and packaging material, patient convenience, and packaging cost; a few of these (either alone or in combination) materials serve as the main ingredient to construct the packaging.

There are some packaging materials and closures as follows,

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

{1} Glass container:-

Glass containers are very commonly used for storing pharmaceutical products. These containers are intended to come into direct contact with pharmaceutical products. Glass containers are used because of their following advantages.

- They can be easily sealed, which can provide hermetic sealing.
- They are impermeable to water vapors, air etc.
- They have an elegant appearance than plastic containers.
- They are available in various sizes and shapes.

- They can be easily labeled.
- They are transparent so the contents can be easily seen from outside for e.g., in case of parental products.
- They can be converted into light-resistant glass by mixing with metal oxides.
- They are able to withstand temperature and pressure during sterilization.
- They have efficient mechanical strength and rigidity.[26]

Disadvantages:-

- This can easily leach alkali to the aqueous solution if preparation treatment is poor.
- Heavyweight
- Fragility

Composition:-

Glass is made up of silica with varying degree of metal oxides, limestone and cullet. Cullet is mainly the broken glass that acts as a fusing agent. The common cations which are found in pharmaceutical glassware are silicon, zinc, boron, alumina, sodium, potassium, zinc etc. the only anion present is oxygen.[26]

Type 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 1 – Borosilicate Glass
Type 2 – Treated Soda-Lime Glass
Type 3 – Regular Soda-Lime Glass
Type NP – General Purpose Soda-Lime Glass

(1) Type 1 -- Borosilicate glass-

Borosilicate glass container contains silica (80%), boric oxide (10%), and small amounts of sodium oxide and aluminum oxide. The presence of boric oxide makes the glass resistant against hydrolysis and releases the least quantity of alkali. In addition, it has the lowest coefficient of expansion that makes it stable in the case of a high thermal shock (Bansal and Doremus, 2013).[27] It is commonly used for pharmaceutical or fine chemical products that are sensitive to pH changes. It's usually used for pharmaceutical or fine chemical products that are sensitive to pH changes.

Borosilicate glass

(2) Type 2 –Treated Soda-lime glass-

Treated soda lime glass contains silica (75%), sodium oxide (15%), calcium oxide (10%), small amounts of aluminum oxide, magnesium oxide, and potassium oxide. Aluminum oxide impacts chemical durability, whereas magnesium oxide reduces the temperature needed throughout molding. This can be associate degree untreated glass with average resistance against chemical reaction and is employed for dry powder and oily solution. It is used for the storage of non-parenteral products and could be used for parenteral products with certain exceptions (Schaut and Weeks, 2017).[28] Before its use for parenteral products, sufficient stability data must be supporting it.

Treated Soda-lime glass

(3) Type 3 - Regular Soda-lime glass-

Regular Soda-lime glass is made from moderately resistant soda lime glass that has been de-alkalized to obtain a great improvement in resistance against hydrolysis by treating the interior surfaces at a high temperature to remove the alkali on or near the glass surfaces. Said process is also known as sulfur treatment (Varshneya, 2013).[29] The undesirable characteristic of Type II Glass is that the treating etches the surface, causing a frosted appearance. This type of glass is suitable for blood products, infusion fluids including neutral aqueous products to most acidic parenteral preparations. alkaline parenteral formulations can even be packed in type II glass with justifiable stability information. Based on product necessities, non parenteral formulation are often hold on in containers of type II glass (Schaut and Weeks, 2017)[28] (Pillai et al., 2016).

Regular Soda-lime glass

(4) Type NP- General purpose Soda-lime glass-

General purpose soda-lime glass container has low hydrolytic resistance. This type of glass containers are not used for products that need to be autoclaved as this will increase the erosion reaction rate of the glass container. It could be used to store topical products and oral dosage forms but

is not suitable for parenteral products. It is reasonably hard, durable, and cost-effective. Glass transmits, reflects, and refracts light and all these qualities can be enhanced by cutting, giving a new shape and polishing to make optical lenses. Soda-lime glass has poor chemical resistance because of the chances of leaching of the mobile nature of sodium and potassium cations from its composition.

General purpose soda-lime glass

{2} Plastic Containers:-

General, plastics are high molecular weight synthetic polymers and sensitive to temperature. But for the packaging of pharmaceutical products few plastic materials are in use having significantly good temperature resistance and can be autoclaved. Example of these polymers are, but not limited to, polyvinyl chloride, polyvinylidene chloride, polystyrene polypropylene, polycarbonate, polypropylene, polyethylene terephthalate (PET), cyclic olefins, Polyamide (nylon), etc (Centea et al., 2015)[31] (Mateescu et al., 2015)[32]. These come under thermoplastic polymers. These thermoplastic polymers are light in weight and mechanically almost as strong as metals. Like glass, these offer transparent properties with relatively less thickness to store the product for long time.

