Unit-V 10 Hours

Cosmetics: Formulation and preparation of the following cosmetic preparations: lipsticks, shampoos, cold cream and vanishing cream, tooth pastes, hair dyes and sunscreens.

Pharmaceutical Aerosols: Definition, propellants, containers, valves, types of aerosol systems, formulation and manufacture of aerosols, Evaluation of aerosols, Quality control and stability studies.

Packaging Materials Science: Materials used for packaging of pharmaceutical products, factors influencing choice of containers, legal and official requirements for containers, stability aspects of packaging materials, quality control tests.

- Cosmetic" means any article intended to rubbed, poured, sprinkled or sprayed on or introduced into, human body or any part thereof for cleansing, beautifying, promoting attractiveness, altering the appearance and includes any article intended for use .
- Cosmetics arise from a Greek word 'kosmeticos' meaning 'adorn'.
- If any material used for beautification or improvement of appearance is known as cosmetics.
- They may be applied to skin, hair and nails for the purpose of covering colouring, softening, cleansing, nourishing, and protection.
- Cosmetics are intended to be applied externally. They include, but are not limited to, products that can be applied to the face: skin-care creams, lipsticks, eye and facial makeup, towelettes, and colored contact lenses; to the body: deodorants, lotions, powders, perfumes, baby products, bath oils, bubble baths, bath salts, and body butters; to the hands/nails: fingernail and toe nail polish, and hand sanitizer; to the hair: permanent chemicals, hair colors, hair sprays, and gels.

A subset of cosmetics is called "makeup", refers primarily to products containing color pigments that are intended to alter the user's appearance. Manufacturers may distinguish between "decorative" and "care" cosmetics.

Cosmetics that are meant to be used on the face and eye area are usually applied with a brush, a makeup sponge, or the fingertips.

- Most cosmetics are distinguished by the area of the body intended for application.
- Cosmetics can be also described by the physical composition of the product. Cosmetics can be liquid or cream emulsions; powders, both pressed and loose; dispersions; and anhydrous creams or sticks.

ADDITIVES

1. Emollients
2. Oil , fats and Wax
3. Humactant
4. Preservatives
5. Binders
6. Surfactant
7. Perfume
8. Color

Emollients

The word emollient is a Latin derivation and implies a material that softens and smooths the skin both to the touch and to the eye.

Emollients should have the effect of reducing the clinical signs of dryness, such as roughness or scaling, and improving sensations, such as itching and tightness.

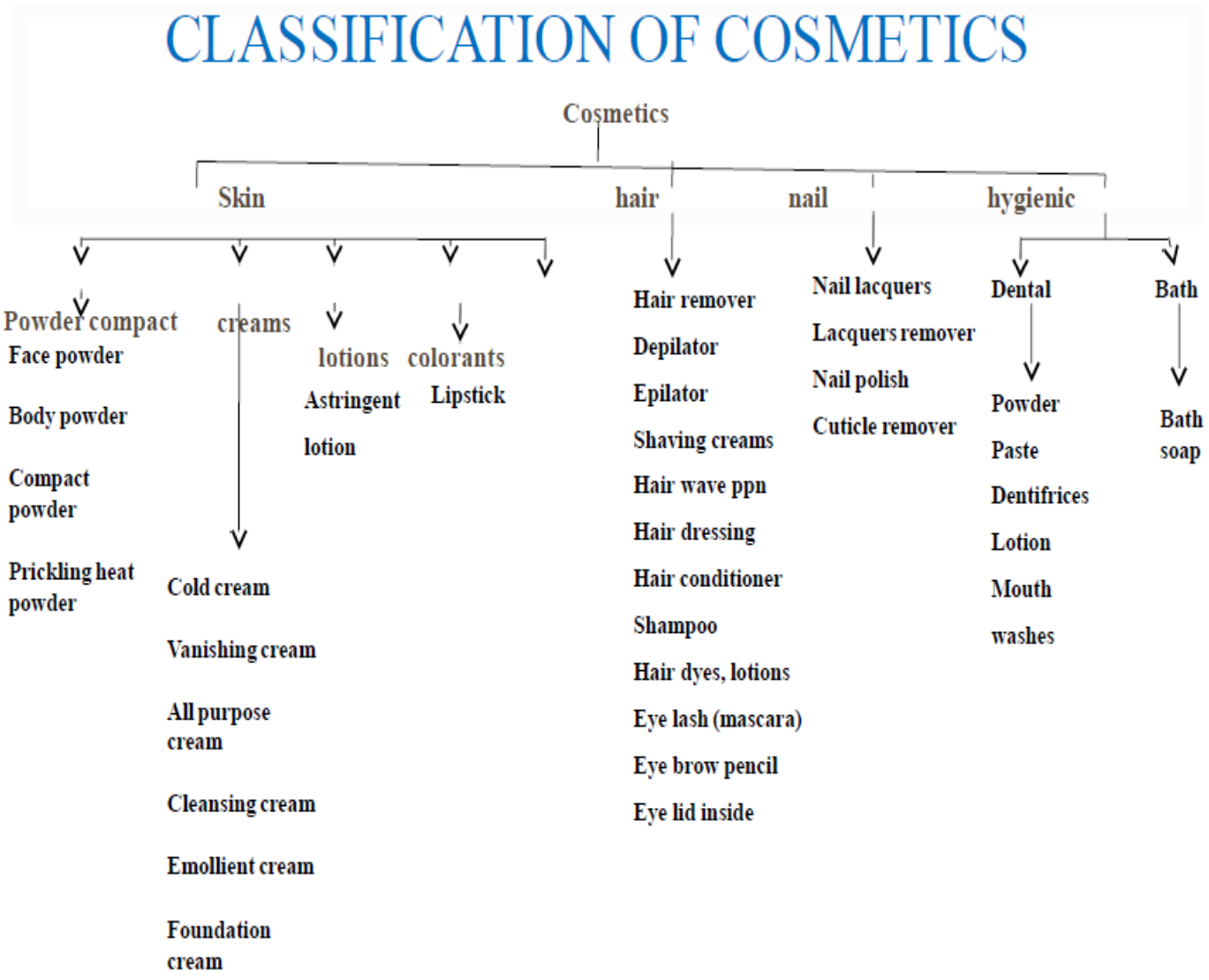
The constituent products of emollients vary hugely, however, all will have some quantity of lipid in them. Lipid is a broad term used to describe fats, waxes and oils

Mode of action

Emollients work to moisturise the skin by increasing the amount of water held in the stratum corneum

Specifically, depending on the constituents of the emollients, they work either by occlusion, 'trapping' moisture into the skin (which slows the evaporation of water), or in an 'active' way by drawing moisture into the stratum corneum from the dermis.

Pharmaceutical Aerosols: Definition, propellants, containers, valves, types of aerosol systems, formulation and manufacture of aerosols, Evaluation of aerosols, Quality control and stability studies.



INTRODUCTION

The aerosol container is referred to as a pressurized package in which the therapeutically active drug is dissolved or suspended in compressed or liquefied gas. The delivery of therapeutically active drug in the form of spray or foam or solid stream is dependent on the ability of the liquefied or compressed gas.

The advantages of aerosols are as follows

- ❖ The drug sensitivity to the effect of oxygen or moisture is protected and stability is enhanced.
- ❖ The drug can be directly applied to the affected areas.
- ❖ Administration of drug by aerosol is a rapid process.
- ❖ It protects the drug from gastrointestinal tract degradation.
- ❖ Hepatic first pass metabolism is avoided.
- ❖ Aerosols are used for both systemic and local application.
- ❖ Easy to apply.
- ❖ A sterile dose of drug is dispensed and also the contamination of drug is prevented.

The delivery of contents of aerosol depends on its valve assembly, containers, and actuators as well as on the propellant. The two components of aerosol are product concentrate and propellant. The product concentrate contains the therapeutically active ingredients. The propellant having vapour pressure greater than atmospheric pressure at 40^{o}C (105^{o}F) is responsible for the development of proper pressure in the container to expel the product concentrate in the desired form like spray, mist, solid, foam, stream etc. Propellant can also act as the solvent or vehicle for the product concentrate. Thus aerosol components are classified as shown in Figure 1 and Figure 2.

LIST OF FIGURES

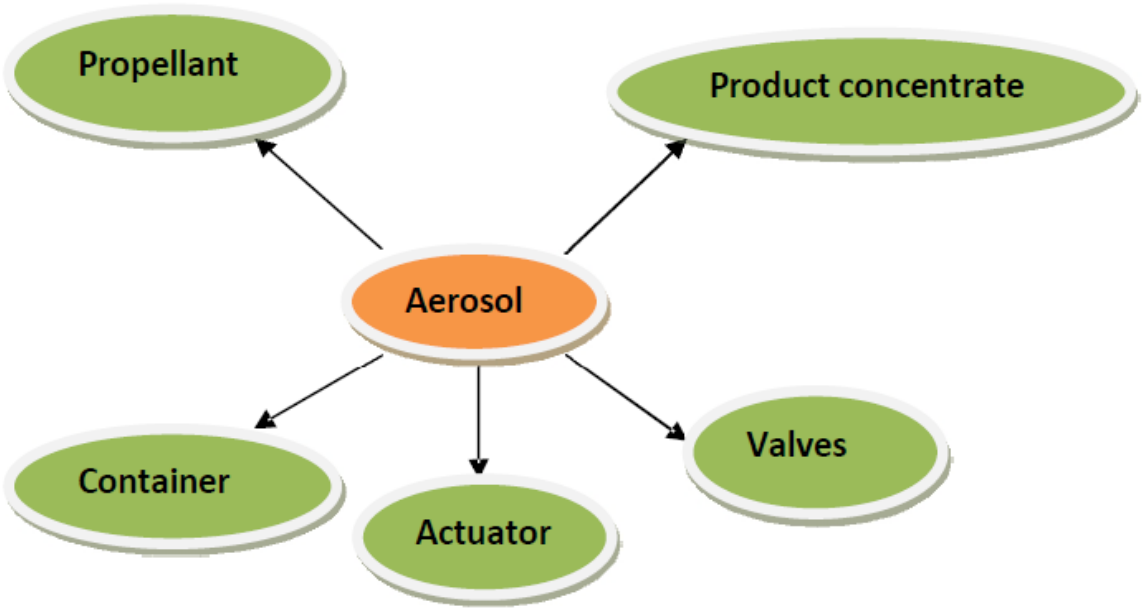


Figure 1: components of Aerosol

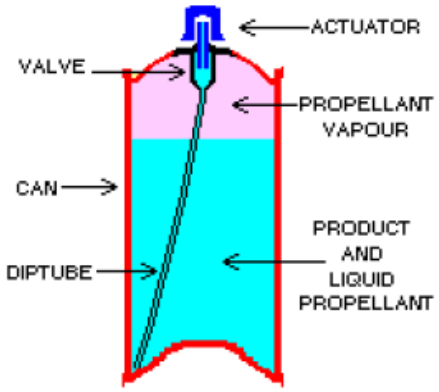
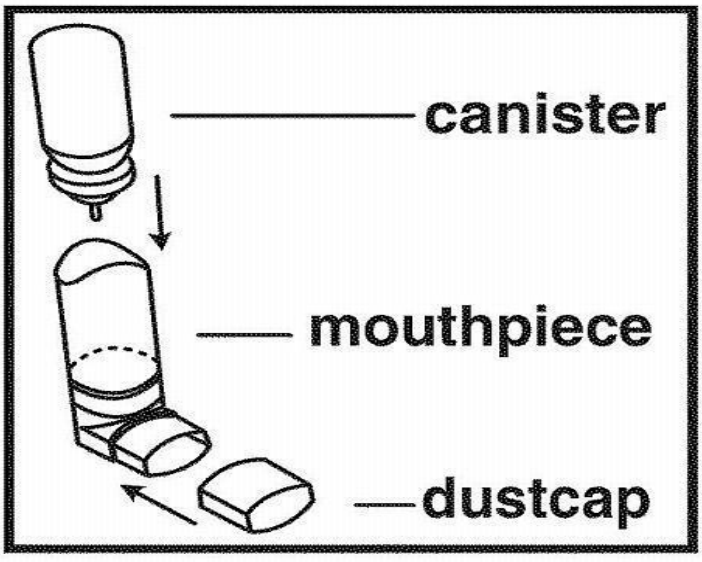
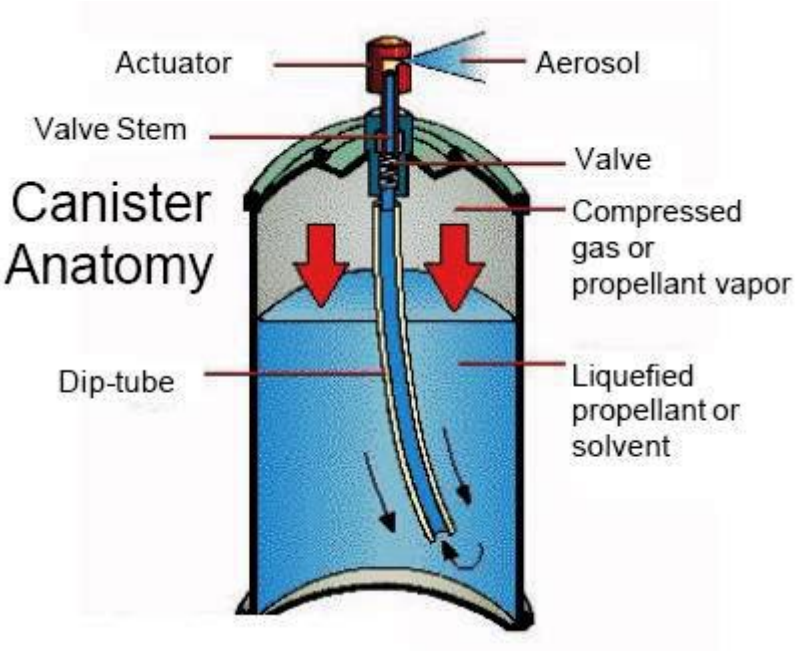


Figure 2: components of Aerosols[9]





- •An aerosol is a suspension of fine solid particles or liquid droplets in a gas.
- •NATURAL AIROSOLS: clouds, fog and smoke.
- •Pharmaceutical aerosol is a suspension of fine solid drug particles or liquid drug droplets in a carrier gas/propellant.
- •Also known as pressurized dosage form as carrier gas/propellant is compressed or liquefied under pressure to expel the contents from the container as a fine solid particles or liquid mists.
- •Also known as Inhalational Drug Delivery systems (IDDS) or inhalants as drug is inhaled through nose / mouth to the lungs.
- •Commonly used for respiratory disease (asthma) and lung disease (emphysema).
- •They are intended for local action in the nasal / throat area, and systemic action also when drugs are absorbed from the lungs in to the blood stream.
- •ALL PHARMACEUTICAL AEROSOLS ARE NOT INHALATIONAL. •E.g Topical aerosol sprays: Local anesthetics, pain reliever spay.

