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RECENT ADVANCES IN PACKAGING MATERIALS FOR PHARMACEUTICAL PRODUCTS AND THEIR QUALITY CONTROL TEST

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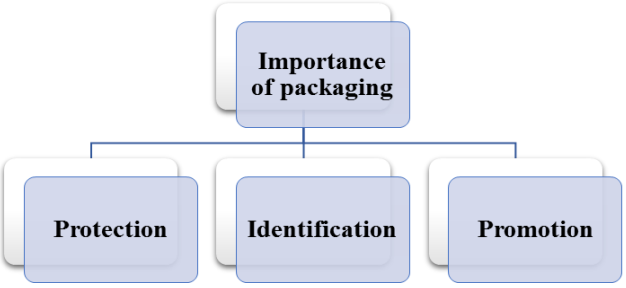
ABSTRACT
The material used in pharmaceutical packaging has a major impact on how long a pharmaceutical dosage form lasts. The dosage form's integrity should be maintained, and the packaging should be made to be naturally inert, robust enough to withstand force, and difficult to break. Glass is the most used material for packing. An important consideration when examining the stability testing of the dosage form is the type of packaging used. Aluminium foil, glass, and plastic are only a few of the materials used in the packaging of pharmaceutical dosage forms. In an effort to lessen the growing pollution problem, packaging materials are produced using biodegradable polymers.[1,2]

KEYWORDS: Packaging material, pharmaceutical dosage form, biodegradable polymers, packaging, product.

INTRODUCTION
As the product is in the process of manufacturing, packaging plays an important and vital role to the product. Without packaging product cannot be complete and commercialized. Packaging should be in the right package for the right product. It means the package should properly cover the product, package should properly protect the product, package should give proper identification and details of the product (such as product name, API that is active pharmaceutical ingredient and other chemical constituent and brand name.). package is the container for the finished product to become final good for commercialization. Package is different for the different material and packaging style is different manufacturers.[3,4]

Packaging is the protective barrier for the product after manufacture from the various factor such as environment, stress, etc. packaging help to purchase self-life of drug. Packaging is important to keep stability of drug.[4]

Packaging material are tested and validate through Q.C. and Q.A. (QUALITY CONTROL AND QUALITY ASSURANCE DEPARTMENT). Quality of the packaging material is important as it may result the degradation of product. Style of packaging may be a container or a closer; it depends upon the product. Package should have proper libelling so we can know the chemical content.[5,6]



WHY PACKAGING IS NEEDED?
Packaging is an important factor which helps the product in

- Protection
- Identification
- Promotion

Protection

Packages protect against parameters such as[5]

1. Environment hazards
2. Mechanical or physical hazards
3. Chemical hazards
4. Misuse
5. Ageing

1. Environment hazards

Environment is an important parameter in the maintaining the stability of the drug. Under the environment parameter there are several individual factors such as temperature, humidity, light, oxygen, water, PH, contamination, etc.

- Temperature – degradation of drug product can be happened due to temperature difference needed for the drug to maintain its originality or stability during the storage. So, the proper packaging is needed.
- Humidity and moisture – humid condition make the drug degrade rapidly and moisture have water molecule which react with the drug and degrade it. If the proper package is done then the degradation can be prevented.[6,7]
- Light – light (such as UV light, IR light, etc.) falls on the photosensitive drug product, API or other chemical constituent which is photosensitive present in the formulation may get exited by getting energy from light and react with each other and degrade itself. It is called photo degradation; it can be prevented by the proper packaging.
- Oxygen- oxidation is the addition of oxygen with the compound from the atmosphere forming oxidised compound which is degradation of the pharmaceutical product. Packaging is the best way to prevent it.
- Contamination- contaminants (such as dust, microorganism, pollutant, etc.) fuse with the product and cause the degradation of the product so if the drug is properly packed then it prevents product from degradation.[8]

2. Mechanical or Physical

Physical or mechanical hazards are unconditional hazards that happens during the transportation of drug in bulk quantity to a distance and for a long-term storage. Physical or mechanical hazards can be identified as

- Shock impact: - shock or impact arises from change in velocity. Product get damaged during long distance transportation or it get drop impact (fall damage) which damage suffered from fall from a hight. It can be prevented by proper packaging.