Materials used for making Plastic containers as follows:-

1) Polyvinylchloride (PVC):-

It has high clarity and smart element barrier. It is created softer & flexible by incorporation of plasticizers. The warmth stability of PVC is extremely poor and its mpt. Is 160°c. It's smart insulation properties however inferior than polythene & plastic. PVC is used for creating containers used for blood & blood components, catheters, bypass sets, dialysis sets etc. the most benefits of PVC include its transparency, light wt., softness, suitableness for sterilization and biocompatibility.

PVC plastic containers

2) Polyethylene:-

Polyethylene is extremely used compound. it's on the market in high density, medium

density and density grades chiefly high density polythene is employed for prescription drugs. It provides protection against wet however poor protection against chemical element & alternative environmental gases. The containers ready from polythene can't be sterilized by heat however is simply sterilized by autoclave. Polyethylene's have freezing point vary of 120-150^{0}c. it's a superb chemical resistance, it suggests that it offer protection against robust acid & alkali. it's wont to prepare bag, plastic films, bottles etc.

Polyethylene plastic containers

3) Polypropylene:-

It is very popularly used in Pharmaceutical container. It has many qualities of polyethylene. It has melting point of 170^{0}c which is higher than polyethylene and make it suitable for sterilization at high temp. It has superb resistance power to most sorts of chemicals. it's superior to density synthetic resin. the most downside of plastic is its less clarity which might be improved by creating skinny walls containers. Other drawback is its brittleness at low temp. which can also be improved by mixing it with some proportion of polyethylene.

Polypropylene plastic container

4) Polystyrene:-

It is made from petroleum. It is non biodegradable, light and rigid. Its main advantages are that it is inexpensive, resistant to acids, strong alkalies & strong oxidizing agents, high heat resistance, expandable etc. The main drawbacck is that it can leach styrene & benzene when come in contact with warm food, oils, alcohols etc. which causes contamination of product.

Polystyrene plastic containers

5) Polyamide (Nylon):-

It is macromolecules having repeated units linked by amide bonds. Nylon is mainly artificially made. It can be produced by interaction of a diamine and a dicarboxylic acid. It has main advantage of excellent

chemical resistance, high strength, sensible toughness, high heat resistance, sensible water resistance etc. it will be autoclaved simply. The most disadvantage is high moisture absorbtivity, attacked by oxidant, strong acids & alkalis etc.

Polyamide plastic containers

6) Polycarbonate:-

Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and acyclic hydrocarbons. It is attacked by strong acids, reducing agents, amines, ketones, aromatic hydrocarbons, and some alcohols. It has highest impact strength and inexpensive. It is clear and very good heat resistance power. Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and acyclic hydrocarbons. It is clear and really and extremely heat resistance power. It's primarily used for producing of surgical equipments. [33 34 35 36 37]

Polycarbonate plastic container closures

Dosage form plastic interaction/Limitations of plastic material:-

1. Permeation
2. Leaching
3. Sorption
4. Chemical modification
5. Alteration on the properties of plastics or product

#1) Permeation

- The transmission of gases, vapors or liquids from the surrounding environment into the plastic container is known as "Permeation".
- Permeation of vapor & oxygen through the plastic wall into the dose type are often problematic If the drug is sensitive to chemical reaction and/or oxidization.
- An increase in temperature will increase permeableness of gases.
- An increase in crystallinity of the fabric decreases permeableness.
- Hydrophilic plastic materials like nylon ar poor barriers to vapor,

whereas hydrophobic materials like synthetic resin ar higher barriers.

- The concentration of medicine in formulations containing volatile ingredients may modification once hold on in plastic containers due to the permeation of 1 or a lot of volatile ingredients through the walls of the plastic containers.
- Plastic containers conjointly have an effect on the physical properties of the merchandise. for instance, once water-in-oil emulsion is hold on in a hydrophobic plastic bottle, there's a tendency for the oil section to migrate & diffuse into the plastic.
- Permeation may have an effect on the shelf-life of a drug.

#2) leaching

- Release of a constituent from the plastic material of the container into the formulation is understood as "leaching".
- For example, specific dyes that are used as coloring agents could migrate into a product, contaminates the product and will cause a toxic result.

#3) Sorption

- The method of extraction / removal of 1 or additional of the constituents from the formulation by the packaging material are said as "Sorption".
- Becomes a significant drawback significantly for form kinds that contain drug and/or different necessary ingredients in the solution form.
- May considerably have an effect on the therapeutic effectively of the formulation containing extremely Potent drug.

#4) Chemical modifications

- Certain ingredients utilized in plastic container producing may chemically react with one or additional parts of a drug product.
- These chemically incompatible substances may alter the looks of the plastic or formulation.

#5) Alteration on properties of plastics or product

- The physical or chemical alteration of the packaging material by the drug product is termed "modification".
- The content could extract the plasticiser, inhibitor or stabilizer, so dynamical the pliability of the container.
- Permeation, natural action or action may alter the properties of the plastic container.

For example:

1. Oils have a softening result on polyethylene;
2. Fluorinated hydrocarbons attack polyethylene & PVC. [13]

{3} Metal containers:-

Metals are very commonly used as packaging material for pharmaceutical containers. These are resistant to heat fluctuation (Tiwari, 2016; Manne et al., 2015). Samples of metals used for this purpose embody chiefly metallic element, lead, tin etc.