COMPONENTS OF AEROSOL PACKAGE

1. Drug Product Concentrates
2. Propellant.
3. Container.
4. Valve and actuator.

(1) Drug Product Concentrates

•Based on the drug product formulation as solution, emulsion, suspension or powder we can have Solutions aerosol, emulsion aerosol or Suspensions aerosols .

•Foams are produced when the product concentrate is dispersed throughout the propellant and the propellant is in the internal phase; i.e., the emulsion behaves like o/w emulsion

PROPELLANT

The development of pressure within the container by the propellant causes the opening of valve which expels the product by atomisation or foam formation.

Types of propellant

Depending on the route of administration and use, the propellant can be classified as given in Table1

Table 1: Types of propellant

Application	Name of propellant
For oral and inhalation	**Fluorinated hydrocarbons** Di-chloro di-fluro methane (propellant 12) Trichloromonoflouromethane (propellant 11) Di-chloro tetra-fluro ethane (propellant 114)
Topical preparation	Propane, Butane, Isobutane
Compound gases	Nitrogen,Carbon dioxide, Nitrous oxide

Table 2: Pressure limitations of aerosol container

Contain Material	Maximum Pressure (psig)	Temperature (^{0}F)
Tin -plated steel	180	130
Uncoated glass	< 18	70
Coated glass	< 25	70
Aluminum	180	130
Stainless Steel	180	130
Plastic	< 25	70

Chlorofluorocarbon (CFC) propellants

The basic characteristics of propellants are chemical inertness, lack of toxicity, lack of flammability and explosiveness. Due to the presence of these characteristics, the chlorofluorocarbon (CFC) propellants P-11, P-12, and P- 114 were used in aerosol products for several years. Now a day their uses have been declined as they cause the depletion of ozone layer. But due to their relatively low toxicity and inflammability, they are still use in low amount in the treatment of asthma and chronic obstructive pulmonary disease (COPD). P-134a and P-227 are now been developed and are being incorporated in aerosol formulations in place of P-12.

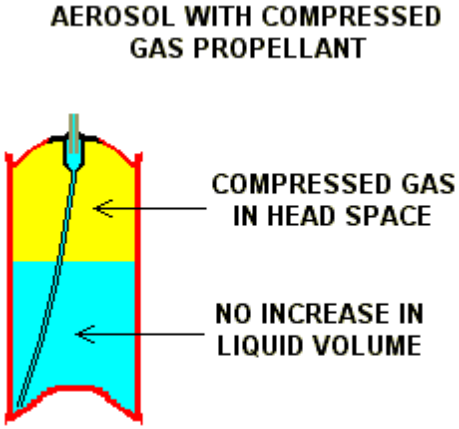
Hydrocarbons Propellants

The environmental acceptance, low toxicity and nonreactivity are the characteristics of hydrocarbons propellants allowing them to be used as the propellant. Hydrocarbons are used in the preparation of water based aerosols as they are not susceptible to hydrolysis due to the absence of chlorine. Since they are immiscible with water, so they remain on the top of water. They provide the force to push the contents out of

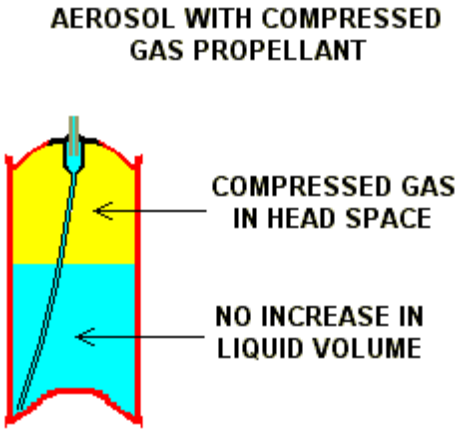
the container. The disadvantage of Hydrocarbon propellant is flammability, explosiveness. It is being reduced by using a blend of propellant. Also the use of vapour tap valve reduces flammability.

Compressed gas propellants

The use of compressed gas like Nitrogen, Nitrogen dioxide and Carbon dioxide as propellant dispenses products in the form of fine mists, foams or semisolid. It produces fairly wet sprays and the foams are not as stable as produced by the liquefied gas propellant. Unlike the aerosol prepared with liquefied gas propellant, there is no propellant reservoir. The compressed gas propellant is contained in the headspace of the aerosol container which forces the product concentrate out of the container. So, higher gas pressure is required in this aerosol. This aerosol finds its application to dispense food products, dental creams, hair preparation and ointments.



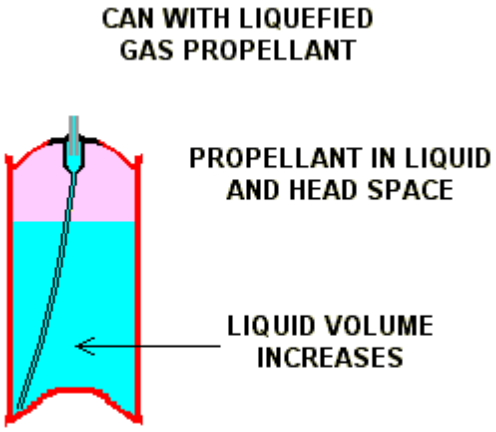
- •Propellants are chemicals with a vapor pressure greater than atmospheric pressure at a temperature of 40˚C.
- •Propellants are simply compressed gas or liquid under pressure that can readily be vaporized into the desired pressurized gas.
- •It is one of the most important components of the aerosol package (It is said to be the heart of the aerosol).
- •It also serves as a solvent for certain active ingredient.
- •It provides the necessary force to expel the contents; it causes the product to be dispensed as foam or mist/spray, depending on the formulation and the type of valve employed.



Compressed gas propellants really only occupy the head space above the liquid product in the can.

When the aerosol valve is opened the gas 'pushes' the liquid out of the can.

The amount of gas in headspace remains the same but it has more pressure space, and as a result the drop during the life of the can. CNN: Eg Carbon dioxide. Nitrous oxide & NITROGEN



As the product is used up, some of the liquid propellant turns to gas and keeps the head space full of gas, pressure in the can remains essentially constant and the spray performance is maintained throughout the life of the aerosol.

PROPELLANTS…..

1. Compressed gas

- –Pressure falls during use;
- –doesn't have any environmental problems

2. Hydrocarbon propellants

- •Most common
- •Cheap,
- •Good solvent
- •Doesn't have any environmental problems (no ozone depletion).
- •Bad taste,
- •Flammable

3. Chlorofluorocarbons

- •Most common
- •Cheap,
- •Good solvent
- •Environmental problems (depletes ozone layer)
- •FDA banned use of CFC
- •Hydrofluorocarbons (HFA
- •Replaced CFC
- •No Environmental problems (does not depletes ozone layer).
- •Very costly.

Principle of releasing out of product concentrates from container

- Liquefied propellant or propellant mixture exists in equilibrium with the product concentrate in a sealed aerosol container. The liquefied propellant vapourises and occupies the upper portion of the aerosol container. As the liquefied propellant exists in equilibrium with the propellant in the vapour phase in an aerosol container, so a constant pressure is maintained within the aerosol container. Hence, it is called as a pressurised aerosol container. The pressure exerted by the propellant is called as vapour pressure, measured in psig; is the characteristic of specific propellant. Upon the actuation of the valve, the pressure exerted by the propellant is distributed equally in all direction in the aerosol container, forcing the product concentrate up the dip tube and out of the aerosol container. As the vapour pressure of the propellant in air is lower than inside the aerosol container, so the propellant evaporates on reaching the air and product concentrates dries up as dry particles.

CONTAINERS

Aerosol containers are generally made of glass, metals (e.g., tin plated steel, aluminium, and stainless steel), and plastics. The materials of aerosol container to be selected should be able to withstand high pressure. Thus the aerosol containers must withstand pressure as high as 140 to 180 psig (pounds per sq. inch gauge)

at 130 0F. Also, the cost, compatibility of the material with the formulation is to be considered. The pressure limitation of aerosol container is as given in Table 2.

Glass

One of the materials is glass whose brittleness limits its use in aerosol containers. Thus glass containers are used in lower pressure and when low amount of propellant are in use such as if the pressure is less than 25psig and propellant content is less than 15%. In order to protect the glass containers against breakage due to high pressure, it is to be coated with plastic coating in two layers. Epoxy and vinyl resins can be used as linings. Vinyl resins are not resistant to high temperature of the steam about 200 0F. But epoxy resins are resistant to steam. These coatings are suitable for low pH water based products.

Metals

Tinplated steel: It provides light and inexpensive aerosol container. The both sides of the tin container are electroplated with sheets of steel plates so as to protect the inside of the container from corrosion and also to prevent the interaction between the tin and the formulation. Oleoresin, phenolic, vinyl, or epoxy coatings are used as the coating materials. The tin plated steel containers are used in topical aerosols.

Aluminium: The aluminium containers are light weight and are less prone to corrosion than other metals. Aluminium is used in most metered dose inhalers (MDIs) and many topical aerosols. Epoxy, vinyl, or phenolic resins coatings are done on aluminium containers to reduce the interaction between the aluminium and the formulation. The seamless aerosol containers manufactured by an impact extrusion process have greater safety against leakage, incompatibility, and corrosion. The container themselves available in sizes ranging from 10 ml to over 1,000 ml.

Stainless steel: As it is strong and resistant to corrosion; no coating is required. Also it can withstand high pressure. The drawback is expensiveness which restricts its sizes to small sized containers.

Plastic

As plastics are highly permeable to vapours and air like oxygen, so interaction with the formulation may occur and also may lead to oxidative degradation of the formulation. Polyethylene tetra phthalate (PET) container as used for some non pharmaceutical products.

VALVES

A valve delivers the drug in desired form and regulates the flow of product concentrate from the container. The valve should be able to withstand the pressure encountered by product concentrate and the container, should be corrosion resistant. The two types of valves available are continuous spray valve and metering

valve. The classifications of aerosol valve components are given in Figure 3.