3. Chemical hazards

Chemical hazard is an important factor that influence the drug stability. It has many individual factors such as temperature, heavy metals, PH, contamination, etc. presence of the chemical substance will increase the toxicity of the product.[9]

4. Misuse

Misuse of drug is a vital point of safety of consumer. The drug is helpful when it is taken according to the advice of doctors. But some drugs common drugs such as pain reliver (aspirin, acetaminophen or paracetamol, ibuprofen), cold and flue medication (cough suppressant, expectorants, etc), anti-histamines (cetirizine, loratadine, etc.), etc are used without doctors' prescription. Some drugs such as sleeping aids(melatonin), benzodiazepines (lorazepam, diazepam) needed proper prescription for drug to distribute as these drugs are misused by others. It can be prevented by proper packaging and proper libelling of drug.[10,11]

5. Ageing

Ageing which is known as degradation of drug, refers to changes happen in the chemical constituent of drug over a the time, which affect drugs potency, safety and efficiency. There are several factors affecting the drug ageing such as temperature, microbial contamination, storage condition, chemical reaction, humidity etc. a proper packaging of drug can prevent the drug from it.[12]

IDENTIFICATION

A proper packaging helps to identify which kind of drug it is. Pharmaceutical products have a marking on it known as packaging marks or pharmaceutical packaging marking. These marks include

- NDC number (National Drug Code number)
- Batch number or lot number
- Manufacturers name and address
- Product name and strength
- Dosage form and route administration
- Control number and serial numbers
- Bar codes

Packaging mark also called libelling on packets plays a crucial role on providing the validation and assurance of the drug. It promotes the safety and efficacy of the product.[13]

Promotion

Packaging laid the ground work for the promotion by

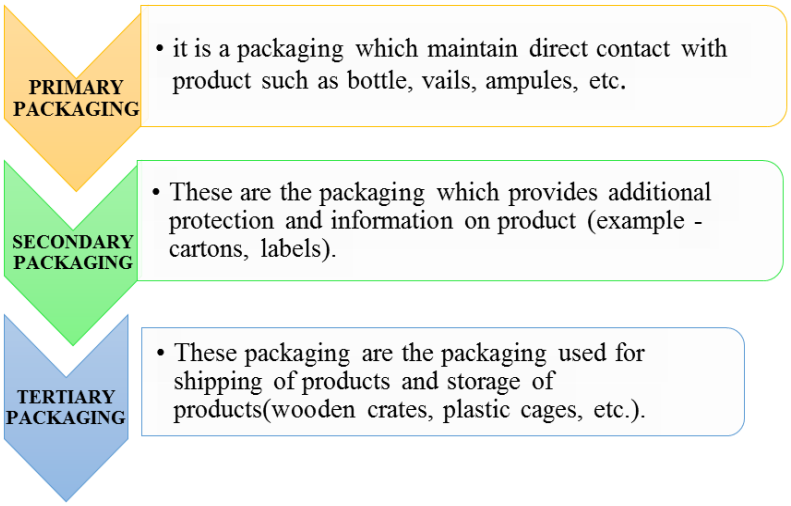
- providing essential information such as dosage instruction, warnings, etc.
- creative packaging style which creates a recognition for brand and easy for customer to use.
- Ensuring the safety of packaging of product, and child resistant packaging.

These are the region why we need packaging.

TYPES OF PACKAGING

Packaging of drug product is divided into mainly three category.[12,14]

- Primary packaging
- Secondary packaging
- Tertiary packaging.



A. Primary packaging

It is a type of packaging which comes in contact with the drug or product. Its main functions are

a. Protect the product.
b. Preserve the product (stability, potency and sterility).

Materials used for primary packaging are

a) Glass bottle or vails
b) Plastic bottle or container (HDPE, PET, etc.)
c) Ampules
d) Tubes (for ointments and cream)
e) Inhalation devices
f) Strip packs (for tablet and capsules)
g) Blister packs
h) Sachets or pouches (for powder and granules)
i) Cartridges
j) Injection syringes.