Advantages:-

- They are light in weight than glass.
- They are strong.
- They are resistant to light, moisture and gases.
- They are elegant in appearance.
- Label can directly print on surface.

Disadvantages:-

- They may react with certain drugs or chemicals and produce toxic product.
- They may leach metal particle in the product.
- They are costlier than plastic.

Metal containers can be prepare by particular material such as Aluminium, tin and lead etc.

Types of metal containers:-

#1) Collapsible tube:-

These are created from metallic element, tin or lead. They're Aluminium pack solid preparation. Metallic element tubes area unit used for dispensing of tooth paste & creams. Lead isn't used for pharmaceutical purpose as a result of risk of lead poisoning. just in case of aluminium collapsible tubes there are chances of minimum contamination of the remaining portion of tube content due to absence of suck back mechanism.

Collapsible tube

#2) Metal container for solid dosage form:-

Aluminium is mainly used for this purpose. So the containers for tablets & capsules are light in weight & also strong enough.

Metal blisters and strips

#3) Metal foil: - These foils are used for wrapping of individual suppositories or pessaries. Mainly aluminum foil is used for this purpose. Metal foil is also used for strip & blister packing of tablets & capsules.[15 38]

{4} Rubber based components:-

Mostly used to make stoppers and bulbs for dropper assemblies.

Examples of rubber for pharmaceutical products include-

1. Natural rubber
2. Neoprene rubber
3. Nitrile rubber
4. Butyl rubber
5. Chlorobutyl rubber
6. Bromobutyl rubber
7. Silicone rubber [13]

{5} Cotton:-

Package type	Remarks
Wadding	In solid preparations to prevent the collision of individual units or to absorb moisture etc.
As	To Prevent absorption of moisture particularly by
Desiccant	tablets & capsules from environment.

{6} Adhesives and inks:-

Some substances, such as cements and lacquers used as label adhesives, are not water based emulsions. They are usually dissolved in toluene, alcohol, naphtha, methyl Ethyl ketone, or other organic solvents. When an adhesive of this type is used on plastics or elastomers, the solvent may allow migration of adhesive components into the formulation. Therefore, appropriate testing Should be performed to determine whether adhesive and ink components migrate through the container. If they do, adequate information to justify the use of the container system in combination with the drug product should be submitted.

For all containers, testing should be conducted on the effectiveness of the adhesive under appropriate challenge conditions (e.g., temperature and humidity).If direct label imprinting is used on containers, such as on containers of injectable drug products, it is necessary that resistant ink be used so that the imprint having the required information resists the normal handling of the containers during their customary conditions of purchase and use. [13]

{7} Closures:-

This is the most critical component of a container. An effective closure system prevents the loss of material from the container, prevents the environmental contamination of the product, and prevents the microbs to enter inside the container.

Design of closure:-

Closures are available in five main designs. Their details are as follows.

1.) Lug cap:-

The difference in lug cap and thread cap is that in thread cap, continuous threads are present but in lug cap threads are present in intermittent fashion. Another difference is that lug cap requires only a quarter turn. Lug caps are mainly used in storage of food products.

Lug cap

2.) Threaded screw cap:-

These are made up of aluminium, tin or plastic. As the name indicates they contain threads which get engaged with the threads present on the neck of container. These types of closures provide the effective seal which protect the product from physical and chemical reaction. Plastic caps are more popular than metal because plastic are resistant to corrosion.

Threaded screw cap

3.) Roll on closures:-

Roll on closure contains the aluminium roll on cap which can be easily sealed, opened and closed. These are available in re sealable, non- sealable & pilfer proof type forms. These are available for use on glass or plastic bottles & jars for food, beverages, chemicals and pharmaceuticals.

Roll on closures

4.) Crown caps:-

These caps are made up of metal and commonly used for beverages bottles. These also provide an effective seal and cannot be open with hands. These cannot be seal again.

Crown caps

5.) Pilfer proof closures:-

In this additional length extends below to threaded portion which forms a bridge. When the closure is removed then the bridge break and the additional portion remains in place on neck of container

which show its opening. [15 39 40]

Pilfer proof closures

Materials used for construction of closures as follows:

Rubber-

Rubber is employed for construction of closures for vials, transfusion bottle fluids etc. many varieties of rubbers are used for this purpose for e.g butyl rubber, nitrile rubber, silicon rubber etc. butyl rubber is extremely ordinarily used attributable to its low absorption property and additionally they're cheaper than alternative rubber however it decompose above on top of.

Rubber is ready by compounding a base chemical compound with additives. The choice of base chemical compound & additives depends upon the kind of rubber properties to be desired. The resultant rubber is non vulcanized compound.

Additives use in construction of rubber closures like Fillers, plasticiser, vulcanizing agent, accelerators, activators

and pigments. [41]

Plastic-

Two types of plastics are used.