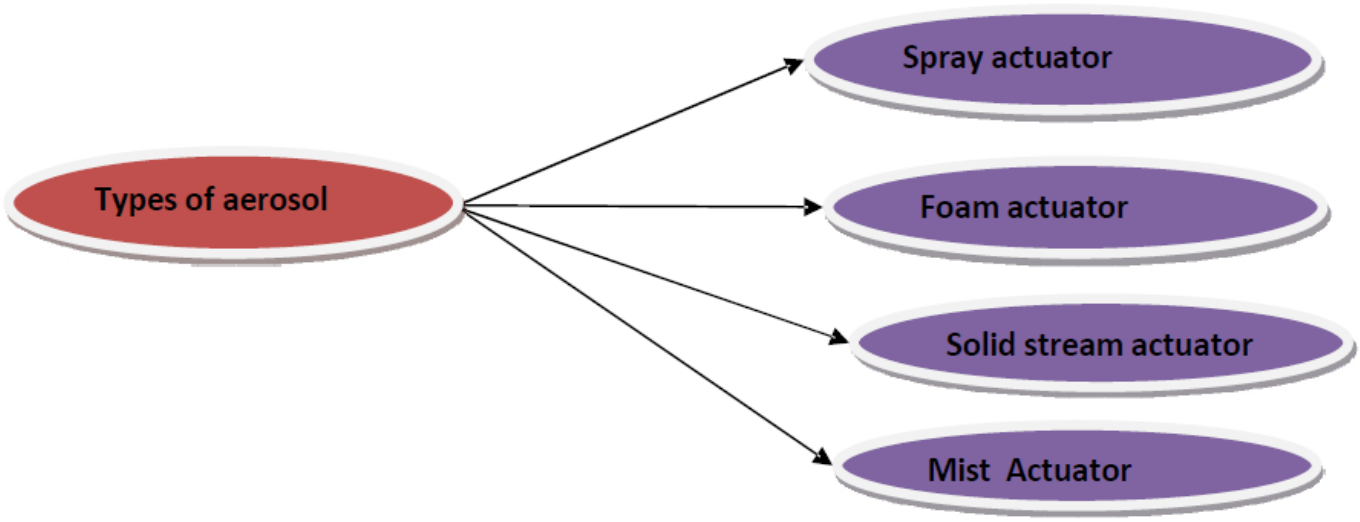
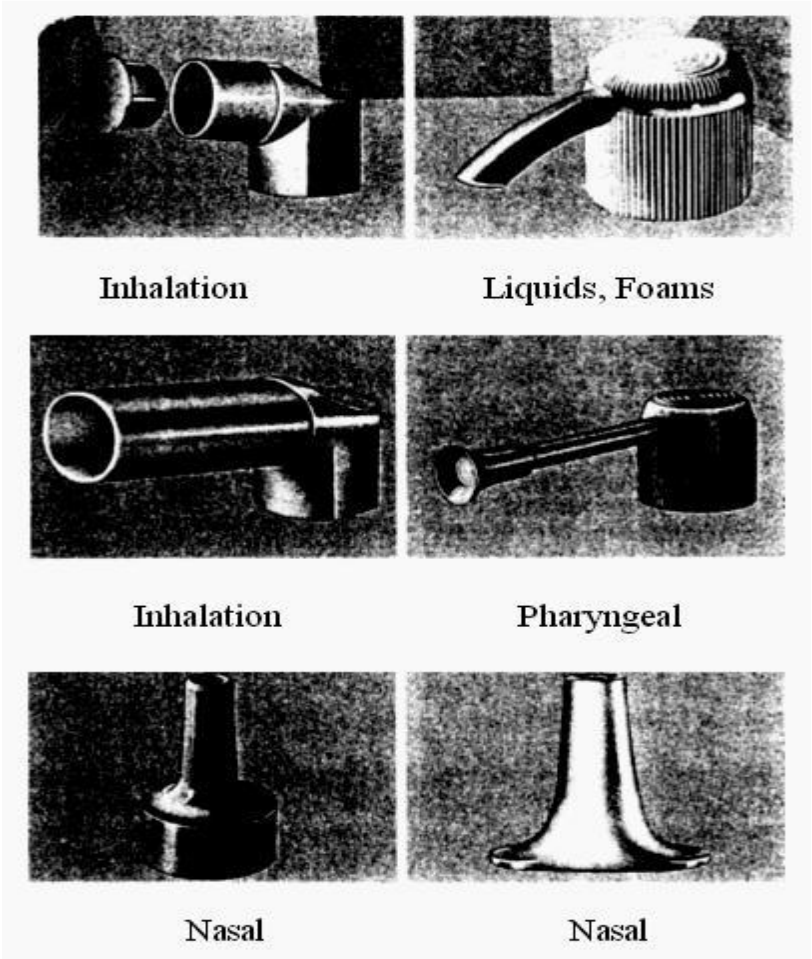
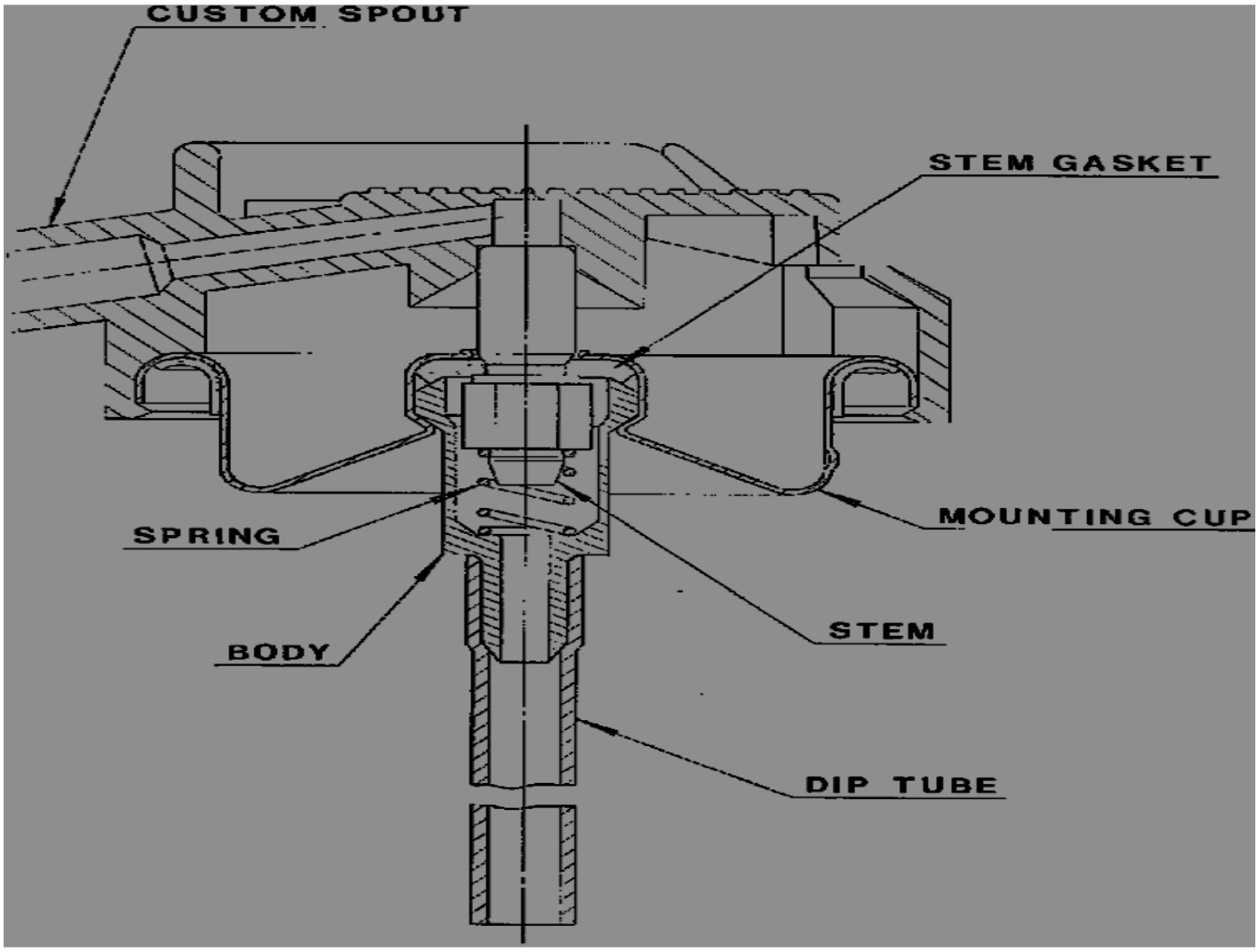


Figure 3: Types of actuator

Actuator: It is the button which the users press to activate the valve assembly and controls the easy opening and closing of valve; also directs the spray to the desired area. The actuator contains orifices of varying size and shapes as well as the expansion chamber which determines the type and quantity of propellant used, actuator design and the physical characteristics of the emitted product concentrate in the form of spray or foam, especially in the case of inhalation aerosols where it is necessary to control the proper particle size of the product concentrate. The types of actuator are given in Figure 4.




Nasal
Nasal
Foams
Dental Spray


CUSTOM SPOUT
STEM GASKET
MOUNTING CUP
SPRING
BODY
STEM
DIP TUBE

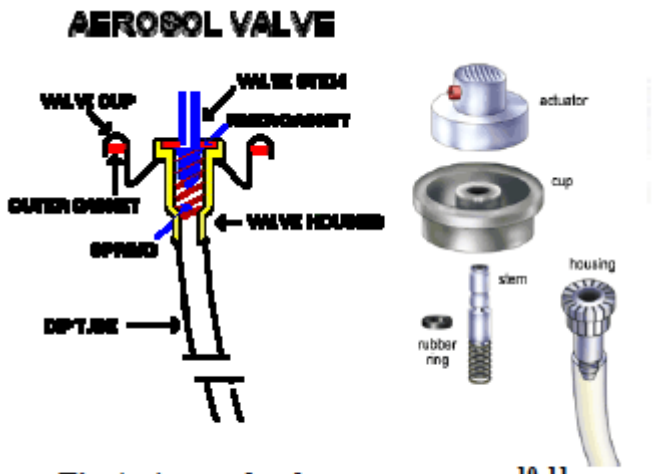
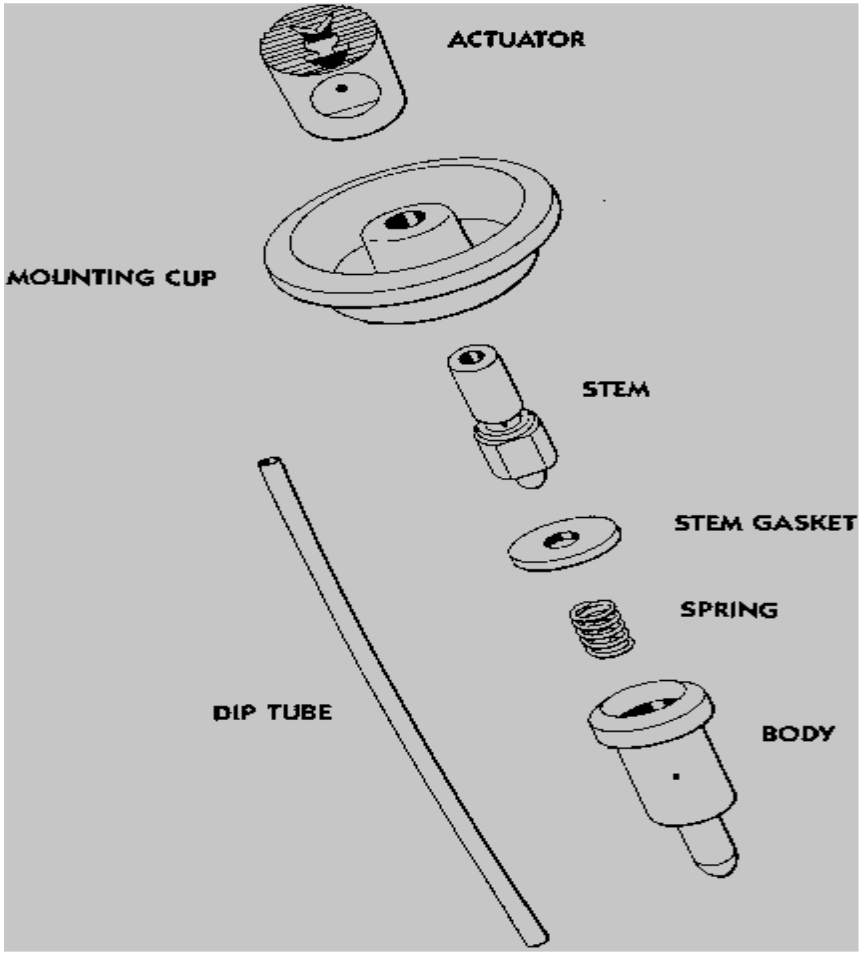


Fig.4: Aerosol valve components [10,11]



Stem: The actuator is supported by the stem and the formulation is delivered in the proper form to the chamber of the actuator by the stem. It is made up of Nylon, Delrin, Brass and Stainless steel.

Gasket: The stem and valve are placed tightly in their place by the gasket and the leakage of the formulation is prevented by gasket. It is made up of Buna N and Neoprene rubber.

Spring: The gasket is held in its place by the spring and also helps to keep the valve in closed position when the pressure is released upon actuation of the formulation.

Mounting Cup or Ferrule: The Mounting cup or Ferrule is generally made up of aluminium which serves to place the valve in its position, and attached to the aerosol container. As the underside of the mounting cup/ Ferrule is exposed to the contents of the container, so it is to be compatible with the contents so as to prevent any interaction. It may be coated with an inert material such as vinyl coating as it prevents any interaction with the contents also corrosion of aluminium is prevented.

Housing or Valve body: The Housing or Valve body located directly below the Mounting cup or Ferrule is made up of Nylon or Delrin work to connect the dip tube and the stem and actuator. The rate of delivery of product and the desired form in which the product is to be emitted is determined by its orifice.

Dip Tube: The dip tube is made up of polyethylene or polypropylene extends from the housing body or valve body down into the product concentrate works to bring the formulation from the container to the valve. The inner diameter of the dip tube depends on the viscocity and the desired rate of delivery of the product. The inner diameter of the dip tube increases with an increase in the viscocity of the formulation. For less viscous solutions, the inner diameter ranges from 0.12 inch to 0.125 inch. While for viscous solution, inner diameter is as large as 0.195 inch.

TYPES OF INHALERS

Depending on the physical state of the dispersed phase and continuous medium, inhaled drug delivery system is classified into three principle categories

1. Pressurised metered dose inhalers (pMDIs)

2. Dry powder inhalers (DPIs)

3. Nebulisers.

1. Metered dose inhaler (pMDIs)

The pressurised metered dose inhalers (pMDIs) as shown in Figure 5; are composed of a canister, and actuator, and sometimes a spacer. The canister is composed of a metering dose valve with an actuating stem. The formulation (containing the active ingredient i.e. drug, a liquefied gas propellant, and a stabilizer) is present in the carnister. The drug may be suspended or dissolved in the liquefied gas propellant. Upon actuation, the metering dose valve is opened which releases a single metered dose of medication alongwith the liquified gas propellant to spray out of a carnister. This process is called cavitation. The liquefied gas propellant is volatile in nature; breaks down into liquid droplets which evaporates rapidly, and the dried micronized drug are inhaled to the lung. But the pressurised metered dose delivery suffers from various drawbacks as follows

a) Till 1990s, various chlorofluorocarbons (CFC) were used as the propellant; it caused depletion of ozone layer; so later it was replaced with hydrofluorocarbons. Hydrofluorocarbons suffer from the drawback of greenhouse effect.

b) As pMDIs is pressurised, it emits the dose at high velocity and gets deposited in the oropharynx.

c) The propellant and the cosolvent may extract some of the organic compounds from the device components and leads to chemical degradation.

d) A careful coordination of actuation and inhalation are required.

e) High chances of pharyngeal depositions.

Later on, the formulation related short comings are reduced by Dry powder inhalers (DPIs).