Primary packaging must follow a strict validation process approved by or set by FDA, European pharmacopoeia, ISO standard for use. It is performed to ensure safety and efficacy of drug product.[16]

B. Secondary packaging

It is a type of packaging which is used to prepare product for distribution, storage, and sale. Secondary packaging includes

a) Cartooning- storing primary packaged product inside it.
b) Labelling- adding label on the cartons.
c) Serializing- assigning unique serial number for tracking and identifying of product.

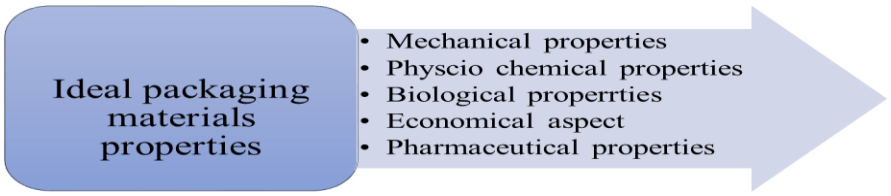
It ensures safety of the product while being transported.

C. Tertiary packaging

It is the outer most layer of packaging. It is also known as bulk packaging. It has several purposes such as protection, convenience, and security. Common example of tertiary packaging pallets, crates, plastic cages. There are no specific guidelines for the tertiary packaging.

FACTOR AFFECTING PACKAGING

I. Characteristic of product.
II. Target of market.
III. Brand identity.
IV. Regulatory requirements.
V. Environmental concern.
VI. Cost and budget.
VII. Consumer convenience.



Mechanical properties

- container should be strong enough to withstand the shock- impact during filling and transportation.
- Container should be heating resistance enough to stand temperature while sterilization.
- Container should be impermeable which should not have leaks, or allow liquids substance to pass through.[17]

Physio-chemical properties

- Container should be non-reactive at any condition with the stored drug.
- Container should be able to protect the light sensitive drug from lights.
- Container should not have any effect to product in colour, taste, and dour.

Biological properties

- Container should not have any toxicological effect.
- Container should withstand the insect attack and prevent from mould attack.
- Container should not affect therapeutic value of drug.

Economical aspect

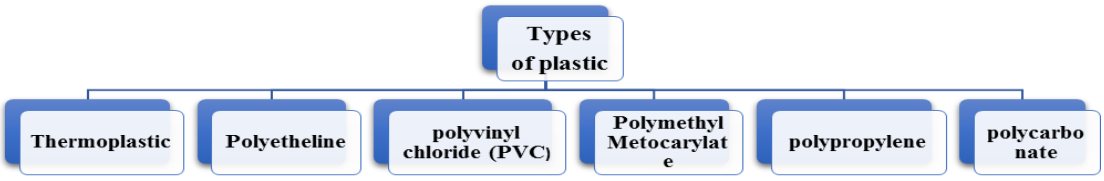
- Cost of packaging should be reasonable and cost effective.

TYPES OF MATERIAL USED IN PACKAGING

I. Plastic
II. Rubber
III. Glass
IV. Metals
V. Paper or cardboard.

Plastic

plastic is a strong, robust, easy to carry, protective, easy to open and use, and temper evident packaging material. Plastic is a group of material which we obtained from natural or synthetic origin, which led to easy to Mold into shape or change into desired shape by applying heat or high temperature. The polymerization is the process in which monomers converted into plastic. Plastics are may be crystalline or amorphous in nature. Crystalline plastic which has low permeability which help in preventing gasses and moisture.[18]



Types of plastic	Details
Thermoplastic [5]	It is a type of plastic which melts and turn into viscous liquid when heat is applied and hardens again when cooldown.
Polyethylene [12]	Melting point about 110°C to 150°C As it has high melting point it is sterilized in the autoclave. It can be divided into two categories HDPE (High density polyethylene) LDPE (Low density polyethylene)
Polyvinyl chloride [14]	It is more flexible than other. It is more permeable to water vapour compared to polyethylene. It is transparent but it is not affected by light. It is used in packaging of eye ointment.
Polymethyl metro-carylate [15]	It is softened at 100°c. It is used for preparation of bottle and tube of pharmaceutical product.
Polystyrene [16]	These plastics are hard, and rigid. Its melting point is at 170°c. In pharmaceutical packaging in bottle and tube.
Polycarbonate [17]	These plastics are very good heat resistance, and have high impact strength.