1. Thermoplastic:-

This type of plastic gets softened to a viscose fluid on heating and then gets hard on cooling. Example includes: Polyethylene, Polypropylene, Polystyrene etc.

2. Thermosetting:-

They are firstly softened under heat and then curved before harden to final state. The shape should be required to be achieve during softening because after softening shaping cannot be done. Thermosetting plastics cannot be re-melt so the closure which are imperfect or improper In shape must be discarded. Example includes Phenolic compounds and Urea.

There are use of additives such as phenolic

compounds and urea.[42 39 43]

Plastic closures

FORMULATION ASPECT OF PACKAGING:-

Formulation specific requirements for packaging material-

1) Compatibility:-

The unacceptability between the packaging material and formulation can be identified during formulation development by container closure studies (Kogawa and Salgado,2016).[44] For example, leakage or accuracy of dose delivery can be identified during development. However, there are a few different types of complex interaction between packaging components and formulation, those are difficult to identify readily during development. In such cases, stability studies are able to explore such unacceptable interactions between the packaging components and formulations. For example, delamination of glass vial and leachable can be identified as an instability (Sloey et al., 2013) [45]

Sterile drug products are very sensitive to external contamination. Packaging components can be the crucial source for such microbiological contamination during storage Therefore, to protect such serious contamination, packaging components shall be capable of maintaining sterility throughout shelf life. Some of the parenteral formulations were packaged in glass containers with rubber stopper/closure and sealed well.

2) Integrity:-

Packaging components shall be identified for the formulation that can protect the formulation from different factors like light, heat, moisture, etc. The nature of the formulation needs to be considered while selecting the packaging components (Ashby and Johnson, 2013).[46] For example, a hygroscopic formulation shall be packaged in air-tight packaging components. Light-sensitive formulations shall be packaged in nontransparent packaging material. Liquid formulations shall be packed in leak-proof packaging systems. Sterile formulations, like injectable or ophthalmic, shall be packaged in such components that can be withstood for the sterilization process. For example, injectable formulations need to be terminally sterilized, e.g., by dry heat, in such cases, plastic containers are not recommended as they cannot withstand heat and may leach or deform during sterilization (Alkers, 2016).[47]

3) Toxicity:-

Formulations packaged in respective packaging components shall be stable throughout the shelf life. If a packaging material is not selected properly then it

may cause toxic potential to the formulation (Pa˚lsson et al., 2013).[48] A few of the components leaching from the packaging material may have a genotoxic nature which again creates safety issues for the patients. This leaching is a crucial concern behind the proper selection of primary packaging material.

4) Leachable:-

Leachables are the compounds that leach into the formulation from container closure as a result of direct contact with the formulation. For drug products, like injection, inhalation, ophthalmic, or transdermal formulations, extensive exploratory studies need to be conducted to identify the leachables which may cause safety concerns to the patients.

5) Dose delivery:-

Any packaging system shall be tested and passed for the dose delivery study. Just like the stability of a product, performance or efficaciousness of the product depends upon the delivered dose by the packaging material. As an example, for an auto-injector which is self administered by intramuscular route, then patients deliver a lower quantity of drug if the dose fully utterly dialed, or if needle size isn't sufficient to go into the intramuscular layer of body. This may decrease the efficaciousness of the product (Lopez et al., 2015).[49]

During stability studies, the dose delivery study should be conducted. Delivered dose is relying upon the varied factors of formulation and device (Mitragotri et al., 2014).[50] Formulation related factors contain viscosity of solution, fill volume, etc. Device-related factors embody setting of device, integrity of device, etc.

6) Administration Feasibility:-

Every formulation is intended to be administered to the patients with its predefined dose and route of administration. The prescription drug User Fee Act (PDUFA) states that one of the goals in drug development ought to be to confirm the safe administration of drug by prospectively planning a drug that minimizes the risk for errors created by supposed finish users (Mullin and Barton, 2017).[51] therefore administration feasibility of a formulation may be a key demand for any drug product. Administration feasibility becomes crucial in associate degree emergency medical condition like hypersensitivity reaction. Few drug product are designed to be self-administrable reception or elsewhere. In these circumstances, it is important that administration of drug product should be

hassle-free. Drug product with device shall allow for the visible inspection wherever

required (Werner-Busse et al., 2014).[52]

7) Durability:-

Each formulation has its own shelf life based on the stability of the formulation along with its packaging components. After manufacturing, the formulation is packaged with its packaging components and transported towards the warehouses of wholesalers or distributors. Nowadays pharmaceuticals manufacturers supply their products globally from respective manufacturing locations. It becomes necessary for packaging materials to be able to withstand the transportation. This supports the global need for quality medicine to patients (Dietrich et al.,

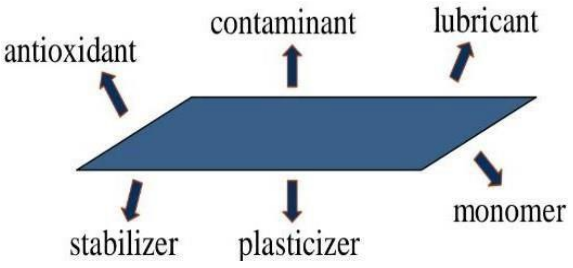
2016).[53]

EVALUATION PARAMETERS OF PHARMACEUTICAL PACKAGING:-

Package analysis is performed to analyze the chemical science interactions that may occur between the product & package. The best package would be fully inert relative to the product & would offer most shelf-life. Therefore, analysis is intended to spot, characterize & monitor these interactions to realize a secure, pure, stable & efficacious product.