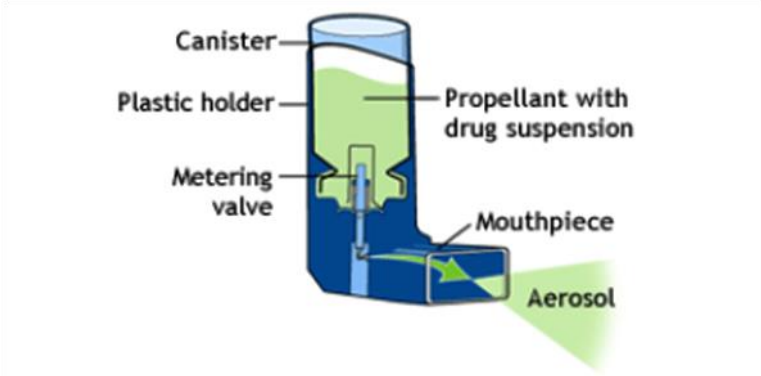


Figure 5: Pressurised metered dose inhalers (pMDIs)

2. Dry powder inhalers (DPIs)

The DPIs are advantageous than pMDIs due to the following reasons:

a) DPIs require little or no coordination of actuation and inhalation as they are activated by patient's inspiratory airflow.

b) DPIs don't extract organic compounds from the device components in contrast to the pMDIs; and the chances of chemical degradation are lesser than pMDIs.

c) The rate of drug delivery is better than pMDIs.

d) DPIs are efficient, more stable than pMDIs and easier to use than pMDIs.

DPIs are composed of micronized powdered drug particles. The micronized powdered drug particles (of sizes < 5μm) are mixed with much larger sugar particles (of size < 30 μm) eg. Lactose monohydrate. The smaller drug particles forms loose aggregate with lactose monohydrate. The micronized powdered drug particles have high cohesive force, so they have a tendency of adhering to each other. The addition of large particle sized lactose monohydrate reduces the cohesive force of the micronized drug particles and form loose agglomerate with the micronized drug particles. It helps in an easy deaggregation of the agglomerates, upon inhalation, the agglomerates get broken down into its constituent particles, with the help of mechanical devices such as screens, on which the particles agglomerates impact. It releases the smaller sized powdered drug particles into the air to be inhaled to the lung. The larger sized lactose monohydrates particles are left behind in the device and in the mouse throat.

The DPIs are classified into two types

ü Unit dose devices

ü Multi dose devices

3. Nebulisers

Nebulizer is a device used to administer aerosolised medication in the form of a mist inhaled into the lungs. Nebulizers use oxygen, compressed air or ultrasonic power to break up medical solutions and suspensions into small aerosol droplets called mists that can be directly inhaled from the mouthpiece of the device. Nebuliser produce a mist of drug containing water droplets for inhalation. The drug is present either in solution form or suspension form in the nebulizer. It is usually of two types:

Electronic nebulizer and Jet or ultrasonic nebulizer. Jet or ultrasonic nebulizer uses a source of pressurised air to blast a stream of ait through a drug containing water reservoir, producing water droplets. In contrast, electronic nebulizers develop mechanical vibration to produce water droplets. The nebulisers are generally used for the treatment of acute conditions (e.g. acute asthma, respiratory infection) or in those patients who have difficulties using other respiratory dosage forms.

Some of the marketed products of nebulizers are as follow:

Omron Microair Nebulizer, DeVilbiss DeVilbiss PulmoMate Compressor / Nebulizer

TYPES OF AEROSOL SYSTEMS

The aerosol systems are classified as shown in Figure 6

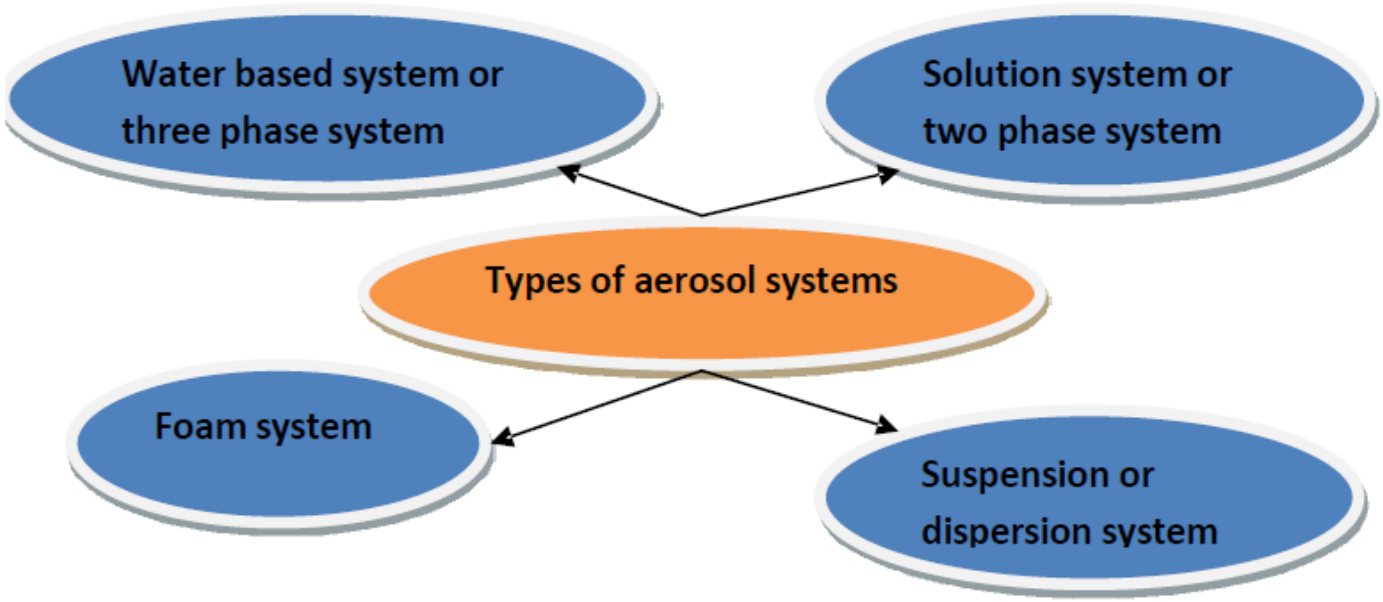


Figure 6: Types of aerosol system

Solution system or two phase system

It is also called two-phase system as it contains both the vapour and the liquid. Based on the desired spray, the propellant can be used single or a mixture of propellants can be used. Propellant 12 is added alone or in mixture. If propellants having vapour pressure lower than propellant 12 is added to propellant 12, a reduction of vapour pressure is achieved but bigger sized aerosol particles are obtained. Also bigger sized aerosol particles are obtained on addition of cosolvents like ethyl acetate, propylene glycol, ethyl alcohol, glycerine and acetone. No other solvent is required if the drug is soluble in the propellant. The solution

system is administered in topical application. Some of the commonly used propellant combinations in solution systems are propellant 12/11 (30:70), propellant 12/114 (45:55), propellant (12/114) (55:45).

Water based system or three phase system

In the water based or three phase system, large quantity of water is present to solubilise the contents. The water is immiscible with the propellant. Generally water based system is a three phase system consisting of a water phase, vapour phase and the propellant. So, the solubility of propellant in water can be increased by adding a cosolvent such as ethanol and also by adding surfactants at a range of composition 0.5% to 2.0 %. The propellant composition ranges from 25 to 60%. The nonpolar surfactants such as esters of Oleic acid, palmitic acid, stearic acids are more preferred than the polar surfactants. The surfactants act by reducing the interfacial tension existing between the water phase and the propellant, and thus produce a uniform dispersion by increasing the solubility of the propellant in the water. The drawback associated with water based system is that the addition of ethanol, not only increases the solubility of propellant in water, but also increases its flammability. The presence of large quantities of water delivers content in liquefied form. The recent advancement is the vapour tap valve and the aquasol valve. In aquasol system, water or the mixture of water and alcohol are used to dissolve the drug. The addition of alcohol increases the solubility of propellant in water. Aquasol system is advantageous than water based system as a vapourised propellant is delivered rather than the liquefied propellant. The vapourised propellant delivers small sized, fine particles and dried contents in the form of fine mist or spray to the site of action. Moreover, the vapourised propellant is non-flammable in nature.

Suspension or dispersion systems

Suspension or dispersion system is the dispersion of the active ingredients in the propellant or the mixture of propellant by adding surfactants or the suspending agents.

Foam system

The liquefied propellant is emulsified. Aqueous or nonaqueous vehicles, propellant and the surfactants are its ingredients. Foam system is further classified as aqueous stable, nonaqueous stable and the quick breaking foam.

Aqueous stable foams: The aqueous stable foam consists of propellant in the range of 3.0 to 4.0 %. A dry spray is produced by the propellant .As the concentration of propellant goes on increasing, more and more contents are delivered in dried form. As the propellant is present in the internal phase, so the concentration of propellant is less. It finds its application in steroid antibiotics.

Non aqueous stable foams: The nonaqueous stable foam contains glycol as the emulsion base and is used as the emulsifying agent.

Quick breaking foams: Here the external phase is propellant. The product will come out as foam which soon merges to form liquid. This type of system can be applied to small area or larger surface. These are used for topical application. Cationic or anionic or non-ionic surfactants are used in the formulation.

Thermal foams: The aerosol which is delivered in the form of foam upon the application of heat is called thermal foam. They are used in shaving creams.

MANUFACTURING OF PHARMACEUTICAL AEROSOLS

The manufacturing of aerosol consists of three types of apparatus

Cold filling apparatus: It consists of an insulated box fitted with copper tubings. The insulated tubings are filled with dry ice or acetone. The copper tubings increase the surface area and cause faster cooling. The hydrocarbon propellant is not to be stored in the copper tubings as it might cause explosion.

Pressure filling apparatus: Pressure filling apparatus consists of a metering burette capable of measuring the amount of propellant to be filled to the aerosol container. The propellant is added through the inlet valve present to the bottom of the valve under its own vapour pressure. A cylinder of nitrogen or compressed gas is attached to the top of the valve and the pressure of nitrogen causes the propellant to flow to the container through the metering burette. The propellant flows to the container stops when the pressure of the flowing propellant becomes equal to the pressure of the container.

Compressed gas filling apparatus: A compressed gas propellant is used. As the compressed gas is under high pressure, so the pressure is reduced by pressure reducing valve. A pressure of 150 pounds per square inch gauge is required to fill the compressed gas propellant in the aerosol container. The product concentrate is placed in the pressure gauge and the valve is crimped in its place. The air is evacuated. The filling head is inserted into the valve opening. Upon the depression of the valve, the compressed gas propellant is allowed to flow into the container. The compressed gas stops flowing when the pressure of the compressed gas flowing to the container from the burette becomes equal to the pressure within the container. In case of increasing the solubility of the gas in the product concentrate and also when an increased amount of compressed gas is required, carbon dioxide and Nitrous dioxide is used. The container is needed to be shaken during and after the filling operation to enhance the solubility of the gas in the product concentrate.

The **filling** of aerosol product into the container is by two methods:

Cold filling method: Two methods are involved:

1. In the first method, the product concentrates are chilled to a temperature of – 30 to – 400 F. The chilled product concentrates are added to the chilled aerosol container. The chilled propellant is added through an inlet valve present under side of the valve of the aerosol container.

2. In the second method, both the product concentrate and the propellant are chilled to – 30 to – 400 F. Then the mixture is added to the chilled container.

In both the above methods, after the aerosol containers are filled, the valves are set in its place and the filled aerosol containers are passed through a water bath in which the contents of the containers are heated to 130 0 F to test for leaks and strength. Then the containers are air dried, capped and labelled. Cold filling method is advantageous for the filling of metering valve containing aerosol container. The pressure filling method is more prominant than cold filling method as most of the formulations cannot be cooled to very low temperatures

Pressure filling method: The product concentrate is filled to the aerosol container through the metering pressure filling burette at room temperature. The propellant is added through the inlet valve located at the base of the valve or under the valve after the crimping of valve. The flow of propellant to the aerosol container continues till the pressure of the filling propellant becomes equal to the pressure within the container. The aerosol container are capped and labelled. The pressure filling methods have the following advantages over the cold filling method:

Ø The emulsion, suspensions are unstable at very low temperature. So the pressure filling method is the preferred method then that of cold filling method.

Ø The absence of moisture reduces the chance of contamination.

Ø The rate of production is high.

Ø The chance of loss of propellant is low.

Concentrate filler, Valve placer, Purger and vacuum crimper, Pressure filler, Leak test tank equipments are used for large scale of production.

QUALITY CONTROL OF PHARMACEUTICAL AEROSOLS

Quality control of pharmaceutical aerosol includes the testing of propellant, valves, actuator and dip tubes, containers, weight checking, leak testing and spray testing.

PROPELLANT

All quality control testings of propellents are accompanied by specification sheets:

A sample is taken out and vapour pressure is determined which then is compared to specifications. The density is also checked when necessary. Other tests include –

- ❖ Identification of two or more blends of propellant by Gas chromatography.
- ❖ Purity of the propellant is checked by moisture, halogen, and non-volatile residue determinations.

VALVES, ACTUATORS, AND DIP TUBES

Both physical and chemical examinations are done. They are sampled according to the standard procedures as found in “Military Standard Mil – STD-105D”.A test method was developed for metered dose pharmaceutical aerosol by Aerosol specifications committee, Industrial Pharmaceutical Technology section, Academy of Pharmaceutical Sciences with an objective of determining the magnitude of valve delivery and degree of uniformity between individual valves.The composition of the test solution is given in Table 3:

Testing procedure

· Take 25 valves and placed on suitable containers.

· The containers are filled with specific test solutions.

· A button actuator with 0.02 inch orifice is attached to the valves.

· The filled containers are placed in a suitable atmosphere at a temperature of 25 ± 1^0 C

· When the products have attained the temperature of 25 ± 1^0 C, the filled containers are actuated to fullest extent for 2 seconds.

· This procedure is repeated for a total of 2 deliveried from each 25 test units.

The valve delivery per actuation in µl = Individual delivery weight in mg/Specific gravity of test solution

The limits for acceptance as given in Table 4

Out of 50 deliveries:

· If 4 or more deliveries are outside limits, then valves are rejected.

· If 3 or more deliveries are outside limits, another 25 valves are tested.

o Lot is rejected if more than 1 delivery is outside specification.