ADVANTAGE[19]

I. Plastic has a very good affinity for mechanical strength.
II. These are non-breakable.
III. Plastic has a very good tensile strength.
IV. It is clear and transparent in nature.
V. There are a very wide range of plastic are available which can carry the need for pharmaceutical packaging.
VI. Plastics are light material which is great use in primary packaging.
VII. Heat conductance of the plastic is low which make it ideal for packaging.

DISADVANTAGE

I. Vapour may permeable in plastic packaging.
II. Plastic may react with the additives use in the product which may cause damage to drug product.
III. Majority of plastic kind are sensitive of heat.

Validation

validation test for plastic packaging material is different for one regulatory authority to other of different

countries. For packaging the manufacturer follows the pharmacopoeia of that country. The European pharmacopoeia is the strict and have detailed about the test requirements.[16,18]

Quality control Tests for plastics[20]

- **Biological test for plastic**

It is a test performed by using various regulatory guidelines such as USP (UNITED STATES PHARMACOPOEIA), EP (EUROPIAN PHARMACOPOEIA), ISO (INTERNATIONAL ORGANIZATION FOR STANDARDIZATION), ATSM (AMERICAN SOCITY FOR TESTING AND METARIALS).

Biological test for plastic is conducted for the assurance of the packaging and its safety of use. This test includes

(i) Cytotoxicity test: - it evaluates the plastics potential toxicity towards the cells of human or animal.
(ii) Genotoxicity: - it evaluates the plastics potential toxicity towards the genetics of human or animal.
(iii) Pyrogenic test: - it detects the plastics contain any pyrogenic substance may present, which can cause fever.
(iv) Biocompatibility test: - it evaluates the plastic whether it is compactable with the leaving being or not.

The goal of the biological test is to ensure that

a) Plastic used does not affect products efficiency and potency.
b) Plastic used does not affect or harm patient.
c) Plastic used does not affect or contaminate the product.

- **Leakage test[20,22]**

it is a test done for both the injectable and non-injectable products.

Procedure

Select 10 bottle randomly.

⬇

Fill these bottles with water up to the top.

⬇

Fit the closure perfectly.

⬇

Keep these bottles at room temperature at inverted position for 14 hours.

⬇

If there is no leakage then it should be approved.

- **Chemical reactivity**

After preparation of plastic, it may interact and provide a unexpected reaction with the ingredient or drug product. Even if it is in the microquantity of reaction it may provide the change in appearance of drug product or other issues.

Glass

Generally, glass is used in the packaging of powder and sterile product in form of glass vail, ampoules, bottles, cartridges, etc. Glasses are primarily composed of sand or silica, soda ash, limestone, and cullet. Glass is the packaging material used over couple of centuries before advent of plastics. In pharmaceutical packaging till date glasses are able to provide superior quality of protection. It is both economical and chemically inert which provide a ideal character for packaging of pharmaceutical product.

Types of glasses used for packaging or making container

I. Type 1 – Borosilicate glass.
II. Type 2 – Treated soda lime glass
III. Type 3 – Regular soda lime glass.
IV. Type 4 – General purpose soda lime glasses.

Type of glasses	Details
Type 1 – Borosilicate glass.	It is a highly strong and resistant glass. It usually has a high melting point. it is chemically inert than most of other glasses. Mostly used for laboratory glass ware. In packaging it is used for (injection and water for injection) sterile products.
Type 2 – Treated soda lime glass.	Regular soda lime glass is treated to remove surface alkali known as treated soda lime glass. Generally, sulphur is used in the treatment. in pharmaceutical packaging it is used for alkali sensitive product.
Type 3 – Regular soda lime glass.	in pharmaceutical packaging it is used for oily injection and solid dosage form.
Type 4 – general purpose soda lime glass.	In pharmaceutical packaging used in case of non-parenteral product. (oral and tropical use).

ADVANTAGES

I. As glass are chemically inert it is a best packaging material.
II. It has practically no effect on odour and taste.
III. Glasses are not corrosive in nature.
IV. Glasses are generally strong and have rigid structure.
V. It is transparent in nature, special case amber glass.

DISADVANTAGES

I. Glasses are generally fragile in nature.
II. It is a heavier packaging material.

Validation

Glasses validation test is conducted on light transmission and hydrolytic resistance. Glasses classification is provided in European pharmacopoeia and united state pharmacopoeia. There is such classification present in Japanese pharmacopoeia.