An important step -- characterizing the materials and therefore the chemicals that may migrate or extract from packaging parts to the drug product.

Figure shows the various types of chemicals that can migrate from polymeric materials. The identities and abundance of these chemicals determine materials suitability.



A number of tests are used to establish initial qualification of the container closure system, and a top quality management arranges will facilitate guarantee compatibility and safety.

To establish suitableness, analysis of 4 attributes is needed: protection, compatibility, safety, and performance/ drug delivery .Suitability refers to the tests used for the initial qualification of the instrumentation closure system with respect to its supposed use.[13]

(1) Glass container:-

Glass containers must be tested for chemical resistance and light transmission according to the described procedures in USP.

***Light transmission test:-**

Spectrophotometer issued for measuring theamount of light transmitted by the glass or plastic. Glass and plastic are of transparent and translucent types. The spectrophotometer with suitable sensitivity and accuracy should be chosen for measuring the amount of light transmitted.

The circular piece of the material is placed in the spectrophotometer with its cylindrical axis parallel of the plane of slit and approximately centered with the slit and measure the amount of light transmitted in the region of 290 to 450 nm. The amount of light transmitted should not exceed 10% at any wavelength for Non parenteral (NP) glass containers and plastic containers for oral formulations.

***Chemical resistance:-**

Chemical resistance of the container is tested for glass containers by using following tests:

1) Powdered glass test
2) Water attack test
3) Arsenic

The degree of resistance is determined by amount of alkali released by attacking the container with the medium at specified conditions. The higher is the resistance the lesser will be the amount of alkali released 12-15.

In the above mentioned three tests for evaluating chemical resistance of glass, the prepared specimen of water (the specimen of water prepared by using the procedure mentioned in the USP monograph 661) should be titrated with 0.020 NH_2SO_4, methylene red issued as an indicator. The amount of acid consumed in the titration should not exceed the limits.

Test of Arsenic:-

Prepare the test solution according to the procedure given in Indian Pharmacopoeia. Compare the absorbance of the test solution with standard arsenic solution (10ppm) at a wavelength of 847nm. The absorbance of test solution should not exceed the absorbance of standard arsenic solution. Hydrazine molybdate reagent is used as a solvent and blank for the qdetermination of absorbance.

(2) Plastic container:-

The following test should be performed on the plastic containers:

1. Light transmission test (According to chapter 661of USP)[54]
2. Water vapor permeation test (According to chapter671 of USP)[55]
3. Physicochemical tests (According to chapter 661of USP)[54]
   - Non volatile residue
   - Residue on ignition
   - Heavy metals
   - Buffering capacity
4. Biological tests

In vitro biological tests (According chapter 87 of USP) [56]

- Agar diffusion test
- Direct contact test
- Elution test

In vivo biological test (According to chapter 88 of USP) [57]

- Systemic injection test
- Intra cutaneous test
- Implantation test

(3) Closures:-

The closures chosen to be used with a selected preparation ought to be specified the elements of the preparation to bear with the closure don't seem to be adsorbate onto the surface of the closure to associate degree extent spare to have an effect on the merchandise adversely. The closure mustn't yield to the merchandise substances in quantities spare to have an effect on its stability or to gift a risk of toxicity.

The closures ought to be compatible with the preparation that they're used throughout the shelf-life of the merchandise.[58 59]

The following tests are to be done on the closure.

1. Appearance of the solution
2. pH of aqueous extract
3. Light absorption
4. Reducing substances
5. Heavy metals
6. Residue on evaporation
7. Volatile sulphides
8. Sterilization tests
9. Fragmentation tests
10. Self-sealability
11. Biological tests.[26]