· If 2 deliveries from 1 valve are beyond limits: another 25 valves are tested.

o Lot is rejected if more than 1 delivery is outside specification.

CONTAINERS

Containers are examined for defects in linings. Quality control aspects include degree of conductivity of electric current as measure of exposed metals. Glass containers examined for flaws.

WEIGHT CHECKING

It is done by periodically adding empty tared containers to filling lines which after filling with product concentrate are removed and reweighed. Same procedure is used for checking weight of the propellant.

LEAK TEST

It is done by measuring the crimp's valve dimension and comparing. Final testing of valve enclosure is done by passing filled containers through the water bath.

SPRAY TESTING

It is done to clear up dip tube of pure propellant and concentrate and to check any defects in the valve and the spray pattern.

EVALUATION TESTS OF PHARMACEUTICAL AEROSOLS

FLAMMABILITY AND COMBUSTIBILITY

It includes Flame projection and Flame extension.

Flame projection: The aerosol product is sprayed to an open flame for about 4 second and the extension of the flame is measured with the help of a ruler.

Flash point: Tag Open Cup apparatus is the standard test apparatus. The aerosol product is chilled to a temperature of about – 25 0 F and transferred to the test apparatus. The temperature of the test liquid is increased slowly and the temperature at which the vapours ignite is taken as the flash point.

Physicochemical characteristics are given in Table 5.

PERFORMANCE TEST

It includes the following tests

Aerosol Valve Discharge Rate: An aerosol product of known weight is taken and its contents are discharged using standard apparatus for a given period of time. The container is reweighed. Then the change in weight per time dispensed is the discharge rate. The discharge rate can also be expressed as grams per second.

Spray patterns: The method involves the impingement of sprays on a piece of paper that has been treated with dye – talc mixture. It gives a record of the spray pattern.

Dosage with metered valves: The doses are dispensed into the solvents or onto a material that absorbs the active ingredients. The assay of the solution gives the amount of active ingredients present. Another method involves accurate weighing of the filled container followed by dispensing of several doses. The container is then reweighed, and the difference in weight divided by the number of doses dispensed gives the average dose. This process is repeated and the results are compared.

Net contents: The tared cans are placed onto the filling line are weighed, the difference in weight is equal to the net contents. The other method is a Destructive method and consists of weighing a full container and then dispensing the contents. The contents are then weighed. The difference in weight gives the amount of contents present in the container.

Foam stability: The life of a foam ranges from a few seconds (for quick breaking foam) to one hour or more depending on the formulation. The methods which are used to determine the foam stability includes visual evaluation, time for a given mass to penetrate the foam, time for a given rod that is inserted into the foam to fall and rotational viscometer.

Particle size determination: Cascade impactor and light scattering decay methods are used for particle size determination. It is based on the principle that for a stream of particles projected through a series of nozzle and glass slides, the larger particles are impacted first on the lower velocity stage and the smaller particles are impacted on the higher velocity stage.

BIOLOGIC TESTING

Therapeutic activity and Toxicity are considered in Biologic testing.

Therapeutic Activity:

For Inhalation Aerosols: The determination of therapeutic activity is dependent on the particle size.

For Topical Aerosols: Therapeutic activity of aerosol products are determined by applying the therapeutically active ingredients topically to the test areas and the amount of therapeutically active substances absorbed is determined.

Toxicity study:

For Topical Aerosols: The topically administered aerosols are checked for chilling effect or irritation in the skin. When aerosol are topically applied, thermistor probe attached to the recording thermometer are used to determine the change in skin temperature for a given period of time.

For Inhalation Aerosols: Inhalation toxicity study is done by exposing test animals to vapours sprayed from the aerosol container.

EXTRACTABLE SUBSTANCES

The composition and the quality of materials used in the manufacturing of elastomeric and plastic components of valve (eg. Stem, gaskets, housing etc) are to selected and checked properly because as organic solvents are the major constituents of the propellant and also used as a vehicle, so it may increase the chance of leaching of constituents from the elastomeric and plastic components of valve into the formulation. This may lead to distortion of the components of valve, changes in the delivery rate of medication, increase in the leak rate and also lead to contamination. So the selected elastomeric and plastic components of valve should be compatible with the formulation. Thus the established profile of each of the elastomeric and plastic components of valve should be correlated to the extractable profile of the aged drug products or placebo, to ensure reproducible quality and purity of the drug product. Specifications and limits for individual and total extractable from different valve components may require the use of different analytical methods.

LABELLING

Medicinal aerosols should contain at least the following warning information on the label as in accordance with appropriate regulations according to USP:

Warning— Avoid inhaling. Avoid spraying into eyes or onto other mucous membranes.

NOTE—The statement "Avoid inhaling" is not necessary for preparations specifically designed for use by inhalation. The phrase "or other mucous membranes" is not necessary for

preparations specifically designed for use on mucous membranes.

Warning— Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120 ^{0}F (49 ^{0}C). Keep out of reach of children. In addition to the aforementioned warnings, the label of a drug packaged in an aerosol container in which the propellant consists in whole or in part of a halocarbon or hydrocarbon shall, where required under regulations of the FDA, bear either of the following warnings:

Warning— Do not inhale directly; deliberate inhalation of contents can cause death.

Warning— Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

Packaging of Pharmaceutical Products: Packaging component types, specifications and methods of evaluation, stability aspects of packaging equipments, factors affecting choice of containers, legal and other official requirements for containers, package testing.

Packaging of Pharmaceutical Product

Ideal packaging requirement

a) They must protect the preparation from environmental conditions.

b) They must not be reactive with the product.

c) They must not impart to the product tastes or odors.

d) They must be nontoxic.

e) They must be FDA approved.

f) They must meet applicable tamper-resistance requirements.

Table 1: Primary and Secondary packaging material

Material	Type	Example of use
Plastic	Primary	Ampoule, vial, infusion fluid container, dropper bottle
Glass	Primary	Metric medical bottle, ampoule, vial
Paper	Secondary	Labels, patient information leaflet
Cardboard	Secondary	Box to contain primary pack

Hazards encountered by package

Hazards encountered by the package can be divided into three main groups

a. Mechanical hazards

b. Climatic or environmental hazards

c. Biological hazards

The only exception is theft, which can be a serious risk with drugs and may demand special protection in certain cases.

a. Mechanical hazards

1- Shock or impact damage

Damage due to shock is usually caused by rsough handling, during transport etc. Cushioning can be provided and a warning label may be useful. Restriction of movement and more careful handling should be made.

2-Compression

Fragile items may be broken or collapsible articles crushed by compression, the usual procedure then being to protect with a rigid outer package. Top pressure or loading can distort inside. The crushing of a carton can make a product un- sealable even though no damage has occurred to the contents. This is more likely to occur during stocking in the ware house or during transport where vibration adds a further hazard. Compression can also occur in other situations like capping on a production line, when being carried home by the user etc.

3- Vibration

Vibration consists of two variables-frequency and amplitude. Considerable vibration may occur during transport, especially with exported items. Sometimes screw caps may be loosen or labels or decorations may abrade etc.

4- Abrasion

Although abrasion results from both regular and irregular forms of vibration , it is listed separately as the visual appearance of the product or package can be affected. eg: rectangular bottle in a carton will move up and down and from side to side. A round bottle in the same circumstances will suffer from an additional possibility of rotation.

b. Climatic or environmental hazards

Environmental conditions encountered by the package are likely to vary considerably, especially in articles for export to the tropical areas. In general, it is extremes of conditions that give rise to problems, and this is especially true of fluctuating conditions.

1- Temperature

Extreme conditions may cause deterioration, low temperatures leading to aqueous solutions freezing and, hence, to fracture of containers. High temperatures increase diffusion coefficients, accelerating the entry of water vapour into hygroscopic products and the loss of volatile components. In addition, high, temperatures increase reaction rates and product breakdowns either by hydrolysis or oxidation. High temperature coupled with a high relative humidity will produce a slower effect if the temperature is lowered sufficiently to reach dew point.

Contamination from liquid moisture can encourage mould and bacterial growth.

2-Moisture

Moisture as liquid or water vapor may cause physical changes (e.g. color fading, softening, hardening etc) or chemical changes (hydrolysis, oxidation, effervescence etc). Although liquid moisture may cause obvious damage, water vapour may penetrate into a package, leading to hydrolysis, without visual changes. It is essential to check the water vapour permeability of materials to be used for packaging moisture-sensitive

products; for example, plastics show considerable variation in this property. It may also act as a carrier for other contaminants like moulds and fungi.

3-Pressure

Decrease in pressure, as in mountainous regions or during flight in non-pressurized transport aircraft, may cause thin containers to burst or strip packs to inflate.

4- Atmospheric Gases

Gases from the atmosphere may diffuse into the package, leading to deterioration. Thus, oxygen will encourage oxidation, while carbon dioxide can cause a pH shift (un buffered solution in plastic bottle particularly Low Density Poly Ethylene (LDPE), which is relatively permeable to carbon dioxide) or lead to precipitation of some products (barbiturates from solutions of their sodium salts). Permeation of the common gases through plastic is typically in the ratio of 1:4:20 for nitrogen, Oxygen and Carbon dioxide respectively, nitrogen being more permeable. Odorous gases or volatile ingredients associated with perfumes, flavors and product formulation may also pass into or out of a package. If a volatile ingredient is lost from a flavor, an unpleasant odor or taste may result.

5-Light

Light consist of wavelengths from the UV zones through the visible to infrared. A number of deteriorations are due to photochemical reactions particularly affected by the ultra-violet band of the spectrum. Such changes may not always be visible. Printed or deteriorated packaging materials may also suffer from discoloration (white may go yellow, deeper colors may fade) and this may be seen as implying a change in the product efficacy or strength. Although light can be excluded by using selected material, tin plate, soil etc opacity and/or color may reduce penetration or filter out selected wavelength. The additional use of UV absorbers in plastics may also restrict light rays entering the packed it should also be noted that many products are protected by a carton, outer etc. Alternatively, an opaque outer packaging may be used, with a warming that the advantage that the latter may be transparent, permitting the contents to be inspected.

5-Solid airborne contamination (particulars)

Particulars matters present in the atmosphere will make the containers dirty during transport or storage. This can be prevented by outer wrappers or by anti-static agents.

c. Biological hazards

Microbiological

The packaging materials must be reasonably clean initially and when put together to form a finished package and restrict any further contamination as much as possible. In the case of sterile products the package and its closure must maintain a 100% effective seal against microbiological contaminants like bacteria, moulds and yeasts. Growth of yeasts is critical with sugar based products as fermentation may occur. Moulds will also grow on cellulose based materials like paper if these are kept under humid conditions. Care should be taken in order to avoid fluctuation in temperature.

Chemical Hazards

The main risk of chemical hazard is due to interaction or in compatibility between the product and package. Compatibility investigations must basically cover any exchange that can occur between the product and the package and vice versa. These may be associated with interaction or contamination, covering migration, absorption, adsorption, extraction, corrosion, etc. where by ingredients may either be lost or gained. Such exchange may be identifiable as organoleptic changes, increase in toxicity/irritancy degradation, loss or gain of microbial effectiveness, precipitation, turbidity, color change, PH shift etc. These external influences may catalyze, induce or even nullify chemical changes.

Function of packaging

The various functions of packaging are

1. Protective function

2. Storage function

3. Loading & Transport functions

4. Identification

1. Protective function

Protective function of packaging essentially involves protecting the contents from the environment and vice versa. The inward protective function is intended to ensure full retention of the utility value of the packaged goods. The packaging is thus intended to protect the goods from loss, damage and theft.In addition packaging must essentially be able to withstand the many different static and dynamic forces to which it is subjected during transport, handling and storage operations. The goods frequently also require protection from climatic conditions, such as temperature, humidity etc. The precipitation and solar radiation may require additional packaging measures in the interior portion of the container.The exterior protection provided by the packaging must prevent any environmental degradation by the goods. This requirement is of particular significance in the transport of hazardous materials, with protection of humans being of primary importance. The packaging must furthermore as far as possible prevent any contamination, damage or other negative impact upon the environment and other goods. The interior and exterior protective function primarily places demands upon the strength, resistance and leak proof properties of transport packaging.

2. Storage function

The materials used for packaging should be stored properly so as to preserve the quality of the material both before packaging and once the package contents have been used.

3. Loading and transport functions

Packaging has a crucial impact on the efficiency of transport, handling and storage of goods. Packaging should therefore be deigned to be easily handled and to permit space-saving storage and stowage. The shape and strength of packages should be such that they may not only be stowed side by side leaving virtually no voids but may also stowed safely one above the other. The most efficient method of handling general cargo is to make up cargo units. Packaging should thus always facilitate the formation of cargo units; package dimensions and the masses to be accommodated should be possibly tailored to the dimensions and load-carrying capacity of standard pallets and containers.

4. Identification

The packaging should give clear identification of the product at all stages. The life of the patient may depend upon rapid and correct identification in emergencies. Packaging also serves as a mean to identify the manufacturer of the product. The manufacturer must consider the packaging requirement for the usage of product in different localities

Selection of the Packaging Materials

Selection is based

1. On the facilities available, for example, pressurized dispenser requires special filling equipment.

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

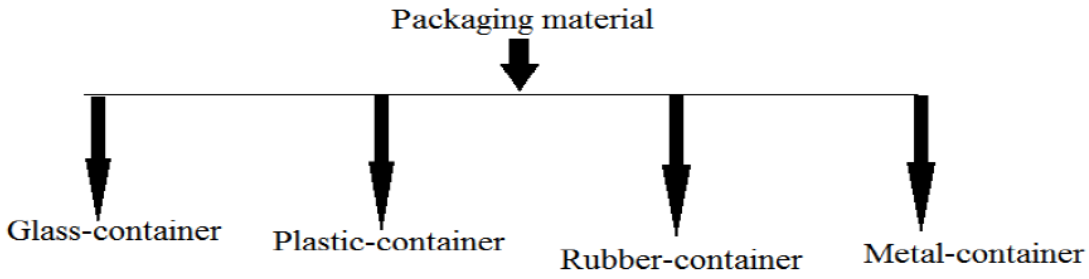
3. On the physical form of the product. For example, solid, semi-solid, liquids or gaseous dosage form.