Quality control test for glass

I. Chemical resistant for glass container

Chemical resistance for the glass container can be done in two procedures,

a) Powdered glass test[22]

Step-1: - preparation of glass specimen: at first clean and reins it properly, dry it in clean stream of air. Then grind it properly by using motor pestle. Separate the size with the help of size no20 and 50.

Step-2: - washing the specimen: take 10gm of the specimen in a 250ml of volumetric flask. Then wash it with 30 ml of acetone.

Procedure: - take 10 gm of sample then add it to50 ml of water contained inside a 250ml of volumetric flask. Place it inside the autoclave for 30 at temperature 131±2°c. then cool it under the running stream of cold water. Decant and transfer it into another flask. Then again wash it in 15 ml of high purity water. Then again decant it and titrate it with 0.02N sulfuric acid. Use indicator methyl red and record it.

b) Water attack test.

It is the procedure which is only applied to treated sods lime glass container. It is also known as water resistance test.

Test involves

- Exposure of glass sample to the water or humid environment under humid condition
- Measurement of alkali amount released into the water.
- Evaluate the surface of the glass.

This procedure include test like arsenic test, thermal sock test, internal brusting pressure test.

II. Leakage test

Procedure: First clean and dry the glass containers. Then set the container as per the instruction. Then perform following test

i) Vacuum decay test.
ii) Helium leak test.
iii) Pressure decay test.
iv) Dye penetration test.

It is approved if there is no visible leakage is found.

Metals

Metal container which are used for packaging relatively stronger, and have unbreakable property, and opaque. Metals have a very high resistivity to heat. Metals cannot directly used for packaging, without coating the metals can give rise to contamination and chemical reactivity. Special coating technique and coating material developed. Metal are usally used in tertiary packaging, sometimes it is also used as closer (such as aluminium foil). Aluminium foil also sometimes used as primary packaging for some tablets and capsule. Tin sheets are also used to store pharmaceutical product such as ointment, powder, tablet, and capsule. Aerosol are stored in the alloy of metals, as they can withstand high pressure when packaging.

Validation

Metals validate through the ISO. It means all the validation test are conducted as per the guideline of or description of ISO.

Rubber

Rubber contains several ingredients, one of which is elastomer. Rubber is mainly used as the closer for the covering the drug container after the filling process. Rubber property why it is used for packaging

I. Elasticity.
II. Chemical resistance.
III. Impermeability and sterilization.

Rubber application in pharmaceutical packaging stopper for vails, seals for syringes and cartridges, rubber closer for infusion system.

Validation

Rubber packaging validate by following the strict regulatory requirements of USP (united states pharmacopoeia), EP (European pharmacopoeia), and FDA (Food and Drug Administration) guidelines. International standards have also been established (ISO 8871).

PAPER AND CARDBOARD

Papers are prepared from organic, natural fibres which is cellulose. It has a diverse application in pharmaceutical packaging such as cartons. The paper can also use to prepare sachets for powder and granules. Package for the patches is prepared.[26,27]

ADVANTAGE

I. These are low cost
II. These are easy to print and libelling.
III. These are easy to use.
IV. These are lighter material.
V. These are bio-degradable.

DISADVANTAGE

I. These are moisture sensitive
II. These are porous.

Validation

Validation of paper packaging indicates the safety and materials are meet the standard to maintain the quality of product. It should be according to the standard of ISO, ASTM or pharmacopoeia standard.[20,21,22]

CONCLUSION

The pharmaceutical industry is significantly dependent on packaging since it protects, preserves, and complies with regulatory standards for its products. Furthermore, attractive packaging can boost customers' trust in the company.

Consider the following while designing pharmaceutical packaging

Hygiene: While preserving a hygienic packaging process, robotic packaging automation can help reduce human interaction.

Environmental factors: The product's packaging should protect it from light, moisture, and air. High-barrier aluminium foil can provide a robust defence against these chemicals.

Quality: The product should be protected from breakage and damage by its packaging, which should also maintain the product's physical characteristics, including its dosage. It should also stop chemical changes and degradation of quality.

Compliance: Packaging must adhere to stringent regulatory criteria.[27]

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