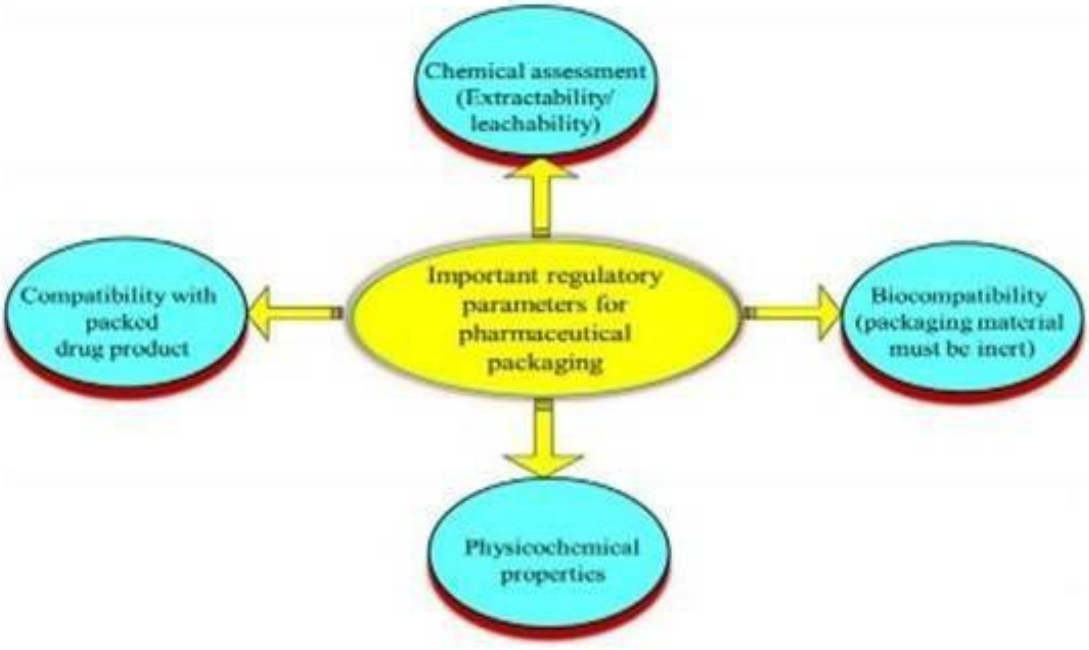
REGULATORY ASPECT OF PHARMACEUTICAL PACKAGING:-

Packaging materials of pharmaceuticals play crucial roles in the marketing of formulations in a regulated market. It is

mandatory for packaging materials to be compliant with respective regulatory recommendations and guidance. Regulatory agencies closely monitor the quality of such packaging materials and eventually drug products by ensuring the adherence of respective manufacturer's compliance with cGMP. Noncompliance of such regulatory recommendations and guidelines results in compromised drug product quality and subsequently recall of drug product from respective market. Examples of such cases are the recall of drug product due to defective container, mispackaged, mislabeled container, etc.[14]

Child Resistant Packaging Regulations in India

Indian Standard Child Resistant Packaging – Requirements and testing procedures for reckonable packages provides the guidance for CR packaging in India, this Indian standard has adopted by Bureau of Indian Standards on the recommendation of the packaging codes sectional committee and approval of the Light Mechanical Engineering Division Council. This guidance provides the requirements and test procedures for reckonable packages. This guidance is intended for type approval only, not for quality assurance purpose.



Regulatory aspects

The American Society for Testing and Materials (ASTM) gives a list of:

Classifications of child-resistant packages

Type I: Reclosable packaging – continuous thread closure

Type II: Reclosable packaging – lug finish closure

Type III: Reclosable packaging – snap closure

Type IV: Unit non-reclosable – flexible (strip/pouch)

Type V: Unit non-reclosable – rigid

Type VI: Unit reclosable packages

Type VII: Aerosol packages

Type VIII: Non-reclosable packages – semi-rigid (blister)

Type IX: Dispensers (not intended to be removed)

Type X: Box or tray package

Type XI: Reclosable packaging – flexible

Type XII: Dispenser (may be removed)

Type XIII: Reclosable packaging – semi-rigid (blister) [13]

Tamper proof packaging

Tamper proof containers are those that resist the tampering of the product before consumer the product.

They help in

- Receiving the products by patients " as manufactured "
- Preventing "product browsing and sampling.
  - Blister or Strip Packs
  - Bubble Packs
  - Heat Shrink Bands or Wrappers
  - Foil, Paper, or Plastic Pouches
  - Bottle Mouth Inner Seals
  - Tape Seals
  - Breakable Caps
  - Sealed Metal Tubes or
  - Plastic Blind-end Heat Sealed Tubes
  - Cans

REGULATION OF PHARMACEUTICAL PACKAGING COMPONENTS

There are a great number of regulatory requirements on pharmaceutical packaging Materials, in

- The pharmacopoeias,
- The GMP regulations, in
- The FDA guidance, &
- other regulatory guidance.

It must be emphasized that packaging preserves the stability and quality of medicinal Products and protects them against all forms of spoilage and tampering.

FDA does not approve containers as such, but only the materials used in the Containers and give them the standard of "Generally Regarded as Safe". (GRAS)

The pharmaceutical manufacturer has to guarantee that only such packaging materials Are used that are Correctly printed, Means it should state what it contain and it should contain what it should state.

In conformity with the specifications and in compliance with the regulatory requirements.

FDA's current focus:-

CMC CC PACKAGING TECHNICAL COMMITTEE:

PACKAGING GUIDANCE COMMITTEE:

CMC CC RECENT PACKAGING INITIATIVE:

->CMC CC- Chemistry, Manufacturing and Control Coordinating Committee

->CMC CC PACKAGING TECHNICAL COMMITTEE

It includes various offices from CDER, CBER and CVM.