4. On the route of administration. For example, oral, parenteral, external, etc.

5. On the stability of the material. For example, moisture, oxygen, carbon dioxide, light, trace metals, temperature or pressure or fluctuation of these may have a deleterious effect on the product.

6. On the contents. The product may react with the package such as the release of alkali from the glass or the corrosion of the metals and in turn the product is affected

7. On the cost of the product. Expensive products usually justify expensive packaging



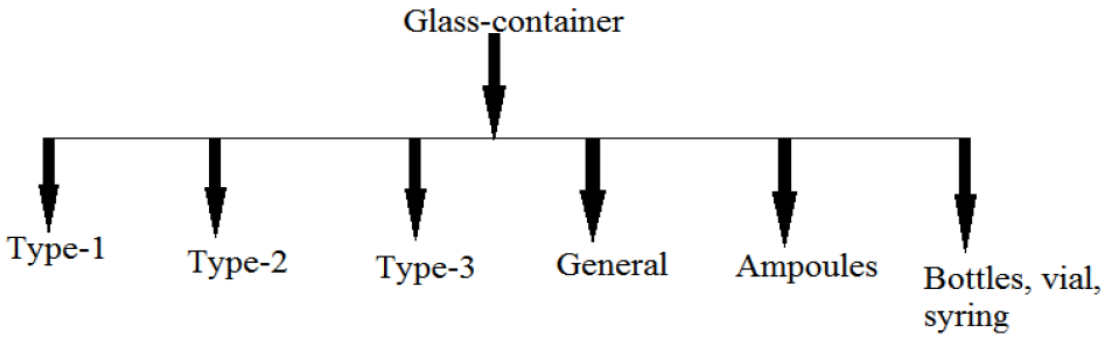
Glass –containers

Manufacture of Glass

Four basic processes are used in the production of glass:-

Blowing uses compressed air to form the molten glass in the cavity of a metal mold. Most commercial bottles and jars are produced on automatic equipment by this method. In drawing, molten glass is pulled through dies or rollers that shape the soft glass. Rods, tubes, sheet glass, and other items of uniform diameter are usually produced

commercially by drawing. Ampoules, cartridges, and vials drawm from tubing have a thinner, more uniform wall thickness, with less distortion than blow-molded containers. In pressing, mechanical force is used to press the molten glass against the side of a mold. Casting uses gravity or centrifugal force to initiate the formation of molten glass in the cavity.



Type 1 —Borosilicate Glass

Borosilicate Glass is a highly resistant glass. In this type of glass a substantial part of the alkali and earth cations are replaced by boron and/or aluminum and zinc. It is more chemically inert than the soda-lime glass, which contains either none or an insignificant amount of these cations. Although glass is considered to be a virtually inert material and is used to contain strong acids and alkalies as well as all types of solvents, it has a definite and measurable chemical reaction with some substances, notably water. The sodium is loosely combined with the silicon and is leached from the surface of the glass by water. Distilled water stored for one year in flint type III glass (to be described) picks up 10 to 15 parts per million (ppm) of sodium hydroxide along with traces of other ingredients of the glass.

Type 2 —Treated Soda-Lime Glass

Type II containers are made of commercial soda-lime glass that has been de-alkalized, or treated to remove surface alkali. The de-alkalizing process is known as "sulfur treatment" and virtually prevents "weathering" of empty bottles. The treatment offered by several glass manufacturers exposes the glass to an atmosphere containing water vapor and acidic gases, particularly sulfur dioxide at an elevated temperature. This results in a reaction between the gases and some of the surface alkali, rendering the surface fairly resistant, for a period of time, to attack by water. The alkali removed from the glass appears on the surface as a sulfate bloom, which is removed when the containers are washed before filling. When glassware is stored for several months, especially in a damp atmosphere or with extreme temperature variations, the wetting of the surface by condensed moisture (condensation) results in salts being dissolved out of the glass. This is called "blooming" or "weathering," and in its early stages, it gives the appearance of fine crystals on the glass. At this stage, these salts can be washed off with water or acid.

Type 3—Regular Soda-Lime Glass

Containers are untreated and made of commercial soda-lime glass of average or better-than-aver-age chemical resistance.

General-Purpose Soda-Lime Glass

Containers made of soda-lime glass are supplied for non parenteral products, those intended for oral or topical use.

1.1.Composition of Glass

The only anion of consequence is oxygen. Many useful properties of glass are affected by the kind of elements it contains. Reduction in the proportion of sodium ions makes glass chemically resistant; however, without sodium or other alkalies, glass is difficult to melt and is expensive. Boron oxide is incorporated mainly to aid in the melting process through reduction of the temperature required.Lead in small traces gives clarity and brilliance, but produces a relatively soft grade of glass. Alumina (aluminum oxide), however, is often used to increase the hardness and durability and to increase resistance to chemical actionGlass is composed principally of silica with varying amount of metal oxides, soda-ash, limestone, and cullet. The sand is almost pure silica, the soda-ash is sodium carbonate, and the limestone, calcium carbonate. Cullet is broken glass that is mixed with the batch and acts as a fusion agent for the entire mixture. The composition of glass varies and is usually adjusted for specific purposes. The most common cations found in pharmaceutical glassware are silicon, aluminum, boron, sodium, potassium, calcium, magnesium, zinc, and barium.

Colored Glass—Light Protection

The USP specifications for light-resistant containers require the glass to provide protection against 2900 to 4500 Angstroms of light. Amber glass meets these specifications, but the iron oxide added to produce this color could leach into the product. Therefore, if the product contains ingredients subject to iron-catalyzed chemical reactions, amber glass should not be used. Manganese oxide can also be used for amber glasses Glass containers for drugs are generally available in clear flint or amber color. For decorative purposes, special colors such as blue, emerald green, and opal may be obtained from the glass manufacturer. Only amber glass and red glass are effective in protecting the contents of a bottle from the effects of sunlight by screening out harmful ultraviolet rays.

Glass for Drugs

The powdered glass test is performed on crushed glass of a specific size, and the water attack test is conducted on whole containers. The water attack test is used only with type II glass that has been exposed to sulfur dioxide fumes under controlled conditions. The USP and NF describe the various types of glass and provide the powdered glass and water attack tests for evaluating the chemical resistance of glass. The test results are measures of the amount of alkalinity leached from the glass by purified water under controlled elevated temperature conditions.

Ampoules

Ampoules are thin-walled glass containers, which after filling, are sealed by either tip sealing or pull sealing. The contents are withdrawn after rupture of the glass, or a single occasion only. These are great packaging for a variety of drugs. The filed – in product is in contact with glass only and the packaging is 100% tamper proof.

The break system OPC (one –point cut) or the color break ring offer consistent breaking force. There are wide variety of ampoule types from 0.5 to 50ml. Up to 3 color rings can be placed the stem or body for identification purpose. Printed ampoules with heavy metal free colors are available.

Some of them are:

• Type B straight –stem

• Type C funnel –tip

• Type D closed

Bottles, vials and syringes

These are more or less thick walled containers with closures of glass or of material other than glass such as plastic materials or elastomers. The contents may be removed in several proportions on one of or more occasions.

Test for glass containers

Test for surface hydrolytic resistance

Surface hydrolytic resistance test is conducted on unused glass containers. The number of containers to be examined and the volume of the test humid necessary for final determination are indicated in the following table.

Table 1:

Nominal capacity of container	Number of containers to b e used	Volume of test solution to be used for titration ml
3 or less	At least 10	25.0
3 to 30	At least 5	50.0
More than 30	At least3	100.0

Initially each container is rinsed three times carefully with carbon dioxide free water. Then the container is allowed to drain and it is filled with the carbon dioxide free water to the required volume. If vials and bottle are used they are covered with neutral glass dishes or aluminum foil which is previously rinsed with carbon dioxide free water. If ampoules are used, they are sealed by heat fusion. The containers are then placed on the tray of the autoclave a containing a quantity of water in such a way that the tray remains clear and temperature is maintained between 100oC to 120o C over 20minutes. Then the temperature is adjusted between 120o-1220C for 60 minutes and finally the temperature is lowered from 120oC for 40 minutes. Remove the containers from the autoclave once the pressure reaches the atmospheric pressure and cool under running tap water Combine the liquids obtained from the containers being examined. The following titration should be carried out within 1 hour after removing the container from the autoclave. Introduce the prescribed volume of liquid in to a conical flask. Add 0.05ml of methyl red solution for each 20ml liquid. Titrate with 0.01M hydrochloric acid taking as the end point the color obtained by repeating the operation using the same volumes of carbon dioxide free water. The result is not greater than the volume state in table

Table 2:

Capacity of container	Volume of 0.01M hydrochloric acid VS per 100 ml of test solution	
	Type 1 or II glass ml	Type III glass ml
Not more than 1	3.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more than 50	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.2

Test for hydrolytic resistance of powdered glass

The Containers to be tested are initially rinsed with water and dried in hot air oven. At least three containers are taken and broken with a hammer to get coarse fragments of about 100g size of the largest fragment should not be greater than 25mm. Transfer a part of the sample to a mortar and insert the pestle and strike heavily once with the hammer. Transfer the contents of the mortar to the coarsest sieve. Repeat the operation sufficient number of times until all the fragment have been transferred to the sieve. The glass is sifted and the portion retained by the 710{mu)m and 423 {mu)m sieve are taken and are further fractured. The operation is respected until 20g of glass is retained by the 710{mu)m sieve. Rejected this portion and the portion that passes through 250{mu)m sieve. Shake the nest of sieve manually or mechanically for 5 minutes. Glass grains that passes through 425{mu)m sieve is taken metal particles are removed by suspending the glass grains in acetone the supernatant liquid is decanted the operation is repeated five times glass grains are speeded on an evaporating dish and allow the acetone to evaporating by drying in an oven at 110oC for 20minutes and allow to cool. 20g of the glass grains to treated is introduced into a 250ml conical flask add 100ml of carbon dioxide free water and weigh In the second flask 100ml carbon dioxide free water serve as blank and weigh. Close the two flasks with neutral glass dish or aluminum foil rinsed with carbon dioxide free water. The flask is then placed in on auto clave and maintain the temperature at 121oC for 30minutes and carry out the operations similar to those described in Test A for surface hydrolytic resistance. After cooling remove the closure, wipe the flask and adjust the original weight by adding carbon dioxide free water. Transfer 50ml (corresponding to 10g of glass grains) of the clear supernatant liquid into a conical flask. 50ml of water is taken in other flask which is used as blank 0.1ml methyl red solution is added as indicator and titrated with 0.001M hydrochloric acid until the color of the liquid is same as that obtained with blank. Subs tract the value of the blank and express the result in millilitres of hydrochloric acid consumed per 10g of glass. Type I glass containers require not more than 2.0ml, Type II or III requires not more than 17.0ml and Type IV glass containers requires not more than 30.0ml of 0.001M hydrochloric acid.

Glass is commonly used in pharmaceutical packaging because it possesses superior protective qualities.

Advantages

a. Economical

b. Readily available container of variety of sizes and shapes

c. Impermeability

d. Strength and rigidity

e. Has FDA clearance

f. Does not deteriorate with age

g. Easy to clean

h. Effective closure and resolves are applicable.

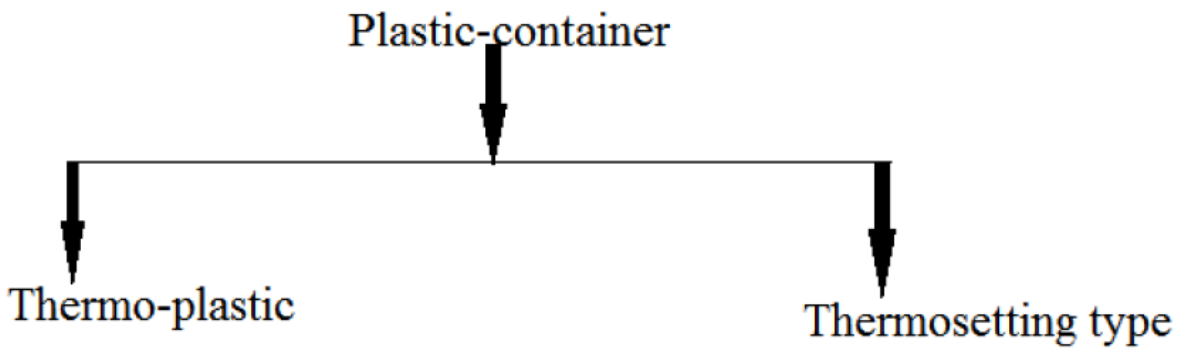
i. Colored glass, especially amber, can give protection against light when it is required.

Disadvantages

a. Fragility

b. Heavy weight

Plastic container



Thermoplastic type

On heating, they are soften to viscous fluid which hardens again on cooling. e.g. polyethylene ,PVC ,Polystyrene ,polypropylene ,Polyamide ,Polycarbonate.

Thermosetting type

When heated, they may become flexible but they do not become liquid. Phenol formaldehyde , urea formaldehyde, melamine formaldehyde Plastics in packaging have proved useful for a number of reasons, including the ease with which they can be formed, their high quality, and the freedom of design to which they lend themselves. Plastic containers are extremely resistant to breakage and thus offer safety to consumers along with reduction of breakage losses at all levels of distribution and use. Plastic containers for

pharmaceutical products are primarily made from the following polymers: polyethylene, polypropylene, polyvinyl chloride, polystyrene, and to a lesser extent, polymethyl methacrylate, polyethylene terephthalate, polytrifluoroethylene, the amino formaldehydes, and polyamides.Plastic containers consist of one or more polymers together with certain additives. Those manufactured for pharmaceutical purposes must be free of substances that can be extracted in significant quantities by the product contained. Thus, the hazards of toxicity or physical and chemical instability are avoided.

Advantages of Plastic Containers

Plastic containers have a number of inherent practical advantages over other containers or dispenses. They are

- Low in cost
- Light in weight
- Durable
- Pleasant to touch
- Flexible facilitating product dispensing
- Odorless and inert to most chemicals
- Unbreakable
- Leak proof
- Able to retain their shape throughout their use.
- They have a unique 'suck-back' feature, which prevents product doze.

Disadvantages

Plastics appear to have certain disadvantage like interaction, adsorption, absorption lightness and hence poor physical stability. All are permeable to some degree to moisture, oxygen, carbon dioxide etc and most exhibit electrostatic attraction, allow penetration of light rays unless pigmented, black etc. Other negative features include

• Stress cracking

A phenomenon related to low density polythene and certain stress cracking agents such as wetting agents, detergents and some volatile oils.

• Paneling or cavitation

Where by a container shows in ward distortion or partial collapse owing to absorption causing swelling of the plastic or dimpling following a steam autoclaving operation.

• Crazing

A surface reticulation which can occur particularly with polystyrene and chemical substances (e.g. isopropyl myristate which first cause crazing and ultimately reaches of total embitterment and disintegration).

• **Poor key of print**

Certain plastics, such as the poly olefins need pre-treating before ink will key. Additives that migrate to the surface of the plastic may also cause printing problem.

• **Poor impact resistance**

Both polystyrene and PVC have poor resistance. This can be improved by the inclusion of impact modifiers such as rubber in case of polystyrene and methyl methacrylate butadiene styrene for PVC.

MATERIALS

Polyethylene

High-density polyethylene is the material most widely used for containers by the pharmaceutical industry and will probably continue to be for the next several years. Polyethylene is a good barrier against moisture, but a relatively poor one against oxygen and other gases. Most solvents do not attack polyethylene, and it is unaffected by strong acids and alkalies.Polyethylene has certain disadvantages that it lack clarity and a relatively high rate of permeation of essential odors, flavors, and oxygen. Despite these problems, polyethylene in all its variations offers the best all-around protection to the greatest number of products at the lowest cost.

The density of polyethylene, which ranges from 0.91 to 0.96, directly determines the four basic physical characteristics of the blow-molded container:

(1) Stiffness

(2) Moisture-vapor transmission

(3) Stress cracking

(4) Clarity or translucency

As the density increases, the material becomes stiffer, has a higher distortion and melting temperature, becomes less permeable to gases and vapors, and becomes less resistant to stress cracking. The molecular structure of high-density material is essentially the, same as that of low-density material, the main difference being fewer side branches.

Polypropylene

Polypropylene has recently became popular because it has many good features of polyethylene, with one major disadvantage either eliminated or minimized. Polypropylene does not stress-crack under any conditions. Except for hot aromatic or halogenated solvents, which soften it, this polymer has good resistance to almost all types of chemicals, including strong acids, alkalies, and most organic materials. Its high melting point makes it suitable for boilable packages and for sterilizable products.

Lack of clarity is still a drawback, but improvement is possible with the construction of thinner walls. Polypropylene is an excellent gas and vapor barrier. Its resistance to permeation is equivalent to or slightly better than that of high-density or linear polyethylene, and it is superior to low-density or branched polyethylene. One of the biggest disadvantages of polypropylene is its brittleness at low temperatures. In its purest form, it is quite fragile at 0°F and must be blended with polyethylene or other material to give it the impact resistance required for packaging.

Polyvinyl Chloride (PVC)

PVC can be softened with plasticizers. Various stabilizers, antioxidants, lubricants, or colorants may be incorporated. Polyvinyl chloride is seldom used in its purest form. PVC is an inexpensive, tough, clear material that is relatively easy to manufacture. PVC must not be overheated because it starts to degrade at 280°F, and the degradation products are extremely corrosive. Polyvinyl chloride yellows when exposed to heat or ultraviolet light, unless a stabilizer is included by the resin supplier. From the standpoint of clarity, the best stabilizers are the tin compounds, but the majority cannot be used for food or drug products Polyvinyl chloride is not affected by acids or alkalis except for some oxidizing acids. Its impact resistance is poor, especially at low temperatures.

Polystyrene

Polystyrene is attacked by many chemicals, which cause it to craze and crack, and so it is generally used for packaging dry products only. To improve impact strength and brittleness, general-purpose polystyrene may be combined with various concentrations of rubber and acrylic compounds. Certain desired properties like clarity and hardness diminish with impact polystyrene. The shock resistance or toughness of impact polystyrene may be varied by increasing the content of rubber in the material, and often these materials are further classified as intermediate-impact, high-impact, and super-impact polystyrene.

General-purpose polystyrene is a rigid, crystal clear plastic. Polystyrene has been used by dispensing pharmacists for years for containers for solid dosage forms because it is relatively low in cost. At present, polystyrene is not useful for liquid products. The plastic has a high water vapor transmission (in comparison to high-density polyethylene) as well as high oxygen permeability. Depending on the methods of manufacture and other factors, polystyrene containers are easily scratched and often crack when dropped. Polystyrene will build up static charge. Polystyrene has a low melting point (190°F) and therefore cannot be used for hot items or other high-temperature applications. Polystyrene is resistant to acids, except strong oxidizing acids, and to alkalies.

Nylon (Polyamide)

As a barrier material, nylon is highly impermeable to oxygen. It is not a good barrier to water vapor, but when this characteristic is required, nylon film can be laminated to polyethylene or to various other materials. Its relative high-water transmission rate and the possibility of drug-plastic interaction have reduced the potential of nylon for long-term storage of drugs. Some of the nylon approved by FDA are Nylon 6, Nylon 6/6, Nylon 6/10, Nylon 11, and certain copolymers. sNylon is made from a dibasic acid combined with a di-amine. Variety of

nylons can be made with different dibasic acids and amines. The type of acid and amine that is used is characteristic and denotes the type of acid and amine used.e.g. nylon 6/10 has six carbon atoms in the

diamine and ten in the acid. Nylon and similar polyamide materials can be fabricated into thin-wall containers. Nylon can be autoclaved and is extremely strong and quite difficult to destroy by mechanical means. Important to the widespread acceptance of nylon is its resistance to a wide range of organic and inorganic chemicals.

Polycarbonate

The plastic is known for its dimensional stability, high impact strength, resistance to strain, low water absorption, transparency, and resistance to heat and flame. Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and aliphatic hydrocarbons. It is attacked by alkalies, amines, ketones, esters, aromatic hydrocarbons, and some alcohols. Polycarbonate resins are expensive and consequently are used in specialty containers. Since the impact strength of polycarbonate is almost five times greater than other common packaging plastics, components can be designed with thinner walls to help reduce cost. Polycarbonate can be made into a clear transparent container. Polycarbonate is expensive and offers some advantage that it can be sterilized repeatedly. The containers are rigid, as is glass, and thus has been considered a possible replacement for glass vials and syringes. It is FDA approved, although its drug-plastic problems have not been investigated adequately. It is only moderately chemically resistant and only a fair moisture barrier.

Acrylic Multipolymers (Nitrile Polymers)

The present safety standard is less than 11 ppm residual acrylonitrile monomer, with allowable migration at less than 0.3 ppm for all food products. These polymers represent the acrylonitrile or methacrylonitrile monomer. Their unique properties of high gas barrier, good chemical resistance, excellent strength properties, and safe disposability by incineration make them effective containers for products that are difficult to package in other plastic containers. Their oil and grease resistance and minimal taste transfer effects are particularly advantageous in food packaging. These type of polymers produce clear container and are less costly. The use of nitrile polymers for food and pharmaceutical packaging is regulated to standards set by the Food and Drug Administration.

Polyethylene terephthalate (PET)

Polyethylene terephthalate is used in food packaging and offers favorable environmental impact system. Polyethylene terephthalate, generally called PET, is a condensation polymer typically formed by the reaction of terephthalic acid or dimethyl terephthalate with ethylene glycol in the presence of a catalyst. Although used as a packaging film since the late 1950s, its growth has recently escalated with its use in the fabrication of plastic bottles for the carbonated beverage industry.

Product-Plastic interactions

Product-Plastic interactions have been divided into five separate categories:

(1) Permeation

(2) Leaching

(3) Sorption

(4) Chemical reaction

(5) Alteration in the physical properties of plastics or products

1) Permeation

Transmission of gases, vapors, or liquids through plastic packaging materials can have an adverse effect on the shelf-life of a drug. Permeation of water vapor and oxygen through the plastic wall into the drug can present a problem if the dosage form is sensitive to hydrolysis and oxidation. Temperature and humidity are important factors influencing the permeability of oxygen and water through plastic. An increase in temperature reflects an increase in the permeability of the gas. Great differences in permeability are possible, depending on the gas and the plastic used. Molecules do not permeate through crystalline zones; thus, an increase in crystallinity of the material should decrease permeability. Two polyethylene materials may therefore give different permeability values at various temperatures. Materials such as nylon, which are hydrophillic in nature, are poor barriers to water vapor, while such hydrophobic materials as polyethylene provide much better barriers. Studies have also revealed that formulations containing volatile ingredients might change when stored in plastic containers because one or more of the ingredients are passing through the walls of the containers. Often, the aroma of cosmetic products becomes objectionable, owing to transmission of one of the ingredients, and the taste of medicinal products changes for the same reason.

2) Leaching

Problems may arise with plastics when coloring agents in relatively small quantities are added to the formula. Particular dyes may migrate into a parenteral solution and cause a toxic effect. Release of a constituent from the plastic container to the drug product may lead to drug contamination and necessitate removal of the product from the market. Plastic containers have one or more ingredients added in small quantities to stabilize or impart a specific property to the plastic and the prospect of leaching, or migration from the container to the drug product is present.

3)Sorption

It is the process involves the removal of drug content from the product by the packaging material. Sorption may lead to serious consequences active ingredients are in solution. Since drug substances of high potency are administered in small doses, losses due to sorption may significantly affect the therapeutic efficacy of the preparation. Sorption is seen mainly with preservatives. These agents exert their activity at low concentration, and their loss through sorption may be great enough to leave a product unprotected against microbial growth. Factors that influence characteristics of sorption from product are chemical structure, pH, solvent system, concentration of active ingredients, temperature, length of contact, and area of contact.

4) Chemical Reactivity

Certain ingredients that are used in plastic formulations may react chemically with one or more components of a drug product. At times, ingredients in the formulation may react with the plastic. Even micro-quantities of chemically incompatible substances can alter the appearance of the plastic or the drug product.

5) Modification

Polyvinyl chloride is an excellent barrier for petroleum solvents, but the plasticizer in polyvinyl chloride is extracted by solvents. This action usually leaves the plastic hard and stiff. Sometimes, this effect is not immediately perceptible because the solvent either softens the plastic or replaces the plasticizer; later, when

the solvent evaporates, the full stiffening effect becomes apparent. The changes in physical and chemical properties of the packaging material by the pharmaceutical product are called modification. Such phenomena as permeation, sorption, and leaching play a role in altering the properties of the plastic and may also lead to its degradation. Deformation in polyethylene containers is often caused by permeation of gases and vapors from the environment or by loss of content through the container walls. Some solvent systems have been found to be responsible for considerable changes in the mechanical properties of plastics. Oils, for example, have a softening effect on polyethylene; fluorinated hydrocarbons attack polyethylene and polyvinyl chloride. In some cases, the content may extract the plasticizer, antioxidant, or stabilizer, thus changing the flexibility of the package.

Constituents of plastic containers

The residues, additives and processing aids that may be used, and therefore possibly extracted from, plastic include

- **Monomer residues**
- **Catalysts**
- **Accelerators**
- **Solvents**
- **Extenders**
- **Fillers**
- **Slip additives**
- **Anti-slip additives**
- **Antistatic agents**
- **Anti-blocking agents**
- **Release agents**

TESTS FOR PLASTIC CONTAINERS

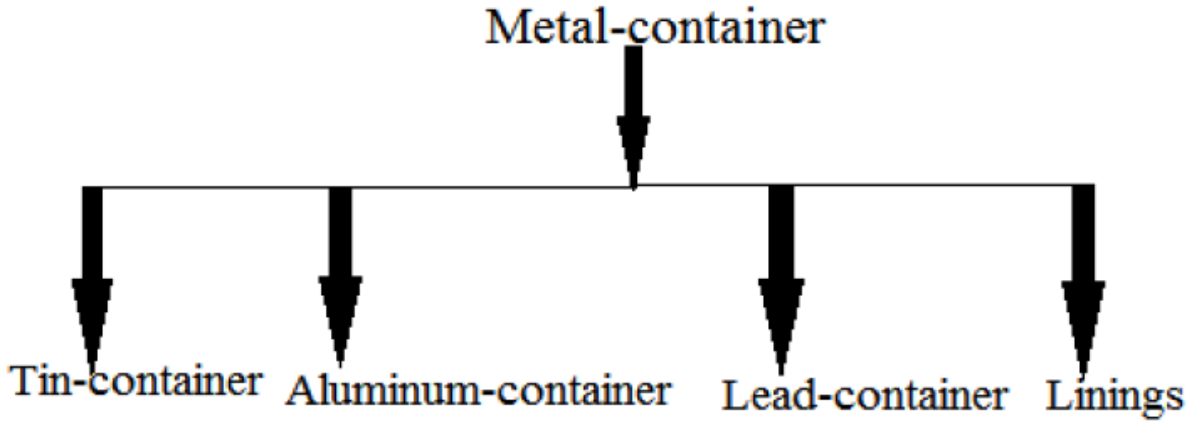
LEAKAGE TEST

The plastic containers (non injectables and injectables 1996 IP): fill 10 plastic containers with water and fit the closure keep them inverted at room temperature for 24 hrs no sign of leakage should be there from any container

WATER PERMEABILITY TEST

Fill 5 containers with nominal volume of water and sealed weigh each container allows to stand for 14 days at relative humidity of 60% at 20-250C reweigh the container loss of weight in each container should not be more than 0.2%.