CDER – Centre for Drug Evaluation and Research

- Office of New Drug Chemistry
- Office of Generic Drug
- Office of Compliance
- Office of Testing and Research
- Quality Implementation Staff

CBER- Centre for Biological Evaluation and Research

- Office of Compliance and Biologics Quality

CVM – Centre for Veterinary Medicine

- Office of New Animal Drug Evaluation

Pharmacopoieal forum:-

It provides information for the following,

- Injection
- Elastomer clouser for injections
- Container
- Cotton filler
- Rayon filler
- Packaging practice:
- Repackaging of single solid oral drug product into unit dose container

Packaging in other guidelines:-

Stability Testing of Drug Substances and Drug Products, draft, 1998 packaging for solid and liquid oral drugs

ICH Common Technical Document-Quality (CTD-Q) S.6 and P.2.4

EN 13427:2004

Packaging - Requirements for the use of European Standards in the field of packaging and packaging waste

The Federal Food, Drug, and Cosmetic Act: Section 501-505

The Code Of Federal Regulation: 21 CFR 211(Subpart E, Subpart F, Subpart G)
16 CFR 1700-1702 – Special Packaging
Compliance policy Guides That Concerns Packaging: Subpart 410, 430, 440-448, 450-457, 480.

Packaging guidance 1999:-

- This document is intended to provide guidance on general principles for submitting information on packaging materials used for human drugs and biologics.
- All necessary documents are submitted to regulatory authority considering the various aspects covered in guideline.
- Also the additional information regarding the contract packager and repackager, if any than should be provided as and when needed.
- Represents Company's current thinking on container clouser systems for packaging of human and biological products.
- Dose not create or confer any rights for or on any person and dose not operate to bind FDA or the public.
- An alternative approach may be used if such approach satisfies the requirement of the applicable status, regulation or both.
- Provide guidance on general principles for submitting information on packaging materials used for human drugs and biologics.

FDA Regulation:-

REGULATORY REQUIREMENTS

The Federal Food, Drug, and Cosmetic Act

(a) Section 501:

A drug or device shall be deemed to be adulterated ``if its container is composed, in whole or part, any poisonous or deleterious substance which may render the contents injurious to the health`` (section 501(a)(3))

(b) Section 502:

A drug or device shall be deemed to be misbranded if it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed manner (502(g))

If it is a drug and its container is so made, formed, or filled as to be misleading (502 (i))

If it is a drug and packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970.

Subpart F: Production & Process Control (21 CFR 211.100-211.115)

Subpart G: Packaging and Labeling Control (21CFR 211.122-211.137)

21 CFR 211.132 describes the Tamper Resistant packaging requirements for OTC Human drug products.

(C) 16 CFR 1700-1702 – Special Packaging

– The U.S consumer Product Safety Commission (CPSC) is responsible for enforcing the Poison Prevention Packaging Act (PPPA) in 1970. The PPPA requires special packaging of hazardous household substance to protect children from serious injury or serious illness from handling, using.

– Which Pdt requires Special Packaging?

–Human oral prescription

–OTC drug preparation

–PPPA regulation establishes performance standards and test methods that determine if a packaging system is child resistant and adult use effective.[1]

Regulatory requirements for labeling:-

Manner of labeling (Rule 96 of D & C act rules) States the minimum requirements to be presented In the labeling. If any drug product is not labeled In the prescribed manner or if its label or Container or anything accompanying the drug bears any statement, design or device which makes any false claim for the drug or which is false or misleading will be considered as misbranded drug.

The following information should be printed or written in indelible ink and shall appear in a conspicuous manner on the label of the inner most container of any drug on every other covering in which the container is packed.

1. The name of the drug- The proper name of the drug shall be printed or written in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name.

2. A correct statement of the net content in terms of weight, measure, volume, number of units of contents, number of units of activity, as the case may be, and the weight, measure and volume shall be expressed in the metric system.

3. The content of active ingredients.

- For liquid orals the content of active ingredient expressed as an amount per single dose where the dose is more than 5mL, if the dose is lesser than 5mL, the content expressed per 1 mL.
- For liquid parenteral preparations ready for administration in terms of 1 mL or percentage by volume or per

dose in the case of single dose container.

- For drugs in solid form which are intended for parenteral administration, in terms of units or weight per milligram or gram.
- For tablets, capsules, pills and the like, in terms of the content in each tablet, capsule, pill or other unit.
- For other preparations, in terms of percentage by weight or volume or in terms of unit per gram or mL Content of the active ingredient is not required to include on the label in of pharmacopoeial preparation where the composition of such preparation is specified in the respective pharmacopoeia and to a preparation included in the National Formulary of India (NF).

4. The name of the manufacturer and the address of the premises of the manufacturer where the drug has been manufactured. If the container is smaller to accommodate all the Details, the name and principal place of manufacture is enough to show on the container.

5. A distinctive batch number. The representation of batch number is preceded by the words, Batch No. or B. No. or Batch or Lot No. or Lot.