Metal-container



Tin

Tin containers are preferred for foods, pharmaceuticals, or any product for which purity is an important consideration. Tin is chemically inert of all collapsible tube metals. It offers a good appearance and compatibility with a wide range of products.

Aluminum

Aluminum tubes offer significant savings in product shipping costs because of their light weight. They provide good appearance.

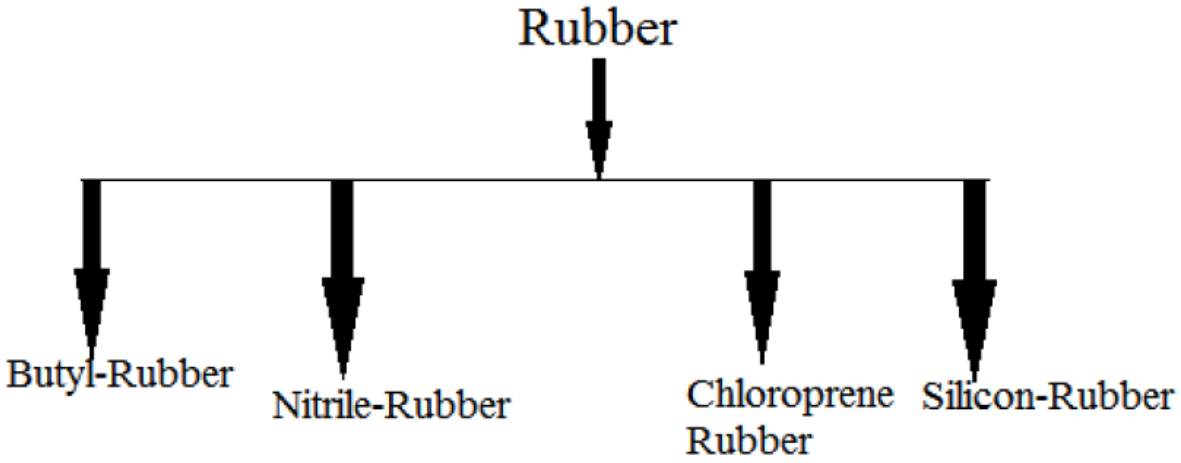
Lead

Lead has the lowest cost of all tube metals and is widely used for nonfood products such as adhesives, inks, paints, and lubricants. Lead should never be used alone for anything taken internally because of the risk of lead poisoning. The inner surface of the lead tubes are coated and are used for products like fluoride toothpaste.

Linings

If the product is not compatible with bare metal, the interior can be flushed with wax-type formulations or with resin solutions, although the resins or lacquers are usually sprayed on. A tube with an epoxy lining costs about 25% more than the same tube uncoated. Wax linings are most often used with water-base products in tin tubes, and phenolics, epoxides, and vinyls are used with aluminum tubes, giving better protection than wax, but at a higher cost.

RUBBER



Rubber

It is used mainly for the construction of closure meant for vials, transfusion fluid bottles, dropping bottles and as washers in many other types of product.

BUTYL RUBBER

Advantages

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

Disadvantages

Slow decomposition takes place above 130 0 C. Oil and solvent resistance is not very good.

NITRILE RUBBER

Advantages

Oil resistant due to polar nitrile group. Heat resistant.

Disadvantages

Absorption of bactericide and leaching of extractives are considerable.

CHLOROPRENE RUBBERS

Advantages

Oil resistant. Heat stability is good.

SILICON RUBBERS

Advantages

Heat resistance. Extremely low absorption and permeability of water. Excellent aging characteristic.

Disadvantages

They are very expensive.

TESTS FOR RUBBER CLOSURES

FRAGMENTATION TEST

Place a volume of water corresponding to nominal volume-4ml in each of 12 clean vials close vial with closure and secure caps for 16hrs pierce the closure with number 21 hypodermic needle(bevel angle of 10 to 140c)and inject 1ml water and remove 1ml air repeat the above operation 4 times for each closure count the number of fragments visible to naked eye Total number of fragments should not be more than 10.

SELF SEALABILITY TEST FOR RUBBER CLOSURES APPLICABLE TO MULTI DOSE

CONTAINERS ONLY

Fill 10 vials with water to nominal volume and close the vials with closures pierce the cap and closures 10 times at different places with no 21 syringe needle immerse the vials in 0.1 %W/v solution of methylene blue under reduced pressure restore the nominal pressure and keep the container for 30 min and wash the vials none of the vial should contain traces of colored solution.

Blister packaging technology

Blister packaging is a type of pre-formed plastic packaging used for small consumer goods. The two primary components of a blister pack are the cavity made from either plastic or aluminum - and the lidding, made from paperboard, paper, plastic or aluminum. The cavity contains the product and the lidding seals the product in the package.

Blister packaging helps retain product integrity because drugs that are pre- packaged in blisters are shielded from adverse conditions. Furthermore, opportunities for product contamination are minimal, and each dose is identified by product name, lot number, and expiration date. Therefore, blister packaging ensures product integrity from the producer directly through distribution to the consumer.

Material used in blister packaging

1. PVC

The most basic material for the forming web is polyvinyl chloride (PVC). The principal advantages of PVC are the low cost and the ease of thermoforming.

2. PCTFE

Polychlorotrifluoro ethylene or PCTFE can be laminated to PVC to obtain very high moisture barrier.

3. **COC**

Cyclic olefin copolymers (COC) or polymers (COP) can provide moisture barrier to blister packs.

Advantages

1. Product integrity.

2. Product protection.

3. Tamper evidence.

4. Reduced possibility of accidental misuse.

5. Patient compliance.

Tamper-evident packaging

(TEP) means packaging that has an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible or audible evidence to consumers that tampering may have occurred.

Tamper-Evidence

The degree to which tampering is apparent to the observer. Tamper-Resistance: The degree to which it is difficult to tamper (and repair) without leaving evidence. A tamper-resistant package has an indicator or barrier to entry which, if breached or missing, can (reasonably) be expected to provide visible evidence to consumers that tampering has occurred.

Tamper- Evident Features

The packaging features listed below are considered to be acceptable forms of TEP provided they are validated in accordance with Clause Whilst these forms of TEP are acceptable, they should not be seen to be exclusive of other forms of TEP or to preclude technological innovation. Tamper-evident packaging must not be regarded as replacing or obviating the need for child- resistant packaging wherever the law requires such packaging. In selecting or developing tamper-evident packaging, consideration should be given to the special.

Film Wrappers

Transparent A transparent film with distinctive design is wrapped securely around the entire product container ensuring the product is completely sealed and a secure tight fit is achieved.

Blister or Strip Packs

Individual doses (for example, capsules or tablets) are sealed in plastic and/or foil. Blister or strip pack seals around individual compartments and the strip as a whole must be intact and complete.

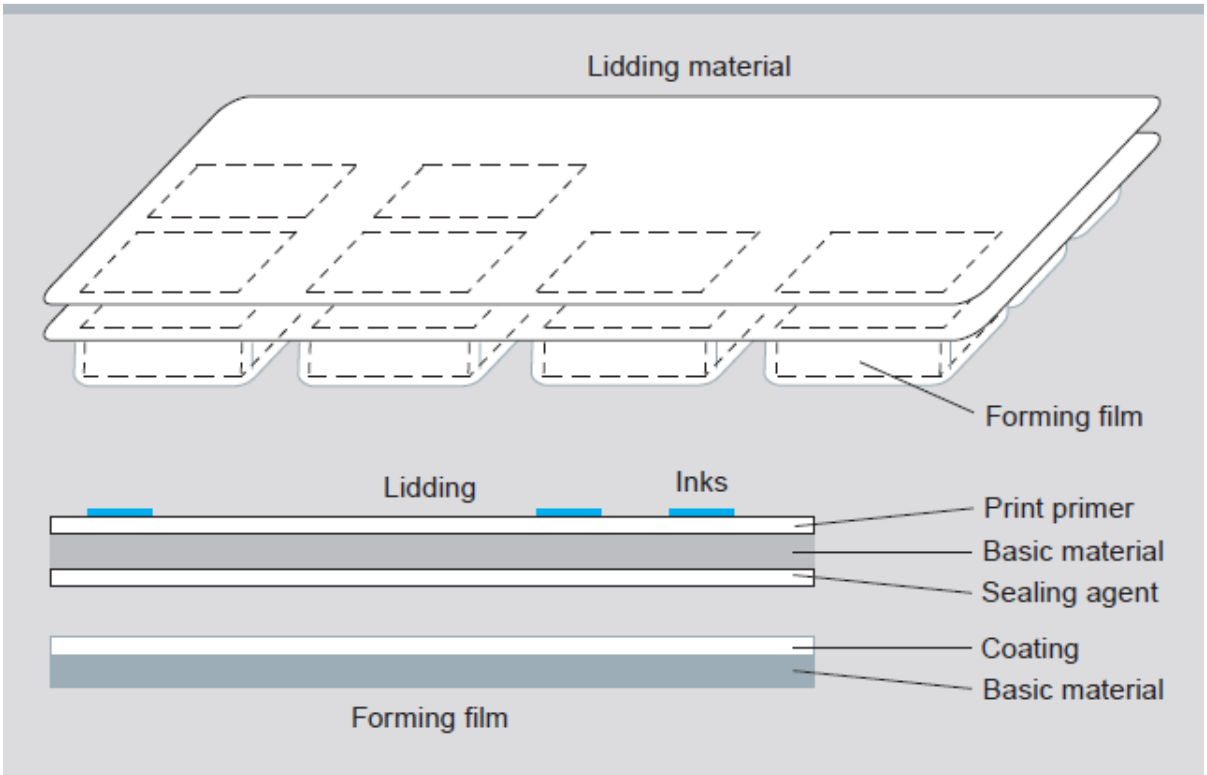


Figure 2: Basic components of blister packaging.

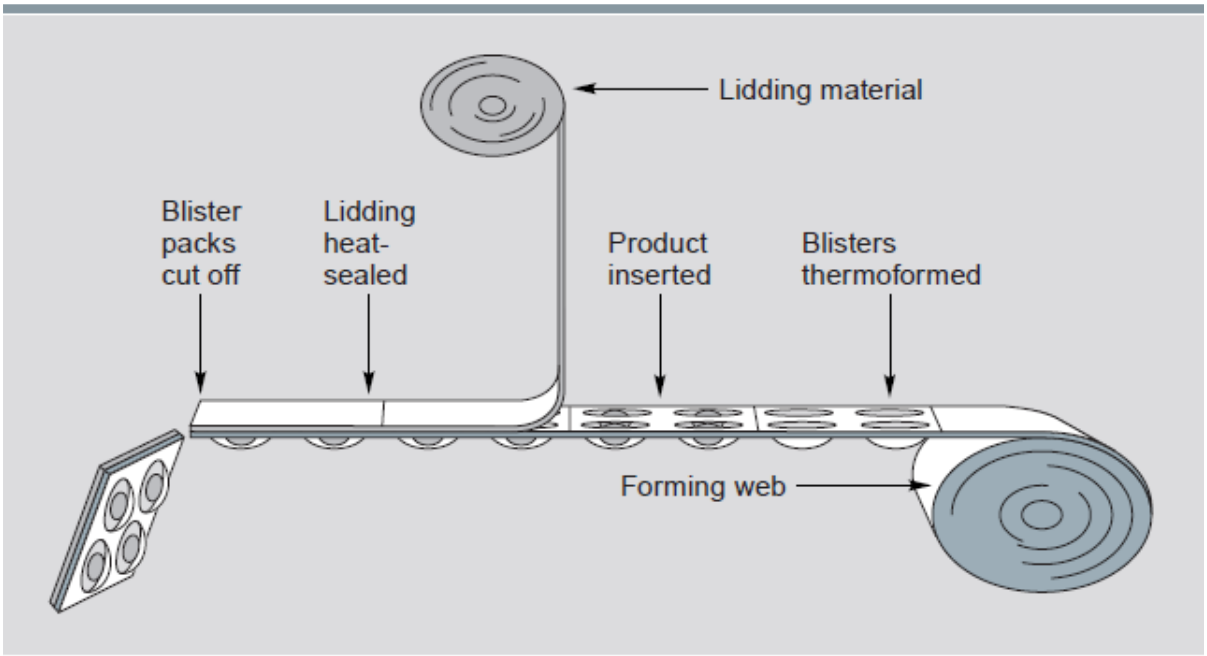


Figure 2: A typical procedure for blister packaging assembly.

Bubble Packs

The product and container are sealed in a plastic bubble and mounted in or on a display card.

Heat Shrink Bands or Wrappers

Bands or wrappers with a distinctive design are shrunk by heat to tightly seal the union of the cap and container.

Pouches, Sachets and Form Fill Seal Packs

The product is enclosed in an individual pouch or sachet that must be ripped, peeled open or broken to gain access to the product.

Container Mouth Inner Seals

Paper, thermal plastic, polystyrene foam, plastic film, foil, or combinations thereof, with a distinctive design is sealed to the mouth of a container under the cap.

Design

During design of TEP, the following aspects must be considered.

a. Suitability of the packaging for its intended purpose.

b. Compatibility of the packaging components.

c. Compatibility of the packaging components with the packaging process.

d. Presence of the required TEP statements on the final pack. The tamper-evident packaging features must be designed to remain intact, when handled in a reasonable manner, during manufacture, distribution and retail display.

Specifications

In recognition of the variability of packaging components, the sponsor must ensure that clear and concise specifications are developed and agreed between the packaging material supplier and the product manufacturer.

Specifications must include functional / performance criteria and must include reference to approved engineering drawings where appropriate.