6. Every drug manufactured in India shall bear on its label the number of the licence under which the drug is manufactured, the figure representing the manufacturing licence number being preceded by the words “Manufacturing Licence Number” or “Mfg. Lic. No.” or “M.L.”

7. Drugs mentioned in Schedule P or Combination of drugs which have schedule P Drugs with it, shall bear the date of manufacture, date of expiry of potency, the period between date of manufacture and date of expiry should not exceed the period mentioned in the schedule for schedule P Drugs, for drugs other than schedule P drug the label should bear the date of manufacture and date of expiry and the date of expiry should not be later than 6months from date of manufacture. The date of expiry shall be in terms of month and year and it shall mean that the drug is recommended till the last day of the month. The date of expiry shall be proceeded by the words 'Expiry date’.

8. If the drugs are imported, the label shall bear the number of license under which it is imported, and preceded by the words ‘Import License’.

9. Every drug intended for distribution to the medical profession as a free sample,

shall, bear on the label of the container the words 'Physician's Sample—Not to be sold' which shall be overprinted.

10. If any preparation contains not less than 3 per Cent by volume of alcohol the quantity of alcohol shall be stated in terms of the average percentage by volume of absolute alcohol finished the finished products.

11. The label of innermost container of the following categories of drugs and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which should not be less than

12. 1mm in width and without disturbing the other conditions printed on the label.

13. Narcotic analgesics, hypnotics, sedatives, tranquilizers, corticosteroids, hormones, hypoglycemic, antimicrobials, antiepileptics, antidepressants, anticoagulants, anticancer drugs and all other drugs falling under schedules 'G', 'H', and 'X'.

14. This requirement is not applicable for ophthalmic products, ear drops, sterile preparations, and preparations for external use and animal use.

15. The above mentioned information should be printed or written in indelible ink either on the label borne by the container, or on the label or wrapper affixed to any package in which the container is issued for sale.

16. The particulars on the label can be etched, painted or otherwise indelibly marked on the container instead of being displayed on the label.

17. According the Rule 97 of the D & C act the label should contain the following cautionary statements.

a) If the container contains the product Specified in schedule G, the label should bear the word 'Caution: It is dangerous to take this preparation except under medical supervision' conspicuously printed and surrounded by a line within which there shall be no other words.
b) If it contains a substance specified in schedule H be labelled with the symbol Rx and conspicuously displayed on the left top corner of the label and be also Labelled with the following words: "Schedule H drug – Warning : To be

sold by retail on the prescription of a registered Medical Practitioner only."

c) If it contains a substance specified in schedule X, be labeled with the symbol XRx which shall be in RED conspicuously displayed on the left top corner of the label and be additionally labelled With the words: Schedule X drug " Warning: To be medical practitioner by retail on the prescription of a Registered Medical practitioner only."

d) If narcotic drugs and schedule H drugs are packaged in the container, the label should bear a symbol NRx which shall be In RED conspicuously displayed on the left top corner of the label and be also labelled with the words: Schedule X drug " Warning: To be sold by retail on the prescription of a Registered Medical practitioner only."

18. The containers for ointments, lotions, etc. should contain the statement in capital letters "FOR EXTERNAL USE ONLY". Annexure I provide various labels with specific statements.

Package insert:-

Package inserts includes adequate directions for use. It is helpful for the physician in making correct decision before prescribing any drug for a particular patient. Package inserts should be written in English.

Package insert is divided into two parts:

1. Therapeutic indications

a) Posology and method of administration
b) Contraindications.
c) Special warnings and special precautions for use, if any.
d) Interaction with other medicaments and other forms of interaction. e. Pregnancy and lactation, if contra-indicated.
e) Effects on ability to drive and use machines, if contra-indicated. g. Undesirable effects/side effects.
f) Antidote for overdosing

2. Pharmaceutical information

a) List of excipients
b) Incompatibilities
c) Shelf life in the medical product as packaged for sale.
d) Shelf life after dilution or reconstitution according to direction.
e) Shelf life after first opening the container.
f) Special precautions for storage.
g) Nature and specification of the container.
h) Instructions for use/handling

CONCLUSION

Packaging plays a vital role in Pharmaceutical Industries. The pharmaceutical packaging market is consistently increasing with annual growth of a minimum of 5 per cent every year within the past few years. Package contains a nice role in protection of Pharmaceutical product. Packaging provide Pharmaceutical elegance, Patient compliance that will increase marketing of Pharmaceutical product. It additionally provides valuable data to the patient. Packaging of oral formulations conforms to needs which have straightforward dispensing, child resistance and senior-friendliness, practical and extremely typically hermetically sealed. However most of the Pharmaceutical packaging has several disadvantages. So, currently a day's eco friendly packaging parts square measure used that square measure perishable in nature and may be reprocessed simply. Food and Drug Administration approval is critical before a new package is to be launch in market and once obtaining approval from Food and Drug Administration no modification will be done without previous permission of Food and Drug Administration. This review article has addressed the vital issues for containers and closures. The article has forced upon the materials used for containers and closures and their benefits and drawbacks and their use.

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